short review

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ASH 2018—Highlights in Multiple Myeloma

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Summary More than 900 abstracts on multiple myeloma were presented at this year's ASH in San Diego. Several trials explored the addition of the monoclonal antibody daratumumab to established treatment regimens in both newly diagnosed as well as relapsed and refractory multiple myeloma. A long-awaited study tried to evaluate the role of double autologous stem cell transplant in multiple myeloma in newly diagnosed transplant eligible multiple myeloma. In relapsed and refractory multiple myeloma updates from several large trials like CASTOR and POLLUX were presented. Another spotlight were lenalidomide-refractory patients, an important patient group that is emerging as an increasingly challenging collective. Finally, abstracts on several novel agents like selinexor, venetoclax, isatuximab, melflufen and AMG420 were presented. Although still very preliminary, these data are already quite promising and illustrate the ever-changing treatment landscape in multiple myeloma.

Keywords ASH 2018 · Newly diagnosed multiple myeloma · Relapsed and refractory multiple myeloma · Autologous stem cell transplant · Experimental treatment

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Take home message

Although this review can only present a small selection of the data presented at last year's ASH, it highlights certain trends for the future. We will see an extension of established triplet to quadruplet regimens as more data on combinations with monoclonal antibodies become available. We will see a diversification of first-line treatment options in transplant-eligible patients as well as the advent of a new standard of care in elderly non-transplant-eligible patients with newly diagnosed MM. Monoclonal antibodies and second-generation PIs are on their way to entering treatment strategies in early disease phases, with acceptable toxicity profile and excellent tolerability. Also, more emphasis should lie on distinct patient groups such as patients with high-risk cytogenetics and the role of early tandem transplantation in these patients. Another cohort of patients that is likely to become more important in the next years is the group of patients refractory to IMIDs and/or PIs. To date, only limited data on alternative treatment options are available but these will be the focus of large future trials. Drugs like selinexor, isatuximab, AMG420, and melflufen are part of a second wave of novel agents that will further diversify treatment options in multiple myeloma in the coming years.

Newly diagnosed transplant eligible

One of the most eagerly awaited presentations was the data from the FORTE trial evaluating the role of carfilzomib in newly diagnosed multiple myeloma (NDMM) patients eligible for autologous stem cell transplantation (ASCT). The study randomized 474 patients into three arms: induction with 4 cycles of carfilzomib, lenalidomide, and dexamethasone (KRd) followed by ASCT, followed by 4 consolidation cycles

with KRd and maintenance with either KR or R. The second arm consisted of 4 cycles carfilzomib in combination with cyclophosphamide/dexamethasone (KCd) followed by ASCT and 4 cycles KCd consolidation followed by maintenance with either KR or R. In the third arm patients received 12 cycles or KRd (KRd12) followed by maintenance (KR vs. R). After a median follow-up of 20 months, KRd-ASCT-KRd was superior to KCd-ASCT-KCd regarding pre-maintenance stringent complete repsonse (sCR, 41.5% vs. 30%), ≥ very good partial response (VGPR, 86% vs. 74%), and minimal residual disease (MRD) negativity 10^{-5} (58% vs. 41%). More interestingly, KRd12 yielded similar rates for sCR, ≥VGPR, and MRD negativity (42, 86, and 54% respectively) to KRd-ASCT-KRd. These results seem promising, also for the transplant-free arm; however, the data are too immature to assess the impact of adding ASCT after KRD induction, since more follow-up time is required to assess whether KRd-ASCT-KRd or KRd12 is better in terms of early relapse rate, sustained MRD negativity, progression-free (PFS), and overall survival (OS) [1].

