Highlights in multiple myeloma

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SUMMARY

With more than 900 abstracts focusing on multiple myeloma (MM), the 2017 annual meeting of the American Society of Hematology (ASH) shows once more the great interest of the myeloma community in identifying new potential targets and developing novel therapeutic strategies for this devastating disease.

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DARATUMUMAB READY TO MOVE TO FRONTLINE THERAPY IN MULTIPLE MYELOMA

Daratumumab (D), a human IgG kappa anti-CD38 monoclonal antibody with a multifaceted immunomodulatory mechanism of action, has been shown to prolong the progression-free survival (PFS) and improve the depth of response in combination with standard of care treatment in relapsed/refractory (R/R) multiple myeloma (MM). This association is now tested upfront with the assumption that treatment-naïve patients may benefit even more from this combination.

Mateos and al. reported on the recent ALCYON phase 3 study, evaluating the safety and efficacy of D in combination with VMP (bortezomib-melphalan-dexamethasone) in patients over 65 not eligible for high-dose melphalan (HDM) followed by an autologous stem cell transplantation (ASCT).[1] A total of 706 patients were randomly assigned (1:1) to receive VMP+/-D and stratified by ISS stage and age. Patients received up to a maximum of nine 6-week cycles of VMP (V: 1.3 mg/m^2 SC on days 1, 4, 8, 11, 22, 25, 29, 32 for cycle 1, and days 1, 8, 22, 29 for cycles 2-9; M: 9 mg/m^2 PO and P: 60 mg/m^2 PO on days 1-4 for cycles 1-9). In the D-VMP arm, D was given at the dose of 16 mg/kg IV qw for cycle 1, q3w for cycles 2-9, and q4w for cycles 10+ until disease progression. The primary endpoint was PFS.

At a median follow-up of 16.5 months, the combination of D with VMP doubled the PFS (HR: 0.50), representing a 50% reduction in the risk of progression or death, with more patients achieving deep responses, including a significantly higher complete response (CR) rate (42.6% *vs.* 24.4%) and a tripling of the minimal residual disease (MRD)-negativity rate (22.3% *vs.* 6.2%) (*Figure 1*). The PFS treatment benefit of D-VMP was consistent across all subgroups, including in patients older than 75 years, patients with ISS stage III disease and in patients with high-risk cytogenetics. No new safety signals were observed with this combination. Although overall survival (OS) data are still immature, these results support the use of a D-based combination, such as D-VMP, upfront for transplant ineligible newly diagnosed (ND) MM.[1]

TRANSPLANTATION: UPFRONT OR DELAYED? SINGLE OR DOUBLE?

The role of transplantation in NDMM, upfront or early at relapse, single or double, continues to be debated in the novel agent era. *Cavo et al*. presented the updated results of an international trial conducted with the European Myeloma Network (EMN02-HOVON65) to prospectively compare ASCT versus proteasome inhibitor (PI)-based intensification therapy (randomization 1, R1), and consolidation therapy versus no consolidation (randomization 2, R2), followed by lenalidomide maintenance for NDMM.[2,3]

In the first part of the study, a total of 1,503 patients were enrolled, with 1,192 being eligible for R1. After 3 to 4 cycles of bortezomib-based induction therapy and subsequent peripheral blood stem cells collection, patients aged ≤65 years were randomized (R1, stratification by ISS stage) to receive HDM plus ASCT or standard-dose intensification treatment with VMP for 4 additional 42-day cycles, each including 8 doses of bortezomib.[2] PFS from R1 was the primary study endpoint for R1. In comparison with VMP, HDM plus ASCT significantly increased the rate of high quality responses, ultimately leading to an improved PFS. This PFS benefit was retained across predefined subgroups of patients at standard- and high-risk. Randomization to ASCT was an independent predictor for improved PFS and significantly prolonged the OS in subgroups of patients with poor prognosis, including

