MultipleMyelomaHub

General MM, Relapsed/refractory patients, Patients eligible for transplant, Patients non-eligible for transplant

EHA 22nd Congress: Novel developments in MM and related diseases

Fiona Chaplin | Jun 29, 2017

The MM Hub team were delighted to attend the 22nd congress of the European Hematology Association held in Madrid from 22nd-25th of June. On Friday 23rd June, 8.30 a.m. - 9.30 a.m. an oral session of the Scientific Working Groups was held, covering the topic of 'Novel developments in Myeloma and related diseases'. The session was chaired by Dr. Martin Kaiser, from The Institute of Cancer Research & Royal Marsden Hospital, London, United Kingdom.

Treatment and sequence in relapsed and refractory multiple myeloma

The session was initiated by Professor Xavier Leleu, from the Hôpital La Milétrie, Poitiers, France. He began by highlighting the major questions for approved drugs in relapsed and refractory multiple myeloma (RRMM) in the EU, according to the number of prior treatments. For patients that have received 3 prior lines of therapy the major regimen is either lenalidomide/dexamethasone (Rd) or bortezomib/dex (Vd), and the major questions are whether to switch regimens or re-treat, whether to choose doublet or triplet therapy, and whether to treat continually until progression.

For patients progressing after at least 2 lines of prior therapy, including one IMiD plus bortezomib and who are refractory to the last line of therapy, pomalidomide-dex-daratumumab (pom/dex/dara) is the major regimen, with the same questions surrounding treatment options, as well as which is the best regimen to pair with pomalidomide.

The revised 2017 ESMO guidelines were then discussed with the two options at first relapse being either IMiD-based induction followed by PI based doublets of Kd/Vd, or bortezomib-based triplets of DaraVD, PanoVD, EloVD or VCD, or bortezomib-based induction followed by Rd doublet or Rd-based triplets of DaraRd, KRd, IRd or ERd. At second or subsequent relapse, there are three major options: pom/dex plus either cyclophosphamide, ixazomib, bortezomib, daratumumab, or elotuzumab. Another option at this stage is daratumumab as either a single agent or in combination, or entering patients into a clinical trial.

The focus then turned towards studies evaluating Rd-based triplets: POLLUX, ASPIRE, ELOQUENT-2 and TOURMALINE. The PFS achieved in high-risk patients has been unprecedented: 23.1, 21.4, and 22.6 median months in ASPIRE-KRd, TOURMALINE-IRd and POLLUX-DRd, respectively. The PI-dexamethasone backbone was then discussed, with this regimen historically used upfront, with PI-dex+Len/Pom and PI-dex plus therapeutic antibodies now commonly used. Currently, lenalidomide is the most common upfront agent, and such was the case with patients recruited to the ASPIRE TOURMALINE-MM1, and POLLUX trials. An update from the CASTOR-1 trial was given, illustrating how adding daratumumab to standard of care (SOC) regimens significantly prolongs PFS.

In some patients, doublets might be an appropriate option, but in general triplet combinations lead to an improved PFS, when compared to doublets, of 1-3 years. Triplet regimens significantly improve the prognosis for high-risk patients and MRD is a feasible objective. The best triplet for a given patient will be selected according to its efficacy (PFS/OS), but also

factors such as safety, QoL, cost and convenience. In frontline therapy, depth and duration of first response must be considered, as well as cases when retreatment with the same agent is feasible. In a concluding slide, the current and future treatment options were outlined:

Finally, Professor Leleu touched upon precision cancer medicine – which encompasses therapies designed to target a specific molecular alteration or pathway that aids cancer development. It is now known that a large proportion of cancers contain at least one plausibly actionable genetic alteration. Therefore, screening patients for these alterations early in diagnosis will hopefully become routine, with such precision therapies likely to feature in future regimens.

Dr. Leleu's concluding remark was to 'Never give up!' For doctors treating RRMM this is certainly a good mantra. With new agents finding their way into clinic at a fast pace, this is a game of re-treating and switching agents, as well as mixing and matching, ultimately buying time for precision therapies that can be patient-tailored, or therapies such as CAR-T that raise hopes for a cure.

You can listen to videos of Professor Leleu talking to the MM Hub in both English and French.

Should imaging be part of MRD?

The next talk was presented by Dr. Elena Zamagni from the Seragnoli Institute of Hematology, Bologna University School of Medicine, Italy, and addressed the question: 'Should imaging be part of MRD?' She answered this with a resounding YES, then put forward her case.

MM patients can relapse with active lesions on imaging despite low disease burden. Newer imaging techniques allow morphological assessments such as the percentage of bone destruction (eg. whole body-MDCT-LDCT and PET/CT) to be evaluated, as well as functional assessments, such as bone marrow infiltration and disease metabolism. Imaging can be used at both diagnosis, to evaluate staging and prognosis, but also after treatment to evaluate treatment response.