The TOURMALINE MM-3 study compared ixazomib vs. placebo as maintenance in NDMM after ASCT. Ixazomib was given until progression or for a maximum of 2 years. After a median follow-up of 31 months, the ixazomib arm had a significantly better PFS (26.5 vs. 21.3 months, $p=0.002$) and a 28% risk reduction for progression or death. The benefit was seen in all subgroups, including patients with high-risk cytogenetics. Also, there was a higher rate of conversion from MRD positivity to negativity during maintenance in the ixazomib arm (12% vs. 7%) [2]. The hazard ratio (HR) for progression or death was 0.72, which is similar to data from the Nordic/German group on bortezomib in this setting [3]. In light of a recent meta-analysis investigating different maintenance regimens, lenalidomide still shows substantially better survival data and should remain standard of care [4].

Several presentations investigated addition of the CD38 monoclonal antibody daratumumab to established triplet combinations in phase 2 studies such as the Griffin study, where data from 16 patients from a run-in phase where presented. They received four cycles of daratumumab, bortezomib, lenalidomide, and dexamethasone (Dara-VRD) followed by ASCT, two consolidation cycles, and DARA-R maintenance for a maximum of 24 months. At the end of consolidation, 100% achieved ≥VGPR and 50% were MRD negative. Infections of any grade were the most relevant toxicity and were seen in 81%, with grade 3/4 in approximately 30% of patients, most commonly pneumonia [5]. The LYRA trial included both NDMM and relapsed and refractory MM (RR-MM) treated with cyclophosphamide, bortezomib, and dexamethasone plus daratumumab, and showed an objective overall response rate (ORR) of 79% in NDMM and 71% in RR-MM. VGPR or better could be achieved in 44 and 56%, respectively [6]. Taken together these data establish daratumumab as a potent and relatively well-tolerated drug in the first-line setting before ASCT with different combination partners. Further results from larger phase 3 trials (e.g., CASSIOPEIA) will further evaluate daratumumab in NDMM.

Michele Cavo presented long-term follow-up data from three phase 3 studies comparing single vs. double ASCT after induction therapy with bortezomib/thalidomide/dexamthason (VTD) or bortezomib/doxorubicin/dexamethasone (PAD). After a median follow-up of 10 years, double ASCT proved superior in terms of PFS and OS, with both benefits remaining significant in patients with high-risk cytogenetics. To further determine which patients should receive double ASCT, a risk score based on ISS stage II+III, high-risk cytogenetics, and failure to achieve complete response (CR) at any time during treatment was developed. The OS and PFS benefits were highest in the ultra-high-risk category, with a median PFS of 35 vs. 14 months (HR 0.45 95% CI 0.21–0.79, $p=0.008$) and a survival probability of 26% vs. 6% at 10 years. In low-risk patients, the differences failed to reach significance. Based on these results, this important study may establish double ASCT as a new standard of care in high-risk patients [7].

CAR-T cell treatment after ASCT was presented as a novel approach for NDMM that achieved partial response (PR) or less after induction therapy. Nine patients first received ASCT and were then infused with BMCA and CD19-positive CAR-T cells 14 to 20 days after ASCT. The ORR was 100% and MRD negativity increased from 37.5% after ASCT to 66.7% after CAR-T cell therapy. Although all patients experienced cytokine release syndrome (CRS) to some degree, no serious CRS was observed [8].

Newly diagnosed not transplant eligible

Several trials on combinations with daratumumab as a first-line treatment were presented. Impressive results were presented in the late-breaking abstract session from the phase 3 MAIA trial, where daratumumab plus Rd was compared with Rd alone in NDMM not eligible for ASCT. The HR for progression or death was 0.55 (95% CI 0.43–0.72, $p<0.0001$) and the rate for CR or better was 47.6% vs. 24.7%, respectively [9]. Updated results from the ALCYONE (daratumumab in combination with VMP) and the early HOVON II trial (daratumumab plus ixazomib/dexamethasone) also showed trends for better ORR and PFS; however, more follow-up data are needed to assess the efficacy of these combinations [10, 11].

Another relatively small trial compared Rd for nine cycles followed by R maintenance (Rd-R) with continuous Rd in elderly NDMM. While the best response rates were similar in both arms, adverse events (AEs) were less frequent in the Rd-R arms, while the event-free survival was significantly better (9.3 vs.

