



American Society of Hematology Annual Meeting 2014: highlights in multiple myeloma

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REVIEWS

American Society of Hematology Annual Meeting 2014: highlights in multiple myeloma

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The American Society of Hematology (ASH) is the world's largest meeting of hematologists worldwide and is held on an annual basis in December

The 2014 meeting was held in San Francisco, CA, USA, from 6–9 December, and with 26,000 attendees, it was the highest attended ASH annual meeting to date

Multiple myeloma (MM) had a major presence at this meeting with 855 abstracts related to MM, 24 oral presentations and 106 posters. This, coupled with the record attendance at this year's meeting, made it a positive year for patients and clinicians alike as much of the presented data are likely to lead to major advances in the field of myeloma. Key areas of focus included: high-risk smoldering disease, minimal residual disease for monitoring response to therapy, novel therapies in clinical trials, including carfilzomib and daratumumab, and imaging modalities for MM.

High-risk smoldering myeloma

In November 2014, the International Myeloma Working Group revised the criteria for diagnosis of smoldering multiple myeloma (SMM) as follows: both serum monoclonal protein (IgG or IgA) $\geq 30\text{g/l}$ or urinary monoclonal protein $\geq 500\text{ mg per 24 h}$ and/or clonal bone marrow plasma cells 10–60%; and the absence of myeloma-defining events or amyloidosis [1]. This was based on a number of studies that had demonstrated that bone marrow plasma cells $>60\%$ was rarely seen in SMM patients (3%) and if so was associated with a high risk of progression within 2 years (95%) [2,3]. Given this new classification published just prior to the American Society of Hematology (ASH) meeting, there was a particular focus on the challenging group of patients with high-risk SMM who lie close to the border of multiple myeloma (MM).

In support of treatment of high-risk SMM, a randomized Phase III trial comparing lenalidomide with low-dose dexamethasone versus observation in high-risk SMM patients [4] was updated by Mateos *et al.* [5]. Duration of remissions was much longer in the treatment

group with 94% of patients alive at 3 years versus 80% in the observation group and there was also a longer time to progression to active MM. Landgren *et al.* presented new data at ASH related to therapy for high-risk SMM in a Phase II pilot study using eight cycles of carfilzomib, lenalidomide and dexamethasone [6]. All patients (12) reached a complete response (CR) with deep responses observed using multicolor flow cytometry, next-generation sequencing and molecular imaging, demonstrating that 92% of patients were minimal residual disease (MRD) negative after eight cycles. The overall consensus at ASH was that patients with ultra-high risk SMM are considered as MM and high risk-SMM patients should be included, where possible, in clinical trials. Questions remaining to be answered in this area relate to optimal timing for initiation of therapy and the duration.

Minimal residual disease

There was also a focus at ASH on the use of novel sensitive tools for the detection of MRD as both a prognostic tool and to guide therapy. Paiva *et al.* presented elegant data using flow cytometry as a method of assessing

MRD in 10 healthy donors and 115 elderly newly diagnosed MM patients [7]. This study demonstrated that patients with less differentiated plasma cells had a higher incidence of extramedullary disease and a significantly inferior progression-free survival (PFS). In another abstract, Paiva *et al.* [8] used a sensitive 8-color multidimensional flow cytometry (MFC) method to monitor MRD among 117 elderly MM patients. It was found that standard-risk patients attaining MRD-negativity had a significantly prolonged time to progression compared to MRD-positive patients (94 vs 58% at 2 years; $p = 0.035$). Additionally, patients with high-risk cytogenetics achieving flow-CR showed significantly superior time to progression (median not reached vs 10 months; $p = 0.001$) validating the prognostic relevance of MRD monitoring. The impact of maintenance therapy on MRD status was addressed by Gambella *et al.* [9] who used both MFC and real-time quantitative PCR to detect MRD in the RV-MM-EMN-441 study. A total of 19/50 patients (38%) achieved MFC-CR after consolidation, while an additional 7/50 (14%) achieved MFC-CR during maintenance, demonstrating that response can be deepened by maintenance therapy with lenalidomide \pm dexamethasone. MRD monitoring is likely to be most beneficial in high-risk patients and new data presented at ASH showed that the depth of MRD response is indeed correlated with overall survival [10]. Questions arising from the MRD data presented at ASH relate to whether or not MRD can be used to define CR and guide maintenance therapy in the future. Bringing MRD monitoring to mainstream clinical utility will require consensus on next-generation methods used to define MRD and further clinical trial validation.

Novel therapies & combinations in the relapsed & upfront settings

Major themes in relation to MM therapy at the 2014 ASH meeting related to the emerging role of immunotherapy, monoclonal antibodies, next-generation proteasome inhibitors and early versus late autologous stem cell transplant. Clinical trials presented at this meeting included most prominently the final results for the 1703 Phase Ib/II study of elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed/refractory MM [11] and the interim results of the ASPIRE Phase III trial, which evaluated carfilzomib, lenalidomide and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd) in patients with relapsed disease [12].

