Malignant disease and the adolescent

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Malignancy affects an estimated one in 800 people in the age group 13–18 years. The majority of these patients are curable, but the cost in terms of physical, intellectual and psychological morbidity can be high for an individual undergoing the developmental transformations of adolescence.

Figure 1 illustrates the most common diagnoses affecting teenagers and young adults in the UK. Compared with adult malignancy, relatively few patients develop tumours of epithelial origin, but compared with paediatric malignancy, they are more common, as are primary bone tumours and lymphomas.

Adolescence is a period of substantial and significant growth and of re-

formation physically and intellectually, as the dependent child moves in stages towards independence. The diagnosis and treatment of a life-threatening illness are likely to disturb and possibly arrest this progress, leaving an individual poorly adjusted to adult life. Hence, the goal of all oncologists must be to cure the patient with minimal morbidity.

Acute problems

General

The effects of a diagnosis of malignancy and of its treatment are profound and may colour the patient’s subsequent ability to overcome the illness. Many sequelae of therapy relate to ‘the system’: prolonged treatment in hospital, family, social and educational disturbance, and the reaction of the adolescent to the acute events experienced whilst undergoing treatment. They must be minimised, which may

Fig 1. Malignant diseases in adolescent patients. GCT = germ cell tumour; NBL = neuroblastoma; NHL = non-Hodgkin’s lymphoma.

![Diagram of malignant diseases in adolescent patients]
require different approaches for different people. Treatment in a specialist oncology unit will overcome many problems, particularly in the early stages when the patient is coming to terms with the diagnosis, and when information in depth is often needed. Paediatric patients with malignant disease, including adolescents below 16 years at the time of diagnosis, are almost always treated in one of the 22 centres affiliated to the UK Children's Cancer Study Group, where a high degree of coordination of initial diagnosis, staging and treatment can be accomplished. It is unfortunate that age is the principal criterion defining entry into the health care system at the present time. There can be no definite cut-off point for a patient to be best treated in an adult hospital.

Having cancer as a teenager leads to loss in many senses: loss of function, of an affected limb or as a result of a brain tumour; loss of normal body image due to alopecia, poor nutrition, operation scars. There is loss of privacy as personal space is repeatedly invaded for examination, cannulation or therapeutic procedures. Independence is also lost, with the adolescent having to rely on others and acquiesce with the regimentation of chemotherapy protocols. The individual may become isolated, losing social contact at school, college or work. For many, a period of grief may be an appropriate reaction to such severe changes.

Surgery

The acute effects of surgery, like chemotherapy or radiotherapy, are well defined and recognised. Surgical intervention in most cases is minimally invasive, and often involves initial biopsy prior to adjuvant therapy. A more limited secondary resection can often then be accomplished, maintaining function and reducing scarring and other complications. Extensive or mutilating surgery is rarely indicated. For example, in most recent studies of treatment of osteosarcoma, amputation is unusual and generally confined to cases of locally highly aggressive disease, for which the overall prognosis is poorer than for conservative, limb-sparing surgery. Patients with amputation may have lower self-esteem and be more socially isolated, but patients who have undergone a limb salvage procedure report more physical complaints.

The outcome for brain tumours more than for any other tumour is determined by the extent of surgical resection. Complete surgical resection is associated with a significantly better outcome (overall and relapse-free survival) in ependymoma and malignant glioma, which comprise a large proportion of tumours in this age group. This situation reflects both operator skill and the nature of the tumour. The danger of pursuing a complete resection is the resulting unacceptable morbidity. Improvements in imaging techniques, stereotactic guidance systems that allow precise location of the tumour, and changing neurosurgical practice (acceptance of adjuvant chemotherapy, radiotherapy and second-look surgery) have improved immediate neurological recovery for many patients and allowed more consistent surgical clearance.