Features of currently available techniques – NGF (next-generation flow), ASO-PCR (allele specific oligonucleotide PCR), NGS (next-generation sequencing) and PET/CT - to monitor minimal residual disease (MRD), were compared, with some major differences such as the time taken differing greatly, as well as the cost. Standardization of techniques is complete for ASO-PCR, almost complete for NGF, and ongoing for both NGS and PET/CT. The inclusion of imaging as part of the IMWG criteria for MRD was outlined, with MRD-negativity defined as the disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT.

The value of PET/CT in measuring metabolic response to therapy before and after ASCT was also described. Complete FDG suppression retained independent prognostic value for PFS and OS in a Cox regression analysis. The use of PET/CT to assess the metabolic response to therapy was discussed, with large differences observed for patients classified as being CR, via either PET/CT or by biochemical assessment. For example, 25-30% of patients in conventionally defined CR were still positive by PET/CT and PET-CT normalization before maintenance was 62% normalized to PFS and OS. Complementarity between imaging and bone marrow (BM) MRD to assess PFS was illustrated, with the use of PET/CT scans now part of the IMWG criteria for MRD assessment, in addition to NGF or NGS. The pros and cons of using either PET/CT and whole body MRI (WBMRI) were covered, with a good correlation with biochemical response observed with PET/CT and prognostic significance, whereas WBMRI has a high sensitivity, but can lead to false positives. Both techniques are still not fully standardized for clinical use, but this is ongoing.

The study by Leo Rasche *et al.*, which linked low expression of hexokinase-2 to the occurrence of false negatives in FDG-PET imaging, was described, with the need for novel biomarkers to increase sensitivity clearly a future requirement. A comparison of current biomarkers can be found in the IMWG consensus statement.

It was concluded that PET/CT and DWIBS-MRI are the preferred techniques for assessing and monitoring response to therapy and are becoming complimentary research tools for detecting MRD, beyond the conventionally defined CR level. However, how and when to incorporate imaging-MRD and BM-MRD analyses after treatment is still an open issue. Comparative studies between PET/CT and MRI are warranted (iTIMM prospective trial is ongoing in UK, with a planned prospective trial within IMWG), whereas implementation of clinical trials with newer imaging techniques will help to standardize the interpretation of results and optimize the use of these tools.

For more information you can listen to Dr. Zamagni summarizing this talk in both English and Italian.

Novel approaches in AL-amyloidosis

Dr. Giovanni Palladini, from the University of Pavia, Italy, spoke about 'Novel approaches in AL-amyloidosis'. AL-amyloidosis is a common complaint in MM, causing a buildup of protein in organs such as the heart, kidney, liver and intestine. Until now, the amyloid clone has been the target of treatment, with AL occurring more frequently in patients with certain genetic abnormalities: gain of 1q21 = 19% AL and associated with a very poor outcome, t(4:14) = 3% AL and t(11:14) = 47% AL.

ASCT is a highly effective treatment in AL amyloidosis, with an overall hematologic response of 71% and a CR of 35-37%. Transplant-related mortality (TRM) is higher in patients with NT-prBNP <500 ng/L, cTnT<0.06 ng/mL who are not candidates for ASCT. In a study by Oliva *et al.* published in Blood this year, the amyloidogenic light chain (LC) was shown to be an intrinsic stressor for plasma cells (PCs), with stress response pathways as therapeutic targets, thus sensitizing towards PIs. Indeed, AL PCs were found to have an unprecedented sensitivity towards PIs and notably higher than that of MM PCs. Therefore, treatment with bortezomib has been highly effective, with a combined regimen of melphalan, dexamethasone and bortezomib (BMDex) assessed for the treatment of AL-amyloidosis patients in a phase III clinical trial.

The current recommendations for intermediate risk patients non-eligible for transplant are: BMDex, CyBorD (cyclophosphamide, bortezomib and dexamethasone) – stem cell sparing and preferred in renal failure or for 1q21 gain, or MDex – preferred in patients with neuropathy or with t(11:14). For patients with advanced cardiac involvement the outcome varied from 3-7 months depending on the regimen used. For high-risk patients, low dose combination regimens are balanced with non-attenuated regimens and intensive care support.

Other combinations discussed include the use of pomalidomide, which resulted with a high hematologic response, and daratumumab, which was used to treat patients previously exposed to PIs, with a median time to response of 1 month. A phase I/II study of ixazomib gave a median hematologic PFS of 14.8 months; 1-year PF and OS rates were 60% and 85%, respectively. Novel approaches targeting the amyloid deposits and the amyloidogenic light chain were outlined. Doxycycline has been shown to disrupt amyloid fibril *in-vitro* and to reduce amyloid load in a transgenic model, and shown promise in early clinical studies too. A randomized phase II/III trial of bortezomib-based therapy plus doxycycline *versus* bortezomib-based therapy alone in cardiac AL is underway. Immunotherapy in AL using anti-SAP antibodies has also shown promise, with a progressive reduction in amyloid load observed with repeat dosing (PRONTO and VITAL studies).

