Speaker abstracts

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Theme: Breast Cancer

The optimal duration of adjuvant endocrine treatment in breast cancer
Thursday, November 18th 2010, 09.00–10.00 (Erato C Hall)
Meet the expert: The optimal duration of adjuvant endocrine treatment in breast cancer
Stephen Johnston

Ways to overcome resistance to endocrine therapies in breast cancer
Thursday, November 18th 2010, 10.15–10.55 (Terpsichore A Hall)
Lecture: Ways to Overcome Resistance to Endocrine Therapies in Breast Cancer
Stephen Johnston

Anthracyclines should remain a component of adjuvant chemotherapy in breast cancer
Friday, November 19th 2010, 16.15–17.00 (ERATO AB)
Lecture: Anthracyclines should remain a component of adjuvant chemotherapy in breast cancer
Norman Wolmark
Co-authors: Luca Gianni, Larry Norton, Thomas M. Suter, Gianni Bonadonna and Gabriel N. Hortobagyi

Purpose: To review data relating to anthracyclines in the adjuvant treatment of early breast cancer.
Design: This is a report from a seminar in which the future of anthracyclines in the adjuvant treatment of breast cancer was considered. In particular, the questions of whether anthracyclines should now be discarded and replaced by taxanes was addressed.
Results: Accumulating data from large randomized trials indicate that genetic markers may have a role in predicting sensitivity to cytotoxic drugs. However, no reliable, validated test is available for predicting sensitivity to anthracyclines in particular. Topoisomerase II alpha amplification and/or deletion, especially in conjunction with human epidermal growth factor receptor-2 amplification, has been proposed to fulfill this role but more data are needed. Currently, only one published trial has shown that a taxane-based regimen may be superior to an anthracycline-based regimen, but several trials indicate that combinations including both anthracyclines and taxanes may be better still. Further studies aimed at optimizing anthracyclines and taxanes in combination, and integrating biologic agents, seem to be the way forward. There is no validated test that can determine whether anthracyclines can be of greater benefit than other agents for individual patients.
Conclusion: Anthracyclines have been extensively tested in clinical trials spanning several decades; currently, there are insufficient data to recommend replacing them in the adjuvant treatment of breast cancer.

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Theme: Breast Cancer & Cancer Screening

Breast cancer screening
Friday, November 19th 2010, 13.30–14.10 (ERATO C)
Lecture: Breast cancer screening
Wendy Chen

Theme: Breast Cancer & Novel Therapeutics

Optimal adjuvant therapy for patients with HER2+ disease
Saturday, November 20th 2010, 12.30–13.15 (ERATO AB)
Lecture: Optimal adjuvant therapy for patients with HER2 positive disease
Valentina Guarneri

HER2 is over expressed or amplified in 15–20% of breast tumors, and confers a more aggressive clinical behaviour. The introduction of the monoclonal antibody against HER2 trastuzumab led to a substantial improvement of prognosis. In the adjuvant setting, the results of six phase III randomized trials have been published or reported so far, exploring the benefit of adding trastuzumab to chemotherapy. Different administrations of trastuzumab in terms of schedule, timing and duration have been tested. Overall, these trials have included more than 10,000 women with HER2 positive breast cancer: five of these trials have demonstrated the superiority of adding trastuzumab to chemotherapy as compared to chemotherapy alone. Therefore, trastuzumab is now an essential component of the adjuvant treatment plan for HER2 positive disease. However, several issues deserve further attention. First of all, adjuvant trastuzumab is commonly prescribed to HER2+ breast cancer patients irrespectively of nodal status, while the majority of the patients enrolled in the adjuvant trastuzumab trials had nodal involvement. Moreover, no data on patients with node negative disease and tumor size less than 1 cm are available. A growing body of literature is showing that patients with T1a-b,N0 HER2+ tumors have a higher rates of recurrence as compared to HER2- tumors. These data indirectly suggest a potential benefit of trastuzumab based therapy for these patients; however,
since this population was not included in the adjuvant trials, the optimal adjuvant therapy is still to be defined. In this perspective, the cardiac safety issue appear even more important. In spite of applying careful patient selection in respect of cardiac function and cardiac morbidities, both symptomatic and asymptomatic cardiac dysfunctions have been reported in the majority of large trastuzumab adjuvant trials. In particular, even if reversible in the majority of the cases, the clinical impact of asymptomatic LVEF decline on long term cardiac morbidity and mortality is still unknown. The optimal trastuzumab duration is still a matter of debate; the choice of 1 year administration in the adjuvant trials have an empirical basis only. The data from the 2-year arm of HERA are still lacking. Exploring potentially less toxic regimens remain a major clinical issue. Several large randomized trials exploring shorter trastuzumab duration are ongoing across several European countries (the Phare trial in France, the Solt trial in Finland and other north European countries, The Persephone trial in UK, and The Short-Her trial in Italy). Other anti-HER2 agents are under evaluation as adjuvant therapy for HER2 positive breast cancer. The dual TK inhibitor of HER1 and HER2 lapatinib is currently approved for the treatment of metastatic breast cancer failing trastuzumab therapy. A large phase III randomized adjuvant study, the ALLTO trial, has completed the accrual. Neratinib, a TK inhibitor of HER1, 2 and 4, is under evaluation in a large randomized, double blind, placebo-controlled adjuvant study in patients who have completed adjuvant trastuzumab no longer than 2 years before and free from recurrence.

Intra-operative radiotherapy for breast cancer; an innovative approach for the 21st century
Friday, November 19th 2010, 09.00–09.40 (ERATO AB)
Lecture: Intra-operative radiotherapy for breast cancer; an innovative approach for the 21st century

Jeffrey Tobias (on behalf of the TARGIT Trialists Group)

Background: Following breast conserving surgery, about 90% of “in-breast” local recurrences occur within the index quadrant, despite the presence of multicentric cancers elsewhere in the breast. We therefore felt that restricting the radiation therapy to the tumour bed might be adequate in selected patients with early breast cancer, with the potential advantage that it might be possible to deliver this form of targeted irradiation as a single intra-operative treatment during the definitive surgical excision, under the same general anaesthetic. This approach would potentially have significant benefits both for patients and also for healthcare systems.

Methods: Having safely piloted the new technique of single dose targeted intra-operative radiotherapy (TARGIT) using Intrabeam [first patient treated at UCH in 1998 and pilot study published 2001], we launched the TARGIT-A trial (www.thelanetc.com/protocol-reviews/99PRT-47) on 24 March 2000. Female patients ≥ 45 years with invasive ductal breast carcinoma suitable for breast conserving surgery were randomly allocated to receive either TARGIT (i.e. ‘Single-shot’ intra-operative radiotherapy), or whole breast external beam radiotherapy (EBRT). Postoperative discovery of predefined factors (e.g., lobular carcinoma) could trigger addition of EBRT to TARGIT, which proved necessary, in the opinion of the supervising team, in about 15% of cases. In other words, in about 85% of patients randomly allocated to the TARGIT arm, no additional EBRT was given. The primary outcome measure of the study, analysed by intention-to-treat, was a non-inferiority margin (2.5%) of local recurrence in the conserved breast. Patients could be treated by TARGIT at the definitive surgical procedure (“pre-pathology group”) or after histological assessment of the excised specimen (“post-pathology group”). Either of these pre-defined policies was acceptable within the trial protocol.

Findings: 2323 patients were randomized from 28 international centres over 10 years. The study has enough patients with a median follow up of more than 4 years to detect the original non-inferiority margin of 2.5% with an 80% power and 95% confidence. Median age was 63 yrs (IQR 57–69), median tumour size 12mm (IQR 9–18mm), lymph node involvement 17% +ve. The overall number of complications and major toxicity (37/1113 TARGIT vs. 44/1119 EBRT, p = 0.44) were equivalent, but radiotherapy toxicity (RTOG grade 3) was lower in the TARGIT group; 6 vs. 23 (p = 0.004). The combined surgical-TARGIT treatment added approx 40 min to the overall operative time, but avoided 15–25 visits (more, in some centres) for treatment, preceded by at least one visit for radiotherapy treatment planning. At a follow-up period of 4 years, there was no significant difference in the Kaplan-Meier estimate of local recurrence in the conserved breast between TARGIT and EBRT (1.2% (95% CI 0.53–2.71) vs. 0.95 (95% CI 0.39–2.3), p = 0.41).

Interpretation: The TARGIT approach is safe. Local recurrence with single dose TARGIT is comparable to EBRT delivered over several weeks in this selected group of patients, at a 4-yr follow-up. Most patients did not require additional EBRT. Long term follow-up is obviously essential, and will continue. We regard these initial results as extremely encouraging, particularly since breast cancer is such a common condition that this single diagnosis constitutes a substantial portion of the workload of most radiotherapy departments.

Theme: Breast Cancer & Translational Research
mTOR inhibitors
Thursday, November 18th 2010, 09.00–10.15 (TERPSICHORE A)
Scientific Symposium: Novel therapeutic approaches in breast cancer
Fabrice André

PI3K/AKT/mTOR pathway is activated in around 30 to 40% of breast cancer. Several molecular alterations can lead to mTOR activation including tyrosine kinase activation (EGFR, Her2, IGFIR...), PI3KCA mutations, PTEN loss. Preclinical studies have suggested that aberrant mTOR pathway activation could lead to resistance to endocrine therapy and trastuzumab. Based on this background, mTOR inhibitors have been evaluated either single agent or in combination with standard. When provided as single agent, everolimus induces a 13% response rate in metastatic breast cancer patients, when administered daily. Two phase I trials have evaluated the tolerability and efficacy of adding everolimus to trastuzumab and chemotherapy. These two trials reported high rate of objective response in patients who were refractory to both chemotherapy and trastuzumab. Finally, one phase II randomized trial has evaluated the benefit of adding everolimus to aromatase inhibitors. In this phase II randomized trial, the everolimus arm was associated with an increase rate of clinical response (p = 0.06) and increased rate of Ki67 normalisation. Based on these early trials, three registration phase III trials have been developed namely BOLETO I, II, III. Two major questions arise regarding the optimal use of mTOR inhibitors. First, preliminary data have suggested that PI3KCA mutations on exon 9 could predict for the efficacy of everolimus when combined with letrozole. Second, several teams have described that inhibiting mTOR could lead to feedback loops that in turn activate intracellular kinase. Based on this observation, the combination between mTOR inhibitors and IGF1R inhibitors has been evaluated and reported to present preliminary signal for efficacy.

Angiogenesis targeting
Thursday, November 18th 2010, 09.00–10.15 (TERPSICHORE A)
Scientific Symposium: Novel therapeutic approaches in breast cancer
David Miles

The concept of angiogenesis as a target for the treatment of cancer has been considered for many years but only with the biological and molecular identification of one of the key mediators of angiogenesis, vascular endothelial growth factor (VEGF), have clinical trials in this field been truly feasible. Inhibition of VEGF, using antibodies to the ligand, its receptor or inhibitors of VEGF receptor tyrosine kinase (TKIs), leads to pruning of vasculature and ‘normalisation’ which may lead to increased delivery of more conventional agents. Such changes have been observed both in animal models and in patients using dynamic contrast MRI.

An open-label, randomised phase III study (E2100) testing an antibody to VEGF (bevacizumab) in addition to weekly taxol, yielded an improvement in response rate and reduced the risk of disease progression (PFS) by about 50%. No improvement in overall survival was observed. Two subsequent
placebo controlled phase III studies with different chemotherapy regimens (AVADO and RIBBON-1) also demonstrated improvements in response rates but with more modest improvements in PFS and again no improvement in overall survival. As a consequence of these findings, the Oncology Drugs Advisory Committee (ODAC) voted against an extension of the accelerated approval of bevacizumab (Avastin) in breast cancer and indeed, voted to remove metastatic breast cancer from the Avastin label. The deliberations of the US Food and Drug administration are currently awaited. Trials of VEGF TKIs have been disappointing. While sorafenib increased PFS when added to capecitabine, trials with sunitinib have demonstrated no benefit or trials were abandoned early because of a likely negative outcome.

Studies examining the role of bevacizumab in the adjuvant setting have either completed recruitment (BEATRICE) or are ongoing (ESi103 and BETH). Clearly the results of these studies are awaited with interest but the negative result of the adjuvant colorectal study (C08), questions our understanding of micro-metastatic disease and its dependence on VEGF.

When considering dynamic imaging studies and aspects of the clinical trial data, it is clear that modulation of tumour vasculature by VEGF inhibition has profound, potentially beneficial effects in terms of tumour control. It is incumbent on the research community to increase our understanding of how these agents may be better targeted to those most likely to benefit, either in terms of clinical characteristics or molecular predictors of response. Similarly, our understanding of the VEGF dependency of micro-metastatic disease must be better understood to design relevant clinical trials in the adjuvant setting.

**Parp inhibitors**

*Thursday, November 18th 2010, 09.00–10.15 (TERPSICHORE A)*

*Scientific Symposium: Novel therapeutic approaches in breast cancer*

**Nicholas Turner**

Poly (ADP-ribose) polymerase 1 (PARP) is an enzyme that promotes DNA single-strand break repair, functioning as a single-strand break sensor that facilitates break repair. Single-strand break repair is required to repair the DNA damage of multiple chemotherapy drugs, and ionizing radiation, and multiple chemical inhibitors of PARP were developed initially as chemotherapies and radiation sensitizers. The clinical development of PARP inhibitors for this indication as anticancer agents was proceeding cautiously with concerns over toxicity, with uncertainty as to whether this approach would increase the therapeutic window. This all changed with the identification that cancers with defective DNA double-strand break repair by homologous recombination (HR) were intrinsically sensitive to PARP inhibitors. This sensitivity, often termed synthetic lethality, reflected the observation that cells with normal DNA repair pathways were not intrinsically sensitive to PARP inhibitors given as single agents, as the other DNA repair pathways, in particular HR, were able to compensate for impaired single-strand break repair. However, if cells were deficient in HR they were unable to compensate for PARP inhibitor–induced DNA damage, and cells became highly sensitive to PARP inhibitors. The tumor suppressor proteins BRCA1 and BRCA2 are both required for HR, and consequently cell lines deficient in these proteins are highly sensitive to PARP inhibitors. Crucially, PARP inhibitors through synthetic lethality targeting of deficient DNA repair targeted only the cancer cells, establishing a substantial therapeutic window.

The demonstration that breast and ovarian cancers arising in women with germ-line mutations in BRCA1 and BRCA2 are highly sensitive to the PARP inhibitor olaparib, with minimal toxicity, has brought PARP inhibitors to the forefront of cancer research. Although germ-line mutations in BRCA1 and BRCA2 account only for 1% to 2% of breast cancers, there are potentially multiple ways in which HR may be lost somatically in cancers. In breast cancer, BRCA1 promoter methylation occurs in 10% to 15% of cancers and results in loss of BRCA1 expression. BRCA1 expression is also suppressed commonly in the basal-like subtype of breast cancers. The suppression of BRCA1 in basal-like cancers may potentially explain the sensitivity of triple-negative breast cancers (of which 80% are basal-like) to the combination of the PARP inhibitor BSI201 in combination with gemcitabine and carboplatin. Recently it has also been shown that in vitro the phosphatase PTEN has unexpected nuclear roles and is required for normal HR. This potentially opens up PARP inhibitors to cancer with loss of PTEN through homozygous deletion or mutation.

Uncertainty exists over whether PARP inhibitors are best used as single agents, or in combination with chemotherapy. It is possible that the combination of PARP inhibitors with chemotherapy may maximize the potential of PARP inhibitors. Further clinical research is required to establish whether there are clinically meaningful differences between the multiple PARP inhibitors in clinical development, and establish if there is long term toxicity associated with PARP inhibition.

**Theme: Cancer Policies**

*Excellence in cancer care: the role of nice*

*Friday, 19th November 2010, 17.00–17.40 (ERATO AB)*

*Lecture: Excellence in cancer care: the role of nice*

**Fergus Macbeth**

The reputation that NICE has in many quarters is as an organisation that rations (or ‘denies’) access to new cancer medicines and by implication, therefore, a block to providing excellent cancer care in England and Wales. This caricature is perhaps understandable but unfair. In the eleven years since its inception it has provided a broad sweep of guidance to the National Health Service about clinically and cost effective care of cancer patients that has contributed significantly to the successful drive to improve services across the country. It has published ten cancer service guidance documents (‘Improving Outcomes in Cancer’) giving blueprints for how services for specific cancers should be configured and delivered. Seven clinical guidelines have been produced and four more are currently in development. Two of these (Metastatic spinal cord compression and Metastatic malignant disease of unknown primary origin) are perhaps the first time that these common but often neglected conditions have been addressed systematically by national guidelines.

The appraisal of cancer drugs has been more controversial, but over 10 years of the 90 or so decisions made about individual drugs for specific indications, the great majority were positive and supportive. A number of them also recommended use but for specific patient subsets or only in research, and so a relatively small proportion did not recommend use. Because NICE appraisal guidance is associated with a ‘funding direction’ which ensures that the drugs must be funded and made available, this has resulted in a significant new investment in direct cancer care. There are clearly challenges for the NHS in providing many of the latest, often expensive new drugs and many of the refusals by NICE recently have been because of very high cost and limited effectiveness. But NICE has for the past two years allowed its committees greater freedom when ‘End of Life’ medicines are considered and the government has encouraged the companies to offer ‘Patient Access’ schemes which provide free or subsidised drugs for limited periods, effectively reducing the price and allowing NICE to approve them.

NICE has a strong reputation within the UK and abroad for producing clear, evidence based guidance. Its decisions may sometimes be controversial but its processes are robust and transparent and engage health professionals and patients at all stages. It has made and will continue to make an important contribution to how cancer care is delivered.

**Theme: Cancer Prevention**

*Vaccination against HPV*

*Saturday, 20th November 2010, 13.10–14.25 (ERATO AB)*

*International Journal of Cancer Session 2: Cancer Prevention*

**Lutz Gissman**

Energy balance and its components (physical activity and body weight) are certain to play a role in the primary prevention of cancer, but may also impact tertiary prevention, affecting well-being and prognosis of cancer.
patients. Low levels of physical activity and overweight or obesity have been associated with various types of cancer, particularly of the colorectum and postmenopausal breast (for physical activity) or the colorectum, postmenopausal breast, liver and esophagus (for obesity). Possible mechanisms include effects on inflammation, immune function, insulin-like growth factors, insulin resistance, steroid hormones, vitamin D levels, and lipid metabolism. A yet unexplored possible mechanism linking energy balance to cancer risk includes effects on DNA repair capacity. Defects in DNA repair function are clearly carcinogenic and intriguing preliminary evidence suggests that regular exercise results in an adaptive response of enhanced antioxidant defenses and DNA repair.

Among cancer patients, initial clinical studies illustrate benefits of exercise training on quality of life or fatigue as well as fitness levels, strength and cachexia. Epidemiologic studies also suggest a positive influence of physical activity on prognosis, particularly for colorectal cancer patients. However, many questions remain regarding causality of the associations, interrelationships between exercise and body weight, and the most appropriate type and timing of exercise training of cancer patients for maximum benefit and minimal risk.

Biomarker in oncology
Saturday, 20th November 2010, 13.10–14.25 (ERATO AB)
International Journal of Cancer Session 2: Cancer Prevention
Magnus von Knebel Doeberitz

Cancer biomarkers are defined as measurable-specific alterations of a cancer cell either on DNA, RNA, protein, or on metabolite level. Ideally, these alterations or distinct expression patterns selectively occur only in the (pre-)cancer cells of interest but not in surrounding cells and tissues. They should enable the unequivocal identification of even very few isolated (pre-)cancer cells in a tissue biopsy or any other clinical sample. The mechanistic understanding of molecular pathways leading to cell transformation and metastatic spread allowed to define candidate biomarkers based on evidence based molecular hypotheses of how a distinct cancer may occur. Prevention of cervical cancer by early detection is since the early success of the Pap-test a paradigm of successful cancer early detection and prevention programs. The Pap test, however, is hampered by important technical limitations. Recent advances in the molecular understanding of how harmless HPV-infections progress into neoplastic lesions allowed defining novel biomarkers that appear to resolve several shortcomings of the currently used early detection techniques in cervical cancer screening.

Recent research allowed to define molecular mechanisms that mediate the switch from harmless transient productive HPV-infections into potentially dangerous transforming HPV-infections. Based on shifts of the epigenetic methylation pattern of HPV-genomes in basal squamous epithelial cells overexpression of the HPV E6 and E7 genes is triggered to initiate cellular transformation. The cyclin dependent kinase inhibitor p16INK4a is strongly up-regulated upon deregulated expression of the viral oncogenes in epithelial stem cells of the basal and parabasal cell layers. Antibodies directed against p16INK4a have been developed and used to highlight HPV-transformed cells in histological section, cytological samples and also for the measurement of the amount of p16INK4a released from dissolved HPV-transformed cells collected as cervical samples. Many clinical studies have shown that this novel biomarker concept substantially improves the sensitivity and specificity of current cervical cancer screening techniques. At the conference we will discuss - as an example - how the elucidation of defined molecular pathways in HPV-associated cancers allows to define molecular biomarkers that are indeed specific for the neoplastic state of cells and their clinical potential clinical impact to improve future cancer early detection and prevention concepts.

Theme: Cancer Staging
Cancer staging and prognosis in the era of personalized cancer treatment
Saturday, 20 November 2010, 15.45–16.30 (TERPSICHERE A)
UICC Session 2: Cancer Staging and Prognosis in the Era of Personalized Cancer Treatment
Mary Gospodarowicz

Cancer staging is an essential element in classifying and measuring the anatomic disease extent of disease. And this measurement is elementary in evaluating the effectiveness of our intervention. Shifts in stage are the earliest indication of effective screening and early detection programs, evaluation of the impact of practice guidelines, and quality of care.

