Highlights in Multiple Myeloma Treatment from EHA2021

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Dr Carmen de Ramon Ortiz
Division of Hematology
University Hospital of Geneva (HUG)
Geneva, Switzerland

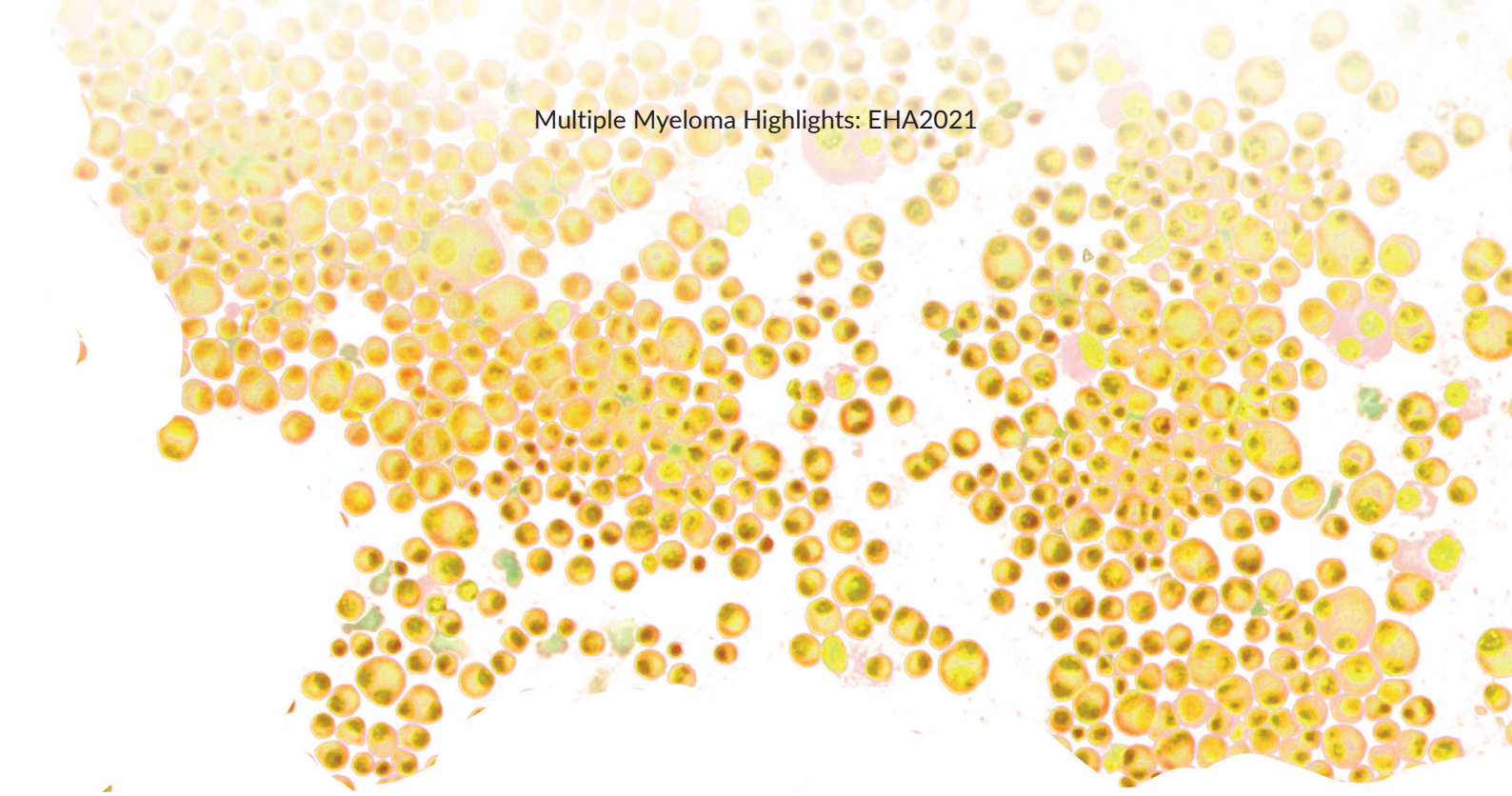
A new quadruplet regimen for the treatment of NDMM