6.6 months). Although there is no difference in PFS or OS to date, this study deserves attention as it opens up the possibility for a less toxic treatment approach, particularly in elderly patients [12].

Relapsed and refractory multiple myeloma

Updated data on the phase 3 CASTOR and POLLUX trials demonstrated a sustained significant PFS and OS benefit in relapsed and refractory multiple myeloma (RR-MM) patients treated with daratumumab containing triplets [13, 14]. Also, a joint analysis from the CASTOR, POLLUX, and MMY1001 trials showed that both the combination of daratumumab with pomalidomide as wells as with carfilzomib showed similar response rates in lenalidomide-refractory patients when compared to non-refractory patients [15]. One of the most important challenges in clinical practice is treatment of patients who have become refractory to lenalidomide, since large trials have only included small cohorts of lenalidomide-refractory patients. Data from the OPTIMISMM trial, which to date is the largest trial that only included patients who have been exposed to lenalidomide (and 71% being refractory to lenalidomide), showed a substantial improvement of PFS (17.8 vs. 9.5 months, HR 0.55, 95% CI 0.33–0.94, $p = 0.0276$) and ORR (85.9% vs. 50.8%) when pomalidomide was added to Vd [16]. Therefore, pomalidomide treatment with or without different combination partners is effective and feasible in patients who have already become refractory to an IMID.

Another interesting aspect concerning relapsed patients similar to maintenance strategies in transplant-eligible patients was addressed in the British MUK FIVE phase 2 study in primary refractory or first-relapse MM. Two different proteasome inhibitors in combination with cyclophosphamide/dexamethasone (6 cycles KCd vs. 8 cycles VCd) followed by maintenance with carfilzomib versus observation for 12 months are under investigation [17]. Not unexpectedly, carfilzomib showed better response rates up to 12 months, but also MRD negativity rates improved in the carfilzomib arm during maintenance. Further results concerning efficacy and tolerability of carfilzomib maintenance phase are awaited [18].

Promising preliminary results were presented from a phase 2 dose escalation study involving the BCL2-inhibitor venetoclax in combination with carfilzomib and dexamethasone. In a cohort of 42 patients, an ORR of 78% and a ≥VGPR rate of 56% were observed. Interestingly, these rates were even higher in cytogenetically high-risk patients (83 and 75% respectively) [19]. Of note, the FDA recently stopped enrollment into venetoclax trials in myeloma following data showing an increased risk for death in the venetoclax arm in the phase III BELLINI trial.

Selinexor, a first-in-class selective inhibitor of nuclear export compound, was combined with daratumumab and dexamethasone in a cohort of heavily pretreated and quad-resistant patients with at least three previous lines of therapy. Once weekly dosing with 100 mg was found to be associated with acceptable toxicity in comparison to biweekly 60 mg, while ORR after 25 patients treated was 74% [20]. The STORM study treated 122 penta-refractory patients with 80 mg selinexor once a week plus 20 mg of dexamethasone. The ORR was 26.2%, with two sCR (both MRD negative). Of note, two patients who relapsed after CAR-T cells achieved PR [21].

Patients in the phase 2 HORIZON trial were treated with melflufen, an enhanced peptidase alkylating melphalan derivative that selectively accumulates in myeloma cells. After at least two cycles, ORR was 32% and clinical benefit rate was 39%. Toxicities, however, were quite severe, with 77% experiencing grade 3/4 adverse events, which were mostly hematological AE (60% neutropenia and thrombocytopenia). Despite this, discontinuation for toxicity was comparably low at 15% [22].

The bispecific anti-BMCA/CD3 antibody AMG420 was evaluated in a dose-finding study at various doses. At 400 µg/d, all 3 treated patients with RR-MM achieved MRD-negative CR [23].

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Conflict of interest G. Jeryczynski and M.-T. Krauth declare that they have no competing interests.

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