The UICC develops the TNM cancer staging classification that is internationally acceptable, clinically relevant, and useful for cancer control efforts. The UICC TNM Prognostic Factor Project provides evidence and consensus based cancer staging classification for worldwide use. Working across the world necessitates engagement while paying attention to the expertise and published evidence. For the classification to be adopted, opinion leaders’ acceptance and engagement is essential. To be relevant to clinical practice, staging must have a significant impact on cancer outcome, or selection of treatment methods. With treatment increasingly being tailored to each patient and improved outcomes, prognostic factors need continuous reevaluation. It is likely that progress will occur along at least two axes. The first is that of improved characterization of cancer biology such as genetic and molecular characteristics of individual cancers, and the second improved characterization of disease extent with improved molecular imaging probes. The knowledge of anatomic disease extent will always be required to minimize treatment exposure. Improved diagnostic methods, and especially more accurate characterization of microscopic disease extent could help define a more homogeneous grouping of patients with similar disease characteristics and tumor-related prognostic factors, for a specified disease. Knowledge of genetic or molecular factors might further add to the improved prediction of outcome and greater individualization of therapeutic interventions. However, grouping of patients into similar categories will continue to be required to assess the impact of new technology in patient assessment and new therapies on outcome.

The UICC TNM Prognostic Factor Project also responds to a growing body of knowledge and growing number of new molecularly defined disease entities, new biomarkers and prognostic factors that are essential in defining treatment and outcomes, and deals with the challenges and impact on taxonomy. With the grant support by CDC, the TNM Project engages through its Global Advisory Group, a growing number of the National Committees on Cancer Staging, extends collaborative initiatives with WHO, AJCC, CDC, Cochrane Collaboration, and other partners.

Theme: Carcinogenesis
Oncogenomics
Thursday, 18th November 2010, 12.15–13.30 (ERATO AB)
International Journal of Cancer Session 1: Carcinogenesis
Peter Lichter

Integrating profiling and functional analysis
Thursday, 18th November 2010, 12.15–13.30 (ERATO AB)
International Journal of Cancer Session 1: Carcinogenesis
Jan Mollenhauer

Nowadays, tumors can be profiled with a broad repertoire of techniques at virtually every molecular level. Expression profiling at mRNA level has been complemented by profiling methods for miRNAs and other non-coding RNAs. Novel breakthroughs in proteomics allow for comprehensive determination of differential proteome profiles in cancer. Finally, chip-based techniques and genome sequencing allow for genetic and epigenetic profiling to uncover predisposing and somatic alterations in cancer. The novel high-throughput sequencing methods additionally allow for expression profiling of miRNAs and non-coding RNAs at unprecedented resolution. A general feature of these profiling methods is that they commonly deliver sets of several hundreds of molecules with differential activity levels in cancer. A functional analysis of such large candidate sets is of critical importance for discerning causal from correlative alterations, because causal alterations can subsequently be used for systematic translation into novel, personalized therapeutic approaches. The concept of cancer stem cells has
profound impact on the question, which profiles might represent the most promising sources for such efforts. From this perspective, somatic mutations recovered by genome sequencing represent a favorable starting point, because these can be assumed to be largely invariant, when comparing “bulk” cancer cells to the cancer stem cells.

Weighing the different in vitro functional genomics strategies against each other, studies of gene function by transient transfection methods rapidly reach a threshold, where they become uneconomic. By contrast, the construction of panels of stable cancer cell lines with targeted engineering of genes and genetic alterations of interest provides a permanent resource for systematic studies of relevant aspects of cancer, such as cancer growth, invasion, and drug resistance. Further, they can directly be forwarded to in vivo studies and systematic drug screens.

We use synthetic biology approaches to engineer systems for the targeted genetic manipulation of cancer cells. By employing recombination-based techniques, these systems allow for the construction of isogenic, i.e. genetically identical, stable cancer cell lines with inducible or constitutive upregulation or knock-down of one or two target genes in any desired permutation. The technique allows operating at the critical scale for coming from molecular profiles to systematic functional analyses. In a prototype screen, we selected from profiling studies a set of 120 candidate genes for melanoma and constructed a panel of 120 isogenic stable cell lines. A targeted functional genomics approach delivered numerous primary hits for new modulators of cancer growth. Follow-ups so far identified one novel oncogene highly upregulated across various cancer types as well as a second promising drug target. Inactivation of the latter causes synthetic lethality selectively in cancer cells with a point mutation in a particular oncogene. This provides an example for how to translate comprehensive molecular profiles into novel conventional and personalized drug targets via systematic functional genomics. Within the Lundbeckfonden Center of Excellence NanoCAN, these efforts are now scaled up to systematically identify new drugs with selective killing activity for cancer stem cells.

Epigenomics and cancer

Thursday, 18th November 2010, 12.15–13.30 (ERATO AB)
International Journal of Cancer Session 1: Carcinogenesis
Carsten Müller-Tidow

Theme: Central Nervous System Tumours
Stereotactic radiotherapy: modalities in de novo and in recurrent disease
Friday, 20th November 2010, 12.30–14.30 (TERPSICHORE A)
Educational Symposium: Glioblastoma Multiforme—New Vistas in Treatment
Carsten Nieder

In newly diagnosed glioblastoma, the landmark phase III trial by the EORTC/NCIC has defined the current standard of care. As published by Stupp et al., postoperative treatment consists of external beam radiotherapy (EBRT, total dose 60 Gy in 30 fractions) with concomitant administration of Temozolomide followed by further chemotherapy with Temozolomide. Chemotherapy might enhance the effect of radiotherapy, aiming either at additive cell kill or true radiosensitization, or treat microscopic out-of-field tumours with more than 300 patients reviewed by our group demonstrates that re-recurrences as long as the total dose is limited to 30–35 Gy. Anti-angiogenic agents such as Bevacizumab might improve delayed radiation effects of alkylating agents.

Cell-cycle pathways: angiogenic-inhibitors and role of targeted agent
Friday, 20th November 2010, 12.30–14.30 (TERPSICHORE A)
Educational Symposium: Glioblastoma Multiforme—New Vistas in Treatment
Marc Sanson

Practical management: steroids, anticonvulsants and pseudo-progression
Friday, 20th November 2010, 12.30–14.30 (TERPSICHORE A)
Educational Symposium: Glioblastoma Multiforme—New Vistas in Treatment
Charles J. Vecht

Neuro-oncology ready for personalized medicine? the MGMT paradigm
Friday, 20th November 2010, 12.30–14.30 (TERPSICHORE A)
Educational Symposium: Glioblastoma Multiforme—New Vistas in Treatment
Michael Weller

Glioblastoma is the most malignant and most common primary intrinsic brain tumor. The standard of care for patients with glioblastoma includes surgical resection whenever feasible, radiotherapy and chemotherapy using the oral alkylating agent, temozolomide. Anaplastic gliomas are differentiated into pure astrocytomas, mixed oligoastrocytomas and pure oligodendrogliomas. Surgery is an accepted standard of care for these tumors, too, but whether radiotherapy can be replaced by chemotherapy as the first-line treatment, or should be combined with chemotherapy upfront, as in glioblastoma, is currently explored in clinical trials. The DNA repair enzyme enzyme, O6-methylguanine-DNA methyltransferase (MGMT), antagonizes the genotoxic effects of alkylating agents. MGMT promoter methylation predicts a
favourable outcome in patients with glioblastoma who are exposed to alkylating-agent chemotherapy, including temozolomide and nitrosoureas. That MGMT promoter methylation uniformly results in MGMT gene silencing and thus loss of MGMT protein expression, has remained difficult to demonstrate. Nevertheless, this biomarker of MGMT promoter methylation may in the future be used for clinical decision making at least in newly diagnosed glioblastoma. At present, it is largely used to stratify or even select glioblastoma patients for clinical trials. For instance, CENTRIC, the registration trial for the integrin antagonist, cilengitide, limits enrolment to glioblastoma patients with MGMT promoter methylation. Conversely, glioblastoma patients lacking MGMT promoter methylation, who may derive little benefit from temozolomide chemotherapy, are eligible for some European trials where novel agents are explored in the newly diagnosed setting in combination with radiotherapy alone. In other subtypes of glioma, such as anaplastic gliomas, the relevance of MGMT promoter methylation might extend beyond the prediction of chemosensitivity, and could reflect a distinct molecular profile predicting responsiveness to radiotherapy as well. A broader clinical use of this biomarker is not yet feasible because major prerequisites for standardized tests have not been met, and difficulties in reproducibility across laboratories persist. Standardization of MGMT testing requires comparison of different technologies across laboratories and prospectively validated cut-off values for prognostic or predictive effects. Future clinical trials are necessary to determine, for each subtype of glioma, the degree to which MGMT promoter methylation is predictive for response to specific treatments, or prognostic for response to genotoxic therapies in a broader sense, and whether testing should become routine clinical practice. At present, except for the repeatedly confirmed prognostic value in newly diagnosed glioblastoma, the prognostic and predictive value of MGMT promoter methylation in patients with different types of glioma treated upfront or at recurrence has remained controversial.

**Theme: Clinical Trials**

**Ethics of new drug trials with focus on phase 0**

**Friday, 19th November 2010, 12.30–14.30 (TERSICHORE A)**

**Educational Symposium: Design and Implementation of Clinical Trials in Oncology**

**Silvia Camporesi**

The drug development process is slow, time consuming and the regulatory burden hampers the recruitment and completion of clinical trials. It currently takes 12 to 15 years from drug discovery until marketing, compared with an average of 8 years in the 1960s. Since 2004, with the publication of FDA Concept Paper titled “Innovation or stagnation?”, regulatory agencies in US and Europe have recognized this problem. As a response, in 2006 new regulatory guidelines concerning early clinical trials have been issued, focusing on pharmacodynamic endpoints, and that require a lesser amount of preclinical data in animals. These are the guidelines on so-called “Phase 0 trials”, which have no intention to treat. From a scientific and regulatory point of view therefore that the pressing need for updating clinical research been recognized. But new guidelines on clinical trials alone are not going to solve the problem. Clinical research requires also the human factor: participants. From 2000 to 2007, 40 % of CTEP-sponsored trials failed to achieve minimum accrual objectives, and delayed study activation was identified as a major culprit behind accrual failure. Not only, but currently, fewer than 5 % of eligible adult patients with cancer participate in clinical trials.

From its start, the ethics of clinical research has been heavily focused on the protection of subjects. This is understandable, as all the clinical research ethical guidelines were written in the aftermath of the WWII. But, as these historical conditions do not hold anymore, and as data demonstrate that increased participation could have beneficial effects on advancing medical knowledge, the ethical foundations of clinical research should also consider the other side of the coin, namely that patients have an interest in participating in research, as they have an interest in its advancement. Several authors have argued in favor of the moral obligation to participate in research, on the basis of the arguments of fairness and reciprocity, and promotion of the public good of biomedical knowledge.

In my talk I will propose a new approach, based on the libertarian paternalistic (LP) view developed by Cass Sunstein and Richard Thaler, to make these ethical arguments more concrete. Within this LP perspective, subjects would be ‘‘nudged’’ towards participation in research: patients who meet the criteria for enrollment and have exhausted standard treatment would be presented with the option to participate in a clinical trial. The respect for their autonomous decision would be preserved by retaining the possibility of opting out. Such a simple change in an initial condition could have striking effects in practice, as a similarly simple change in the default option in the context of organ donation shows. As Phase 0 trials do not offer any therapeutic benefit to the participant, they could represent the paradigmatic case of this shift in the ethics of clinical research, which envisages researchers and subjects as partners in the promotion of the common good of biomedical knowledge.

**Real examples of clinical trial design from the IEO breast programme**

**Friday, 19th November 2010, 12.30–14.30 (TERSICHORE A)**

**Educational Symposium: Design and Implementation of Clinical Trials in Oncology**

**Giuseppe Curigliano**

Conduction of clinical trials in Europe is approaching a state of crisis. Layers of bureaucracy at participating institutions and other government agencies slow the review process from concept to protocol approval. Some trials remain uncompleted because of poor enrollment, lack of interest, excessive administrative burdens, and inadequate funding. Current protocol initiation is plagued by inefficiencies, overlapping oversight, and lack of standardized collaboration between the research groups and industry. Many steps in the review process are redundant, and there are many oversight committees with different objectives and responsibilities. At European Institute of Oncology (IEO) we implemented strategies to improve clinical research. Specific changes have been done in several areas: 1) Speed and efficiency of the design, launch, and conduct of trials. 2) Innovation in translational science and trial design. 3) Trial prioritization according to scientific strength and according to disease subpopulation, selection, support, and completion. 4) Incentives for patient and physician participation. We created a scientific steering committee (Strategic Scientific Committee) to better define the trials with the highest priority. Validated biomarkers and maintenance of tissue banks will be necessary for all the future personalized medicine studies. With many established standard-of-care therapies already in place and hundreds of potential therapies in the arena, innovative trial designs are mandatory. This is the main approach of trial design in our breast cancer program. We selected and implemented research according to innovative trial design. Real-life examples of these designs include: 1) Multigroup and multistage design. Uses intermediate outcomes and tests new agents and combinations against a single control group. 2) Adaptive trial design. Uses Bayesian analysis during trial to allow study groups to be eliminated and patients requirements to be reduced. 3) Predictive biomarker trial. Stratifies patients according to biomarker status. 4) Progression free survival (PFS) trial. 5) Randomized phase II trials. 6) Simultaneous multigene trials. All trials are designed for subpopulation of breast cancer patients. Our program’s success depends on increased participation of patients in the studies. Obstacles to physician participation include the time required, a lack of academic recognition for participation, inadequate teaching and mentoring for clinical trialists, and inadequate cost reimbursement. These factors can be addressed by involving young investigators and mentoring them for a career development program. For patients, obstacles include fear of clinical trials, variable coverage of care expenses, ignorance of trial options, complex eligibility requirements, and geographic distance from trial sites; all these potential limitations are rectified by straightforward improvements in expenses coverage and electronic tools that provide information about available trials. During the talk a specific trial we’ll be presented (inflammatory breast cancer model) with results and discussion.
Meta-analyses of clinical trials
Friday, 19th November 2010, 12.30–14.30 (TERSICHORE A)

Educational Symposium: Design and Implementation of Clinical Trials in Oncology

Sara Gandini

Meta-analysis is a statistical procedure that integrates the results of several independent studies considered to be “combinable.” Well conducted meta-analyses allow a more objective assessment of the evidence than traditional narrative reviews, provide a more precise estimate of a treatment effect, and are useful tool to investigate between-study heterogeneity. They are used to generate hypotheses for future trials, to study the consistency of trials with similar goals, and to obtain more precise estimates of effect.

The main difficulty in integrating the results from various studies regards the variability in terms of study design, methods employed and types of populations. Those who perform meta-analyses are aware of these problems and have proposed a number of guidelines to minimize their impact. First of all, a formal protocol should be written specifying the exact question under investigation and describing the studies that will be included in the analysis. Secondly, meta-analytic techniques should be used to investigate heterogeneity, validity of inclusion/exclusion criteria, and possible sources of bias, including publication bias. Thirdly, all eligible studies must be included in the meta-analysis. Data must be free of biases—such as those due to selection or exclusion criteria. In fact, if a conscious decision is made to exclude some, there is always a suspicion that this was done in order to achieve a desired result.

The Quality of Reporting of Meta-analyses (QUOROM) conference published a checklist that suggests items to be included in a meta-analysis report that can systematically influence estimates of treatment effects. This initiative also acted as a catalyst for improving the methods by which meta-analyses are conducted. Fixed and random effects models are used to combine studies. The former is based on the hypothesis that the true magnitude of the effect is assumed to be a constant, the latter that the effect can vary between studies. Such analyses are becoming increasingly popular in medical research where information on efficacy of a treatment is available from a number of clinical studies. If considered separately, any one study may be either too small or too limited in order to generalize conclusions about the effect of treatment. Combining the findings across such studies represents an attractive alternative to strengthen the evidence about the treatment efficacy and investigate reasons for the variability in the results. For healthcare managers and clinicians, careful reviewing of published meta-analyses and a balanced assessment of their deficiencies is likely to become an increasingly important way of resolving therapeutic uncertainty.

Historical look and vision for new trial design
Friday, 19th November 2010, 12.30–14.30 (TERSICHORE A)

Educational Symposium: Design and Implementation of Clinical Trials in Oncology

J. Gordon McVie

Theme: Cup
Diagnosis using molecular profiling assays—retrospective studies in patients with cup
Saturday, 20th November 2010, 12.30–14.30 (TERPSICHORE B)

Educational Symposium: Cancer of Unknown Primary Site

Frank Greco
Co-author: John D. Hainsworth

Cancer of unknown primary site (CUP) is a syndrome consisting of many types of cancers, and as diagnostic techniques improve patient management continues to evolve. Molecular profiling of tumors may aid in defining the primary site of origin. Several molecular assays are reasonably accurate (80–90%) in recognizing known primary cancers, and the accuracy and clinical utility of these assays in CUP classification has been the subject of recent clinical research.

Indirect validation studies of several assays in CUP have correlated clinical features and immunohistochemical (IHC) staining patterns, and suggest the assays are reasonably accurate (average positive correlations 85%). One study provided a direct measure of accuracy, by evaluating the initial biopsy in a select group of CUP patients who months to years later had their latent primary site discovered, thus providing a direct validation of the assay (75% accurate; 15 of 20 tumors).

To further determine if molecular profiling adds to the standard pathologic evaluation in CUP, and to define the outcome in the subset of patients with a ‘‘cancerous profile’’ we completed one retrospective evaluation and continue a prospective study of the BioTheranostics RT-PCR molecular assay (Cancer TYPE ID). In the prospective evaluation 149 CUP patients had the assay successfully performed on their diagnostic biopsy, and 97% had a primary site predicted (20 different sites; intestine in 16%; non-small cell lung 11%; breast 9%; liver 6%; ovary 5%; pancreas 5%). In 59 patients, a single primary site was predicted by IHC staining, and in this group the molecular assay diagnosis was obtainable in 52, and matched the IHC prediction in 40 (77%). The correlations in breast (100%), intestinal-colorectal (93%) and lung adenocarcinoma (74%) are notable. In the other 97 patients in whom IHC was consistent with 2 or 3 possible primary sites the assay matched one in only 45%. In 21 CUP patients with a colorectal diagnosis the response rate to site-specific chemotherapy were 80% and the median survival about 20 months.

The retrospective study reviewed 42 patients with CUP and a ‘‘cancerous molecular profile.’’ The standard clinicopathologic features were frequently consistent with an occult colorectal primary, and 32 patients received either first or second-line regimens used for colorectal cancer; response rates were 50% and the median survival was 27 months.

Molecular profiling can accurately predict the primary site of origin in a majority of CUP patients. When a single primary site is predicted by IHC staining, the correlation with the molecular profile diagnosis is good, and the molecular assay may not be necessary. In the majority of patients IHC staining is not specific and molecular profiling assays can provide additional valuable information. The impact of site-specific therapies in CUP based on molecular assay diagnosis appears promising, particularly in the colorectal subset and the selected use of these assays in concert with the clinical features and IHC stains will likely change the therapeutic approach to many CUP patients. Additional prospective studies in CUP of molecular profiling directed therapy to determine if patient outcome is improved are necessary and ongoing.

Carcinoma of unknown primary site: current management and treatment
Saturday, 20th November 2010, 12.30–14.30 (TERPSICHORE B)

Educational Symposium: Cancer of Unknown Primary Site

John Hainsworth

Carcinoma of unknown primary site (CUP) is a common clinical syndrome, accounting for approximately 3% of all cancer diagnoses. After metastatic cancer is documented, usually on the basis of a biopsy of a metastatic lesion, further clinical and pathologic evaluation is indicated for the purposes of: 1) identifying a primary site or tissue of origin, if possible, 2) establishing whether the patient fits into a favorable treatment subset, and 3) establishing the extent of disease and prognosis.

The initial clinical evaluation includes a complete medical history, physical examination, chemistry profile, complete blood counts, urinalysis, and computed tomography scanning of the chest, abdomen, and pelvis. PET scanning also detects some occult primary tumors, although its benefit has been incompletely evaluated in this setting. All women should have mammography; men should have measurement of serum PSA. Additional evaluation should be based on clinical signs/symptoms or specific pathologic findings.

Improved methods of diagnosis are the most exciting new development in the management of CUP, and will be discussed more completely in other sections of this symposium. Traditional pathologic evaluation has included an assessment of histology, followed by pertinent immunohistochemical (IHC) staining. Although excellent at differentiating carcinomas from other cell lineages, the identification of specific adenocarcinomas, other than...
prostate cancer (PSA stain) has been problematic. New IHC stains are somewhat more specific, although most still require interpretation in context of other clinical and pathologic features. In addition, molecular tumor profiling is under intense investigation currently, and will undoubtedly be of future use in establishing the tissue of origin in many of these patients.

Even if no primary site is identified, some patients can be categorized into one of several treatable subsets, on the basis of clinical and/or pathologic features. Subsets include: 1) women with axillary node metastases, 2) women with peritoneal carcinomatosis, 3) young men with features of extragonadal germ cell tumor, 4) squamous carcinoma involving neck nodes, 5) squamous carcinoma involving inguinal nodes, 6) neuroendocrine carcinoma, 7) carcinoma presenting with a single metastatic lesion, 8) men with elevated serum or tumor levels of PSA, 9) patients with ‘‘colon cancer profile’’.

Details of treatment in these patient subgroups will be presented.

For the group of patients who do not fit in to any of the treatable subsets, a trial of empiric chemotherapy is the current treatment standard. Although no phase III randomized trials exist, several ‘‘modern’’ regimens are generally accepted to be more active than either best supportive care or older regimens. These regimens include combinations of taxane/platinum, gemcitabine/platinum, or gemcitabine/taxane. With current regimens, response rates range from 30–40% in most reported series, with median survivals of 8 to 11 months. Limited experience with targeted agents exists, and has indicated some activity with inhibitors of the VEGF and EGFR pathways. However, the role of agents with these targets or others is currently undefined.

### Treatment directed by molecular profiling results: preliminary report of a prospective study

**Saturday, 20th November 2010, 12.30–14.30 (TERPSICHOIRE B)**

**Educational Symposium: Cancer of Unknown Primary Site**

**John Hainsworth**

Increasing evidence supports the ability of molecular tumor profiling to correctly identify the tissue of origin in the majority of patients with CUP. However, there is little data regarding the use of these putative diagnoses to select first-line therapy for these patients. Indeed, there is skepticism that established treatments for cancers of known primary site will be effective in CUP patients, due to fundamental differences in tumor biology. However, increasing anecdotal data, in addition to the retrospective data in patients with ‘‘colon cancer profile’’, suggests that at least a portion of patients with CUP will respond to treatment in a predictable way.

