



Multiple myeloma: my highlights at ASH 2020

Eberhard Gunsilius

Received: 14 May 2021 / Accepted: 25 June 2021 / Published online: 13 August 2021
 © The Author(s) 2021

Summary The meeting focused in particular on new strategies such as chimeric antigen receptor (CAR)-T cells and bispecific antibodies. Updates of clinical trials regarding induction treatment in transplantable and non-transplantable status were presented. Furthermore, minimal residual disease negativity (MRD) or, in other words, a status characterized by no measurable disease, using standardized multicolor-flow cytometry or next-generation sequencing techniques becomes increasingly important as an endpoint in clinical trials. A subjectively assessed overview of the current contributions to the treatment of multiple myeloma is given here.

Keywords Multiple myeloma · Minimal residual disease · Modern treatment · CAR-T cells · Bispecific antibodies

First-line treatment in transplant-eligible patients

The randomized phase-II GRIFFIN trial compared induction with bortezomib-lenalidomide-dexamethasone (VRD)+daratumumab (VRD+D), followed by autologous stem-cell transplantation (ASCT) and consolidation with VRD+D and lenalidomide+D maintenance with VRD, ASCT, VRD consolidation and lenalidomide maintenance in 207 newly diagnosed transplant-eligible multiple myeloma (MM) patients. Daratumumab was given intravenously (subcutaneous daratumumab is given in the randomized phase-III PERSEUS trial VRD vs VRD-D in transplant-eligible newly diagnosed MM [NDMM]). Updated results presented at ASH 2020 showed that,

at the 12-month maintenance cut-off, the percentage of patients in stringent complete response (sCR) was 63.6% in the D-arm vs. 47.4% in the control arm [1]. The frequency of MRD-negative patients was 62.5% (durable ≥ 6 months 37.5%) in the daratumumab arm and 27.2% (durable ≥ 6 months 7.8%) in the control arm. Toxicity was mainly hematologic with 43% grade III/IV neutropenia in the daratumumab arm and 24% in the control arm. Grade III/IV thrombocytopenia was 15% and 9%, respectively. Upper respiratory tract infections occurred in 68% (5% grade III/IV) of patients receiving D-VRd and in 50% (2% grade III/IV) in the control arm. In all, 43% of patients in the D-VRd group and 6% in the control arm experienced infusion-related reactions. Thus, the addition of daratumumab substantially improved the depth of response in newly diagnosed patients in this patient group with manageable toxicity. The risk of infections has to be kept in mind when daratumumab is administered over a long time period.

In the three-armed FORTE trial carfilzomib-lenalidomide-dexamethasone (KRd) induction-ASCT-KRd consolidation (KRd-ASCT) was compared to KC (cyclophosphamide) induction-ASCT-KCd consolidation (KCd-ASCT) or 12 cycles of KRd (KRd12). In the transplant arms, four cycles were given for both induction and consolidation. In a second randomization maintenance treatment with KR versus R, both until progression, was compared.

After a follow-up of 45 months, the progression-free survival (PFS) in the KRd-ASCT arm was not reached at 57 months in the KRd12 and 53 months KCd-ASCT arm [2]. The superiority of KRd-ASCT was especially beneficial in patients with high-risk cytogenetic features. KR maintenance improved PFS (3-year PFS after the second randomization 75% vs. 68%), showing for the first time the benefit of adding a proteasome inhibitor to lenalidomide maintenance in a randomized

E. Gunsilius (✉)
 Department of Hematology & Oncology, Medical University
 Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria
eberhard.gunsilius@i-med.ac.at

setting. A total of 46% of patients that were MRD-positive at the beginning of maintenance treatment converted to a MRD negative status compared to 32% of patients receiving maintenance with lenalidomide alone. Achieving negative MRD disease was associated with prolonged PFS and overall survival (OS).

Additional evidence for the superiority of ASCT comes from the updated data of the IFM 2009 trial, which compared VRD induction (three cycles) followed by ASCT and two cycles VRD consolidation to eight cycles VRD without ASCT [3]. Both arms received lenalidomide maintenance for 12 months. With a follow-up of nearly 8 years the median PFS was significantly longer in patients receiving ASCT (47.3 months) compared to 35 months in the patients receiving lenalidomide, bortezomib, and dexamethasone (RVd) alone. Achieving MRD negativity predicted a longer PFS and OS. Median overall survival was not reached in both groups, the 8-year OS rate was 62.2 months in the ASCT group and 60.2 months in the non-ASCT group. In the EMN02/HO95 trial 1197 patients were randomized either to upfront ASCT after 3–4 cycles of VCD (bortezomib, cyclophosphamide, dexamethasone) induction or to four cycles of bortezomib-melphalan-prednisone (VMP) and, in a second randomization, to consolidation with two cycles of bortezomib, lenalidomide, dexamethasone or no consolidation, both followed by lenalidomide maintenance. The overall survival after 75 months was significantly longer in the transplant arm (69% vs. 63%) [4].