Elotuzumab is mAb that targets SLAMF7, a cell surface glycoprotein that is highly expressed at the surface of plasma cells [13]. The 1703 trial reported data for 73 patients randomized to elotuzumab 10 or 20 mg/kg intravenous in combination with lenalidomide (25 mg) and low-dose weekly dexamethasone (40 mg) with a primary end point of overall response rate (ORR). This study reported an impressive ORR in relapsed/refractory patients, with at least three prior therapies, of 84% (92% in the 10 mg/kg group and 76% in the 20 mg/kg group) with a median PFS of 29 months (32.5 months in the 10 mg/kg group).

The results of the ASPIRE trial were eagerly awaited at ASH 2014 [14]. This was a randomized, open-label, multi-center Phase III trial, including 792 patients, evaluating carfilzomib (27 mg/m²), which is an irreversible epoxyketone proteasome inhibitor approved by the US FDA as a single agent in relapsed/refractory MM. There was an unprecedented median PFS in the KRd group of 26.3 versus 17.6 months in the Rd group ($n = 396$ /group). The ORR was also significantly improved in the KRd group (87 vs 67%), overall significantly more patients achieved \geq CR (31.8 vs 9.3%) and there is a trend towards improved overall survival at 24 months in the KRd group (73 vs 65%).

Daratumumab is a mAb that binds CD38 and is effective in killing MM cells via multiple mechanisms of action, including complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity [15]. A Phase I/II trial presented at ASH 2014 [16] evaluated the safety and efficacy of daratumumab (2–16 mg/kg) in combination with lenalidomide and dexamethasone in relapsed/refractory MM and reported an ORR of 100% with a CR rate of 31% and very good partial remission of 46% in the first dose-escalation phase. SAR650984 is also an anti-CD38 mAb, which appears to be effective in heavily pre-treated patients, many of whom were lenalidomide refractory, when used in combination with Rd – ORR: 64.5%, PFS: 6.2 months [17].

An oral presentation [18] of data on a multi-center, open-label, dose-escalation Phase Ib/II study evaluating oprozomib, an irreversible oral epoxyketone proteasome inhibitor, as a single agent in MM and other hematological malignancies provided new data on two different dosing schedules – a 2/7 schedule with an ORR of 31% and a 5/14 schedule with an ORR of 23%. This, and other studies, reported gastrointestinal side effects and bleeding as dose-limiting toxicities reflecting a tight therapeutic index of irreversible proteasome inhibitors. Ixazomib (MLN9708) is an oral reversible proteasome inhibitor that was evaluated as maintenance following ixazomib, lenalidomide and dexamethasone induction in patients with previously untreated MM in the Phase II setting [19]. This study reported that 48% of patients improved their depth of response during maintenance therapy and impressively the rate of CR plus nCR increased from 24% after induction to 62%, making this an effective and feasible maintenance therapy for up to 1.9 years.

For elderly MM patients, new data were presented at this year's meeting by Mateos *et al.* [20] evaluating Sequential Versus Alternating Administration of Bortezomib, Melphalan, Prednisone (VMP) and Rd in 242 newly diagnosed MM patients. Both regimens were identical in CR rate (42 and 44%) and both regimens were equally well tolerated. Median PFS was 30 months in both groups with a 3-year survival of 94% in patients who achieved stringent CR making this an active and feasible regimen in elderly patients.

Scientific highlights

An interesting highlight from the oral scientific abstracts, presented by Dr Morgan's group, relates to the prognostic value of mutational status and copy number abnormalities at

diagnosis in MM patients. Data were presented on 463 newly diagnosed MM patients, which revealed that the mutational landscape of MM is dominated by RAS (43%) and NF- κ B (17%) pathway mutations that do not impact survival, but interestingly, a strong interaction was shown between the mutational status and the cytogenetic profile (e.g., $t[4;14]$ with FGFR3), which can be incorporated into a predictive score of outcome allowing greater prognostic discrimination useful for identifying high-risk populations [21].

Concluding the highlights of ASH 2014 would not be complete without mentioning the wonderful Hamm Wasserman lecture delivered this year by Prof. Jesus San Miguel entitled 'Multiple Myeloma: A Modern Model for Scientific and Clinical Progress'. This lecture is traditionally given by an individual from outside the USA who has made a major contribution to our understanding of an area of hematology. This lecture

addressed the genomic complexity of MM cells and provided a comprehensive insightful summary of the MM landscape as it exists in 2014, with a particular focus on intraclonal heterogeneity and disease prognostication and monitoring tools. Prof. San Miguel highlighted the ever-growing need to minimize toxicity and cost of MM therapies as we work toward optimizing the treatment duration and maintenance for standard and high-risk patients.

Financial & competing interests disclosure.

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