In 2008, we began a prospective trial to evaluate the use of a molecular assay (Cancer TYPE ID; BioTHERANOSTICS, Inc.) in identifying the tissue of origin and directing first-line treatment for patients with CUP. Patients with the diagnosis of CUP and formalin-fixed biopsy tumor specimens available were eligible. Patients with specific treatable subsets of CUP were excluded. Patients who were given a specific tissue of origin by the Cancer TYPE ID assay were treated with standard treated regimens for that particular type of cancer, while those without a specific tissue of origin were treated with an empiric CUP regimen as the current treatment standard.

To date, 110 patients have enrolled and have had the molecular profiling assay performed; 98 patients had specific diagnoses rendered, and 66 patients (60% of the total) received assay-directed therapy. The assay was unsuccessful due to inadequate tissue in 12 patients (11%); the remaining patients did not receive assay-directed therapy for other reasons (eg. rapidly declining performance status, refusal of assay-directed therapy, treatment considered urgent and initiated prior to assay result). Of the patients who received assay-directed therapy, 61 had specific primary sites identified, while 5 had molecular profiles that were non-diagnostic. Eighteen different primary sites were identified by the assay; most common groups included pancreas (11 patients), colorectal (8), urinary bladder (8), non-small cell lung cancer (5), and ovary (4).

Patient subsets are currently relatively small to evaluate separately for treatment efficacy. Of the 8 patients with colorectal cancer profiles, all received FOLFIRI/bevacizumab; 6 of 8 patients had partial responses or stable disease for greater than six months. The median overall survival for the entire group of patients was 12.9 months. The study is ongoing, with the goal of treating sufficient patients in the common subsets to be able to make a more definitive statement regarding the efficacy of site-specific therapy.

### The search for a molecular CUP ‘‘signature’’

**Saturday, 20th November 2010, 12.30–14.30 (TERPSICHOIRE B)**

**Educational Symposium: Cancer of Unknown Primary Site**

**George Pentheroudakis**

Carcinoma of unknown primary site (CUP) ranks as the fourth most common cause of cancer deaths and represents both a diagnostic and a management challenge. In CUP, the regression or dormancy of the primary tumor, the development of early, uncommon, systemic metastases, and the resistance to therapy are hallmarks of this heterogeneous clinical entity. Still, no consensus exists on whether CUP is simply a group of metastatic tumors with unidentified primaries or a distinct entity with specific genetic/phenotypic aberrations that define it as ‘‘primary metastatic disease.’’ Karyotypic analyses as well as single-gene, single-protein studies done on the expression of oncogenes, tumor- or metastasis-suppressor genes, as well as angiogenesis effectors did not identify a molecular aberration that is specific for CUP rather than metastatic malignancies. These studies showed frequent expression of oncoproteins, lack of activating epidermal growth factor receptor/c-Kit mutations or amplification, uncommon presence of tumor- or metastasis-suppressor gene mutations and highly active angiogenesis in CUP. Informative as they may be, these data have been observed in several solid tumors of known primary and failed to identify a CUP-specific molecular signature. The latter, if it exists, probably consists of a multigene expression pattern not captured by single-gene studies. Gene and protein microarray technologies offer promise for the unraveling of complex genetic programs that would either identify each CUP’s primary tissue of origin or instead define the CUP-specific molecular signature. Confirmation of one of the two hypotheses would either improve primary disease– oriented therapy or develop CUP-oriented treatments targeting molecular aberrations that drive neoplastic growth/dissemination.

### Identification of a new treatable subset: the colon cancer ‘‘profile’’

**Saturday, 20th November 2010, 12.30–14.30 (TERPSICHOIRE B)**

**Gauri Varadhachary**

Carcinoma of unknown primary (CUP) accounts for about 3–5% of all new cancers and is a challenging heterogeneous disease entity with an unmet research need. Over the last decade there has been an increased availability of sophisticated diagnostics including newer imaging and immunohistochemistry (IHC) options and more recently molecular profiling techniques, although innovative therapeutic interventions have lagged. Traditionally, patients with CUP have been treated with empiric chemotherapy doublets. There are at least two potential approaches that can be used to define CUP subsets and improve on therapy options for our patients. In the ‘‘target-based’’ approach, all CUP tumors may be evaluated for over-expression of molecular markers such as EGFR mutations, Her-2, Kras and others. It has not yet been established that this approach will benefit CUP patients given the variable correlation between marker over expression and therapeutic response although additional insight into novel targets that drive CUP biology may allow us to consider appropriate tests. The alternative ‘‘site-of-origi-” approach attempts to use IHC or gene expression studies to help identify CUP subsets with molecular profiles consistent with putative site of origin. This approach could potentially leverage the substantial development work focused on site-specific tumors. Our recent experience with this latter approach has been encouraging. In the last few years, we have come to recognize a new ‘‘favorable’’ CUP subset in association with a colon-cancer profile (CCP-CUP). Recognizing this group of patients is important with apparent therapeutic implications. Unlike most favorable CUP cancers which are based on anatomical distribution and histopathology, CCP-CUP may be best identified by pathologic evaluation including IHC and molecular profiling. By definition, these patients have a negative colonoscopy. Our retrospective and prospective studies suggest that patients with CCP-CUP have
immunohistochemical features, molecular profile, clinical presentation and course that resemble colon or appendiceal carcinoma. CCP-CUP is identified by CK 20 and CDX2 positive and (often, though not always) CK 7 negative IHC, and a molecular profile that is consistent with the profile of patients known to have metastatic colon cancer. Our early work suggests that these patients show substantial benefit from the use of specific therapeutic approaches developed for patients with metastatic colorectal tumors. There are limitations to IHC as have been described in known colorectal cancers including a decreased or even absent CK 20 expression as reported in microsatellite high (MSI-H) colon tumors and poorly differentiated tumors. We are also beginning to recognize the limitations of profiling assays. Our best approach is to present an integrated cost and clinically effective algorithm based on IHC and profiling so that they complement each other to provide our CCP-CUP patients with the best management options.

**Conclusion**

- Sparing the salivary glands through use of IMRT preserves salivary flow and significantly reduces the incidence of xerostomia in patients with pharyngeal tumors.

**Results**

- 129 patients with pharyngeal tumors (T1–4, N0–3, M0).
- Patients received 65Gy in 30 fractions over 6 weeks delivered using either CT planned parallel opposed lateral fields or parotid-sparing IMRT.
- Stratification in on area of the world accurately reflect results in other regions.

**Methods**

- The PARSPORT trial compared two radiotherapy delivery methods in the treatment of patients with pharyngeal tumours (T1–4, N0–3, M0).
- PARSPORT investigated the role of IMRT in reducing xerostomia in patients with head and neck cancer.
- Secondary endpoints included acute toxicities (CTCAE v3) and other late RTOG and LENT-SOMA radiation toxicities.
- Saliva collection was attempted from both parotid glands.

**Results**

- 94 patients (47 RT, 47 IMRT) were randomised between 2003 and 2007 from six UK centres.
- 80 patients had oropharyngeal tumours and 14 hypopharyngeal.
- Radiotherapy was given as primary treatment in 71 patients and post-operatively in 23, 22 patients had AJCC stage III disease.

**Results**

- Median follow-up was 44.0 months (IQR: 30.0–59.7).
- Twelve month LENT-SOMA ≥G2 xerostomia was reported in 74% (26/35) of RT and 39% (15/39) of IMRT patients (p = 0.002).
- Corresponding values at 24 months were 83% (20/24) and 29% (9/31) (p = 0.001).
- On the RTOG scale, 12 month ≥G2 xerostomia was reported in 65% (22/34) RT vs 39% (15/39) IMRT patients (p = 0.04).
- The 24 month incidence was 75% (18/24 RT vs 19% (6/32) IMRT (p = 0.001).
- Acute radiotherapy related ≥G2 fatigue was more prevalent in the IMRT group (65% vs 40% p = 0.02).
- No differences in acute mucositis or pain scores were seen. At 12 months, no statistically significant differences were seen in other late toxicities.

**Conclusions**

- Sparing the salivary glands through use of IMRT preserves salivary flow and significantly reduces the incidence of xerostomia in patients with pharyngeal tumors.

**Results**

- Results of a phase III multi-centre randomised controlled trial of intensity modulated (iMRT) vs conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN48243537; CRUK/03/005)
- Current Issues in Oncology (Organized by ESTRO): New challenges in head and neck cancers

**Aisha Mah**

**Background:**

- Xerostomia is the commonest late toxicity of RT to the head and neck. IMRT dose distributions reduce the dose delivered to parotid gland.
- PARSPORT investigated the role of IMRT in reducing xerostomia in patients with head and neck cancer.

**Methods:**

- The PARSPORT trial compared two radiotherapy delivery methods in the treatment of patients with pharyngeal tumours (T1–4, N0–3, M0).
- Patients received 65Gy in 30 fractions over 6 weeks delivered using either CT planned parallel opposed lateral fields or parotid-sparing IMRT.
- Stratification was by site of tumour and centre. The primary endpoint was incidence of LENT-SOMA ≥G2 xerostomia one year after treatment. Secondary endpoints included acute toxicities (CTCAE v3) and other late RTOG and LENT-SOMA radiation toxicities.
- Saliva collection was attempted from both parotid glands.

**Proportions of patients with ≥G2 toxicity were compared using exact tests.**

**For secondary endpoints a significance level of 1% was used.**

**Results**

- 94 patients (47 RT, 47 IMRT) were randomised between 2003 and 2007 from six UK centres. 80 patients had oropharyngeal tumours and 14 hypopharyngeal.
- Radiotherapy was given as primary treatment in 71 patients and post-operatively in 23, 22 patients had AJCC stage III disease.

**Plenary Lecture: Applying Research Lessons to the Treatment of Advanced Colon Cancer**

**John L. Marshall**

The treatment of colon cancer has undergone a recent revolution. Having moved from a 5FU only world and a median survival of 10–12 months to having 7 approved agents (in the US) and overall survivals reaching nearly 3 years, we are claiming great success. Indeed we should be pleased but we must recognize that we have not yet cured the disease, and we still use the “trial and error” method of treating patients. In essence, our treatment strategy is to give all the patients all the drugs, knowing that each treatment will only help a subset of patients. However, we are just entering the next revolution, and one that will realize the true benefit of targeted therapy. Centered around mutations in the EGFR pathway, we now recognize which subset of patients will NOT respond to the EGFR agents. This information results in only positive outcomes for patients: those who receive the drugs have a much greater chance of benefit and we no longer give these drugs to patients who will not benefit from them saving them time and toxicity. This new revolution will also be the key to the rapid, successful development of the next generation of cancer agents being tested today. Importantly, we must re-analyze the tools we currently utilize. Prime among them is the tumor sample, but newer data suggests that unless we control the conditions of tumor collection, we will not have accurate results. The concept of ischaemia time will be briefly explored. This overview represents only a small fraction of novel approaches being investigated for the treatment of colon cancer. With the successes targeting EGFR and VEGF pathways, with our increasing comprehension of the need for personalized medicine (not all treatments are for all patients), we will increase our dependence on tumor tissue, on measuring specific pathways, of determining which pathways our tumors are dependent upon (oncogene addiction). When asked what are the most promising future targets and agents, I actually answer they all will play a key role once we find the right patients to treat. The future is bright but highly challenging. New trial designs will be required. Cooperation among competitors will be required. Our goal should be returned to curing cancer, not merely prolonging survival by a few months. Cure is the expectation of our patients and society, and we should do our best to meet this goal. Cancer is a global problem but likely has local genetics. We recognize that gastric cancers vary around the world, but is the same true for colon cancer? Do the results of trials performed in one area of the world accurately reflect results in other regions.
evolved from single-center retrospective observational studies, to reports from rectal excision. Over time, there is ample evidence that surgical science has open technique, and investigated bladder and sexual (dys)function after mesorectal excision (TME) for rectal cancer, the 1990s reported a number of landmark studies demonstrating the survival effect of training and implementing this universal technique as well as hospital and surgeon volume on patient survival. Then, during the later part of the 1990s and early 2000s, papers investigating prognostic risk factors followed, including defining the circumferential resection margin and the role and timing of pre- and post-operative adjuvant chemo-radiation. Later came the definition of high-resolution MRI of the rectum to allow for preoperative identification of important surgical and pathological prognostic factors followed, including defining the circumferential resection margin and the role and timing of pre- and post-operative adjuvant chemo-radiation. Later came the definition of high-resolution MRI of the rectum to allow for preoperative identification of important surgical and pathological prognostic factors. The past decade has seen trials comparing laparoscopic vs open technique, and investigated bladder and sexual (dys)function after mesorectal excision. Over time, there is ample evidence that surgical science has evolved from single-center retrospective observational studies, to reports from national registries to prospective, multicenter studies and randomized clinical trials. With continued clinical investigation and refined research questions new milestones papers will appear in the management of rectal cancer and most likely an important share of them will be published in the BJS. This talk will illuminate some of the milestones made in rectal cancer over the past decades as envisioned by a presentation of selected papers published in the BJS.

**Update on EGFR targeting**

*Br J Surg,* 1982

**Current issues in Oncology (Organized by ESTRO): New challenges in head and neck cancers**

Aisha Miah

**Challenges in the diagnosis and treatment of HPV-related oropharyngeal cancer**

*British Journal of Surgery Sessions: Milestone Papers on Rectal Cancer in the BJS*

Jens Overgaard

**BJSS-milestone papers on rectal cancer in the BJS**

Kjetil Søreide

Progress in the management and outcome of patients with rectal cancer has been an endeavour across disciplines over the past decades. Obviously, success has derived from building on bricks of information and puzzling together the pieces of scientific progress one after another. However, some major leaps in understanding principles of disease have been made by a few owing to the works of many. A retrospective view of papers published in the British Journal of Surgery over the past half century may identify studies that have been deemed particularly valuable in the management of rectal cancer. Further, the evolution of the studies published in a high-ranked surgical journal over time, reveals that not only has understanding of the disease evolved but also the scientific approach to investigation has developed. According to the Web of Science, papers on rectal cancer in the major general surgical journals were scarce prior to the early 1980s. However, over the past decades there has been an almost exponential increase in papers covering this topic with BJS taking a definite lead in terms of number of papers published (>500 articles), total times cited (>15,000 citations), average citations per article (>30 per article per year) and the accumulated average citations per year for the topic (>260) in addition to having the most cited paper among the surgical journals for the topic (Heald et al. The mesorectum in rectal cancer surgery - the clue to pelvic recurrence? *Br J Surg,* 1982). Following the introduction of the principles of total mesorectal excision (TME) for rectal cancer, the 1990s reported a number of landmark studies demonstrating the survival effect of training and implementing this uniform surgical technique as well as hospital and surgeon volume on patient survival. Then, during the later part of the 1990s and early 2000s, papers investigating prognostic factors followed, including defining the circumferential resection margin and the role and timing of pre- and post-operative adjuvant chemoradiation. Later came the definition of high-resolution MRI of the rectum to allow for preoperative identification of important surgical and pathological prognostic risk factors for better selection and assessment of patients undergoing preoperative therapy. The past decade has seen trials comparing laparoscopic vs open technique, and investigated bladder and sexual (dys)function after mesorectal excision. Over time, there is ample evidence that surgical science has evolved from single-center retrospective observational studies, to reports from national registries to prospective, multicenter studies and randomized clinical trials. With continued clinical investigation and refined research questions new milestones papers will appear in the management of rectal cancer and most likely an important share of them will be published in the BJS. This talk will illuminate some of the milestones made in rectal cancer over the past decades as envisioned by a presentation of selected papers published in the BJS.

**Theme: Gastrointestinal (Colon/rectal) Cancer & Cancer Genetics**

**Hereditary colorectal cancer**

*Plenary Lecture: Hereditary Colorectal Cancer*

Astrid T. Stormorken

Introduction: Colorectal cancer (CRC) is the 3rd leading cause of death in the Western world. Environmental factors play a dominant role in the aetiology of most CRCs, but inherited predisposition can be a major risk factor. Familial colorectal cancer accounts for 10 to 15 % of all CRCs and about 5% are caused by mutations in high penetrant genes. The discovery of inherited mutations in genes associated with increased risk of cancer enables more accurate risk assessment, targeted surveillance, preventive measures and tailor-made treatment for high risk persons.

**Purpose of the lecture:**

*Give a brief summary of some of the hereditary CRC syndromes with identified germline mutations as Lynch syndrome (Hereditary non-polyposis colorectal cancer, HNPPC), Familial adenomatous polyposis (FAP), attenuated FAP (AFAP), MUTYH—associated polyposis (MAP), Peutz-Jeghers Syndrome and Juvenile polyposis. Address cancer risk in individuals who have families with clustering of CRC but who do not have one of the high risk cancer syndromes. Clinical features, genetics and management recommendations will be covered.

**Conclusions:**

Unlike many types of tumours, tumours of the colon and rectum are highly accessible through the use of endoscopy. Surveillance can prevent the development of advanced CRC and can also have implications for treatment. This makes it important to identify high risk individuals.

**Theme: Gastrointestinal (Noncolorectal) Cancer**

**Systemic chemotherapy for metastatic gastric or EGJ (cardia) adenocarcinoma: which drugs, which regimen, how many lines?**

*Educational Symposium (Organized by ESDO): Gastric and eso-gastric junction (cardia) adenocarcinoma in 2010 at the light of the expert conference held in Barcelona June 2010 (ESMO-WCGIC joined congress)*

Andrés Cervantes

Several drugs have been considered as active agents for the treatment of advanced gastric cancer. This is the case for 5-fluorouracil and some oral fluoropyrimidines, such as capecitabine or S1, doxorubicin or epirubicin, cisplatin and oxaliplatin, docetaxel, tritomotecan and more recently the anti-HER2 antibody trastuzumab. However, among those agents only cisplatin, docetaxel and trastuzumab have shown to be better than other therapies in trials designed for a superiority endpoint. On the other hand, oxaliplatin and capcitabine have been found to be acceptable agents in noninferiority trials or in meta-analyses.

The role of anthracyclines is largely debatable. Trials using them as single agents showed low responses and most of them were published during the eighties, when response assessment was mostly performed by WHO criteria, accepting the use of liver ultrasonography, as a tool. Data from the meta-analysis published by Wagner et al, suggests a significant survival benefit when anthracyclines were added to other combination schedules. However, this meta-analysis is not based upon individual data from patients included in those trials. Despite this, epirubicin has been used in the ECF regimen, giving consistent and reproducible results over several randomised trials, including more than thousand patients at Royal Marsden. Nevertheless, the specific value of the addition of epirubicin is difficult to assess with the currently available information.
The addition of docetaxel to a conventional doublet of cisplatin and 5FU in the DCF regimen was also shown to offer better survival for advanced gastric cancer patients. However, it use it is not very extended, due perhaps to toxicity constraints, especially in patients with poor performance status. The combination of a platinum agent, cisplatin or oxaliplatin plus 5FU or capcitabine could be considered as an accepted practice. If HER2 is overexpressed, Trastuzumab should be added to the chemotherapy selected schedule. Docetaxel is added as a third drug more frequently for young patients with good performance status. DCF, ECF, or its variants ECX or EOX could be acceptable as standard comparators when designing phase III randomised studies.

In our current practice, a significant proportion of patients with advanced gastric cancer do progress after first line chemotherapy with a good performance status. A German randomized trial with a limited number of patients showed that second line chemotherapy with irinotecan could improve survival over supportive care alone. This trial supports the use of second line chemotherapy in good performance status individuals. Schedules using FOLFIRI or docetaxel combinations are more commonly employed and could prolong disease control in advanced gastric cancer patients.

**Adjuvant treatment to surgical resection?— post-operative chemotherapy (or radio-chemistry) in gastric and EGJ (cardia) cancer: is it standard or optional?**

**Friday, 19th November 2010, 12.30–14.30 (TERPSICHORE B)**

Educational Symposium (Organized by ESOO): Gastric and eso-gastric junction (cardia) adenocarcinoma in 2010 at the light of the expert conference held in Barcelona June 2010 (ESMO-WCGIC joined congress)

Roberto La Bianca

**Pre-operative work-up and principles of the surgery in gastric cancer**

**Friday, 19th November 2010, 12.30–14.30 (TERPSICHORE B)**

Educational Symposium (Organized by ESOO): Gastric and eso-gastric junction (cardia) adenocarcinoma in 2010 at the light of the expert conference held in Barcelona June 2010 (ESMO-WCGIC joined congress)

Christophe Penna

**Adjuvant treatment to surgical resection? - pre or peri-operative chemotherapy in gastric and EGJ (cardia) cancer is it a new standard?**

**Friday, 19th November 2010, 12.30–14.30 (TERPSICHORE B)**

Educational Symposium (Organized by ESOO): Gastric and eso-gastric junction (cardia) adenocarcinoma in 2010 at the light of the expert conference held in Barcelona June 2010 (ESMO-WCGIC joined congress)

Philippe Rougier

Surgery is the standard and main treatment for GC-EGJC without metastases, however most patients develop recurrences despite R0 resection and strategies to prevent recurrences and improve overall survival are warranted. Adjuvant chemotherapy (ACT) is not standard in absence of clearly positive trial and is feasible in only 50% of the patients because post-ump complications or poor nutrtional status, and results in a less than 10% benefit in overall survival (OS) in the most appropriate meta-analyses using individual data (HR = 0.81; p < 0.0001) (Paoletti X et al. JAMA, 2010; 303:1753.). Adjuvant chemo-radiotherapy (CRT) (US standard) seems more active but is limited to patients in excellent post-prooperative nutritional status. Peri-operative chemotherapy (POC) was developed because the low efficacy of ACT, the high percentage of patients unable to receive it, the ability to test the CT efficacy, and the down-staging of the tumour allowing more curative resection rate (R0).