At EHA2021, Prof. Katja Weisel presented the updated interim analysis of the phase II GMMG-CONCEPT trial that aimed to investigate isatuximab plus carfilzomib, lenalidomide and dexamethasone (Isa-KRd) in patients with high-risk newly diagnosed multiple myeloma (NDMM).[1] The trial was conducted in 20 German centers and included 153 patients with high-risk newly diagnosed multiple myeloma (NDMM). Eligible were patients with high-risk disease, defined by either del(17p), t(4;14), t(14;16), or >3 copies of 1q21, together with an International Staging System (ISS) stage II or III. In addition, patients were required to have adequate organ function and no more than one prior anti-myeloma treatment. Transplant-eligible patients (n=117) (arm A) received 6 cycles of Isa-KRd induction, 4 cycles of Isa-KRd consolidation and Isa-KR maintenance, while patients who were transplant-ineligible or ≥70 years of age (n=36) (arm B) received 2 additional cycles of Isa-KRd. The primary endpoint was minimal residual disease (MRD: threshold: 10^{-5}) negativity after consolidation and the secondary endpoint was progression-free survival (PFS). In the present report, data of the first 50 patients are presented (arm A: n=46; arm B: n=4). At baseline, high-risk cytogenetics including del(17p), t(14;4), t(14;16) and >3 copies of 1q21 were present in 52%, 38%, 12% and 42% of patients, respectively. After 6 induction cycles, the overall response rate (ORR) was 100%, with 90% of patients in arm A achieving very good partial response (VGPR) or better, and 46% achieving a complete response (CR)/stringent CR. After a median follow-up of 24.9 months, the median PFS of the total population was not reached, with PFS rates of 79.6% after 12 months and 75.5% after 24 months. Regarding safety, the most common treatment-emergent adverse events (TEAEs) of grades 3 and 4 were mostly hematological and included neutropenia (34%), lymphopenia (28%) and leukopenia (26%). Conclusively, the quadruplet treatment regimen of Isa-KRd is an attractive potential treatment option as a new standard of care (SOC) for patients with NDMM. However, a longer follow-up of these patients is required to confirm the results.

Diagnostic Biomarker in Transplant-eligible Multiple Myeloma

Achieving better outcomes for multiple myeloma (MM) patients is not solely dependent on improving treatment options but also on developing diagnostic tools. An interesting study on circulating tumor cells (CTCs) as a diagnostic biomarker in transplant-eligible MM patients was presented by Dr Juan José Garcés.[2] The Spanish GEM2012 trial included transplant-eligible MM patients with available CTCs assessment (n=374). CTCs were determined in peripheral blood by next-generation flow cytometry (sensitivity: $2x10^{-6}$) and displayed as % CTC out of total peripheral blood (PB) leukocytes. Transplant eligible patients were given bortezomib plus lenalidomide plus dexamethasone (VRd) for 6 cycles followed by autologous stem cell transplant (ASCT) conditioned with busulfan plus melphalan versus melphalan and posttransplant consolidation with 2 cycles of VRd. Patients were stratified into three risk groups according to their CTC percentage: 0%, <0.24%, ≥0.24% CTCs. Both PFS and overall survival (OS) outcomes are significantly better in the patient group with 0% CTCs, resembling the great prognostic potential of CTCs as a biomarker. The PFS was not reached in the 0% CTCs patient group while it was 78 months and 44 months in the patient groups with <0.24% and ≥0.24% CTCs. Accordingly, OS rate at 5-years was 100%, 81%, and 67% for patients with 0%, <0.24% and ≥0.24% CTCs. Interestingly, patients who do not achieve complete response or better (≥CR) or MRD-negativity but do have undetectable (0%) CTCs, still show high PFS rates. Additionally, among patients showing ≥CR and MRD-negativity, patients with 0% CTCs achieve superior outcomes. Similarly, patients with 0% CTCs at the beginning of treatment achieved better outcomes. Therefore, elevated CTC levels predict poor survival regardless of other baseline prognostic factors.

In the same Spanish GEM2012 study, the sensitivity of mass spectrometry (MS) versus serum and protein electrophoresis (SPEP) after immunofixation (IFE) for detection of the monoclonal component (MC) as a biomarker for disease progression in MM



was assessed.[3] MS and SPEP/IFE were performed at three different time points: after induction therapy with 6 cycles of VRd after ASCT and after 2 cycles of VRd-consolidation. At all three time points, MS yielded a higher percentage of patients with detectable MC than SPEP/IFE (63% vs 52% post-induction, 46% vs 36% post-ASCT, and 35% vs 27% post-consolidation). Complete response (CR) was defined as undetectable MC. Patients who achieved CR after consolidation by both SPEP/IFE and MS assessment showed a significantly higher PFS than those who showed undetectable MC by SPEP/IFE but not by MS analysis. Conclusively, MS identified the presence of paraprotein in a higher proportion of patients throughout the screening and identified the residual disease in a cohort of patients in standard CR but at increased risk of progression.