Chemotherapy and radiotherapy

Chemotherapeutic drugs carry significant side effects both in the acute and long term. These are summarised in Table 1. Historically, nausea and vomiting were of major significance, and occasionally this remains the case. Drugs such as cisplatin, anthracyclines and alkylating agents may present difficulties in control of nausea, but the appropriate use of anti-emetic agents can usually achieve this goal. Inhibitors of 5-hydroxytryptamine (5-HT)3 receptors, with the synergistic use of dexamethasone, and the addition of agents such as metoclopramide (butyrophenone), chlorpromazine (phenothiazine) lorazepam (benzodiazepine) or nabilone (cannabinoid) may be required.

The acute effects on nutrition of chemotherapy, abdominal surgery or radiotherapy may be profound, and the patient may take months or years to recover fully. Enteral and parenteral nutrition is increasingly adopted to avoid such changes, with the result that patients are better able to tolerate the increasingly aggressive protocols. Nevertheless, a nasogastric tube is often unacceptable to a teenage patient, and parenteral nutrition requires hospital admission. Significant weight loss is still a major concern in oncology. The incidence of protein energy malnutrition is reported to be between 6 and 50%; it is higher in patients with extensive, progressive or unresponsive disease, those receiving intensive chemotherapy, abdominal or pelvic irradiation.
abdominal surgery, or in patients with psychiatric depression.

The acute complications of chemotherapy (nausea, vomiting, alopecia, weight loss, bone marrow suppression, infections) may lead to problems with compliance and acceptance of particular regimens. This is not common in the author’s experience, but information, discussion and acceptance by oncology staff of an individual’s preferences or difficulties in compliance are vital both acutely and in the reduction of the overall long-term psychological impact of treatment on the patient.

Long-term problems

The late sequelae of therapy are of major consequence to all patients. Most adolescent patients are cured; for some groups with localised Hodgkin’s disease or testicular germ cell tumour, cure approaches 100%. Recent strategies for the treatment of many tumours have been to reduce or avoid late morbidity altogether, but such goals must be balanced against the possibility of reduced chances of cure. For some patients, cure with severe morbidity may be acceptable.

Late effects of treatment reflect end-organ damage produced by chemo- or radiotherapy and sometimes surgery. These may be specific and have well defined manifestations which require intervention at a later date. For example, radiotherapy of a limb at a young age may leave the patient with a shorter or poorly functioning arm or leg which needs surgical correction. Effects may sometimes be subtle, and only defined by close examination or screening, or they may be the end result of multiple problems which together lead to significant disability. Follow-up is particularly important for the latter group, for whom intervention has historically often been poor.

Cardiac

Patients who receive radiotherapy, anthracycline chemotherapy and some other forms of chemotherapy are at risk

| Drug            | Tumour                      | Side effects                                      |
|-----------------|-----------------------------|---------------------------------------------------|
| **Alkylation agents** |                             |                                                   |
| Cyclophosphamide | Sarcoma, Hodgkin, NHL, NBL | Second malignancy, Infertility, BM, Emesis         |
| Ifosfamide       | Sarcoma, Germ cell          | Cystitis, Cardiac                                 |
| Melphalan        | Sarcoma, NBL, ALL           | Cystitis, Renal, Encephalopathy, Fits, Mucositis  |
| Procarbazine     | Hodgkin, Brain              | Mucositis, Skin                                   |
| Temozolomide     | Melanoma, Brain             |                                                   |
| Cisplatin        | Germ cell                   | Renal, Peripheral neuropathy, Ototoxicity         |
| Carboplatin      | Brain, NBL                  |                                                   |
|                 | (Osteo)                     |                                                   |
| **Antimetabolites** |                             |                                                   |
| 6-mercaptopurine | Leukaemia                   | BM                                                |
| 6-thioguanine    | Leukaemia                   |                                                   |
| Methotrexate     | Leukaemia, NHL, Osteo, Brain|                                                   |
| Cytarabine       | Leukaemia, NHL              |                                                   |
| 5-flourouracil   | Carcinoma                   |                                                   |
| **Antibiotics**  |                             |                                                   |
| Actinomycin D    | Sarcoma                     |                                                   |
| Bleomycin        | Germ cell                   |                                                   |
| **Anthracyclines and related agents** |                 |                                                   |
| Daunorubicin     | Leukaemias                  | Cardiac                                           |
| Doxo, Epi, Ida   | NHL, NBL                    | Mucositis                                        |
| mAMSA            | Sarcoma                     | Vescitant                                         |
| Mitoxantrone     |                             |                                                   |
| **Plant alkaloids** |                             |                                                   |
| Etoposide        | Leukaemia                   | BM                                                |
| Teniposide       | NHL, NBL                    | Second malignancy, Hypersensitivity               |
|                  | Sarcomas                    |                                                   |
|                  | Brain, Germ cell            |                                                   |
| Vincristine      | ALL, Hodgkin                | Vescinant                                         |
| Vinblastine      | NHL, NBL                    | Neuropathy                                        |
|                  | Sarcomas                    | SIADH (BM)                                        |
|                  | Brain                       |                                                   |
| **Others**       |                             |                                                   |
| Asparaginase     | ALL, NHL                    | Allergy                                           |
|                  |                             | Coagulopathy (Stroke)                            |
| Prednisolone     | ALL, NHL                    | Pancreatitis                                      |
| Dexamethasone    | NHL                         | Liver                                             |
|                  |                             | Weight, Behaviour                                |
|                  |                             | Hyperglycaemia                                   |
|                  |                             | Growth (Hypertension)                            |