Two large randomized trials have demonstrated the efficacy of POC:

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial evaluated POC (ECF regimen) on OS of 503 resectable GC-EGJC (stomach adenocarcinomas 74% of patients) and reported an increased OS after POC with a 5-year survival rate of 36% versus 23% (HR for death, 0.75; p = 0.009) and in the PFS (HR for progression or death, 0.86 < p = 0.001). (Cunningham D, et al. N Engl J Med 2006;355:11.)

The FNLC-FPCD trial conducted on 224 resectable GC-EGJC (lower oesophagus-GGC 74% of cases; GC 26% of cases) randomized to receive a preoperative chemotherapy (2–3 cycles: monthlu FU-P regimen) followed by surgery (n = 113) and postoperative chemotherapy (n = 111). POC resulted in a better 5-year OS (38% vs 24%; death HR: 0.69; p = 0.02); and 5-year DFS (34% versus 19%; HR 0.65; p = 0.003); in multivariate analysis : POC (p = 0.01) and distal site of the GC (p <0.01) were the only 2 independent prognostic factors and R0 resection rate was improved (84% vs 73%, p = 0.04). Toxicity was manageable (gr3/4 observed in 38% of patients) without increase in postoperative morbidity (Boige V et al. ASCOabstract: JCO 2007;25 : 4510; submitted for publication).

An EORTC trial reported an increase in R0 resection after preoperative chemotherapy and a recent meta-analysis was positive for OS (Ronellenfischt U et al. ASCO2010; JCO 2010:28:306s).

In conclusion, in case of potentially resectable GC-EGJC, POC must be considered because it significantly increases chances to get a curative resection and better DFS and OS. In the future better tolerated and more efficient chemotherapy will be tested and biologics will be tested (MAGIC2 trial & trastuzumab in HER2 positive) as well as different combinations of CRT.

**Gastroenteropancreatic neuroendocrine tumours**

**Thursday, 18th November 2010, 10.00–11.00 (ERATO C)**

Meet the Expert: Gastroenteropancreatic Neuroendocrine Tumours

**Bertram Wiedenmann**

Neuroendocrine tumors (NET) of the gastroenteropancreatic system have significantly increased over the past decades with a current incidence of approx. 5/100 000 and prevalence similar to gastric carcinomas (Modlin et al. 2008). Likely causes are an improved awareness among doctors, better diagnostic modalities such as improved immunohisto- and sero-diagnostics and also advanced imaging modalities, such as double balloon enteroscopy, MR Sellink, capsule endoscopy, PET-CT, etc.. Other causes may be also related to environmental and dietary factors.

Similar to adenocarcinomas, NET have to be subdivided according to their primary tumor location, histological state of differentiation, tumor extent and hormone activity/functionality. The latter is observed in less than half of all cases. Natural courses and excessive release (hypersecretion) of peptide and biogenic amines differ considerably between primaries. For example, pancreatic primaries are characterized by a faster tumor progression and the hypersecretion of peptide hormones, such as gastrin, insulin and VIP, whereas ileal NETs are slower growing and show a hypersecretion of biogenic amines in approx. half of all cases leading to the carcinoid syndrome.

In order to categorize and also treat NET better than in the past, a new TNM classification has been proposed by the European Neuroendocrine Tumor Society (ENETS), including the first-ever grading system (Rindi et al., 2006, 2007). A number of centers have already demonstrated that this new TNM classification is applicable in daily routine (e.g. Pape et al. 2008).

In recent years, an impressive spectrum of treatment options has evolved esp. for pancreatic NETs. Current treatment includes new biologicals and small molecules such as the mTOR inhibitor everolimus and the TKI sunitinib, which has shown to be efficacious esp. in the case of pancreatic primary tumors of grade 1 and 2 (Kulke et al., 2008; Yao et al. 2008). In addition, novel orally available chemotherapeutics such as temozolomide and capcitabine have shown to be efficacious in pancreatic G1 and G2 NET (Kulke et al., 2010). Furthermore, FOLFOX can also lead in poorly differentiated G3 NET to remissions, as well as to prolonging time to tumor progression (Pape et al., 2006). Biotherapeutics such as somatostatin analogues (SSA, esp. octreotide) have gained renewed attention based on their newly demonstrated antiproliferative action in midgut tumors (Rinke et al., 2009). In addition, the new SSA pasireotide has been shown to control the carcinoid syndrome in patients who had been refractory to conventional therapies such as...
Cytoreductive nephrectomy (CN) has been shown to improve overall survival in patients with metastatic RCC treated with interferon-alpha. Combining targeted therapy with CN in the metastatic setting has the potential to improve efficacy and tolerability relative to cytokine therapy and prospective studies are underway. Presently, there is no definitive evidence supporting changes in the current treatment paradigms. In the absence of prospective randomized data, CN remains a part of the treatment algorithm for patients with metastatic disease, a favourable or intermediate prognosis, good performance and a resectable tumour. This view is largely based on two randomized studies that have demonstrated that CN is associated with a survival advantage in selected mRCC patients treated with IFN-a. By contrast, patients with poor performance, large metastatic burden or highly aggressive subtypes such as sarcomatoid features are unlikely to benefit from CN, and may be better off with systemic therapy first. Two phase III randomized studies are now open for accrual, addressing respectively the questions of the role and the timing of nephrectomy. The CARMENA trial is a phase III randomized study comparing nephrectomy plus sunitinib versus sunitinib without nephrectomy in first-line metastatic RCC. Primary end point is overall survival. Rather than investigating indiscriminately whether or not CN is of benefit, another approach is to identify those individuals in whom CN alters the natural course of mRCC. Such identification would require understanding of new clinical and molecular predictors. Therefore, there is a rationale for trials of presurgical targeted therapy and investigation of pretreated primary tumour tissue. The EORTC 30073 trial is a randomized phase III trial comparing sunitinib followed by nephrectomy in case of non-progressive metastases followed by sunitinib versus nephrectomy followed by sunitinib in patients with synchronous metastatic renal cell carcinoma. Primary endpoint is progression free survival. In addition to CN increasing evidence suggests that presurgical targeted therapy may have a role in metastasectomy by selecting responders and reducing the extent prior to resection. For patients with non-metastatic disease and large advanced primary tumours, use of targeted agents to downsize tumours is under investigation. However, the degree of primary tumour shrinkage and the rate of surgically relevant down-staging seen with the current generation of agents is not sufficiently high to justify their regular use. Finally, the tolerability and safety of targeted agents used perioperatively must be considered, particularly in the adjuvant setting where long-term therapy to prevent recurrence or metastasis is currently under investigation.

The changing role of surgery in the TKI ERA

Thursday, 18th November 2010, 09.00–11.00 (TERPSICHORE B)

Educational Symposium: Renal Cell Carcinoma

Axel Bex

Targeted agents for RCC have improved the outcome in metastatic patients, and there is increasing interest in multimodal approaches integrating the efficacy and safety of these drugs in combination with surgery in both early and advanced disease. The encouraging responses observed in both primary tumours and metastases may lead to a change in the role and sequence of surgery in the treatment of RCC.

Optimal selection of patients for surgery. advances in surgery

Friday, 19th November 2010, 16.15–17.45 (TERPSICHORE B)

Current Issues in Oncology: Optimal Selection of Patients for Surgery. Advances in Surgery

John Davis

The evaluation of the man with newly diagnosed, clinically localized prostate cancer should begin with question as to whether or not the patient is best suited for immediate curative therapy versus active surveillance. In absence of randomized studies, the combination of Sorafenib with IL-2 was feasible but there was not an overall benefit from the combination compared to Sorafenib alone.

In conclusion, the role of immunotherapy in the era of targeted therapy is still evolving. Although a minority of patients may still benefit from upfront IL-2, the combination of with novel antiangiogenic agents seems to be a promising way of still widely using immunotherapy in this disease.
of better screening tools, serum PSA screening results a large fraction of men diagnosed with early, low-grade cancer that are likely to be over-treated with a policy of immediate therapy. Active surveillance is not a perfect strategy, but the current literature indicates that upwards of 70% of men with early, low-grade disease can be managed with surveillance, provided they are willing to undergo repeat evaluations, and delayed therapy for evidence of increased risk. For men with higher volume tumors, or any intermediate to high grade findings, the patient should be counseled regarding standard curative therapies (surgery and radiation) and the possibility of alternative treatments (cryotherapy, high-frequency ultrasound, etc.). Comparison of surgery and radiation can be done using American Urological Association and/or European Association of Urology guidelines that offer state-of-the-art reviews of levels of evidence, and point by point review of oncological and functional outcomes. Most surgeons will point out the advantages of surgery to include pathological staging, opportunity for post-operative radiation, simplified PSA-based monitoring, and perhaps a greater understanding of long-term (>15 year) durability of cure. Discussions on quality of life should include the known trends in sexual, urinary, and bowel side effects; no one therapy has been shown to be superior. In the United States, and a growing number of worldwide centers, the selection for surgery may include whether or not robotic approaches should be utilized; and strong trends have been observed for physician and patient-directed referrals to high volume surgeons. The literature on open surgery demonstrates clear improvements in outcomes by training and volume, and performance of robotic surgery should be similar. The only clear evidence of benefit for a robotic approach includes lower blood loss, shorter hospital stay; fewer complications, and fewer urinary strictures. Oncologic and functional outcomes are not well studied, and likely are influenced by surgeon experience more than the tools selected. Current high volume surgeons should be able to present to a prospective patient a program for and adaptive, and agenda-based approach to improving outcomes including reducing positive margins, improving selection for nerve-preservation with imaging and nomograms, improving urinary control, reducing complications, and selecting patients for extended pelvic lymph node dissections. Furthermore, the results of surgical training should be quantifiable, and surgical simulation is being developed. Ultimately, optimized outcomes should be achievable by open or robotic approaches; however the latter approach seems to have more promise regarding reducing the wide variation in results demonstrated from open surgery. A high volume surgeon should be able to adapt their technique to almost any patient-specific situation, although recent trends in utilization of drug eluting stents mandating anti-coagulation, and morbid obesity remain possible contraindications.

State of the art in the management of testicular germ-cell tumours
Friday, 19th November 2010, 09.40–10.20 (ERATO AB)
Lecture: State of the Art in the Management of Testicular Germ-Cell Tumours
Alan Horwich
Most germ cell cancers are highly curable. They occur in young adults and the risk of long term treatment toxicities are important in considering options for management. Both seminomas and non seminomas have a pathognomonic chromosome signature of an isochromosome 12p, and immunohistochemical analyses can aid diagnosis by stains for AFP, HCG, PLAP or OCT3/4. The tumours usually arise from pre-existing non invasive carcinoma in situ, and both this lesion and the malignancy are more common in those with a history of testicular maldescent or when the testis is atrophic. There is a genetic component to the aetiology and the cancer is 5x more common in brothers of a case than in the general population of males. The analysis of levels of alphafetoprotein (AFP) and Human Chorionic Gonadotrophin (HCG) in the blood help diagnosis, prognosis and monitoring. Lactate Dehydrogenase is also a tumour marker, useful in prognostication. Stage I seminomas have traditionally been treated by adjuvant radiotherapy to abdominal and pelvic lymph nodes. This policy should be reconsidered since either surveillance or adjuvant carboplatin are likely to have a lower risk of causing second cancers. Stage I non-seminomas can be managed by orchidectomy and surveillance. It seems that PET does not aid the specificity of staging. Adjuvant chemotherapy is an effective alternative and a single cycle reduces recurrence risk to less than 5%. Metastatic germ cell tumours have been classified using an internationally agreed system. Good prognosis (estimated 5 year survival 92%) is defined for non seminoma by low markers, poor prognosis (5 years survival 48%) by high markers or non pulmonary visceral metastases or mediastinal primary site; intermediate prognosis has a 5 year survival of 80%. For seminoma all are good prognosis unless there are non-pulmonary visceral metastases (5 year survival 86% vs 72% for intermediate prognosis). Most good prognosis patients are treated with 3 cycles of BEP chemotherapy (bleomycin, etoposide, cisplatinum). Intermediate prognosis is treated by 4 cycles of BEP chemotherapy and poor prognosis by either 4 cycles of BEP or an investigational and usually higher-intensity protocol.

Residual masses are common after chemotherapy for bulky seminomas, and a negative PET scan is reassuring, however false positive scans are not uncommon, presumably due to macrophage activity. Following chemotherapy for non-seminoma consideration should be given to resection of residual masses in case they contain active malignancy or mature teratoma which is subject to late malignant change if left. Patients are best evaluated within a multidisciplinary team.

Patients who relapse after first line BEP chemotherapy can still be cured in approximately 40–50% of cases. Second-line chemotherapy regimens incorporate paclitaxel and ifosfamide and usually a platinum drug. Again, it is important to incorporate resection of any residual masses and a multidisciplinary approach is recommended. The role of high dose chemotherapy in salvage remains unproven, though good results have been reported in some retrospective series including two or three high dose cycles.

Optimal selection of patients for radiation. advances in radiation
Friday, 19th November 2010, 16:15–17:45 (TERPSICHORE B)
Current Issues in Oncology: The Challenge of Prostate Cancer; Part II: Optimal Application of Therapies for Patients with Localised Prostate Cancer
Deborah Kuban
Molecular basis of disease & animal models
Thursday, 18th November 2010, 09.00–11.00 (TERPSICHORE B)
Educational Symposium: Renal Cell Carcinoma
Athena Matakidou
Kidney cancer accounts for ~3% of all adult cancers. Its incidence is increasing in most western countries and despite recent advances in our understanding of the underlying biological processes and the development of new therapeutic approaches its associated mortality remains high. Renal cell carcinomas (RCC) arise from renal tubular epithelial cells and account for ~85% of all kidney tumours. Most cases of sporadic RCC are of clear cell histology (75%), followed by papillary (12%), chromophobe (4%), oncocytoma (4%) and collecting duct carcinomas (<1%). Molecular efforts in RCC research have focused upon several hereditary syndromes that predispose to the disease, including von Hippel-Lindau, hereditary papillary renal carcinoma, Birt-Hogg-Dube, hereditary leiomyomatosis and tuberous sclerosis complex. Somatic mutations in the genes associated with these syndromes (VHL, c-Met, BHD, FH, TSC-1, and TSC-2 respectively) have been identified in sporadic RCC. Indeed, defects in the VHL gene appear to be responsible for ~60% of the cases of sporadic clear-cell RCC. Studies of the cellular consequences of these specific genetic mutations associated with hereditary RCCs have spawned much of our current understanding of tumourigenesis from renal tubular epithelia. However, these well studied genetic events do not account for the totality of sporadic tumourigenesis in RCC, suggesting that additional causative mutations remain unidentified. Studies of RCC pathogenesis have been limited by the paucity of genetically defined animal models. Mice with genetic disruptions of VHL, c-Met, or FH

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do not develop kidney tumours. Similarly, combined conditional inactivation of VHL and the PTEN tumour suppressor genes, in the mouse kidney, elicits cyst formation reminiscent of the human VHL phenotype but no overt neoplasia. To date, only mutation of BHD, TSC-1, TSC-2, or the APC and NF2 tumour suppressor genes yields tumours reminiscent of RCC in genetically engineered animals. However, mutation of these genes is rare in sporadic RCC, and these animal models do not provide an accurate picture of the diverse molecular mechanisms implicated in this disease. Moreover, none of these models is ideal for studying renal tumorigenesis, owing to high neoplastic mortality (BHD, APC, NF2), long latency of tumour development (TSC-1), or lack of tissue-specific targeting (TSC-1, TSC-2). Additional and improved animal models of RCC offer prospects for advancing basic and preclinical studies of renal epithelial neoplasia.

Recently, a new form of somatic mutagenesis (forward genetics) was developed to generate novel tumour models and instantaneously identify the causal loci. These transposon-based methods provide an unbiased approach for the generation of novel models of RCC and the identification of causative genes.

Summary of findings and optimal application. future direction

PSA Screening 2010—what are the consequences?
Friday, 19th November 2010, 12.30–13.30 (ERATO C)
Debate: The Challenge of Prostate Cancer; Part I: Perspectives on screening—Prostate Cancer: a Unique Disease with Special Challenges
Kurt Miller

In 2009 two randomized screening studies have been published (Andriole, Crawford et al. 2009; Schroeder, Hugosson et al. 2009). While several flaws make it difficult to assess the results of the PLCO trial, the ERSPC study suggests a significant reduction of prostate cancer specific mortality, when PSA testing is applied for early detection. One problem is still the high numbers needed to screen and to treat. However, a recent report suggests, that these numbers will decrease substantially, if a longer follow-up will be available (Hugosson, Carlsson et al. 2010). The most relevant problem however is, that PSA screening leads to a dramatic overdiagnosis of clinically insignificant prostate cancer. Earlier calculations of the ERSPC study suggest an overdiagnosis rate of close to 50 % (Draisma, Boer et al. 2003). Overdiagnosis per se is irrelevant if it does not result in overtreatment. Hence one of the consequences of these data are to introduce active surveillance (AS) as one of the standard approaches to low risk screen detected prostate cancer. Midterm data from AS studies suggest excellent prostate cancer specific survival rates (Klotz 2007; van den Bergh, Roemeling et al. 2008). On the other hand, there is an inherent risk to underestimate the tumor with the information set (Biopsy, PSA, DRE) currently available (Suardi, Capitanio et al. 2008). So a ‘narrow path’ exists between overtreatment an understereimation, reflecting the psychological burden of active surveillance on one side versus the potential morbidity of radical treatment on the other side. In daily practice this often leads to rather choose radical treatment over active surveillance thus avoiding lengthy and burdensome discussions with the patient. In any oncology setting overtreatment is not uncommon and ‘feels’ better than undertreatment with its potentially life threatening hazards.

Currently there are few solutions to this dilemma. Focal therapy, providing a lower morbidity profile, is still in its infancy and not recommended for routine clinical use. On the other hand ‘active surveillance’ of suspicious PSA values without enforcing a diagnosis by biopsy may take the psychological burden off the patient but has all other intrinsic disadvantages of AS with the established diagnosis of prostate cancer.

The unmet need for providing a more accurate prognosis for the individual patient has often been stressed with little progress actually being made over the last 20 years or so. Molecular makers like PCA3 seem to provide incremental progress (Deras, Aubin et al. 2008) and more work is in progress (Schostak, Schwall et al. 2009; Sreekumar, Poisson et al. 2009). For the immediate future however, the dilemma is here to stay and we need to seek the best choice for the individual patient on the limited information available.

References
Andriole, G. L., E. D. Crawford, et al. (2009). ‘‘Mortality results from a randomized prostate-cancer screening trial.’’ N Engl J Med 360(13):1310–1319.
Deras, I. L., S. M. Aubin, et al. (2008). ‘‘PCa3: a molecular urinary assay for predicting prostate biopsy outcome.’’ J Urol 179(4):1587–1592.
Draisma, G., R. Boer, et al. (2003). ‘‘Lead times and overdiagnosis due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer.’’ J Natl Cancer Inst 95(12):868–878.
Hugosson, J., S. Carlsson, et al. (2010). ‘‘Mortality results from the Goteborg randomised population-based prostate-cancer screening trial.’’ Lancet Oncol 11(8):725–732.
Klotz, L. (2007). ‘‘Active surveillance for favorable risk prostate cancer: rationale, risks, and results.’’ Urol Oncol 25(6):505–509.
Schostak, M., G. P. Schwall, et al. (2009). ‘‘Annexin A3 in urine: a highly specific noninvasive marker for prostate cancer early detection.’’ J Urol 181(1):343–353.
Schroeder, F. H., J. Hugosson, et al. (2009). ‘‘Screening and prostate-cancer mortality in a randomized European study.’’ N Engl J Med 360(13):1320–1328.
Sreekumar, A., L. M. Poisson, et al. (2009). ‘‘Metabolomic profiles delineate potential role for sarcosine in prostate cancer progression.’’ Nature 457(7231):910–914.
Suardi, N., U. Capitanio, et al. (2008). ‘‘Currently used criteria for active surveillance in men with low-risk prostate cancer: an analysis of pathologic features.’’ Cancer 113(8):2068–2072.
van den Bergh, R. C., S. Roemeling, et al. (2008). ‘‘Outcomes of Men with Screen-Detected Prostate Cancer Eligible for Active Surveillance Who Were Managed Expectantly.’’ Eur Urol.

Summary of findings and optimal application. future direction

Perspectives on screening for prostate cancer—Summary of findings and optimal application of screening tests
Friday, 19th November 2010, 12.30–13.30 (ERATO C)
Debate: The Challenge of Prostate Cancer; Part I: Perspectives on screening - Prostate Cancer: a Unique Disease with Special Challenges
Fritz H. Schröder

Screening for prostate cancer saves lives. This has been shown by the European Randomized Study of Screening for Prostate Cancer (ERSPC) [1,2] and by the publication of the Gothenburg screening trial, which is a partner of ERSPC [3]. However, there are uncertainties and downsides to screening. The uncertainty includes the number needed to screen and number needed to treat that can be achieved with longer follow-up in the multi-center setting of the ERSPC study and, above all, the independent problem of overdiagnosis and overtreatment that results from present screening algorithms.

Prostate-specific antigen (PSA). Prostate-specific antigen is prostate specific and not prostate cancer specific. This results in overlap of increases of serum PSA due to benign enlargement and carcinoma of the prostate, specifically in the critical PSA range <10 ng/ml in which biopsies are indicated if early diagnosis is to be achieved. This dilemma has not yet resolved.

The ERSPC study. Interim results of the ERSPC study were reported in [1]. The analysis is based on 162,378 men age 55–69, 2- and 4-year screen intervals were used. The study shows after 9 years of follow-up a 20% reduction in prostate cancer mortality in favor of screening and, after adjustment for non-compliance and contamination, a 31% mortality reduction for those men who were in fact screened. The number needed to screen amounted to 1,410, the number needed to treat to 48. These findings were considered the main downsides, together with the large amount of overdiagnosis.

The Gothenburg screening trial. The Gothenburg screening trial [3] was initiated independently of the ERSPC in 1993 but joined the ERSPC as a partner shortly thereafter. The study reported an absolute reduction of prostate cancer mortality at 14 years of 0.40%. The relative reduction of prostate cancer mortality amounted to 44% in the intention to screen analysis and to 56% if those who were in fact screened are considered. With a follow-up of

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14 years the number needed to be invited for screening decreased to 293 and the number needed to treat to a very acceptable 12.