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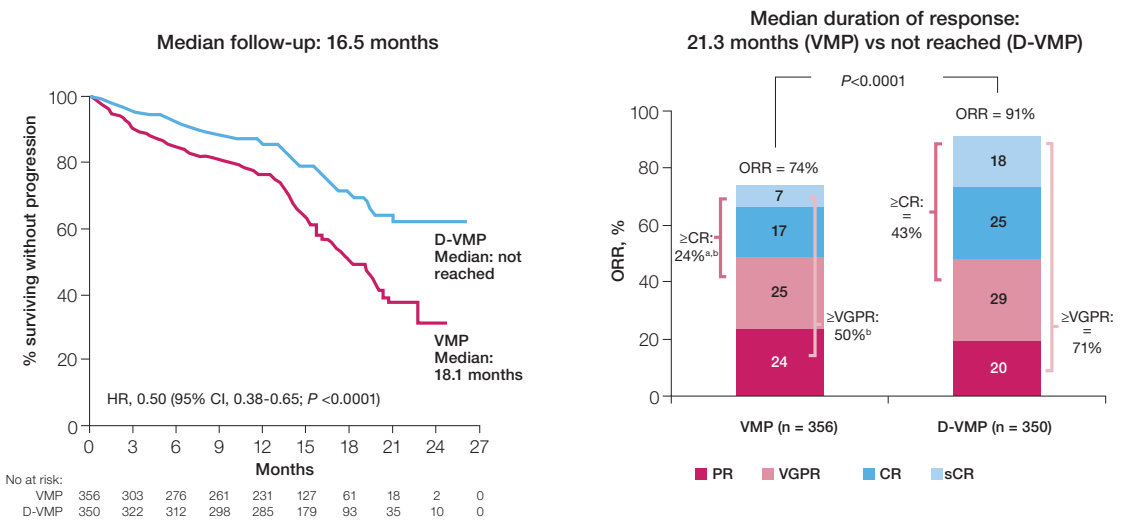

FIGURE 1. Progression free survival and overall response rate in the phase III ALCYONE trial.[1]

patients with R-ISS stage III and patients carrying a t(4;14) ± t(14;16) ± del(17p).[2]

The second part of the study focused on the role of single versus double ASCT.[3] In centres committed to a double ASCT policy, patients were randomized to receive VMP, single ASCT (ASCT-1) or double ASCT (ASCT-2) performed 2-3 months apart (1:1:1), in an attempt to prospectively compare both strategies. Among the 618 patients who were diagnosed in centres with a double ASCT policy, 203 were randomly assigned to VMP, 208 to ASCT-1 and 208 to ASCT-2. Randomization to ASCT-2 was superior over ASCT-1 reflected by a prolonged PFS and OS for the overall patient population and for poor prognosis patient subgroups (advanced R-ISS disease stage and carrying a high-risk cytogenetic profile). Incorporation of bortezomib into ASCT-2 abrogated the increased risk of progression or death imparted by t(4;14) ± t(14;16) ± del(17p), and in particular by del(17p) positivity. This study confirms the necessity to still consider transplants as an option to improve the outcome of patients.[3]

MINIMAL RESIDUAL DISEASE TESTING IS INTEGRAL TO TREATMENT SUCCESS

Evaluation of MRD in MM has become an important trial endpoint. With the current intensive approaches, the complete remission rates are up to 80%, making conventional evaluations of response quite useless. More sensitive techniques are needed to monitor the actual remaining disease burden. *Avet-Loiseau et al.* applied both flow cytometry and NGS techniques to the IFM/DFCI 2009 trial.[4] In this trial, 700 NDMM patients were randomized to receive HDM and ASCT or not, after a VRD induction, followed by 12-month lenalidomide maintenance.[5] MRD was assessed before and after maintenance with a very sensitive technique, the immunoglobulin gene NGS that allows to detect 1 tumor cell in 1.000.000 bone marrow cells. Results were correlated to PFS and OS. MRD was evaluated in the 269 patients who achieved at least a very good partial response (VGPR). Patients who did not achieve a VGPR were considered as MRD positive. Patients achieving a MRD level below 10^{-6} presented a significantly better PFS compared to those not achieving this level. Therefore, 10^{-6} was chosen as the cutoff for MRD negativity. At a median follow-up of 55 months, with this cutoff, the median PFS was not reached for patients achieving MRD negativity, compared to 29 months for those not reaching this goal. In addition, patients able to achieve MRD negativity without transplant presented a similar outcome than those transplanted. Similarly, high-risk patients who achieved MRD negativity presented a significantly better outcome than standard risk patients who did not achieve MRD negativity, meaning that "high-risk" is a dynamic concept that should be re-evaluated during treatment. Finally, achievement of MRD negativity was associated with a significantly longer OS.[4] Therefore, MRD should be proposed in the near future as a novel surrogate biomarker for trial

evaluation. The best sensitivity associated with the best discrimination in terms of PFS and OS suggested that 10^{-6} is the optimal cutoff.