New triplet regimen for transplant-ineligible patients with NDMM

At EHA2021, Prof. Thierry Facon presented updated efficacy and safety results from a prespecified interim overall survival (OS) analysis of the multicenter, randomized, MAIA trial assessing daratumumab plus lenalidomide and dexamethasone (Rd) versus Rd alone in transplant-ineligible patients with NDMM. Overall, 737 patients were randomized 1:1 to receive either daratumumab (16 mg/kg once per week in cycle 1–2, every second week in cycle 3–6 and once every 4 weeks thereafter) plus Rd (R: 25 mg on days 1–21; d: 40 mg on days 1, 8, 15 and 22) (n=368) or Rd alone (n=369) until disease progression.[4] The additional follow-up continued to demonstrate deeper responses with daratumumab plus Rd versus Rd alone at a median follow-up of 56.2 months. Similar to previously published data, the overall response rate (ORR) was 93% in patients receiving daratumumab plus Rd and 82% in patients receiving Rd alone, with a stringent complete response (sCR) rate of 35% and 15%, respectively. In this updated analysis, the significant PFS benefit of daratumumab plus Rd versus Rd alone was maintained. After a median follow-up of 56.2 months, the median PFS for patients receiving daratumumab plus Rd was not reached, while it was 34.4 months for those receiving Rd alone (HR: 0.53 [95% CI: 0.43–0.66]; p<0.0001). The 5-year PFS rate with daratumumab-based regimen was 52.5% versus 28.7% with Rd alone. Furthermore, the median OS was not reached in both treatment arms, with a 5-year OS rate of 66.3% with daratumumab plus Rd and 53.1% with Rd alone (HR: 0.68 [95% CI: 0.53–0.86]; p=0.0013). This benefit is consistent across patient subgroups except for patients with impaired baseline hepatic function. Remarkably, the PFS and OS data have been achieved in a population with 44% of patients aged between75–90 years. Taken together, the updated results strongly support the use of daratumumab plus lenalidomide and dexamethasone as a standard of care for patients with transplant-ineligible NDMM.

Improving clinical outcomes with triplet therapy in RRMM

At EHA2021, Dr Aurore Perrot reported the updated interim analysis of the efficacy and safety data of the phase III ICARIA-MM trial, which assessed isatuximab with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM). The multicenter, open-label, randomized trial included a total of 307 relapsed/refractory RRMM patients previously treated with ≥2 prior lines of therapies, including lenalidomide and a proteasome inhibitor (PI). Patients underwent 1:1 randomization to receive either isatuximab (10 mg/kg once weekly in cycle 1, then every other week) plus pomalidomide (4 mg on days 1–21) and dexamethasone (20–40 mg once weekly) (Isa-Pd) (n=154) or Pd alone (n=153), until disease progression or unacceptable toxicity.[5] The primary endpoint was progression-free survival (PFS), determined by an independent response committee (IRC). This preplanned second interim analysis assessed longer-term outcomes, including time to next treatment (TTNT), overall survival (OS), time from randomization to disease progression on first subsequent therapy or death (PFS2) and safety.

At the time of primary analysis, the trial met its primary endpoint.[5] At a median follow-up of 11.6 months, Isa-Pd versus Pd was associated with significant improvement in PFS (11.5 months vs 6.5 months; HR: 0.596 [95% CI: 0.436–0.814]; p=0.001).

At a median follow-up of 35.3 months, Isa-Pd versus Pd alone was associated with significantly prolonged median PFS (11.1 months vs 5.8 months; HR: 0.599; p<0.0001) and median TTNT (15.5 months vs 8.9 months; HR: 0.555 [95% CI: 0.418–0.737]; p<0.0001). The results further showed that Isa-Pd significantly improved PFS2 (17.51 months vs 12.88 months; HR: 0.759 [95% CI: 0.582–0.989]; log-rank p=0.0202), while there was a strong trend in OS benefit with a 7-month improvement in the median OS (24.57 months vs 17.71 months; HR: 0.760 [95% CI: 0.574–1.008]; log-rank p=0.0280).[6] After additional 2 years of therapy, the responses continued to deepen, with an ORR of 63% with Isa-Pd versus 33.3% with Pd alone. Interestingly, this study showed that daratumumab monotherapy following Isa-Pd appears to be less effective than after Pd. However, no difference in response was observed when daratumumab was given as a combination therapy. In conclusion, the longer follow-up confirmed Isa-Pd as a standard of care for patients with RRMM.