**Overdiagnosis and overtreatment.** As already mentioned above, the problem of overdiagnosis and overtreatment is independent of an eventually achievable low number needed to screen and number needed to treat. It is task of our urological profession to work on this further and to develop methodology to decrease overdiagnosis. Obviously, a new marker replacing PSA would be desirable.

**Conclusion.** There is no question anymore that screening reduces prostate cancer mortality. Overdiagnosis and overtreatment can be decreased by screening less aggressively and more selectively. Well-informed men who wish to undergo early diagnosis cannot be refused. The introduction of population screening as a health policy will depend on improving on the downsides of screening, mainly on the reduction of overdiagnosis and overtreatment.

1. Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Clatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis L, Recker F, Berenguer A, Määttänen L, Bangma CH, Aus G, Villers A, Rebillard X, van der Kwast Th, Blijenberg BG, Moss SM, de Koning HJ, Auvinen A, for the ERSPC investigators. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009 Mar 26;360(13):1320–8.

2. Roobol MJ, Kerkhof M, Schröder FH, Cuzick J, Sasieni P, Hakama M, Steman UH, Clatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis L, Recker F, Berenguer A, Ruutu M, Kujala P, Bangma CH, Aus G, Tammela TL, Villers A, Rebillard X, Moss SM, de Koning HJ, Hugosson J, Auvinen A. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). Eur Urol. 2009 Oct;56(4):584–91.

3. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Bergdahl S, Lilja H. Mortality results from the Göteborg randomized population-based prostate-cancer screening trial. Lancet Oncol. 2010 Aug;11(8):725–732.

**Theme: Gynaecologic Cancer**

**Intraportaline chemotherapy for ovarian cancer (pro)**

**Friday, 19th November 2010, 13.15–14.00 (ERATO AB)**

**Debate: Intraportaline Chemotherapy for Ovarian Cancer**

**Deborah Armstrong**

The cumulative body of evidence from multiple randomized trials of IP vs IV studies indicates that the average effect of IP therapy is to reduce the death rate by approximately 20%. This is the conclusion from an NCI overview of IP therapy, and from a Cochrane overview. While most, but not all of these studies also showed increased toxicity and decreased quality of life during treatment, these measures largely equalize after treatment is complete. IP therapy in GOG 172 produced the longest survival reported to date from a randomized phase III trial in advanced ovarian cancer. Yet this therapy has not gained widespread acceptance.

Some have argued that the benefits of treatment given in GOG 172 are due to the differences in the dose intensity of the regimen. The IP regimen was designed to provide an intensive therapy that cannot be delivered IV thus the argument that different doses of agents were used on the IV and IP arms is a circuitous argument; the ability to give higher and more frequent dosing when using the IP route is one of the benefits of IP therapy and this dose-intensity/dose-density cannot be delivered using the IV route. While toxicities were greater on the IP arm, there was no increase in toxic deaths and quality of life measures were similar between the IV and IP arms one year after therapy was complete. Less toxic toxicities are indeed preferable when clinical outcomes are equal however the benefit seen with IP therapy in GOG 172 is an important advance, not equivalence. More recent studies have shown that with contemporary supportive care measures and an experienced and dedicated treatment team, the majority of patients can complete IP therapy. Furthermore, modifications of the IP chemotherapy regimen, significantly improve tolerability and ease of administration.

Critics have also suggested that there are only two possible explanations for the improvement in overall survival are that patients who relapse after IV therapy live longer because the nature of the treatment has altered the biology of their disease or that they are able to receive more effective 2nd-line treatment. A treatment that provides either or both of these beneficial outcomes is desirable. However, there are two additional potential explanations for the improved survival. One is that patients who relapse later are more likely to be sensitive to second line treatment and that some patients who would have relapsed after IV therapy are prevented from relapsing (i.e. are cured) by the use of IP therapy.

**The role of consolidation and maintenance therapies in ovarian cancer**

**Thursday, 18th November 2010, 12.30–13.30 (ERATO C)**

**Meet the Expert: The Role of Consolidation and Maintenance Therapies in Ovarian Cancer**

**Jonathan Ledermann**

Ovarian cancer is one of the most chemosensitive solid malignancies and more than 75% of advanced tumours will respond to platinum-based chemotherapy. More than 50% of patients with widespread disease can expect to be in a complete clinical remission following surgery and chemotherapy, usually with carboplatin and paclitaxel. This regimen has remained the standard of care for more than a decade despite attempts to improve outcome by adding in a third or fourth agent. The duration of remission with any of these regimens remains remarkably constant, with a median progression-free survival rate of 18 months. Residual microscopic disease, resistant to these drugs is the key issue affecting the long-term survival of ovarian cancer patients in remission.

Maintenance therapies have been investigated in an attempt to eradicate residual disease, or suppress its growth. The first question addressed was whether chemotherapy given for longer would extend survival. Randomized trials with maintenance or consolidation courses paclitaxel or topotecan have produced mixed results. Long-term paclitaxel has shown to prolong progression-free survival but the results need to be interpreted in the context of overall survival. Nevertheless, new ongoing trials are investigating less toxic taxane analogues. An alternative strategy is to use a novel molecular targeting drug to consolidate remission. A randomised phase II evaluation design has been developed to ‘screen’ several agents that might be useful for larger-scale studies. One of these drugs, BIBF 1120, a triple angiokinase inhibitor has been identified as an active compound in ovarian cancer and a trial is now being performed using this drug in first-line therapy in combination with carboplatin and paclitaxel, and as maintenance therapy.

Anti-angiogenic drugs appear to be the most promising group of agents in ovarian cancer. Angiogenesis plays a key role in the growth and progression of ovarian cancer. Non-randomised studies with bevacizumab, a monoclonal antibody targeting circulating VEGF have shown good single agent activity in recurrent drug-resistant ovarian cancer and prolongation of the progression-free survival. Two large-scale international studies of chemotherapy in combination with bevacizumab followed by maintenance therapy with this antibody have been completed. The first, GOG 218, presented at ASCO 2010 showed a significant prolongation in progression-free survival in patients receiving up to 15 months of therapy with bevacizumab. The results of a similar study, ICON 7 will be presented in Autumn 2010, and the results will be available for discussion. A third trial of maintenance therapy with pazopanib, a small molecule multikinase inhibitor following carboplatin and paclitaxel has completed recruitment but the results are not yet available. A further study, ICON 6 with cediranib, a VEGFR tyrosine kinase inhibitor is being performed in platinum-sensitive relapsed ovarian cancer. The results of GOG 218 have clearly demonstrated the importance of anti-angiogenic therapy in ovarian cancer and indicated maintenance therapy is likely to be the best strategy. However, critical interpretation of the results is needed in order to understand how to use anti-angiogenic therapy most effectively to improve the outcome of ovarian cancer.
Traditionally maintenance treatment in oncology refers to the continuation of systemic therapy in patients who have responded to remission induction with the aim prolonging the remission. Within this broad definition there are at least 2 scenarios with quite different implications concerning the mechanism of action of maintenance therapy. In the first scenario an agent (or agents) that has been used in induction, and hence presumed to have contributed to the response, is continued in the hope that the tumour retains sensitivity to it. In the second scenario an agent not used in remission induction is commenced on completion of first-line induction therapy in the hope that exposing the tumour to a different agent (or agents) will prolong the remission perhaps through non-cross-resistance. This scenario might be called early second line therapy. This distinction is important because patients with advanced non-small cell lung cancer (NSCLC) can deteriorate rapidly from the cancer itself or from comorbidities that prevent them from ever receiving further therapy. So one might anticipate benefit from the early administration of 2nd line therapy during remission as ‘maintenance’ rather than waiting for progression. Support for this hypothesis comes from data showing that only around 50% or fewer of patients in clinical trials ever receive 2nd line therapy. Furthermore a trial comparing immediate with delayed 2nd line docetaxel did report some benefits from the immediate use of the drug. Until recently the weight of evidence has supported discontinuation of chemotherapy in advanced NSCLC after 4–6 cycles of induction therapy. Additionally it is only in recent years that agents without serious cumulative toxicity have become available as realistic maintenance agents. Discontinuing after induction allows patients with limited life expectancy a ‘treatment holiday’. However, there has been renewed interest in the concept of maintenance from trials with pemetrexed and erlotinib. Both these agents can be given for long periods without serious cumulative toxicity in most patients. Both trials have shown significant extension of progression free survival in placebo controlled trials. In the case of pemetrexed a statistically significant 5-month prolongation of overall survival in non-squamous NSCLC has been reported in cases not receiving pemetrexed as induction therapy. Treatment was well tolerated. This effect may reflect the early administration of an active second line agent and it remains to be seen whether similar benefits will accrue to patients having pemetrexed as induction therapy. A trial is currently underway testing this. Finally, retrospective analysis of both trials testing maintenance erlotinib and pemetrexed demonstrated that the benefit accrued only to those cases who had stable disease after induction, and not to those achieving partial or complete remission. This apparently counter-intuitive observation needs testing prospectively, and explaining biologically as we learn more about the role of maintenance therapy in advanced NSCLC.

The current optimal paradigm for palliative systemic therapy in advanced NSCLC

Friday, 19th November 2010, 16.15–18.15 (TERPSICHORE A)

Educational Symposium: Lung Cancer; Non Small Cell Lung Cancer

Thierry Le Chevalier

Non-Small Cell Lung Cancer mostly includes squamous cell carcinoma, adenocarcinoma and large cell carcinoma. These three subtypes represent 85% of lung tumors, the leading cause of death from cancer in the world. Median age at diagnosis is 69 years in the Western countries. More than two third of patients present with locally advanced or metastatic disease and around 50% of those with an initially limited disease will eventually fail distant. So the vast majority of NSCLC patients will be potential candidates for a palliative, systemic treatment during the course of their disease. The individual data-based meta-analysis published in 1995 established the superiority of chemotherapy over supportive care in patients with advanced NSCLC. These results have been recently updated and confirmed in 2714 patients from 16 trials with an overall survival benefit of 9% at 1 year. Chemotherapy also improves quality of life and controls symptoms in patients with good performance status. It is classically recommended to use platin compounds in combination with third generation agents including vinorelbine, gemcitabine, taxanes or pemetrexed (in non-squamous NSCLC). Integrating palliative care at an early stage of the...
treatment also prolongs survival and improves quality of life. The addition of antiangiogenic monoclonal antibodies (bevacizumab) or antiEGFR monoclonal antibodies (cetuximab) to standard platinum based chemotherapy may prolong survival in some cases but the selection of patients remains unclear and we have presently no predictive test to guide our therapeutic decision. Second line chemotherapy with docetaxel or pemetrexed has also been showed active even if the benefit on overall survival remains modest. The use of biological markers such as ERCC1, RRM1, beta-tubulin or thymidylate synthase has not yet proven efficacy on the choice of cytotoxic agents. The addition of targeted TKIs to standard chemotherapy is disappointing and has never showed superiority toer chemotherapy alone in the general population. In the recent years, several targets have been identified, particularly among the growing population of adenocarcinoma. Several targeted agents have been developed in second line (as single agents or in combination with other specific drugs); In a large chemo-naive population, it has been demonstrated that, in patients with mutations of Exons 19–21, the use of first line EGFR TKIs offered a better outcome compared to a classical cytotoxic chemotherapy. More recently, it has been reported that inhibition of c-Met and ALK might also have an impact on survival of some selected patients with adenocarcinoma.

In conclusion, platinum-based chemotherapy remains the standard treatment for patients with advanced NSCLC. The addition of antiangiogenic monoclonal antibodies prolongs survival in some cases. Substituting targeted agents for cytotoxic chemotherapy may be appropriate in selected patients; it constitutes the major challenge of the coming decade.

What is the role of surgery in SCLC?

Friday, 19th November 2010, 09.00–11.00 (TERPSICHORE A)

Educational Symposium: Lung Cancer; Small Cell Lung Cancer

Eric Lim

Combined modality therapy using chemotherapy and thoracic irradiation is currently the standard of care for limited-stage small cell lung carcinoma, but the long term results are poor. The cumulative results from 25 years of North American chemoradiation trials report a current median survival of 17 months and data from the Surveillance, Epidemiological and End results (SEER) programme of the National Cancer Institute (Bethesda, Maryland, USA) reported an overall 5 year survival of 10%. Previous major randomised trials of surgery for small cell lung cancer were performed in the era prior to PET, with clinical staging and preoperative selection based on either plain chest film or CT scanning, and in part accounts for the high proportion of exploratory thoracotomies by the inclusion of patients not currently accepted to be suitable for surgery. In light of published evidence, surgery for small cell lung cancer is not an established treatment modality. Current surgical series however report excellent survival. In selected patients with small-cell lung cancer at the Royal Brompton Hospital was associated with a 5-year disease free survival of 52%. Similar results have been achieved with multimodality treatment that included surgery by Eberhardt et al with 5 year overall survival of 63% and a 5-year survival of 39% by the Toronto group. However there is no available evidence on the prognosis of a similar group of patients treated with the current standard of concurrent chemo-radiotherapy.

In view of the current data, surgery should feature more prominently as part of multimodality management, and British Guidelines will be advocating a broader remit for the consideration of surgery in patients with small cell lung cancer.

References

1. Janne PA, Freidlin B, Saxman S, Johnson DH, Livingston RB, Shepherd FA, Johnson BE. Twenty-five years of clinical research for patients with limited-stage small cell lung carcinoma in North America. Cancer. 2002;95(7):1528–1538.

2. Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, Spitznagel EL, Piccirillo J. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol. 2006;24(28):4539–4544.

3. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. Lancet. 1975;2(7820):63–65.

4. Lad T, Piantadori S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest. 1994;106(Suppl):323S–323S.

5. Lim E, Goldstraw P. Surgery for small-cell lung cancer: time to re-evaluate. J Clin Oncol. 2007;25(18S):438S.

6. Eberhardt W, Stamatis G, Stuschke M, Wilke H, Muller MR, Kolks S, Flaschke M, Schutte J, Stahl M, Schlenzer L, Budach V, Greschuchna D, Struben G, Teschler H, Sack H, Sebber S. Prognostically orientated multimodality treatment including surgery for selected patients of small-cell lung cancer patients stages IB to IIIB: long-term results of a phase II trial. Br J Cancer. 1999;81(7):1206–1212.

7. Shepherd FA, Ginsberg RJ, Feld R, Evans WK, Johansen E. Surgical treatment for limited small-cell lung cancer. The University of Toronto Lung Oncology Group experience. J Thorac Cardiovasc Surg. 1991;101(3):385–393.

8. Turrisi AT, Kim K, Blum R, Sause WT, Livingston RB, Konnari R, Wagner H, Aisner S, Johnson DH. Twice-Daily Compared with Once-Daily Thoracic Radiotherapy in Limited Small-Cell Lung Cancer Treated Concurrently with Cisplatin and Etoposide. N Engl J Med. 1999;340(4):265–271.

9. Lim E, Baldwin D, Beckles M, Duffy J, Entwistle J, Faiivre-Finn C, Kerr K, Macieh A, McGuigan J, Padley S, Popat S, Screenom N, Snee M, Waller D, Warburton C, Win T. Guidelines on the radical management of patients with lung cancer. Thorax. 2010 (in press).

Systemic therapy for SCLC: is platinum/etoposide the limit?

Friday, 19th November 2010, 09.00–11.00 (TERPSICHORE A)

Educational Symposium: Lung Cancer; Small Cell Lung Cancer

Paul Lorigan

Outcomes for patients with small-cell lung cancer remain poor and advances in treatments have not kept pace with those seen for other cancers. The main improvements in outcomes have been related to use of radiotherapy, though chemotherapy remains the cornerstone of treatment for the majority of patients. A platinum-based chemotherapy regimen is the standard of care, based on the data from 4 meta-analyses and systematic reviews. However, a recent Cochrane review of 29 randomised controlled trials reported no significant survival benefit for platinum based treatment at 6, 12 or 24 months. It is unclear whether cisplatin and carboplatin can be used interchangeably, and the only study to address this was not powered for equivalence.

Combined modality treatment with cisplatin-based chemotherapy and early concurrent radiotherapy remains the standard of care for patients with limited stage disease, based on a number of randomised controlled trials and systematic reviews. Any new drug would almost certainly need to be deliverable with concurrent radiotherapy to make a significant impact in limited stage disease. The role of maintenance chemotherapy remains unclear, with concerns about toxicity. However, a meta-analysis of 14 randomised studies encompassing 2550 patients reported a 4% survival benefit at 2 years. For patients with extensive stage (EDSCLC) disease but a good performance status, 4-6 cycles of platinum based chemotherapy is a standard of care. There is no clear benefit to adding a third of fourth drug to standard treatment, or to alternating treatments. Strategies to evaluate new agents in EDSCLC have usually involved either addition of the new drug to the platinum-etoposide combination, or substitution for etoposide. There is no clear benefit to the combination of platinum topotecan over platinum-etoposide in first line treatment, thought topotecan is the only drug licensed for second line therapy, and showed a clear benefit in quality of life and survival over best supportive care. Two studies evaluating the addition of paclitaxel to platinum-etoposide reported increased toxicity but no survival benefit. The combination of carboplatin-pemetrexed was found to be inferior to carboplatin-etoposide and a
large phase 3 study was closed early by the Data Safety Monitoring Committee. The median overall survival was 8.1 months for carboplatin-pemetrexed and 10.6 months for carboplatin-etoposide. Irinotecan has shown activity in an Asian population of patients, but no benefit was seen in a large phase 3 study carried out by SWOG. A recent meta-analysis reported that platinum-irinotecan is not inferior to platinum-etoposide. Amrubicin, a synthetic anthracycline has shown significant activity in the second-line setting, both in the sensitive and resistant/refractory patients. A recent first line randomised phase II study showed a response rate of 77% for cisplatin-amrubicin versus 63% for cisplatin-etoposide. A large phase III study in second-line setting comparing amrubicin with topotecan has completed accrual and the result of this will impact on future study design in the first-line setting.

Platinum-etoposide chemotherapy remains the standard of care for the majority of patients with small cell lung cancer.

Biology of SCLC: are there new therapeutic targets?

Friday, 19th November 2010, 09.00–11.00 (TERPSICHORE A)

Educational Symposium: Lung Cancer; Small Cell Lung Cancer

Gary Middleton

Optimal use of radiation in SCLC

Friday, 19th November 2010, 09.00–11.00 (TERPSICHORE A)

Educational Symposium: Lung Cancer; Small Cell Lung Cancer

Ben Slotman

Although the incidence of small cell lung cancer (SCLC) is declining, it still comprises 10–15% of all lung cancers. Approximately two-thirds of all SCLC patients present with distant metastases (ES; extensive stage). In this presentation, the current status and future prospects on the role of thoracic and prophylactich cranial irradiation will be discussed.

Standard treatment for patients without distant metastases (LS; limited stage) is combined radiochemotherapy. Outcomes of a number of studies indicate that radiotherapy should start early, and be given concurrently with chemotherapy (Pignon, 1992, De Rujisscher, 2006). Twice daily radiotherapy may enable the delivery of required radiation doses in a short time with acceptable toxicity. In the ongoing CONVERT-trial, twice-daily radiotherapy (45 Gy in 30 fractions in 3 weeks) is being compared with once-daily fractionated radiotherapy to doses of 66–70 Gy. The CALGB-30610/RTOG-0538 study will investigate whether high dose (mainly once-daily) treatment is beneficial compared to the twice-daily 45 Gy in 3 weeks regimen. In this trial, the high-dose arm delivers 70 Gy in 35 fractions in 7 weeks, or 61.2 Gy (1.8 Gy once daily for 16 days followed by 1.8 Gy twice daily for 9 days).

In all patients with LS who do not show evidence of disease progression, prophylactic cranial irradiation (PCI) should be given after completion of chemotherapy. This not only reduces the risk of brain metastases but also leads to improved survival rates (Auperin, 1999). Neuropsychological evaluations have not shown any difference in neuropsychological functioning between patients who received and who did not receive PCI. A recent study on dosing of PCI did not reveal a benefit of increased PCI doses (36 vs 25 Gy) and 25 Gy in 10 fractions remains the standard (Le Pechoux, 2009). The results of PCI in LS in combination with the even higher risk of brain metastases in patients with ES, have prompted us to investigate the role of PCI in responding ES patients as well. In these patients, PCI not only significantly reduced the risk of brain metastases, but it also increased survival rates (Slotman, 2007).

Intra-thoracic failure is an important problem in patients with ES. Both the Dutch Lung Cancer Group and the RTOG, have initiated a trial on the role of thoracic radiotherapy in patients with ES SCLC who respond to first-line chemotherapy. In the CREST study, patients receive 30 Gy in 10 fractions to the thoracic lesions after completion of chemotherapy. In the RTOG-0937 study, a dose of 45 Gy in 15 fractions in 3 weeks is delivered to the thorax and a maximum of 3 other extracranial sites.

Histological classification of NSCLC in the small biopsy and molecular era

Friday, 19th November 2010, 16.15–18.15 (TERPSICHORE A)

Educational Symposium: Lung Cancer; Non Small Cell Lung Cancer

William D. Travis

With some exceptions, the field of lung cancer pathology has been relatively static over the past several decades with few major practice-changing advances. The diagnosis of non-small cell lung cancer (NSCLC) based on small biopsies and/or cytology, an area of lung cancer diagnosis where a paradigm shift has occurred for both pathologists and clinicians.

This topic is important because the majority patients with lung cancer present with unresectable disease and the diagnosis is established based on such small specimens. Moreover, with increasing use of minimally invasive biopsy methods, pathologists are being asked to do more with less tissue.

The World Health Organization (WHO) classifications of lung tumors through the 1999 edition did not address lung cancer diagnosis based on small biopsies and cytology, as these were recommendations for the histologic classifications of resection specimens. In the 2004 WHO classification, cytology was addressed for the first time, but classification in small biopsies was not.

There is currently no internationally recognized standard of criteria or terminology for the diagnosis of lung cancer in small biopsies.

