MINIMAL RESIDUAL DISEASE IN PERIPHERAL BLOOD ASSESSED BY MASS SPECTROMETRY

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Despite the high rates of complete response (CR) achieved with the current treatments, patients with multiple myeloma (MM) continue to relapse due to the presence of undetected disease. Disease identification in patients with standard CR using more sensitive techniques (flow cytometry and sequencing) has been named “minimal” or “measurable” residual disease (MRD) and numerous studies have demonstrated its capacity to identify patients at a higher risk of progression and/or death. However, the evaluation of MRD in BM might ignore distant foci or extramedullary disease and hemodiluted BM samples could produce false negative results. Further, the procedure to obtain a BM sample is painful, which prevents to perform it frequently. Therefore, there are alternative methods for MRD assessment in more accessible and representative samples, such as peripheral blood (PB) need to be tested. Mass spectrometry (MS) is an analytic method based on the measurement of mass-to-charge ratio of ion species. Each monoclonal protein (MP) is characterized by a unique sequence of amino acids that is specific to each plasma cell clone (MM and MM patient), thus permitting single-clone tracking overtime with high sensitivity and specificity. The Spanish Myeloma Group GEM/PETHEMA has investigated the use of QIP-MS to assess treatment response vs standard and BM-based MRD analysis by next generation flow (NGF). In the GEM-CESAR trial for patients with high-risk smoldering MM, the presence of an MP was evaluated by QIP-Ig, QIP-FLC, QIP-MS and conventional immunoglobulins (QIP-lg-MS) or in combination with free light chains (FLC; QIP-FLC-MS) vs conventional serum protein electrophoresis (SPEP) and immunofixation (sIFE) in 77 patients. When the analysis of FLCs was added to QIP-lg-MS, the percentages of positive cases increased from 80% to 85% post-induction, from 60% to 68% post-ASCT and from 56% to 63% post-consolidation. Importantly, among patients achieving at least CR, the percentage of positive cases by QIP-lg-MS + QIP-FLC-MS was 60%, 38% and 43% post-induction, post-ASCT and post-consolidation, respectively. More recently, results from 186 newly diagnosed MM patients enrolled in the GEM2012MENO65 trial have been presented. As compared to SPEP/IFE, QIP-MS detected the paraprotein in a higher proportion of cases at each time point: 63% vs 52% post-induction, 46% vs 36% post-ASCT and 35% vs 27% post-consolidation. Importantly, QIP-MS identified the MP in a cohort of patients in standard CR and this was associated with a significantly shorter progression free survival (PFS) (p=0.0008). As compared to NGF, the percentage of concordant results was around 80% at all time points analyzed and both techniques exhibited a similar prognostic value in terms of PFS throughout the treatment: post-induction (VNGF: p=0.012; QIP-MS: p=0.015), post-ASCT (NGF: p=0.015; QIP-MS: p=0.057) and post-consolidation (NGF: p=0.001; QIP-MS: p=0.005).

In conclusion, from our results, MS-based methods can detect the MP in serum with a higher sensitivity as compared to conventional SPEP/IFE. As compared to NGF in BM, MS in PB displays a fair degree of concordance and is associated with a comparable prognostic value. However, more data are needed to define the final role of MS in the follow-up of patients with MM.

HOW TO INCORPORATE MRD IN CLINICAL TRIALS
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Depth of response is the key element to evaluate treatment efficacy and predict survival. Eradicating all tumor cells is necessary to cure most malignancies and this requires achieving and maintaining the deepest response possible. Both next generation flow (NGF) cytometry, and next generation sequencing (NGS) affords a sensitivity of 10-6. Patients that achieve a negative MRD status at the level of 10-5 or 10-6, display significantly longer progression-free (PFS) and overall survival (OS) when compared to those with positive MRD. The prognostic impact of MRD apply to newly-diagnosed transplant eligible and ineligible MM as well as relapsed/refractory Multiple Myeloma: Analyses of High-Risk Subgroups in the KarMMa Study. Blood 2020 supl: 3234a.
months to minimize the risk of false-negative results. Mass spectrometry is also emerging as a potent technique to detect low levels of paraprotein as a surrogate for residual disease. In addition imaging techniques, particularly PET-CT, has an important role for MRD assessment outside of the BM. Currently MRD has been incorporated in numerous clinical trials with different aims: 1. to evaluate treatment efficacy; 2. to compare two treatment approaches; 3. adapted therapy intensity according to MRD follow-up; 4. to adapt maintenance duration; 5. to introduce Early Rescue Intervention (ERI) strategies. The implantation of MRD should help in avoiding over and under treatment and may become a surrogate biomarker for accelerated drug development and operational cure.

**HOW TO TREAT HIGH RISK PATIENTS**

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Whilst outcome has improved for most multiple myeloma patients, the treatment of high-risk and ultra-high-risk disease remains challenging. Recent evidence regarding molecular diagnostics as well as retrospective and novel prospective data regarding improvements with innovative treatment approaches will be discussed in this presentation.