Expanding the treatment armamentarium of RRMM

With the current standard of care therapies in MM, patients who are refractory to the cereblon-targeting drugs lenalidomide and pomalidomide, have only limited options. A novel drug targeting cereblon, iberdomide, has recently proven activity in pomalidomide and lenalidomide refractory myeloma cell lines.[7] It's efficacy and safety is being assessed in the CC-220-MM-001 study, including a phase I dose-escalation study and a phase II dose expansion study. At the EHA2021, results from cohorts E, F, and G from the phase I, CC-220-MM-001study were presented by Dr Sagar Lonial. Patients included in these cohorts had RRMM with ≥2 prior lines of therapy, including lenalidomide and pomalidomide as well as PIs and whose disease progressed on or within 60 days of last anti-myeloma therapy. Patients were treated with iberdomide (Iber) plus daratumumab (D) plus dexamethasone (d) (n=43) (cohort E), Iber plus bortezomib (V) plus d (n=25) (cohort F) or Iber plus carfilzomib (K) plus d (n=9) (cohort G). All patients were heavily pretreated with a median time since diagnosis of >6.5 years and 30%–40%% of the patients were triple-class refractory. At a median follow-up of 3.9 months for patients treated with IberDd, 5.5 months for those treated with IberVd and 5.1 months for those treated with IberKd, the ORR was 45.9%, 56.0%, and 50.0%, respectively. Of note, the occurrence of non-hematological treatment-emergent adverse events (TEAEs) was low, with fatigue, rash, and gastrointestinal disorders being the most common grade 3–4 TEAEs. The recommended phase II dose (RP2D) is 1.6 mg for patients receiving IberDd, while it was not yet determined in the other cohorts. Overall, the results support further investigation of iberdomide-based combination therapies in phase III studies.

Finally, to further expand the possibilities in MM treatment, novel agents with different mechanisms of action are of great interest. Currently, the bispecific B-cell maturation antigen (BCMA) - and CD3-directed off-the-shelf antibody, teclistamab is evaluated in the first-in-human, multicenter, phase I study MajesTEC-1.[8] In the open-label, single-arm trial, eligible patients (n=157) had measurable MM, were relapsed or refractory or intolerant to established therapies, had not received any prior BCMA-targeted therapy, and fulfilled the following criteria: hemoglobin ≥8 g/dL, platelets ≥75x10⁹/L, absolute neutrophil count ≥1.0x10⁹/L. Teclistamab was administered intravenously (range 0.3–19.2 µg/kg [once every 2 weeks] or 19.2–720 µg/kg [once per week]) or subcutaneously (range 80–3000 µg/kg [once per week]) in different cohorts, with step-up dosing for 38.4 µg/kg or higher doses. In fact, 1,500 g/kg was the determined subcutaneous RP2D. The median number of prior therapies was 5.0 in both the total SC cohort (n=73) as well as the RP2D SC cohort (n=40). Of those patient groups, nearly 80% were triple-class refractory, 38% were penta-drug-refractory, and approximately 80% were refractory to the last line of therapy. Regarding TEAEs, 60% of patients in the SC total and 70% of patients in the RP2D cohort experienced cytokine release syndrome (CRS), however, all CRS events were of grade 1 or 2 and therefore manageable. There was only 1 case of neurotoxicity and grade 3–4 cytopenia was generally confined to step-up dosing and in cycles 1 and 2. Infections were reported in 51% of SC-treated patients, including 21% of patients experiencing grade 3–4 infections. Keeping in mind that the patient population was heavily pretreated, a promising ORR of 65% in the RP2D SC cohort was achieved, including 40% of patients showing ≥CR. In patients, who received other SC doses (n=32), an ORR of 59.4% was achieved. After a median follow-up of 7.1 months 22/26 (85%) responders in the RP2D SC group, were still alive and continuing treatment. In conclusion, teclistamab is a well-tolerated agent and no new safety signals were detected. The observed responses were durable and deepened over time, representing a promising starting point for future studies to evaluate teclistamab in earlier-line MM as well as in combination therapies.

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