The most important decision for pathologists in small biopsies and cytology, historically, has been the crucial distinction between small cell lung cancer (SCLC) and NSCLC, as it defines patients with completely different clinical tumor behavior and management. Within NSCLC, important clinical reasons to separate squamous cell carcinoma from adenocarcinoma and other histologic types have not existed.

In a literature review spanning 25 years of clinical studies evaluating chemotherapy in advanced NSCLC, there was some weak association between histology and therapeutic outcomes, but none of these studies reported a formal test of treatment by histology interaction. Therefore, in older studies, there was no clear evidence that histology had a prognostic (independent of treatment) or a predictive role (associated with the effectiveness of a specific treatment) for patients with NSCLC.

Recently, this has all changed. Three clinical observations in advanced lung cancer patients have provided a reason for pathologists to change their practice and make a better attempt to distinguish adenocarcinoma from squamous cell carcinoma. First, patients with advanced lung cancer treated with bevaciuzumab are at increased risk for life-threatening hemorrhage if they have squamous cell carcinoma. Second, patients with adenocarcinoma or NSCLC, not otherwise specified (NSCLC-NOS; reported as large cell carcinoma in some of these studies) respond significantly better to pemetrexed than those with squamous cell carcinoma. Third, EGFR mutation is strongly associated with adenocarcinoma histology and patients with advanced NSCLC and EGFR mutation have a better outcome and response to tyrosine kinase inhibitors (TKI’s) as first line therapy, while patients without EGFR mutations seem to have a better outcome with chemotherapy.

Importantly, in all of these studies, the histologic classification was based solely on light microscopy with or without mucin stains. No immunohistochemistry or other special techniques were utilized to classify the tumors further.

A new Lung Adenocarcinoma Classification has just been published by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS) and European Respiratory Society (ERS). In this new classification, presents an algorithm with recommended terminology, special stains and approaches to tissue management.

References

1. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. Pathology and Genetics. Tumours of the Lung, Pleura, Thymus and Heart. Lyon France: IARC Press; 2004.

2. Travis WD, Colby TV, Corrin B, Shimoshato Y, Brambilla E. Histological Typing of Lung and Pleural Tumors. Berlin: Springer; 1999.

3. Hirsch FR, Spreafico A, Novello S, Wood MD, Simms L, Papotti M. The prognostic and predictive role of histology in advanced non-small cell lung cancer: a literature review. J Thorac Oncol 2008;3:1468–81.
4. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184–91.

5. Scagliotti G, Hana H, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. Oncologist 2009;14:253–63.

6. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543–51.

7. Giuleau T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432–40.

8. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.

9. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121–8.

10. Travis WD, Brambilla E, Noguchi M, et al. The new IASLC/ATS/ERS classification of lung adenocarcinoma. J Thoracic Oncol 2010; 5:821–49.

What is the optimal management of stage III NSCLC
Friday, 19th November 2010, 16.15–18.15 (TERPSICHORE A)
Educational Symposium: Lung Cancer; Non Small Cell Lung Cancer
Jan P . van Meerbeeck

More than 80% of the 213,000 incidental cases of lung cancer in the US are of the non-small-cell variant (NSCLC) and approximately 37% of these will present at diagnosis with locoregional involvement [1]. The latter means that the tumor has spread out of the confines of the lung into the surrounding structures without clinical evidence of dissemination. This extension varies from tumors locally abutting the chest wall, diaphragm or mediastinum (T3) to frank invasion of the mediastinal tissues and organs (T4), and nodal invasion in either the ipsilateral lymph nodes (N2) or the supraclavicular or contralateral mediastinal lymph nodes (N3) [2]. Although some of these extensions are no formal barrier for radical surgery (e.g. T3N0/1)- preferably followed by adjuvant chemotherapy-, most T4 lesions and clinical mediastinal lymph node invasion are considered beyond the limits of immediate surgery. They are referred to as stage III NSCLC and subclassified in IIA whenever N2 nodes are involved (or T3N1 tumors) or IIIB whenever any N3 or T4 involvement is present. The surgical-radiological correlation of the mediastinal lymphnodes has been recently described [3].

The overall five year survival rate for locally advanced lung cancer is 16% [1]. In the past decade, meta-analyses have gradually shifted the standard of care in selected patients with stage III NSCLC from radical local treatment only, over sequentially administered systemic and locoregional treatments to the present concurrent chemoradiotherapy [4, 5]. The role of surgery as local treatment following induction chemo(radio-)therapy in stage IIA-N2 has recently been challenged by 2 large randomized trials, showing no no statistically significant improvement in overall survival as compared to definitive radiation therapy (RT) [6, 7]. The role of surgery, if any, in stage III with clinical nodal involvement is hence to be considered limited [8, 9].

Present day survival figures for selected patients with stage III NSCLC treated with concurrent chemoradiotherapy average a median of 17 months and a 3 year rate of 25%, versus 14 months and 18% with a sequential approach. Factors predictive of outcome are performance status, stage (IIIA/ B), weight loss and pathological downsizing of the mediastinum and/or the tumor with induction treatment. Relaps pattern typically shows that both modalities do not completely control the tumor in 80% of patients, with equal numbers of patients failing intrathoracically, extrathoracically and both [10]. Improvements in combined modality outcome should hence come from improvements in local and systemic therapies.

Successful interventions to increase local control with RT include dose escalation, altered fractionation and the integration with concurrent chemotherapy [11]. These interventions increase the tumor cell kill by a variety of mechanisms, inflicting more initial radiation damage, decreasing repair or counteracting the effects of cancer-cell proliferation.

Conclusion: The optimal treatment in locally advanced NSCLC is by itself a moving target. There is a strong conviction that modern radiotherapy as part of a multimodality approach of stage III patients, will further improve the outcome. The last decade has seen the advent of several novel radiation techniques which are likely to improve the local control by the delivery of higher radiation doses to smaller volumes, allowing for lesser toxicity. These techniques are not mutually exclusive but instead are complimentary to each other. Further implementation of these techniques will need well-designed clinical trials in appropriately selected patients and taking into account as much of the different variables present and options available.

References
1. Jemal A, Siegel R, Ward E, et al. CA Cancer J Clin 2007;57;43
2. Mountain CF. Chest 1997;111:17l0
3. Chapet O, Kong FM, Quint LE, et al. Int J Radiat Oncol Biol Phys 2005;63:170
4. NSCLC Collaborative Group. Brit Med J 1995;311:899
5. Aupérian A, Rolland E, Curraj WN, et al. J Thor Oncol 2007; 2(8): S310 (abstract A1–05)
6. van Meerbeeck JP, Kramer GWP, Van Schil PEY et al. J Natl Cancer Inst 2007;99:442
7. Albain KS, Swann RS, Rusch V, et al. Lancet Oncol 2009;374:379
8. Johnson DH, Rusch VW, Turrissi AT. J Natl Cancer Inst 2007;99:415
9. Robinson LA, Ruckdeschel JC, Wagner H, Stevens CW. Chest 2007;132:243
10. Le Chevalier T, Arriagada R, Tarayre M, et al. J Natl Cancer Inst 1992; 84:58
11. Blackstock AW, Govindan R. J Clin Oncol 2007; 25:4146

Lung cancer in never smokers
Friday, 19th November 2010, 14.00 -14.40 (ERATO AB)
Lecture: Lung Cancer in Never Smokers
Heather Wakelee

Tobacco exposure is by far the most common cause of lung cancer, but the disease is also seen in those without a smoking history. In fact, for women with lung cancer the percentage of those with no history of smoking ranges from approximately 20% in the United States to over 80% in some Asian countries. Given the overall prevalence of lung cancer this means that lung cancer in never-smokers has a higher incidence than disease entities such as cervical cancer, and mortality rates that dwarf many other malignancies. Many speculate that the incidence of lung cancer in never-smokers is on the rise, though data is difficult to obtain due to a lack of cancer registries that capture smoking data and published literature is contradictory. Less contradictory is the data indicating that never-smokers constitute a higher percentage of women with lung cancer than men with lung cancer, the higher prevalence of adenocarcinoma compared to squamous cell carcinoma in never-smokers with lung cancer, and that there are racial/ethnic differences with the disease with higher rates seen in Asia. Causes of lung cancer in never-smokers remain elusive and are postulated to include secondhand smoke, exhaust from vehicles, cooking fumes in poorly ventilated kitchens, radon exposure, other environmental toxins such as asbestos, and to a lesser extent genetic factors. Regardless of cause, exciting research has identified specific ‘driver’ mutations in certain genes that account for approximately half of lung cancer in never-smokers. The best characterized are those of the epidermal growth factor receptor (EGFR). Tyrosine kinase inhibitors of EGFR were developed about a decade ago and dramatic responses seen preferentially in patients without a smoking history led to the discovery of specific
mutations in EGFR in approximately 10% of patients with NSCLC. The percentage is closer to 30% in never-smokers and as high as 60% in Asian never-smokers with lung cancer. In these patients, the mutation leads to the protein being constitutively turned on, which in turn drives the lung cancer. Turning the switch off with an EGFR-TKI such as erlotinib or gefitinib leads to dramatic responses, though unfortunately resistance develops over several months to years. More recently the EML4-ALK (anaplastic lymphoma kinase) fusion protein has been identified in <5% of lung cancer patients, but closer to 15–20% of those with no smoking history, particularly in the very young with the disease. The drug crizotinib works dramatically in this patient population, though again resistance develops over time. Other molecular differences between never-smokers with lung cancer and those with a smoking history have also been identified with ongoing research identifying more. Lung cancer in never-smokers is an important disease entity and exciting research into the molecular underpinnings of the disease has led to dramatic therapeutic advances. Hopefully these will lead to therapeutic advances for all lung cancer patients and a reduction in the stigma associated with the disease.

Theme: Lung Cancer & Cancer Staging
The impact of the new lung cancer staging system on clinical practice and clinical research
Thursday, 18th November 2010, 13.30-14.10 (ERATO AB)
Lecture: The Impact of the New Lung Cancer Staging System on Clinical Practice and Clinical Research
Peter Goldstraw
The publication of any new TNM classification is always a major event for those clinicians and researchers involved in the study and treatment of a particular cancer. This was especially the case with the launch of the 7th Edition of the TNM Classification for Lung Cancer(1,2), being the first revision for 12 years and the most radical for 35 years. Unfortunately the scientific rigour of the analytical process required that it broke with the convention that each new edition was retrospectively compatible with earlier editions(3), and this will almost certainly be the case with future revisions. The collection of raw data is recommended to “future proof” data in the long term.

Once the 7th edition was enacted on January 1st 2010 all new cases of lung cancer should be classified by the new edition. It has been estimated that for 1 in 6 cases this would result in a different stage being assigned compared with the 6th edition(4). The 7th edition is the first to incorporate carcinoid tumours into the TNM classification, and to emphasise the use of TNM in the clinical management and trial design for small-cell lung cancer (SCLC).

It provided pathologists with the first standardised definition of “visceral pleural invasion” and provided clinicians and researchers with an internationally agreed nodal map, reconciling the discrepancies between previously used maps. There are now precisely defined anatomical boundaries for each nodal station, which alongside the new map, are recognised as the recom- used maps. There are now precisely defined anatomical boundaries for each nodal station, which alongside the new map, are recognised as the recom-

References
(1) Goldstraw P. IASLC Staging Handbook in Thoracic Oncology. 1st ed. Florida, USA: EditorialRx Press; 2009.
(2) Goldstraw P. IASLC Staging Manual in Thoracic Oncology. 1st ed. Florida, USA: EditorialRx Press; 2009.
(3) Goldstraw P, Crowley JJ, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: Proposals for revision of the stage groupings in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2, 706–714. 2007.
(4) Kassis ES, Vaporiyian AA, Swisher SG, Correa AM, Bekele BN, Erasmus JJ, et al. Application of the revised lung cancer staging system (IASLC Staging Project) to a cancer center population. Journal of Thoracic and Cardiovascular Surgery 138, 412–418. 2009.

Theme: Lymphomas
State of the art in the treatment of hodgkin lymphoma
Saturday, 20th November 2010, 11.45–12.30 (TERPSICHORE A)
Plenary Lecture: State of the Art in the Treatment of Hodgkin Lymphoma
Volker Diehl
Hodgkin Lymphoma (HL) is a monoclonal B-cell-lymphoma. In Asia HL is rare, 0.6/100.000 new cases/annuo, whereas in Western countries the annual incidence is 2–3/100.000.

Historical Aspects of Management: In the years 1950–1970 radiotherapy was the mainstay of therapy, yielding cure rates in localized Ann Arbor stages I-II in up to 80%. The advent of polychemotherapy regimen MOPP, and later the ABVD regimen made cures possible in about 60–70% even in advanced stages. However, unexpected toxic short- and long-term side effects, of radiation and drug-co-carcinogens (mustard, cyclophosphamide, procarbazine: MOPP) induced secondary leukemias and solid tumors that amounted after 30 years to nearly 20–30%, mitigating the therapeutic breakthrough!

Modern Management Strategies for HL Patients in 2010: Today modern strategies of treatment reach cure rates of 90% in nearly all stages of the disease and serve as a model for management strategies of other cancers! Treatment decision is based on an immune-histological/molecular-genetic diagnosis based on a sufficiently representative biopsy (not Fine-Needle-Airation!) and on the anatomical extent of the lymphoma lesions catagorized according to the ANN ARBOR-stages I,IV, A or B (without or with systemic symptoms).

Stages I-II without risk factors* (Early Stages)

| Stage | Treatment | PFS | OS |
|-------|-----------|-----|----|
| I     | ABVD      | 85% | 80%|
| II    | ABVD      | 85% | 80%|

*Risk Factors: (bulk > 7 cm; high ESR (A > 50, B > 30); > 3 lymph node areas; extranodal involvement; (EORTC; age >50ys) are treated with 2 courses of ABVD + 20–30 Gy IF-RT, the PFS after 5 years is 95%, OS is 97% (German Hodgkin Study Group experience in HD7,HD10, HD13 trials with more than 3000 pts recruited).

Stages I-II, A,B with risk factors (Intermediate Stages)
2 BEACOPP escalated + 2 ABVD + 20–30 Gy IF-RT (GHSG-HD14)) or 4 ABVD + 30 Gy IF-RT (USA)

In intermediate stages according to the GHSG experience PFS is 97% at 3ys (HD14) and OS 98%.

The USA-Intergroup data with 4–6 ABVD are around PFS 85% and OS 80%.

Stages III B LMM; III-IV,A,B (Advanced Stages)
6–8 ABVD +/- 30 Gy IF-RT (USA, Canada)
6–8 BEACOPP escalated +/- 30 Gy IF-RT

In advanced stages (GHSG HD9, HD12,HD15, ca.3500 recruited patients): PFS: at 5 ys 87%; OS 91%
USA/Canada: 6–8 ABVD +/- RT: at 5 ys PFS 70%, OS 80%

Future Perspectives: Multiple international cooperative studies are ongoing to evaluate the role and impact of early response assessment with FDG-PET after...
2 courses of ABVD or BEACOPP to tailor therapy for the individual risk of the patient to relapse/progress and the need for escalation or de-escalation to preserve the high cure rates and minimize the long term sequelae like secondary neoplasias, endocrine, gonadal or cardiac or pulmonary complications. New horizons are open for targeted therapies in HL with lenalidomide, mTOR inhibitors, HDAC-inhibitors or anti CD30-/CD40-/CD25- antibodies. Multiple studies have started globally to test these promising molecules/antibodies in relapse settings as well as in induction therapies.

**Theme: Malignant Melanoma**

**Intermediate dose/low dose regimens**

*Friday, 19th November 2010, 16.15–17.00 (ERATO C)*

**Debate: Adjuvant Immunotherapy in Malignant Melanoma**

**Alexander Eggermont**

The following phase III adjuvant interferon (IFN) therapy trials with Intermediate Dose IFN (IDI, 5–10 MIU) and Low Dose IFN (LDI, 1–3 MIU) have been conducted as tabulated below:

| Trial      | Stage | Treatment                                      | DFS     | OS    |
|------------|-------|-----------------------------------------------|---------|-------|
| EORTC 18952 | II-III | IFNα2b, 10 MIU/ wk, sc,24mts or + 3x10MIU/ wk,sc,24mts | 4.65-yr; HR = 0.88; p = 0.40 | 4.65-yr; HR = 0.88; p = 0.40 |
| NORDIC 18952 | II,III | IFNα2b, 10MIU/ wk,sc,4 mths or + 3x10MIU/ wk,sc,24mths | 6 yr; HR = 0.83; p = 0.05 | 6 yr; HR = 0.88; p = 0.47 |

**Low dose IFN**

| Trial | Stage | Treatment                                      | DFS   | OS   |
|-------|-------|-----------------------------------------------|-------|------|
| French II 459 pts | IFNα2a, 3x3MIU/ wk,18mths | 5-y; HR = 0.75; p = 0.035 | 5-y; HR = 0.72; p = 0.059 |
| Austrian II 311 pts | IFNα2a, 3MIU/wk, 12mths | 3.4 yr; HR = 0.62; p = 0.02 | 3.4 yr; HR = 0.83; p = NS |
| Scottish II, III 95 pts | IFNα2b, 3x3MIU/ wk,6mths | 2 yr; HR = 0.72; p = 0.05 | 2 year; HR = 0.81; p > 0.2 |
| ECOG 1690 II,III 428 pts | IFNα2b, 3x3MIU/ wk,24mths | 5 yr; HR = 0.90; p = 0.17 | 5 year; HR = 0.93; p = 0.81 |
| UKCCR II,III 674 pts | IFNα2b, 3x3MIU/ wk,24mths | 5 yr; HR = 0.94; p = 0.6 | 5 year; HR = 0.91; p < 0.3 |
| WHO-16 III 424 pts | IFNα2a, 3x3MIU/ wk,36mths | 5 yr; HR = 0.95; p = 0.5 | 5 year; HR = 0.96; p = 0.5 |
| German III 291 pts | IFNα2b, 3x3MIU/ wk,24mths | 4-yr; HR = 0.69; p = 0.018 | 4-year; HR = 0.62; p = 0.0045 |
| EORTC 18871 II-III 484 pts | IFNα2b, 3x1MIU/ wk,12mths | 8 yr; HR = 0.96; p > 0.5 | 8 yr; HR = 0.96; p > 0.7 |

Interestingly the three smallest trials (Scottish (95 pts), Austrian (311 pts) and German (293 pts) had the best HR (0.62; 0.72; 0.69) which is cause for concern in view of the consistently worse outcome in the large trials. The two largest trials EORTC1892 and Nordic have virtually identical HR (0.81, 0.83) for the IDI trials. Interestingly this is virtually identical with the HR of 0.82 for RFS in the EORTC18991 (1256 pts) trial with PEG-IFN. Overall LDI and IDI are more effective in stage II, stage III and Stage III(SN++) only. There is very little evidence of efficacy in stage III palpable nodal involvement. The larger trials do provide the most consistent data regarding the impact of IFN on DFS, DFIand RFS as well as on OS. Interestingly lower stage and ulceration of primary were independent predictive factors of outcome in the EORTC 18952 + 18991 meta-analysis.

**High-dose regimens**

*Friday, 19th November 2010, 16.15–17.00 (ERATO C)*

**Debate: Adjuvant Immunotherapy in Malignant Melanoma**

**Helen Gogas**

Although cutaneous malignant melanoma is the least common form of skin cancer, it accounts for 75% of skin cancer deaths. The therapeutic management of cutaneous melanoma is one of the most challenging issues for oncologists. Because melanoma is among the solid malignancies most refractory to medical therapy, it makes early diagnosis and surgical removal of the primary tumor virtually the only curative approach currently available.

In patients with high-risk melanoma, that is, with American Joint Committee on Cancer (AJCC) TNME stage II (T2–4N0M0) and stage III (TanyN+M0) disease, the rate of disease recurrence ranges between 20% and 60%, with 5-year overall survival (OS) varying between 45% and 70%. The only agent currently approved for the adjuvant therapy for such patients is interferon alpha (IFN-α). Dosages, schedules and routes of administration have varied considerably among the various trials. For purposes of interpretation, it is useful to consider them under the subheadings of high-dose, intermediate-dose, and low-dose trials, where high dosages are defined as dosages of 10MIU/m2/day subcutaneously and/or 20MIU/m2/day intravenously, and low dosages are defined as dosages of 3 MIU/day or lower—and all between are defined as intermediate.

The high-dose IFN-α (HDI) regimen designed by ECOG is a unique schedule comprising an initial “high-dose” intravenous induction phase lasting 4 weeks, followed by a prolonged, self-administered, subcutaneously administered, high-dose treatment for 11 months. The rationale behind the development of this regimen was twofold: to deliver maximally tolerable doses of IFN-α over a finite period of time and to decrease the potential to form anti-IFN antibodies through the administration of a high-dose intravenous component. This regimen has now been tested in four randomized ECOG and Inter group trials. The first of these (E1664) was the pivotal study accepted by the FDA Oncologic Drug Advisory Committee as the basis for licensure of IFN-α-2b (Intron A) as the first effective adjuvant therapy of melanoma following resection of disease in patients with deep primary (T4, AJCC stage IIB) or regional lymph node metastatic disease (N1, AJCC stage III) disease. The first randomized trial of the high-dose IFN-α regimen, ECOG trial E1684 enrolled 287 patients between 1984 and 1990. At a median follow-up of nearly 7 years, median survival was significantly prolonged, from 2.8 to 3.8 years, and relapse-free survival from 1.0 to 1.7 years (P = 0.02, 0.02, respectively) for the overall trial. The toxicity of this regimen was considerable, and dose modification or delays were required in nearly two thirds of patients during the first month of treatment and again in more than half of subjects during the last 11 months of therapy. In the second Intergroup trial E1690 642 patients were accrued. This was completed in June 1995. A lack of overall survival benefit for HDI was observed despite an improvement in relapse-free survival. The lack of an overall survival benefit in E1690 generated significant controversy regarding the benefits of the HDI regimen. Data from a third trial addressing the adjuvant use of IFN-α-2b over patients who had been assigned to the GMK vaccine. The current efforts of the US and
The liver is the most common site for blood-borne metastasis from colorectal cancer. Liver metastases are often the stepwise pattern of metastatic progression and often the cause of death, thus justifying local treatment and often its association with systemic treatment.