A CURATIVE STRATEGY FOR SMOLDERING MULTIPLE MYELOMA

Smoldering multiple myeloma (SMM) is an asymptomatic plasma cell disorder that affects patients with different risks of progression to MM. In SMM patients with a high-risk of progression, the Spanish group has already demonstrated that early treatment with Rd (lenalidomide-dexamethasone) resulted in a significant benefit in terms of progression to MM and survival.[6]

Mateos and al. designed a phase 2 "curative" strategy for high-risk SMM (GEM-CESAR), defined by a sustained MRD negativity for at least 5 years. They enrolled 90 SMM patients at high-risk of progression (>50% at 2 years), under the age of 70 and transplant eligible. High-risk was defined by the presence of both ≥10% aberrant plasma cells and serum M-protein ≥3g/dl, or in the presence of one of these criteria, by a proportion of 95% immunophenotypically aberrant bone marrow plasma cells and immunopharesis. Patients received six 4-week cycles of KRd (carfilzomib-lenalidomide-dexamethasone) (K: 36 mg/m^2 twice a week; R: 25 mg on days 1-21; D: 40 mg weekly), followed by HDM and ASCT, 2 cycles of KRd consolidation and Rd maintenance (R: 10 mg on days 1-21; D: 20 mg weekly) up to 2 years. MRD was evaluated by next-generation flow cytometry after induction, ASCT, consolidation, and annually thereafter. The 43 patients who completed induction were evaluable for response, and showed a 98% ORR, including ≥CR in 46%, VGPR in 37% and MRD negativity in 38%. The depth of response improved along with the duration of treatment, with ≥CR in up to 85% of patients who completed induction, ASCT and consolidation. The associated safety profile was acceptable. Although longer follow-up is required, this "curative strategy for high-risk SMM" seems to be encouraging.[7]

SMOLDERING MYELOMA: SHOULD WE STILL WAIT TO TREAT?

Hofmeister and al. suggested treating MM in its early stage using D as a strategy to prevent organ damage and provide the best prognosis for cure. He reported preliminary data from the CENTAURUS phase 2 study that evaluated 3 D dosing schedules in patients with intermediate or high-risk SMM.[8] Eligible patients had a SMM diagnosis of <5 years, aberrant bone marrow plasma cells between 10% and 60% and at least one high-risk criterion. Patients with one or more SLiM-CRAB MM-defining events were excluded from the trial. D was administered in monotherapy either on a "long" intense dosing regimen (weekly in cycle 1, every other week in cycles 2-3, every 4 weeks in cycles 4-7, every 8 weeks up to cycle 20), an "intermediate" intense dosing regimen (weekly in cycle 1, every 8 weeks up to cycle 20) or a "short" intense dosing regimen (weekly for one cycle). Patients were monitored for biological response using the IMWG criteria and followed by magnetic resonance imaging every 6 months for the first 3 years. The primary endpoints were the rates of CR and PD/death. A total of 123 patients were enrolled. The median time since initial SMM diagnosis was 6.83 (0.4-56) months. After a median follow-up of 9.6 (range, 0-17.9) months, the ORR was numerically higher in the "long" dosing regimen than what was seen with the 2 other schedules. The median PFS was not reached in any treatment arm, but the 12-month PFS rates were 95% with the "long" schedule, compared to 88% and 81% with the "intermediate" and the "short" dosing schedules, respectively. The rate of hematologic treatment-emergent adverse events (TEAEs) was less than 15% across all arms and the rate of grade 3/4 infections was under 5%. One death related to disease progression was reported in the "short" arm. Safety data were consistent with those reported in other single-agent D trials.[8] Follow-up for efficacy is ongoing, but these results have already triggered a phase 3 trial to evaluate "long" intense dosing with subcutaneous administration of D in high-risk SMM patients.

ANTIBODY DRUG CONJUGATE AGAINST B-CELL MATURATION ANTIGEN

B-cell maturation antigen (BCMA) is a cell surface receptor of the TNF superfamily required for the survival of long lived plasma cells, that is also expressed on MM cells. GSK2857916 is a humanized IgG1 anti-BCMA antibody bound to a microtubule disrupting agent that is rapidly internalized and exhibits enhanced antibody-dependent cell-mediated cytotoxicity and potentially induces MM cell death. In this first in human phase I, open-label study, this compound was investigated in 35 heavily pretreated RRMM patients who had undergone an ASCT if eligible, and who had already been exposed to (at least) alkylators, PI, and immunomodulators (IMiDs).[9] Most patients were refractory to PI or IMiDs or both, and 57% had received ≥5 prior lines of therapy, including monoclonal antibodies. Given in monotherapy, this antibody drug conjugate demonstrated a very high response rate of 60%, with 1 sCR, 2 CR, 15 VGPR and 3 PR. Responses were deep (51% ≥VGPR) and durable (duration of response not reached) with an unprecedented median PFS of 7.9 months, compared to any approved drug in this heavily pretreated setting. Side effects were manageable with thrombocytopenia and low grade corneal events being