ALL = acute lymphoblastic leukaemia; BM = bone marrow suppression; doxo = doxorubicin; epi = epirubicin; ida = idarubicin; mAMSA = amsacrine; NBL = neuroblastoma; NHL = non-Hodgkin’s lymphoma; Osteo = osteogenic sarcoma; SIADH = syndrome of inappropriate antidiuretic hormone release.
of developing significant cardiac toxicity. The risk is dose- and schedule-related and may take several years to become manifest, sometimes appearing only at times of extreme physical effort. The death of healthy young adults cured of malignancy can be avoided by limiting the cumulative chemotherapy or radiotherapy dose to the chest, administering anthracyclines as prolonged infusions rather than bolus injections, and possibly by the co-administration of cardioprotective agents such as ICRF 187 (Cardioxane). Careful follow-up of patients with ECG and echocardiography is essential in order to identify potential clinically significant toxicity at an early stage. Echocardiography can accurately determine long-term outcome in patients receiving cardiotoxic drugs.

Infertility

Germinal epithelium of the normal testis and of ovarian tissue is highly sensitive to radiotherapy and chemotherapy. Testicular radiotherapy is uncommonly used except in patients with testicular leukaemia and some primary testicular tumours, although 'spill over' radiation of ovaries in patients with other abdominal or pelvic malignancy may be unavoidable. Chemotherapy with cyclophosphamide or high-dose cytarabine is associated with a high risk of male infertility. It is normal practice to offer patients the option of sperm storage. This may be a satisfactory solution for adult and older adolescent patients, but for younger teenagers it may cause considerable distress at the onset of treatment. At present, no reliable method is available for many patients. It is uncertain whether options such as testicular slice harvesting or electro-ejaculation may reach normal practice.

The issue of fertility for women is somewhat different. The ovary appears to be relatively resistant to the effects of chemotherapy, and specific measures may not be necessary at the time of diagnosis. High-dose therapy, such as autologous or allogeneic bone marrow transplantation, is associated with infertility, a result of high-dose alkylator chemotherapy, total body irradiation or both, which are used in conditioning regimens for BMT, although occasional pregnancies do occur.

When storage of ovarian tissue is desirable, there may be considerable difficulties both technically and ethically. A patient presenting with malignant disease is often unwell, anxious and malnourished. It is unlikely that she will have normal menstrual cycles or that ovarian stimulation could be safely accomplished before treatment begins. Ovarian slice harvesting has been successfully performed, and recently shown to restore cycling in a postmenopausal woman. However, to date, no fertilised zygote has been produced from such stored tissue. Furthermore, it is possible that re-implanted ovarian tissue may retain malignant cells and perhaps cause a relapse.