The data from these studies support once more the established practice of offering high-dose chemotherapy and ASCT to eligible patients as a first-line treatment.

First-line treatment in transplant-ineligible patients

An update of the randomized MAIA trial, which compared lenalidomide-dexamethasone-daratumumab (DRd, $n=368$) and lenalidomide-dexamethasone (Rd, $n=369$) as induction treatment in NDMM patients not eligible for autologous transplantation was presented (median age 73 years). The treatment duration was until progression or unacceptable toxicity. The median treatment duration was 43 months in the DRd arm and 23 months in the RD arm. After a median follow up of 48 months 34% of the patients in the DRd arm had sCR and the PFS was 60% in the DRd arm and 38% in the RD arm [5]. Older patients ≥ 75 years and patients with high-risk characteristics also benefited from the addition of daratumumab in terms of PFS. Duration of response was not reached for DRd and 44.3 for RD. At this 48-month update, 31% of the patients in the daratumumab arm were MRD-negative (23% of patients with high-risk cytogenetics) compared to only 10% of patients in the control arm (2% of patients with high-risk cytogenetics). Sustained

MRD negativity for >12 months was achieved in 13% (DRd) and 3% (Rd), respectively. The triplet was well tolerated. In all, 11% of patients in the DRd arm and 22% in the RD arm discontinued treatment due to adverse events. The most important grade 3/4 adverse events were neutropenia (DRd/Rd; 53%/37%), pneumonia (18%/11%), lymphopenia (16%/11%) and infections (40%/29%). These data support DRd as a standard for first-line treatment in transplant non-eligible myeloma patients.

The randomized phase-III TOURMALINE-MM2 trial compared the oral proteasome-inhibitor ixazomib in combination with lenalidomide and dexamethasone (IRd) and lenalidomide-dexamethasone (Rd) alone in transplant-ineligible patients with NDMM. The PFS was 13.5 months longer in the IRd arm, although not statistically significant [6]. Despite this lack of significance, this total oral combination can be an option for some patients.

An update of the randomized phase-III ALCYONE trial comparing D-VMP (daratumumab, bortezomib, melphalan, prednisone) including daratumumab maintenance and VMP as induction treatment in transplant non-eligible patients with NDMM showed that D-VMP significantly increased the rates of \geq complete remission (CR) (46% vs 25%) and MRD negativity (28% vs 7%), as well as progression-free and overall survival [7]. The \geq CR rate improved from 44% at the start of daratumumab maintenance treatment to 64% and 68% at 1 and 2 years, respectively.

Relapsed/refractory disease

The anti-CD38 antibody daratumumab in combination with pomalidomide and dexamethasone (DPd) versus pomalidomide dexamethasone alone was tested in a randomized setting in the phase-III APOLLO trial which included 304 patients [8]. Initially, daratumumab was given subcutaneously, after an amendment (i.v. patients also switched to s.c.). Treatment was given until progression or unacceptable toxicity in both groups. The mean age of the patients was 67 years and approximately 20% were ≥ 75 years old. The International Staging System (ISS) stage was I in 45% of patients in both groups. The median number of prior treatments was two. Remarkably, 80% of patients were, by definition, refractory to lenalidomide and 80% of patients were refractory to their last treatment. In all, 50% were refractory to proteasome inhibitors, and 42% were refractory to both substance classes.

Overall response rates were 69% for DPd and 46% for Pd, in which the \geq CR rates were 24% vs. 4%. For patients receiving DPd the 12-month PFS was 52% (median PFS: 12.4 months) compared to 35 for Pd (median PFS: 6.9 months). The risk of progression or death was reduced by 37%. For those that were refractory to lenalidomide, median PFS was 9.9 months with D-Pd vs 6.5 months with Pd. No new safety signals

were observed. Hematotoxicity was the most common adverse effect with grade III/IV neutropenia in 58% (DPd) and 51% of patients. The infection rate was higher in the DPd arm (70% vs. 55%). A total of 5% of patients experienced mild infusion-related reactions. These data, together with the results of the MM-014 trial (DPd in patients that progressed under lenalidomide as their direct prior treatment [9]), show that DPd is an option for pretreated patients that are refractory to lenalidomide, which is used in many patients in the first-line setting. The benefit in terms of PFS of another anti-CD38 antibody, isatuximab, when added to pomalidomide and dexamethasone, has already been shown in the IKARIA trial in relapsed/refractory MM (RRMM) patients after at least two prior lines of treatment [10].