Hepatic intra-arterial chemotherapy (IAHC) takes advantage that the liver vascularization is 30% arterial and 70% portal, while tumor growing in the liver are nearly exclusively fed by the arterial blood. IAHC with 5 FU or FUDR have demonstrated a better response rate for IAHC than for IV treatments. However only two trials have demonstrated a moderate benefit in survival [Meta-Analysis Group in Cancer, 1996 #20]. Intra arterial chemotherapy with oxaliplatinum in heavily pretreated patients offered a promising 45% response rate. More recently, IAH OXaliplatin through, plus IV 5FU and cetuximab (KRAS wild) as a first line therapy demonstrated a 90% overall response rate, and conversion to surgical patient of 48%. A similar 84% response rate and 47% surgical conversion has been reported with HIAC FUDR combined with systemic oxaliplatin and irinotecan. Percutaneous insertion of catheter for IAHC demonstrated a 97% feasibility with better overall permeability than surgical ones (9.18 vs 5.95 courses).

Chemoembolization, a combination of arterial drug delivery and vascular occlusion experimentally demonstrated better pharmacologic profile than IAH or IV injection when using drug eluting beads. response rate with response rate between 75 and 78% s, with 90% improvement of quality of life and 21% adverse reactions.

Radiomodelization is injection of Yttrium-90 loaded on glass or resin microspheres. Salvage therapy in heavily pretreated patients with unresectable colorectal liver metastases who had failed 3 lines of chemotherapy in 208 patients, demonstrated a median survival of 10.5 months for responders but only 4.5 months in non-responders (p<0.01). Morphologic response was found in 35% of patient according to RECIST, and CEA level decreased in 70% of patients. A RCT with 74 patients studying IAHC FUDR vs IAHC FUDR +Y- 90 showed 24% and 50% response rate, 7.6 and 12 months of time to progression respectively. Today a large scale (450 patients) randomized controlled trial (SIRFLOX) comparing FOLFOX±bevacizumab vs Y-90+ FOLFOX±bevacizumab in first line treatment is ongoing.

Indication and timing of intra-arterial therapies within the course of the non surgical liver metastatic disease remains discussed today. These treatments moved from salvage therapy towards more early use in the course of the disease with the hope to propose as early as possible the more efficient treatment, able to downstage patient and convert non surgical candidates to surgical candidates, which could be achieved in more than 45% of cases two recent studies. Indeed today surgery remains the only curative treatment of colorectal cancer metastases

Chemoembolization as downstaging and neoadjuvant treatment for patients considered for transplantation

Saturday, 20th November 2010, 09.45–11.15 (TERPSICHERE B)

Current Issues in Oncology: Interventional Radiology in Cancer
Christos Georgiades

Introduction: Currently, in the Western countries, approximately one-fourth of all liver transplants are performed for Hepatocellular-Carcinoma (HCC). The drop off risk for patients awaiting liver transplantation for HCC stands at 22%. Transplant liver availability is expected to worsen, resulting in longer waiting times and increased drop off rates. Our aim was to determine whether chemoembolization can reduce this risk and maintain patients until a donor liver becomes available.

Patients & Methods: 87 consecutive HCC patients listed for liver transplant (according to Milan criteria) underwent statistically comparable adjustability using the propensity score (Wilcoxon, Fisher’s and Chi-square tests). HCC was diagnosed after a biopsy or in cirrhotic patients with a hypervascular liver mass and an AFP > 400. Treated patients (selection criteria) had tumors 2 cm or larger and lesion within 1 cm of a planned surgical plane. 43 non-chemoembolization patients and 22 chemoembolization patients were comparable for C-P

State of the art in the use of biologics in the adjuvant setting in colon cancer

Saturday, 20th November 2010, 10.30–12.30 (TERPSICHERE A)

Plenary Lecture: State of the Art in the Use of Biologics in the Adjuvant Setting in Colon Cancer
Aimery de Gramont

The goal of an adjuvant therapy is to increase the cure rate in early-stage cancer by eradicating residual micrometastasis. Benefit of adjuvant therapy in colon cancer has been shown with fluoropyrimidines alone, then in combination with oxaliplatin, after having demonstrated an anti-tumor activity in first-line advanced disease. Albeit a proven efficacy in metastatic disease, irinotecan in combination with 5-FU could not show any advantage in terms of survival in adjuvant setting.

The NSABP C-08 and the AVANT BO17920 phase III trials have evaluated bevacizumab in combination with an oxaliplatin-based chemotherapy in patients with stage II-III colon cancer. The NSABP C-08 trial compared the fortnightly modified FOLFOX6 regimen for 6 months to the same regimen with bevacizumab (5mg/kg every 2 weeks) then bevacizumab alone as maintenance therapy (5 mg/kg every 2 weeks) for an additional 6 months. Contrary to advanced disease, nor arterial ischemic events, nor GI perforation, nor hemorrhage were associated with higher frequency in the bevacizumab arm than in the control arm. Toxicities significantly increased with bevacizumab were hypertension, pain, proteinuria, and wound complications. The addition of bevacizumab to modified FOLFOX 6 did not result in a statistically significant prolongation in DFS, with a 3-year DFS of 77.4% vs. 75.5% respectively (HR = 0.87; p = 0.08), in spite of a transient benefit in DFS during the first year when bevacizumab was utilized. The AVANT study compared FOLFOX4 (6 months) vs FOLFOX4 (6 months) with bevacizumab (12 months) vs XELOX (6 months) with bevacizumab (12 months) in 3451 patients with stage II or III colon cancer. The adverse event profile was comparable to the safety profile in metastatic disease and in the NSABP C-08 trial. The efficacy results should be available late 2010.

Both US Intergroup N0147 and European PETACC8 trials are evaluating FOLFOX chemotherapy for 6 months with or without a weekly administration of cetuximab in patients with stage III colon cancer whose tumor was completely removed by surgery. Results of N0147 were presented at ASCO 2010. Patients with wild type KRAS tumor had no benefit of cetuximab. Three-year DFS was 71.4% in the mFOLFOX6 arm and 73.3% in the cetuximab plus mFOLFOX6 arm, HR 1.18, p = 0.33. The same trend was observed for 3-year overall survival. Furthermore, patients over 70 years and patients with mutated KRAS tumor experienced worst outcome with cetuximab than with chemotherapy alone. Of note, cetuximab added significant toxicities to chemotherapy. The results of the PETACC8 trial are not yet available.

Thus, preliminary results of the first trials failed to improve survival, even though these drugs were active in metastatic disease. Benefit of adjuvant therapy might not be predicted by anti-tumor activity in the advanced setting. We should determine better signal(s) to launch adjuvant trials. How could we prevent those failures in adjuvant setting before recruiting a large number of patients? We should definitely improve understanding of mechanisms of action of drugs and tumor biology. Looking at biomarkers to select populations or to predict those who can benefit of therapy could be more cost-effective than the too large adjuvant trials.

Int. J. Cancer: 128, Supplement 1, 1–29 (2011) © 2011 UICC
and MELD scores, tumor size/number, AFP levels and cause of cirrhosis. We calculated the risk of dropping off the transplant list by assigning a transplant time to those who dropped off (equal probability with patients who were on the list longer than the patient in question). The significance level was obtained by calculating the simulation distribution of the difference over the permutations of chemoembolization vs. non-chemoembolization assignment of the patients. Kaplan-Meier estimators (log-rank test) were used to determine survival rates. Chemoembolization was performed by experienced interventional radiologists using a triple chemotherapy cocktail (Doxorubicin, Mitomycin C and Cisplatin, followed by 100–300 micrometer embosphere embolization). The procedure was repeated every 4–6 weeks if the follow up MRI showed residual viable tumor (more than 25% enhancement, using EASL criteria).

Results: Median follow up was 187±110 weeks (range 38–435, from date of diagnosis). The chemoembolization group had an 80% drop-off risk reduction (15% non-chemoembolization vs. 3% chemoembolization, significant with a p = 0.078). Though survival was also better for the chemoembolization group, it did not reach statistical significance. This is likely because our study was underpowered for survival analysis, which was not the objective. Specifically, 2-year survival for the non-chemoembolization and chemoembolization group was 57.3 ± 7.1% and 76.0 ± 7.9%, respectively (p = 0.078).

Conclusions: Chemoembolization appears to result in a significant reduction in the risk of dropping off the liver transplant list for patients with HCC. Chemoembolization should be considered for all HCC patients awaiting a liver transplant and whose lesion is ≥ 2 cm or larger or close to a planned surgical plane. Though not reaching statistical significance, there was a tendency towards longer survival in the treated group.

Current status of combination chemoembolization—systemic chemotherapy for hepatocellular carcinoma
Saturday, 20th November 2010, 09.45–11.15 (TERPSICORE B)

Current Issues in Oncology: Interventional Radiology in Cancer
Jean-Francois Geschwind

Ablation for lung, liver malignancies
Saturday, 20th November 2010, 09.45–11.15 (TERPSICORE B)

Current Issues in Oncology: Interventional Radiology in Cancer
Clotilde Della Pina

The term “image-guided tumor ablation” is defined as the direct application of chemical or thermal therapies to a specific focal tumor (or tumors) in an attempt to achieve eradication or substantial tumor destruction. Although tumor ablation procedures can be performed at laparoscopy or surgery, most procedures are performed with a percutaneous approach. Hence, several authors refer to these procedures as “percutaneous therapies”. The concept of image guidance is stressed in the title to highlight that image guidance is critical to the success of these therapies. Over the past 25 years, several methods for chemical or thermal tumor destruction have been developed and clinically tested. The thermal ablative therapies involved in clinical practice can be classified as either hyperthermic treatments— including radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation— or cryoablation. The thermal damage caused by heating is dependent on the tissue heterogeneity and the duration of heating. Heating of tissue at 50–55°C for 4–6 minutes produces irreversible cellular damage. At temperatures between 60°C and 100°C near intermediate coagulation of tissue is induced, with irreversible damage to mitochondrial and cytosolic enzymes of the cells. At more than 100°C–110°C, tissue vaporizes and carbonizes. On the other hand, the freezing of tissue with temperatures between ~20°C and ~60°C followed by rapid thawing results in cell membrane disruption and induces cell death. For adequate destruction of tumor tissue, the entire target volume must be subjected to cytotoxic temperatures. Among these methods, RFA is currently established as the primary ablative modality at most institutions. RFA is accepted as the best therapeutic choice for patients with early-stage hepatocellular carcinoma when liver transplantation or surgical resection are not suitable options and is considered as a viable alternate to surgery for inoperable patients with limited hepatic metastatic disease, especially from colorectal cancer. Recently, RFA has been demonstrated to be a safe and valuable treatment option for patients with unresectable or medically inoperable lung malignancies. Resection should remain the standard therapy for non-small cell lung cancer (NSCLC) but RFA may be better than conventional external-beam radiation for the treatment of the high-risk individual with NSCLC.

Initial favorable outcomes encourage combining radiotherapy and RFA, especially for treating larger tumors. In the setting of colorectal cancer lung metastases, survival rates provided by RFA in selected patients, are substantially higher than those obtained with any chemotherapy regimens and provide indirect evidence that RFA improves survival in patients with limited lung metastatic disease. Novel non-thermal techniques for tumor ablation—including irreversible electroporation and light activated drug therapy—seem to have potential to overcome the limitations of RFA and warrant further clinical investigation. The efficacy of combination therapies, including ablation plus administration of drug-eluting beads or thermal sensitive drug carriers is also currently being explored.

Theme: Novel Therapeutics & Translational Research
Clinical data with large molecular angiogenesis inhibitors: current data and future questions
Thursday, 18th November 2010, 12.45 – 14.00 (TERPSICORE B)

Scientific Symposium: Antiangiogenic Therapeutic Strategies in Cancer - Large-molecule Inhibitors
Dirk Arnold

Why are Fc receptors so important to the immune response?
Thursday, 18th November 2010, 12.30 – 14.00 (TERPSICORE A)

Scientific Symposium: Cancer vaccines—Overcoming Translational Dilemmas that Diminish Cancer Vaccine Efficacy
Madhav V. Dhodapkar

Monoclonal antibodies (mAb) have emerged as effective therapies for several cancers. Recent studies in several preclinical models have shown that the Fc portion of the antibodies is critical for their anti-tumor efficacy in several settings. Engagement of Fc receptors by mAb opsonized cells leads activation of antibody dependent cytotoxicity. In prior studies, we and others have shown that FcR dependent pathways are also critical for activation of adaptive immunity. FcR mediated uptake of opsonized tumor cells leads to marked increase in cross-presentation and generation of tumor immunity by dendritic cells. The Fc receptor system is a balance of activating and inhibitory receptors. Under steady state conditions, signaling via the inhibitory receptors dominates and plays an important role in mediating immune tolerance. Alteration of this balance towards reduced inhibitory signaling leads to activation of immune cells such as dendritic cells (DCs), and activation of type I interferon response. This pathway has major effects on immune stimulatory properties of DCs. Balance of activating/inhibitory receptors can therefore play a role in regulating immune effects of mAb therapies. Indeed, FcR polymorphisms have been strongly linked to survival following some antibodies, such as Rituximab therapy of lymphoma. Together, the emerging data suggest that clinical efficacy of mAb therapy may be determined not only by direct effects on tumor cells, but also the nature of recruited immunologic mechanisms, which depend in a large part on the Fc portion of antibody. These considerations also provide the biologic basis for rational combinatorial therapies as well as antibody engineering to improve the efficacy of antibody therapies.

Another concept with major implications for immunotherapy of cancer is the importance of self renewal pathways or stemness in cancer. We and others have recently shown that T cells targeting pathways involved in regulating stemness are highly effective in inhibiting the growth of tumor cells in culture. Preclinical studies also support targeting putative cancer stem cells in mice. The presence of spontaneous T cells response against SOX2, an embryonal stem (ES) cell gene, is a strong predictor of favorable outcome in patients with monoclonal gammopathies / myeloma. Immunity to some of the core ES genes (such as OCT4) may be much more common than previously thought and readily detected in healthy individuals. Harnessing immunity to genes...
important for self renewal of tumor cells may be an important requirement for eliciting durable and protective immunity with cancer vaccines.

Angiopoietin -2 as a potential biomarker in metastatic colorectal cancer

Thursday, 18th November 2010, 12.45–14.00 (TERPSICHERE B)

Scientific Symposium: Antiangiogenic Therapeutic Strategies in Cancer - Large-molecule Inhibitors

Ulrich Hacker

Glycans as a bridge between innate and adaptive immunity

Thursday, 18th November 2010, 12.30–14.00 (TERPSICHERE A)

Scientific Symposium: Cancer vaccines—Overcoming Translational Dilemmas that Diminish Cancer Vaccine Efficacy

Thomas Kieber-Emmons

Update on mechanisms of angiogenesis and antiangiogenesis: from basic concepts to clinical insights

Thursday, 18th November 2010, 12.45–14.00 (TERPSICHERE B)

Scientific Symposium: Antiangiogenic Therapeutic Strategies in Cancer - Large-molecule Inhibitors

Sonja Loges

Is there more to multimodality than meets the eye?

Thursday, 18th November 2010, 12.30–14.00 (TERPSICHERE A)

Scientific Symposium: Cancer vaccines—Overcoming Translational Dilemmas that Diminish Cancer Vaccine Efficacy

Hans W. Nijman

In the first part of this presentation the interaction of tumor cell death due to chemotherapy and radiotherapy on one hand and induction of anti-tumor immune responses induced by this cell death on the other hand to achieve the optimal result in tumor eradication will be elucidated. It is postulated by Zavo-gel et al that activation of the calreticulin exposure pathway is an important mechanism of activation of the immune system after treatment with classical therapies like chemotherapy. The thought that chemotherapy in general results in a strong reduction of major components of the immune system and thereby harming the immune system ready to attack the tumor does not hold true anymore. An evolving amount of evidence is showing the opposite. Immunotherapy in combination with chemotherapy might be a very effective strategy to induce long lived antigen specific memory T cells. Cephalolin next to paclitaxel and doxorubicin, drugs often used in gynecologic malignancies, make tumor cells more susceptible for Granzyme B dependent killing by cytotoxic T cells. Not only chemotherapy, but also radiotherapy can prime an immune response. Proof of principle has been shown in diseases like prostate and cervical cancer.

In the second part of this presentation enhancement of immunotherapy by treatment with monoclonal antibodies will be discussed. One examples is treatment with an anti death receptor 5 monoclonal antibody (anti-DR5 mAb) in combination with E7 specific memory T cells. Cephalolin next to paclitaxel and doxorubicin, drugs often used in gynecologic malignancies, make tumor cells more susceptible for Granzyme B dependent killing by cytotoxic T cells. Not only chemotherapy, but also radiotherapy can prime an immune response. Proof of principle has been shown in diseases like prostate and cervical cancer.

In this presentation results will be presented on the immunological microenvironmement changes occurring in cancer patients during conventional therapies and vaccination and discussed in light of possible implications in designing new vaccination strategies and propose novel criteria and biomarkers for the evaluation and monitoring of immunotherapeutic clinical trials.

Theme: Psycho-Oncology

Screening for distress

Thursday, 18th November 2010, 11.30–12.45 (TERPSICHERE B)

Scientific Symposium: Cancer vaccines—Overcoming Translational Dilemmas that Diminish Cancer Vaccine Efficacy

James Brennan

Background: Thanks to the emergence of hospices and palliative care, the physical suffering associated with cancer has never been better controlled. It is the psychosocial suffering associated with cancer that bears a much closer resemblance to historical images of the disease as wasting and painful. At the

2/neuT transgenic mice a combination treatment of anti-DR5 mAb with anti-ErbB-2 antibodies had a synergistic effect in suppressing spontaneous arising tumors. Bortezomib, a proteasome inhibitor, further promoted cancer cell death if combined with anti-DR5 mAb. Whether this combination would enhance or suppress an immunological response needs to be elucidated.

In the end patients might benefit from a combined treatment modality, including immunotherapy, radiotherapy and chemotherapy with or without further targeted therapies.

Lessons learned from localized immunotherapy

Thursday, 18th November 2010, 12.30–14.00 (TERPSICHERE A)

Scientific Symposium: Cancer vaccines—Overcoming Translational Dilemmas that Diminish Cancer Vaccine Efficacy

Marianna Nuti

The vast amount of information and novel knowledge in the field of tumor immunology has in the last years, increased the interest in defining immunotherapeutic strategies to be applied in cancer therapy. Immunotherapy is today an increasing attractive option for the treatment of cancer. Although malignancies presuppose a failure of the host responses, patients develop innate and adaptive immune response in the course of their disease. In fact measurable immune prognostic signatures can define the immunological history of cancer progression and are becoming important markers to be used in defining prognosis and establishing timing for immunotherapy intervention. Immune activation appears to begin early during tumor development and progression and can be easily boosted by vaccination. However the effect on tumors is not rapid or at least is not comparable to the timing of a chemotherapy treatment, needing more time to activate cognate multiple interactions that will ultimately lead to tumor cell killing. Moreover this type of treatment can be particularly efficacious only in the presence of minimal residual disease since a heavy tumor burden is a condition opposing strongly the type of immunological killing based on a cell-to-cell contact while it does not profit of the advantage of lymphocytes to recirculate through tissues to find their target. Uniform expression of target antigen by the cancer cells may also not be essential since the mechanism of epitope spreading has been shown to occur in both mice and humans and contribute significantly to tumor rejection. Finally it is very important to address the question of the interactions between the standard therapies (gold standard) and immunological intervention. Until now these approaches have been considered in some ways opposite. Chemotherapy was detrimental to blood cells and therefore considered as a separate option from immunotherapy. Today anti neoplastic drugs are being studied as inducers of immunological deaths, and outcomes from pure chemotherapy trials are been revised as a result of the combination of two effects, the cell chemical cytotoxicity and the consequent immune activation. Moreover surgery can be considered as an optimal and unique way to reduce tumor derived immunosuppression that is particularly relevant in gynecological cancers. For example in ovarian cancer, cyto reduction appears to exert a beneficial systemic effect by reversion immunosuppression and restoring immunological fitness in the patient.

In this presentation results will be presented on the immunological microenvironment changes occurring in cancer patients during conventional therapies and vaccination and discussed in light of possible implications in designing new vaccination strategies and propose novel criteria and biomarkers for the evaluation and monitoring of immunotherapeutic clinical trials.
International Psycho-Oncology Society (IPOS) Board Meeting held in Vienna in 2009, members unanimously endorsed the idea that distress be named the 6th Vital Sign in Oncology. Over past decades a number of attempts have been made to respond to cancer distress. The field has gradually moved away from the idea that distress can be sensibly equated it with psychopathology, and these days it is generally agreed that distress is a multi-factorial concept involving physical, psychological, social, and spiritual causes. But if hard-pressed oncology services are to respond to distress, as the 6th Vital Sign, then the challenge is to do so efficiently and effectively yet humanely.

In the UK a number of regional cancer centres have adapted the US NCCN Distress Thermometer and developed it as the basis of both a screening measure and a form of triage. This paper will describe these and associated developments and report data from a study to validate the multi-factorial problem list (PL) of the screening tool.

Method: Published versions of the PL items, along with modifications made by UK researchers, were scrutinised by focus groups comprising ex-patients and clinical staff. These groups examined the intelligibility, ambiguity, and potential redundancy of items, sometimes making alternative suggestions or pooling items. The resulting 46 candidate items were then sent by post to participants, asking them to endorse any items that had been ‘a source of concern or distress’ during their recent treatment. This resulted in a 42-item PL.

Participants: 735 mixed cancer patients who had recently finished treatment. Responses were obtained from 395 (53%) of those written to, of whom 65% were female.

Results: The most frequently endorsed items were ‘Fatigue, exhaustion or extreme tiredness’ (70%), ‘Worry, fear or anxiety’ (45%), and ‘Sleep problems’ (38%). Some new items were commonly endorsed: ‘Memory or concentration’ (30%) and ‘Loneliness or isolation’ (15%), suggesting that these items should be routinely included in any screening PL.