Growth

Short stature is a common problem in patients treated for malignancy at a young age. There may be direct and indirect effects on growth, and multiple factors may combine to affect final adult height. Brain tumours are often associated with significant loss of height, most commonly those affecting the hypothalamic-pituitary axis. Hypothalamic gliomas, germ cell tumours and cranio-opharyngiomas are typical tumours affecting this region. The most frequent hormone to be lost is gonadotrophin releasing hormone, and therefore also growth hormone (GH), but destruction associated with the primary tumour, neurosurgical resection and subsequent radiotherapy often leave a patient deficient in all pituitary hormones.

Patients receiving radiotherapy at a young age are likely to enter puberty early, and the rapid growth associated with this may be attenuated or lost. GH deficiency is universal in patients who receive a radiation dose of 30 Gy to the hypothalamic-pituitary axis, and variable - but likely - in patients receiving less than 30 Gy. In addition, radiotherapy affects spinal growth directly, and is associated with an estimated 5.5 cm loss in adult height when given at age 10 years.

GH replacement therapy prevents further loss of adult height, where this has been recorded, but does not reverse such loss. The onus is therefore on paediatricians and oncologists to identify patients at risk of growth problems before these become manifest as the patient moves through puberty.

Neuropsychological (educational)

The neuropsychological impact of malignancy has been underestimated for many years. This occurs principally in patients who have received therapy for brain tumours, but also in those treated for leukaemia or given central nervous system (CNS)-directed therapy for other reasons. Sequelae to a child's developing brain may become apparent only with the changing circumstances of adolescence. Without structured long-term follow-up, the problems of the adolescent patient treated for malignancy as a young child may pass unnoticed.

Normal brain myelination is complete at approximately 2–3 years, and radiotherapy administered to children below this age has profoundly damaging effects. For example, in patients treated with craniospinal radiotherapy for medulloblastoma, Johnson et al. reported full-scale IQ between 41 and 89. For those treated before the age of three years, mean full-scale IQ was 65, compared with 80 for those treated over the age of three years. Reports are variable for acute lymphoblastic leukaemia (ALL) for which patients have received less than 24 Gy. In a series of 28 patients treated for ALL, Eiser found a mean 13-point loss in full-scale IQ in irradiated patients, most noticeable in performance skills and less so in verbal skills. Deficits become more pronounced over time, and are well established by 2–5 years. Others have reported no significant deficit, although most indicate a moderate loss of IQ.

Damage to a developing brain may be apparent but be underestimated in
early life, with major consequences only at adolescence. The increased complexity and range of challenges made on young adults may exceed an individual’s ability to cope, and teenagers may remain dependent indefinitely upon their parents. Radiotherapy is not the sole cause of neurological impairment — indeed, multiple craniotomies, postoperative seizures, obtundation at the time of diagnosis, CNS infection and prolonged hydrocephalus are all adverse prognostic factors in determining outcome. Nevertheless, improved radiotherapy techniques have led to more precise targeting of brain tumours, and it is to be hoped that sequelae will be less profound.

Second primary malignancy

The development of a second primary neoplasm remains a significant risk as young patients reach adulthood. Second malignancy represents a side effect of the original therapy (chemo- and radiotherapy), the original tumour or both. The cumulative lifetime risk of a second primary malignancy for a patient treated successfully for Hodgkin’s disease is approximately 15–20%. By 15–20 years after therapy, the cumulative mortality from a second malignancy will exceed the cumulative mortality from Hodgkin’s disease.

Although a second tumour is a catastrophic event, it appears that curability is as high for some of them (eg radiotherapy-induced osteogenic sarcoma) as when the tumour arises de novo. For others, as with acute myeloid leukaemia arising following etoposide therapy, the outlook is poor.

Conclusions

Adolescence presents many and varied problems to the individual, and the diagnosis of a life-threatening illness at this time may exceed the individual’s ability to cope. Late effects of treatment as a child may appear only in the teenage years, and the full effects may not be assessed until years after the patient has reached adulthood. The goal for all oncologists must be to reduce both immediate distress and late complications, and to allow adolescence to progress as normally as possible.

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