An update of the CANDOR trial was also presented at ASH 2020. Patients with RRMM and 1–3 prior treatment lines were randomized between daratumumab + carfilzomib-dexamethasone (KDd, $n=312$) or carfilzomib/dexamethasone (KD, $n=154$) [11]. The median PFS was nearly doubled in the KDd arm (28.6m. vs 15.2m.), whereby patients with early relapse (<1 year after the last therapy) comparably benefited from the treatment. Also, patients with high-risk features do better with the triple combination.

The second novel anti-CD38 antibody isatuximab was tested in the randomized phase-III trial IKEMA together with carfilzomib and dexamethasone (IKd) against carfilzomib and dexamethasone alone in RRMM patients after 1–3 prior treatment lines. The median PFS was not reached in the IKd arm after a median follow-up of 20.7 months and after 19.2 months in the KD arm ($p=0.0007$). The rate of MRD negativity was doubled in the isatuximab arm (30% vs 13%). As in other studies, MRD negativity was associated with prolonged PFS [12]. Treatment with isatuximab was well tolerated with 0.6% grade III/IV infusion-associated reactions (grade I–IV 45.8%). Interestingly, if the response assessment was performed using mass spectroscopy, the rate of CRs increased by 6% due to the interference of the anti-CD38 antibody with immunofixation (can produce false positive immunofixation results).

Novel treatment strategies

An important focus of the last ASH meeting was again the implementation of CAR-T cells, bispecific antibodies and drug-immunoconjugates in the treatment. The predominant target for such strategies is the B-cell maturation antigen (BCMA) expressed on malignant plasma cells.

An update of the phase-I CRB-401 trial “Idecabtagene Vicleucel (Ide-cel, bb2121), a BCMA-Directed CAR T Cell Therapy, in Patients with Relapsed and Refractory Multiple Myeloma” was presented [13]. The patients had received a median of six previous lines of therapy (range: 3–17) and 64% were triple-refractory

to immunomodulatory drugs (IMiDs), proteasome inhibitors and an anti-CD38 antibody. Roughly a third had high-risk cytogenetics. The presented data confirmed the high response rate of 76% in heavily pretreated RRMM patients ($n=62$). The rate of complete responses was 39% and 30 out of 37 evaluable patients became MRD-negative. Three quarters of the patients experienced cytokine-release syndrome (CRS) and 42 neurotoxicity (NT). Grade III/IV CRS and NT was observed in 7% and 2%, respectively.

Data from the CARTITUDE-1 trial (ciltacabtagen Autoleucel; Cilta-Cel), a phase-I/II trial ($n=113$ with a median of six pretreatments, 88% triple-refractory) showed an impressive response rate of 97% with 67% stringent remissions. The median time to first response was 1 month. The 1-year PFS for patients in sCR was 84.5%. Grade \geq III/IV infections were seen in 19.6% and grade III/IV CRS in only 4.1% and grade III/IV neurotoxicity in 9.3%. Virtually 90% of the patients received steroids and/or tocilizumab for CRS, which resolved in 99% within 14 days. Of 14 deaths during the trial, five were due to progressive disease and six deaths due to a combination of infections, CRS, and neurotoxicity. After Cilta-CEL cytokine release syndromes occur later than after Ide-Cel and the duration of cytopenia is shorter.

Another promising immunotherapeutic strategy are bispecific antibodies, called BITEs (bispecific-T-cell enhancer), which target T-cells and an antigen on myeloma cells (e.g., BCMA) simultaneously, thereby creating an “immunological synapse” that leads to the killing of myeloma cells. One advantage of BITEs is the “off-the shelf” availability of the products, their disadvantage being the necessity of repeated dosing. One of these BITEs, shown here as an example, is teclistamab, a CD3/BCMA-targeting antibody that can be applied subcutaneously, which is convenient for the patients. An update of a phase-I trial in 149 patients with a median pretreatment of six lines (five lines in the 33 patients that received the recommended phase-II dose of 1500 μ g/kg s.c.) [14]. Nearly 70% of the patients were penta-exposed and 90% were refractory to their last line of therapy. In the s.c. group, the overall response rate was 73%, with \geq very good partial response (VGPR) in 55%. CRS occurred in 50% of those patients and was exclusively grade I/II.

The data presented at the meeting show the enormous potential of CAR-T cells and BITEs to control disease in heavily pretreated myeloma patients. Although no definitive plateau in the curves is currently visible, immunologic strategies are highly efficient and the future will tell us if the results are durable, especially if these treatments are applied in earlier stages of disease.

Funding Open access funding provided by University of Innsbruck and Medical University of Innsbruck.