Discussion: If health services are to respond to cancer distress they must first be asking the right questions of their patients and, in view of patients’ reluctance to volunteer their concerns, be prepared to be proactive in doing so. It is also essential that screening for distress is acceptable to patients and that the language used is easily understood by them. The screening methods presented in this paper offer a potentially efficient way of identifying and responding to cancer distress that has thus far been warmly welcomed by patients and staff alike.

Men, communication and clinical trials—an overview
Thursday, 18th November 2010, 11.30–12.45 (TERPSICHORE B)

Scientific Symposium (Organized by IPOS): Breaking New Developments in Psycho-oncology
Clare Moynihan

Background: Relatively little work has been carried out with men with cancer while women are overwhelmingly represented in all aspects of psychosocial oncology. This is surprising considering that an Equality Act has been finally passed this year in the United Kingdom stating the importance of attending to gender; to both men’s and women’s needs with respect to cancer care. Moreover relatively little is known regarding the ways in which men participate and adhere to randomisation into clinical trials that involves the important question of communication. The little that is known rests on a ‘deficit model’ of patient-hood. Patients have been shown to ‘misunderstand’ important concepts and procedures and reasons for accepting and declining randomisation have become an important focus of interest. Participants: While background data will be presented from work that has been carried out with men with prostate cancer and who were invited to join clinical trials, a recent qualitative study that investigated men with bladder cancer and who were invited to join a complicated randomised trial, will form the main thrust of this talk.

Results: In general men and women may have similar needs in terms of communication. However there are areas where men appear to prefer certain ways of being attended to. This is particularly evident in terms of clinical trials. In the study we carried out, many men made rational and self serving decisions to decline randomisation. However, others were shown to ‘misunderstand’ concepts and procedures that led to both acceptance and refusal to be randomised, casting doubt on the validity of the trial. This was not because they were incapable of understanding but because of faulty communication procedures that did not appear to match men’s needs, coercion, a lack of time to make decisions and information ‘overload’.

Discussion: Rather than utilising a ‘deficit’ model of the ways in which patients comprehend concepts and procedures of clinical trials, it is important to address the ways in which men may wish to participate, not only in trials but in cancer care in general. By doing so, clinicians and other health professionals are required to be reflexive—to look at their own practices when conveying complicated messages in situations that are, in most part, entirely new to consumers of cancer care.

Cancer and the elderly
Thursday, 18th November 2010, 11.30–12.45 (TERPSICHORE B)

Scientific Symposium (Organized by IPOS): Breaking New Developments in Psycho-oncology
Maggie Watson

Background: By 2030 the number of older cancer patients is expected to double. Older patients are perceived as an under-served group but will become the majority used group for cancer services in the future. Recent changes in European law require that cancer patients receive optimal care regardless of age. Why examine age issues? There are few studies clarifying support needs according to age. Different physical and social circumstances mean that the needs of older patients are likely to differ from younger patients. Differences in functional impairment, social support networks, lower income and other co-morbidities associated with aging will contribute to different support and psychosocial needs. The issues will be introduced and briefly overviewed. Alongside is reported details of a study aimed at clarifying support care needs in elderly cancer patients. Research questions:

1. Do psychosocial, information and support care needs in the elderly differ from younger patients?

2. What are the points of difference according to age?

Method: Prospective Questionnaire survey methodology using [1] Support Care Needs Survey (SCNS), [2] Information Satisfaction Questionnaire: Short Form (ISC), [3] EORTC QLQ: functional and global QL subscales

Participants: N = 400 patients (n = 200 seniors; n = 200 non-seniors) assessed at 3 (baseline) and 9 months (follow-up) post-diagnosis. Includes; breast, GI, GU, and lung cancer patients.

Results: Data are presented on baseline characteristics (3 months post-diagnosis) of the sample and comparisons between seniors and non-seniors during this early period following diagnosis.

Discussion: Findings will help guide the development of age-appropriate care in oncology to meet the growing needs of an aging population. While age per se must not be the only criterion for care decision-making, it is recognised that the elderly may have specific needs and oncology services will need to be increasingly tailored to these needs.

Theme: Supportive Care

Standard of care in the treatment of chemotherapy induced nausea and vomiting (CINV)
Saturday, 20th November 2010, 09.00–09.45 (TERPSICHORE A)

Plenary Lecture: Standard of Care in the Treatment of Chemotherapy Induced Nausea and Vomiting (CINV)
Matti Aapro

Vomiting and, especially, nausea, continue to be two of the most distressing side effects of cancer chemotherapy in spite of all the progress that has been
made since the early 1980’s. Recommendations on the optimal antiemetic pro-
phylaxis in patients submitted to chemotherapy and radiotherapy have been sug-
gested by many groups, and the Multinational Association for Supportive Care in
Cancer has recently published along with the European Society for Internal Medecine a position paper. This presentation is based on the conclusions of this
paper, and will also discuss some of the questions that still need to be addressed.
Defining the emetogenicity of chemotherapy agents is a framework defining antiemetic treatment guidelines. The principles for use of antiemetic
drugs to prevent nausea and vomiting induced by chemotherapy are the follow-
ing: - use the lowest tested fully effective dose, - no schedule better than a sin-
gle dose beginning before chemotherapy, - the adverse effects of these agents are
comparable, - intravenous and oral formulations are equally effective and safe.
To prevent acute nausea and vomiting following chemotherapy of high
emetnic risk (including anthracycline cyclophosphamide combinations) a 3-drug
regimen including single doses of a 5-HT3 receptor antagonist, dexamethasone, and [lo[aprepitant given before chemotherapy is recommended. Guidelines rec-
mand that all patients receiving highly or moderately emetogenic chemother-
aphy should receive antiemetics that prevent delayed nausea and vomiting. Polo-
noetron is superior to other 5-HT3 receptor antagonists when an NK, receptor
antagonist is not available. Therefore, to prevent acute nausea and vomiting induced
by non-AC moderately emetogenic chemotherapy a combination of palonosetron
plus dexamethasone is recommended as standard prophylaxis. Dexamethasone
or can be substituted by other corticosteroids where it is not available. If aprepitant
is not available, women receiving a combination of anthracycline plus cyclo-
phosphamide should receive a combination of palonosetron plus dexamethasone.
Only a few small studies have been carried out in patients receiving multiple
day chemotherapy. It is preferable to use maximally effective antiemetics as first
line therapy rather than withholding more effective antiemetics for later use at
the time of antiemetic failure. Rescue antiemetic treatment is done with a num-
ber of approaches including switching to a different 5-HT3 receptor antagonist
or adding other agents such as dopamine antagonists or benzodiazepines. Antici-
pathy nausea and vomiting is widely believed to be a learned response to chemother-
aphy that develops in up to 20% of patients by the fourth treatment
cycle and is difficult to control by pharmacological means. Therefore, it is rec-
ommended that the best approach to the treatment of anticipatory emesis is the best
possible control of acute and delayed emesis.

Pharmacologic management of cancer pain
Saturday, 20th November 2010, 09.45–11.15 (TERPSICHORE A)

Current Issues in Oncology: Management of Cancer Pain
Janet L. Abrahm

Pain can be relieved without excessive sedation in over ninety-percent of
cancer patients. The initial steps include a comprehensive patient assessment
and making a “diagnosis” of the cause of the pain, even in patients in
whom the underlying cause cannot be reversed. Patient reports of pain may
reflect underlying tissue damage, but they may also reflect other sources of
suffering, including emotional, psychological, spiritual and existential inju-
rines. The “meaning” of the pain alters its intensity: a post-surgical pain fol-
lowing a curative resection is likely to be much better tolerated than a pain
arising from progressive disease. Oncologists and oncology nurse practi-
tioners must therefore address pain from all sources, collaborating with social
workers, psychologists, nurses and clergy who are crucial to relieving other
causes of distress that presents as or exacerbates the experience of pain. Pharma-
cologic agents of several classes are usually required if patients are to achieve
pain relief: non-steroidal anti-inflammatory agents (NSAIDs), glucocorticoids,
adjutant agents specific for bone or neuropathic pain, and opioids. Opioids
available to Greek physicians who obtain the required permit include: short-act-
ing oral and intravenous morphine, oral sustained-release morphine, and trans-
dermal sustained-release fentanyl. Because another speaker will discuss the
treatment of bone pain, this presentation will review the utility and side effects
of agents useful for pain caused by muscle or tissue injury, or for neuropathic
pain. These agents include: NSAIDs, glucocorticoids, neuropathic adjutant
agents, and opioids. Fear of addiction can prevent cancer patients from taking
the opioids they need, but in actuality, cancer patients rarely become addicted to
opioids used to relieve their pain. I will discuss the distinction between addic-
tion and physiologic tolerance and ways to encourage cancer patients to acquire
the permit needed to take pain-relieving opioids despite their and their families’
fears. I will also review how to (1) manage a patient in a pain crisis (using oral
or intravenous morphine), (2) convert a patient whose pain is relieved by intra-
venous morphine to the equi-analgesic dose of oral sustained-release morphine
or transdermal fentanyl (e.g. Duragesic™ and vice versa), and (3) prevent and
treat common opioid-induced side effects (i.e. constipation, nausea, and seda-
tion). Pain must also be distinguished from delirium, and many of the agents
used to relieve pain also cause delirium. I will also review, therefore, the meta-
bolic, pharmacologic, and other predisposing factors that cause delirium, the
clinical presentation of hypo- and hyperactive delirium, and what can be done to
reverse the delirium. Since pain can be exacerbated by anxiety and depres-
sion, I will briefly review anti-anxiety agents and anti-depressants.

Viral infections
Friday, 19th November 2010, 09.00–11.00 (TERPSICHORE B)

Educational Symposium: Infections in Cancer Patients
Mickael Aoun

Overshadowed for long by the more fulminant bacterial and fungal infections,
viral agents have witnessed in cancer patients increased awareness during the
last decade. New approaches to diagnosis based on molecular biology methods
and new antiviral therapeutical modalities have been developed. Either directly
by causing end-organ damage or indirectly through facilitation of bacterial or
fungal infections, viral agents contribute to increased morbidity and mortality in
cancer patients. Although susceptible to the same common viruses that infect the
general population, but with more complications, cancer patients are prone to
devastating diseases generated by several chronic or latent viral infections.
There are no global epidemiological data on viral infections in cancer patients.
Several studies are focused on haematological malignancies, mainly on hematopo-
etic stem-cell transplantation (HSCT). In our last review on causes of fever in
cancer patients, viral causes represented 3.9 %. However, this is an under esti-
mation since many viral infections are not documented microbiologically.
The main sites of involvement include the respiratory tract, the gastro-intestinal
tract and the central nervous system. Pneumonia is one of the most common in-
fecious complications in cancer patients receiving chemotherapy. Respiratory
viruses are being increasingly recognized as important pathogens and responsi-
bly for severe lower respiratory tract infections. Multiplex real-time polymerase
chain reaction (RT-PCR) and other nucleic acid sequence based amplification
methods, have markedly improved our detection of respiratory viruses includ-
ing the old ones such as influenza and param influenza viruses, respiratory syncri-
tial viruses (RSV), adenoviruses and the new ones such as human metapneumo-
virus, coronavirus and rhinoviruses. The associated mortality in cancer patients
is highly variable with the highest rates reported in hematopoietic stem cell
transplant recipients. Anti-influenza vaccination and contact isolation are im-
portant prevention measures. High-dose oseltamivir and IV peramivir are being
evaluated for severe influenza pneumonia, and IV or oral ribavirin is increas-
ingsly used for parainfluenza, RSV, human metapneumovirus and adenovirus
Viral gastro-intestinal infections are more frequent in the pediatric cancer
population. Although there is no specific treatment for epidemic viral gastroen-
teritis caused by norovirus, rotavirus, or astrovirus, identification is important
for infection control measures in order to avoid nosocomial transmission. Her-
petic mucositis is very common in cancer patients and early treatment with acy-
clovir has almost eliminated the end-organ damage previously reported with
Herpes simplex such as pneumonia or hepatitis. Ulcerative esophagitis may be
uncommonly associated with herpetic mucositis and on rare occasions in highly
immunosuppressed patients, cytomegalovirus could be the causative agent. Viral
colitis is either due to cytomegalovirus, human herpes virus 6 or enteric aden-
virus and could be either localized or part of a disseminated disease.
Viral hepatitis in cancer patients is of major concern. It could be either associ-
ted to a disseminated disease due to cytomegalovirus, adenovirus, HHV6, EBV or
due to reaction of hepatitis viruses A, B, C, and E. There is increasing
evidence showing that carriers of hepatitis B who are candidates for chemo-
therapy, should receive pre-emptive therapy with lamivudine or adefovir.
Viral encephalitis or meningitis in cancer patients is the most serious complication. Several viruses have been implicated including herpes virus such as Herpes simplex, varicella-zoster, CMV, HHV6 and EBV. Polymavirus JC is responsible of progressive multifocal leuco-encephalitis, occurring in haematological malignancy patients such as LLC, Hodgkin lymphoma and post-allogenic HSCT.

**Usage of growth factors**

**Friday, 19th November 2010, 09.00–11.00 (TERPSICHORE B)**

Educational Symposium: Infections in Cancer Patients

Jean Klastersky

Lung cancer, of which 75 % are non-small cell tumors (NSCLC) is presently the leading cause and accounts for more than 30 % of cancer-related deaths. A first progress in the management of NSCLC was the demonstration of a favourable impact of platinum or carboplatin-based therapy on survival and quality of life. Today a combination of a platinum derivative with any of the following agents: docetaxel, paclitaxel, gemcitabine, vinorelbine or perempted continues to be the standard of care for advanced or metastatic NSCLC. Another important advance has been the demonstration that adjuvant platinum-based chemotherapy prolonged survival in a significant proportion of patients with stage I, II or IIA NSCLC who underwent a successful resection of the tumor. A recent major step to words a better management of NSCLC has been the recognition that the epidermal growth factor (EGF) family played an important role in the tumorigenic process and that the EGF-receptor was frequently overexpressed in the development and progression of NSCLC.

Actually somatic mutations have been identified in the tyrosine kinase domain of EGFR that predict significant responses to EGFR inhibitors such as gefitinib and erlotinib. Many other genetic abnormalities (VEGF overexpression, KRAS and BRAF mutations, TITF-1 amplification, ERCC1, etc) not only provide a better understanding of NSCLC carcinogenesis but could be used as prognostic factors or targets for therapy. Hopefully, therapy of NSCLC will increasingly become more personalized, based on specific features of the tumor and of the patient.

The tremendous laboratory and clinical efforts to achieve a better management of NSCLC should not however cloud that in the majority of cases, lung cancer is due to tobacco use, which makes it a self-induced and highly preventable disease.

**Erythropoiesis stimulating agents (ESAS) in cancer patients; where do we stand today?**

**Thursday, 18th November 2010, 15.15–16.00 (TERPSICHORE A)**

Plenary Lecture: Erythropoiesis Stimulating Agents (ESAS) in Cancer Patients; Where Do We Stand Today?

Iain Macdougall

Anemia is common in cancer patients and is exacerbated by chemotherapy. This has a negative effect on survival and contributes to the fatigue associated with cancer. Many patients require top-up red cell transfusions. The advent of ESA therapy brought hope that there may be an effective treatment for anemia that would reduce the need for blood transfusions and also decrease anemic complications. There are four relevant issues in relation to the use of ESAs in cancer:-

(1) Do ESAs enhance tumour progression due to stimulation of tumour cell EPO receptor?
(2) Do ESAs increase the risk of venous thromboembolism in malignancy?
(3) Do ESAs impact on survival in cancer?
(4) Do ESAs improve quality-of-life in patients with cancer?

Over the last few years, we have begun to elucidate some of the answers to these questions.

(1) Early studies in breast cancer and head & neck malignancy, raised some safety concerns with ESA therapy. Although studies have shown that mRNA can be isolated from tumour cells, it has been much harder to definitively show the presence of EPO receptor protein due to a lack of specific antibodies against the erythropoietin receptor. It is also questionable whether the erythropoietin receptor on tumour cells is functional and although there is some in vitro evidence showing enhanced tumour growth with erythropoietin, in vivo studies are less convincing.

(2) Thromboembolism is a common event in cancer patients, and a leading cause of death. Data from both the oncology, as well as the nephrology literature suggest an enhanced risk of thromboembolism with ESA therapy, and this may be due to the effect on platelet function, endothelial cell activation, and nitric oxide scavenging.

(3) Data from both the nephrology and oncology literature suggest that there may be reduced survival with the use of ESA therapy with current malignancy or a previous history of cancer. Part of the reason for this is the increased risk of thrombotic events associated with the use of ESA therapy.

(4) Anemia is associated with reduced quality-of-life in cancer patients, and ESA therapy may improve fatigue and energy scores in cancer patients with chemotherapy-induced anemia. Various tools have been used to assess this, including the FACT-An and the LASA scores. Most of the improvement in quality-of-life occurs between 8 and 11 g/dl, and above 12 g/dl, there is less additional improvement in quality-of-life. There is also evidence that the use of ESA therapy will reduce the requirement for, and adverse affects associated with, blood transfusions.

As with many therapies, the use of ESAs in cancer patients is a fine balance between risk and benefit. There are certainly potential benefits for many patients, but the risks associated with their use in this setting must be acknowledged, particularly the increase in thromboembolism and reduced survival. We have come a long way since the early 1990s when three studies enrolling a total of 413 patients were conducted to satisfy the FDA into granting approval for the use of recombinant erythropoietin in cancer patients) to the present day, when several large Cochrane meta-analyses have been performed in tens of thousands of cancer patients. Because of the possible risks, ESA treatment should be used within the constraints of its label.

**Bone cancer pain: from animal models to targeted therapy**

**Saturday, 20th November 2010, 09.45–11.15 (TERPSICHORE A)**

Current Issues in Oncology: Management of Cancer Pain

Patrick W. Mantyh

**Infections due to resistant bacteria**

**Friday, 19th November 2010, 09.00–11.00 (TERPSICHORE B)**

Educational Symposium: Infections in Cancer Patients

Kenneth V. Rolston

**Introduction:** Patients with cancer develop bacterial infections frequently especially (but not exclusively) during episodes of neutropenia (1). Currently, gram-positive organisms are the predominant bacterial pathogens, causing ~80% of bacteremic infections and 45–50% of bacterial infections overall. Gram-negative and polymicrobial infections are less frequent, but are associated with great morbidity and mortality. Heavy microbial usage in many cancer patients creates selection pressures leading to the emergence of resistant organisms. As high-lighted in several recent reports, therapeutic options for multi-drug-resistant organisms are limited, and new drug development is at a standstill (2). Consequently, antimicrobial stewardship has become an important aspect in the management of these patients.

**Gram-Positive Bacteria:** Staphylococci are the predominant gram-positive organisms causing infection in cancer patients. Almost all coagulase-negative-staphylococci and methicillin -resistant, and >50% of S. aureus isolates are methicillin resistant. Vancomycin used to be the agent of choice for the treatment of infections caused by methicillin-resistant staphylococci (9). Recently clinical failures to vancomycin have been encountered even in...
In the 90’s the new lipid and liposomal formulations of amphotericin B gave new possibilities to treat a wide spectrum of fungal diseases. These formulations are still in use as effective therapeutic modalities. The production of newer azoles such as voriconazole, that made the difference in the treatment of aspergillosis, and posaconazole, that has a very broad spectrum, offered new weapons against IFIs. The new class of echinocandins, that includes caspofungin, micafungin and anidulafungin, broadened even further the antifungal armamentarium. However, despite the development of effective drugs the cancer patient remains a sensitive host. Immunosuppression minimizes the activity of antifungal agents. Hence, the infectious diseases community is looking forward to new compounds as well as to the results of ongoing clinical trials assessing the activity of combination antifungal treatments. It must be emphasized, however, that restoration of the immune system, if possible, remains the cornerstone for the treatment and prophylaxis of fungal infections of patients with neoplastic diseases.

**Does neoplastic therapy improve cancer pain?**

*Saturday, 20th November 2010, 09.45–11.15 (TERPSICHORE A)*

**Current Issues in Oncology: Management of Cancer Pain**

*Jamie H. Von Roenn*

Pain is one of the most feared and common complications of advanced cancer. Fortunately, the majority, up to 90%, of patients achieve effective relief of pain utilizing standard approaches to pain management. For the minority of patients with metastatic disease and curable cancer, effective antineoplastic therapy cures the cancer and generally leads to resolution of cancer-associated pain. Unfortunately, the majority of patients with metastatic disease are not cured with currently available therapies. For patients with incurable cancer and pain, management of the pain is an essential component of optimal cancer care. The most frequent type of pain in patients with metastatic disease is bone pain secondary to osseous metastases. While the mainstay of treatment is analgesics, antineoplastic treatment does provide significant benefit. The Radiation Therapy Oncology Group has demonstrated that external beam radiation therapy, whether given as a single or multiple fractions, provides complete to partial relief of pain from osseous metastases for about 60% of patients. Overall, the results are better for single sights of pain than for treatment of extensive multifocal osseous metastases. Bisphosphonates decrease and delay the occurrence of skeletal fractures from metastatic bone disease, but improve pain control to only a limited degree. For cancer pain not related to bone metastasis, radiation therapy is not usually the treatment of choice. Pharmacologic treatment is the treatment of choice for patients with advanced disease and multiple sites of pain. A purported goal of chemotherapy for patients with advanced disease is to provide symptom palliation. However, the majority of clinical trials of pharmacologic agents assess the effectiveness of treatment in advanced disease based on tumor shrinkage. In patients with metastatic breast cancer, a randomized trial evaluated the association between symptom improvement and objective tumor response. Pain was one of the symptoms that improved in those patients who had a complete or partial response to treatment. The relationship between objective tumor response and symptom improvement has not been evaluated for most disease sites. Data on the impact of chemotherapy on cancer-related pain is limited and outcomes may vary by primary site. There are a number of excellent examples of pain relief from pharmacologic treatment of cancer. The acceptance of gemcitabine as a treatment for pancreatic cancer is based on its impact on symptom control and quality of life utilizing a composite measure of pain, performance status and weight. Trials of prostate cancer have incorporated palliative endpoints, including pain control, as a primary outcome measure. Some data are also available in other tumor sites.
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