the most frequently reported adverse events. When we look back at the 30% ORR reported with D single agent a few years ago in a similar setting, the 60% ORR observed with this single agent is nothing less than very promising.[9] The FDA has already granted this compound a breakthrough therapy designation for the treatment of patients with RRMM who have failed at least 3 prior lines of therapy, including an anti-CD38 antibody, and who are refractory to a PI and an IMiD.

CAR T-CELL THERAPY ONGOING IN MULTIPLE MYELOMA

Immunotherapy with CAR T-cells has recently taken center stage in several hematological cancers. Achieving acceptable benefit/risk profiles with these strategies depends on several factors, including the specificity of the antigen target and the characteristics of the CAR itself. To test the safety and efficacy of CAR T-cells in RRMM, *Berdeja et al*. designed a second-generation CAR construct targeting BCMA to redirect T-cells to MM cells.[10] In a multicenter phase 1 dose escalation trial, this compound was proposed to RRMM who had received at least 3 prior regimens, including a PI and an IMiD, or were double-refractory. Also, 50% of BCMA expression had to be present on malignant cells. Peripheral blood mononuclear cells were collected by leukapheresis and shipped to a central facility for transduction, expansion, and release testing prior to being returned for infusion. Patients underwent lymphodepletion with fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) given daily for 3 days before receiving a single CAR T infusion in different doses, ranging from 5 to 80 x 10^7 cells. The primary outcome was the incidence of side effects, including dose-limiting toxicities (DLT). Quality, duration of response (DoR), MRD evaluation, OS and PFS were also evaluated. Among the 21 patients infused, 18 were evaluable for clinical response. They received a median of 7 prior lines of therapy (range 3-14), all with prior ASCT, and 67% had a high-risk cytogenetic profile. After a median follow-up after CAR T infusion of 15.4 weeks, no DLT or TEAEs grade 3 or higher neurotoxicities as those reported in other trials had been observed. Cytokine-release syndrome (CRS), primarily grade 1 or 2, was reported in 71% of the patients but was manageable (eventually with anti-IL6 therapy) and rapidly resolved. One death (cardiac arrest) occurred 4 months after CAR T infusion in a patient in sCR with an extensive cardiac history and was declared to be therapy unrelated. The ORR was 89% but increased to 100% for patients who received a higher, active dose of CAR T-cells. Ten patients achieved a CR, with a MRD negative response in 9 of them. These outstanding results support the potential of CAR T-cell therapy as a new treatment paradigm in RRMM.

NOVEL ONCOGENES AND TUMOR SUPPRESSOR GENES IN NEWLY DIAGNOSED MULTIPLE MYELOMA

Oncogene activation through mutation is common in MM. They directly affect the clinical behaviour of the disease and its prognosis, and can define new targets for therapy. *Walker et al*. established a set of 1,277 NDMM samples for which whole exome sequencing was available.[11] A total of 26 statistically significantly mutated genes were identified, including mutations in 11 previously identified genes (*KRAS, NRAS, DIS3, BRAF, TP53, MAX, TRAF3, CYLD, RB1, FAM46C, HIST1H1E*) as well as 9 new mutations associated with oncogene activation including *PTPN11, IDH1, IDH2,* and *SF3B1*. Compared to tumour suppressor genes, mutations in oncogenes are more clonal and, are therefore, associated with early events in the natural history of the disease. Fully characterizing driver genes in MM will enhance our ability to manage the disease more effectively.

CONCLUSION

The most exciting news at ASH 2017 probably came from a diverse class of therapies targeting the B-cell maturation antigen (BCMA) through different mechanisms. CAR T-cells developed in MM along with antibody drug conjugates focus on this target with very exciting and promising results. This "next generation of MM treatment" will probably shift the treatment paradigm from purely "survival-focused" to "quality of life-focused". With the landscape of MM treatment moving so rapidly, with more and more potent therapeutic options proposed, physicians will face the difficult task to choose the most adequate therapy for their patients. There is no doubt that biomarkers in MRD and cytogenetic characteristics will be of great help in redefining goals of therapy and in selecting appropriate treatments. Finally, treatment in earlier stages of the disease will also affect the way we approach MM.

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