Conflict of interest E. Gunsilius declares that he has no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Kaufman JL, Laubach JP, Sborov D, Reeves B, Rodriguez C, Chari A, et al. Daratumumab (DARA) plus lenalidomide, bortezomib, and dexamethasone (RVd) in patients with transplant-eligible newly diagnosed multiple myeloma (NDMM): updated analysis of griffin after 12 months of maintenance therapy. *Blood*. 2020;136(Supplement 1):45–6.
- Gay F, Musto P, Rota Scalabrini D, Galli M, Belotti A, Zampagni E, et al. Survival analysis of newly diagnosed transplant-eligible multiple myeloma patients in the randomized forte trial. *Blood*. 2020;136(Supplement 1):35–7.
- Perrot A, Lauwers-Cances V, Cazaubiel T, Facon T, Caillot D, Clement-Filliatre L, et al. Early versus late autologous stem cell transplant in newly diagnosed multiple myeloma: long-term follow-up analysis of the IFM 2009 trial. *Blood*. 2020;136(Supplement 1):39–39.
- Cavo M, Gay F, Beksac M, Dimopoulos MA, Pantani L, Petrucci MT, et al. Upfront autologous hematopoietic stem-cell transplantation improves overall survival in comparison with bortezomib-based intensification therapy in newly diagnosed multiple myeloma: long-term follow-up analysis of the randomized phase 3 EMN02/HO95 study. *Blood*. 2020;136(Supplement 1):37–8.
- Kumar SK, Facon T, Usmani SZ, Plesner T, Orlowski RZ, Touzeau C, et al. Updated analysis of daratumumab plus lenalidomide and dexamethasone (D-rd) versus lenalidomide and dexamethasone (rd) in patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM): the phase 3 Maia study. *Blood*. 2020;136(Supplement 1):24–6.
- Facon T, et al. The phase 3 TOURMALINE-MM2 trial: oral ixazomib, Lenalidomide, and Dexamethasone (Ird) vs placebo-rd for transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM). In: ASH 2020, virtual edition, abstract 551. 2020.
- Rodriguez-Otero P, Boccadoro M, Hajek R, Fujisaki T, Lee JH, Martinez-Lopez J, et al. Long-term outcomes and health-related quality of life (HRQoL) by response status for Bortezomib, Melphalan, and Prednisone (VMP) ± Daratumumab (DARA) in alcyone. *Blood*. 2020;136(Supplement 1):43–4.
- Dimopoulos MA, Terpos E, Boccadoro M, Delimpasi S, Beksac M, Katodritou E, et al. Apollo: phase 3 randomized study of subcutaneous Daratumumab plus Pomalidomide and Dexamethasone (D-Pd) versus Pomalidomide and Dexamethasone (Pd) alone in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *Blood*. 2020;136(Supplement 1):5–6.
- Siegel DS, Schiller GJ, Samaras CJ, Sebag M, Berdeja JG, Ganguly S, et al. Pomalidomide, Dexamethasone, and Daratumumab after Lenalidomide treatment in relapsed refractory multiple myeloma: updated results from an open-label, multicenter, phase 2 trial. *Blood*. 2020;136(Supplement 1):16–7.
- Attal M, Richardson PG, Rajkumar SV, San-Miguel J, Beksac M, Spicka I, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomized, multicentre, open-label, phase 3 study. *Lancet*. 2019;394(10214):2096–107.
- Dimopoulos MA, Quach H, Mateos M-V, Landgren O, Leleu X, Siegel DS, et al. Carfilzomib, Dexamethasone, and Daratumumab versus Carfilzomib and Dexamethasone in relapsed or refractory multiple myeloma: updated efficacy and safety results of the phase 3 candor study. *Blood*. 2020;136(Supplement 1):26–7.
- Moreau P, et al. Isatuximab plus Carfilzomib and Dexamethasone vs Carfilzomib and Dexamethasone in relapsed/refractory multiple myeloma (IKEMA): interim analysis of a phase 3, randomized, open-label study. In: ASH 2020, virtual edition, abstract 2316. 2020.
- Lin Y, Raje NS, Berdeja JG, Siegel DS, Jagannath S, Madduri D, et al. Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, in patients with relapsed and refractory multiple myeloma: updated results from phase 1 CRB-401 study. *Blood*. 2020;136(Supplement 1):26–7.
- Garfall AL, Usmani SZ, Mateos M-V, Nahi H, van de Donk NWCJ, San-Miguel JF, et al. Updated phase 1 results of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in relapsed and/or refractory multiple myeloma (RRMM). *Blood*. 2020;136(Supplement 1):27–27.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



► For latest news from international oncology congresses see: <http://www.springermedizin.at/memo-inoncology>