The outcome for patients with AL-amyloidosis is rapidly improving, as a result of early diagnosis, novel agents, biomarker-guided treatment and monitoring, although advanced cardiac AL-amyloidosis remains an unmet need. Dr. Palladini concluded that, 'combination therapy reducing the concentration of the amyloidogenic light chain with chemotherapy, while also targeting the amyloid deposits, is likely to further improve survival and overall quality of life'.

Is NGS of value for clinical practice?

Dr. Klaus Kortüm from The Mayo Clinic, Rochester, USA, spoke about the value of NGS in clinical practice. Current diagnostics for MM still rely on conventional cytogenetics such as karyotyping or FISH. NGS has not yet been included in clinical assessments, although it has application in prognosis by potentially identifying and defining high-risk patients, as well as during treatment by identifying novel targets to drive patient-tailored regimens, and also response assessment by tracking clonal evolution, MRD and resistance mechanisms.

Dr. Kortüm began by heralding the use of NGS a huge success story in MM so far, due to its many different applications. The decreasing costs of NGS have enabled the analysis of thousands of MM genomes, revealing the mutational landscape of untreated MM and the identification of numerous actionable mutations, such as those occurring in the MAPK pathway (NRAS, KRAS, BRAF, 40%), NF-kappaB (TRAF3, CYLD, 20%), DNA repair (TP53, ATM, ATR), DIS3, FAM46C and B cell differentiation pathways. For example, patients with BRAFV600E mutated MM may respond rapidly and durably to targeted vermurafenib treatment.

The clonal evolution of MM over time has been studied using NGS, which is helpful in identifying the appearance of actionable mutations over time. In addition, the occurrence of spatial heterogeneity has been studied using WBMRI, which revealed a mixed response in one patient - dramatic shrinkage of two lesions and an accelerated growth of others; investigational PET tracers also allow imaging of spatial heterogeneity.

Screening with the MM specific Gene-Panl (M^3P) can help to identify recurrently mutated genes, different MM pathways, potential drug targets or resistance mechanisms, as well as minor subclonal detection by increased sequencing depth. The mutational landscape of untreated MM differs significantly from treated MM, with new mutations occurring in 40% of treated MM patients. Genes associated with drug responses are commonly mutated in relapsed MM. Several examples were given to show the utility of NGS in detecting potential drug resistance mechanisms: PI-related genes = *PSMD1, XBP1, PSMB5,* and *PSMB9*; and IMiD-related genes = *CRBN, IRF4, IKZF1, IKZF3,* and *CUL4B*. Mutations in PSMB5 cause PI-

resistance, and cells chronically exposed to PIs develop *PSMB5* mutations. Detailed studies analyzed the appearance of PSBM5 mutations over time and as well as the selection of resistant clones. The mutation locus in PSMB5 was found to impact both pan- or selective- PI resistance (bortezomib, carfilzomib and ixazomib).

The mechanism by which CRBN mutations (that predominantly occur in binding regions) drive resistance to IMiDs in myeloma was given, followed by an example of a patient that developed 7 CRBN mutations. The patient had received thalidomide/dex induction, lenalidomode/dex maintenance after ASCT, then did not respond to pom/dex when repeatedly treated. Another patient was under a PI/IMiD regimen and developed an IKZF3 G159R mutation.

It was concluded that NGS is needed to overcome clonal heterogeneity in MM and to allow for precision medicine progression. Several layers of genomic analysis need to be addressed, including mutations and structural variations, copy number variations, methylation status and RNA expression. He was confident that NGS will become part of standard diagnostic workflows in the very near future, but standardization, functional analysis and validation of hypotheses within clinical trials are still needed.

Dr. Kortüm was asked to comment on clinical situations in which NGS could change treatment for the better. He replied that a possible survival benefit could be obtained using NGS to identify key targets and thus intensifying treatment, because prolonged maintenance therapy adds selective pressure and can induce mutations.

References

1. Leleu X. Treatment and sequence in relapsed and refractory multiple myeloma. 22nd Congress of the European Hematology Association; 2017 June 22–25; Madrid, Spain.
2. Zamagni E. Should imaging be part of MRD? 22nd Congress of the European Hematology Association; 2017 June 22–25; Madrid, Spain.
3. Palladini G. Novel approaches in AL-amyloidosis. 22nd Congress of the European Hematology Association; 2017 June 22–25; Madrid, Spain.
4. Kortüm K. Is NGS of value for clinical practice? 22nd Congress of the European Hematology Association; 2017 June 22–25; Madrid, Spain.