**HOW TO TREAT UNFIT AND FRAIL PATIENTS**

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Therapeutic options have greatly expanded over recent years defining new standards of care in multiple myeloma (MM). However, MM is a heterogeneous disease as are the patients it affects. As the median age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that may have more difficulty tolerating and recovering from systemic therapy, thus being in need of treatment delivery modifications. Recently developed clinical scoring systems which are able to delineate patients into fit, unfit & frail groupings, with respective differences in PFS and OS in clinical trials have been highlighted. To date these have been proven to be prognostic biomarkers yet not evidence exists as to their potential as predictive biomarkers and thus used in the clinic to direct treatment decisions. Consequently, such identified limitation have led to a study in the front-line setting using frailty scoring to prospectively adapt therapy (UKMRA Myeloma XIV trial). Dose and delivery modifications may be pertinent to patients with altered performance if we are to attain similar outcomes as with younger patients in the current era of novel agent combinations. The potential exists for improving performance (senolytics, exercise, nutrition) as well as how we measure performance more accurately through establishing digital phenotypes.

Such clinical frailty scores may allow for better prediction of toxicity but there is a need for the development of additional, biological-based tools to reflect the processes of accelerated aging and how they impact on tolerance of cancer treatment and survivorship. Identifying specific biologic determinants of frailty may allow physicians to become even more adept at identifying patients at risk of excessive toxicity and provide the opportunity to target these processes therapeutically to help improve tolerability, quality of life and survival outcomes for older patients with cancer. Host response biology (HRB), is the measurable pathophysiological processes resulting from the impact of disease and accelerated aging on an individual’s biological function. Biomarkers of HRB can include end-organ damage parameters, clinical scoring systems of fitness, immune system quantitation (immunosenescence) and serial markers of age-related inflammation (inflamming). Less fit patients represent a substantial proportion of newly diagnosed patients requiring treatment. Whilst age does not necessarily equate to fitness to tolerate therapy nonetheless age-related inflammation is perhaps the most important physiologic correlate of the age-related frailty syndrome.

There is a need to design clinical trial research going forward, cognisant of a number of disease and patient related determinants, realising the mantra that “one size doesn’t fit all” which will inevitably allow us to deliver Better Research, Better Impact.

**TREATMENT AT RELAPSE: WHAT TO DO FIRST?**

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Over the last years and because of the introduction of novel drugs, autologous stem cell transplant as well as maintenance as part of the first line of therapy, together with the better knowledge of the disease biology and new techniques to measure the residual disease, the duration of the response after the diagnosis is longer than in the past. However, most patients will finally progress and we have to consider some patients and disease-based factors in order to make the right choice: i) chronological age; ii) frailty; iii) organ function; iii) risk status; iv) life style and family support and vi) treatment history.

The first consideration at the moment of the relapse is if we should treat biochemical or clinical relapses and it is highly recommended to treat at the biochemical relapse with the only exception of indolent diseases at the diagnosis (ISS-1, anaemia as the only myeloma defining event….). The second consideration is to evaluate the treatment history and the refractoriness to the previous drugs. Today, most patients at the moment of first relapse, are exposed to proteasome inhibitors and immunomodulatory drugs and refractory to lenalidomide and over the last months, some patients are also exposed to the anti-CD38 monoclonal antibodies. According to the most recent guidelines and phase 3 clinical trials, if the patient is eligible for anti-CD38 monoclonal antibodies because the patient is naive or sensitive, the optimal choices are carfilzomib-dexamethasone plus either daratumumab or isatuximab or pomalidomide-dexamethasone plus daratumumab. If the patient is not eligible for anti-CD38 monoclonal antibodies, the possibilities would be either pomalidomide-dexamethasone plus bortezomib or Selinexor-dexamethasone plus bortezomib. Of note, venetoclax-dexamethasone alone or in combination will be reserved for patients with t(11;14). These recommendations would be applicable to patients in first relapse. There are some other combination recommended for third line and beyond, and based on pomalidomide-dexamethasone, if the patient has not been previously exposed, in combination with either isatuximab or elotuzumab although it is also possible to combine with cyclophosphamide.

In summary, we have to follow the current guidelines for the management of MM at first relapse although the treatment landscape is rapidly evolving and phase 3 trials are ongoing with the objective of incorporating the BCMA-targeted therapy at first relapse.

**AL AMYLOIDOSIS: MECHANISMS OF DISEASE AND BIOMARKERS**

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Light chain (AL) amyloidosis is caused by usually small B cell, usually plasma cell, clones that produces a monoclonal light chain (LC) causing organ toxicity, aggregating and forming deposits in tissues. Biomarkers of clonal and organ involvement play a key role in the diagnosis, treatment stratification and in the therapeutic strategy, including response assessment. Serum and urine immunofixation (IFE) and free LC (FLC) measurements are used to detect the amyloid LC. Investigation of chromosomal abnormalities in plasma cells offers precious information for the choice of treatment. Patients with t(11;14) have poorer outcomes with bortezomib and dexamethasone (BDex) with/without cyclophosphamide. These patients can be treated with BDex plus melphalan, daratumumab-bortezomib combinations, and possibly in the future with venetoclax. On the other hand, gain1q21 is associated to a dismal outcome after first-line melphalan and dexamethasone or after lenalidomide or daratumumab-bortezomib-based regimens in relapsed/refractory disease. Patient survival is best predicted by cardiac biomarkers that are also used for stratification of clinical trials and to adjust dose and drug efficacy. Proteinuria and estimated glomerular filtration rate are used to assess the risk of dialysis. The replacement of 24h-proteinuria with urinary albumin/creatinine ratio for renal staging has been recently proposed. Hematologic response (HR) is assessed by IFE and FLC measurement and organ response (OR) by changes in NT-proBNP and proteinuria,