MultipleMyelomaHub

62nd ASH Annual Meeting and Exposition

Practice-changing abstracts in multiple myeloma (MM)

December 5–8, 2020

The Multiple Myeloma Hub Steering Committee members shared their insights on the abstracts presented at ASH 2020 about multiple myeloma (MM) that could impact your clinical practice in the near future.

Here, you can find the key messages from world-leading experts on MM about the role of autologous stem cell transplant (auto-SCT) in the novel agents' era, and the latest updates on new combinations and therapy-sequencing strategies to achieve deeper and more durable responses.

Click the articles to view

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#62 Discordances between Immunofixation (IFx) and Minimal Residual Disease (MRD) Assessment with Next-Generation Flow (NGF) and Sequencing (NGS) in Patients (Pts) with Multiple Myeloma (MM): Clinical and Pathogenic Significance

"The study raises speculation that discordances between the immunofixation (IFE) and MRD assessments, as well as NGS and NGF testing, could be related to more immature clonotypic B cells. Because such cells do not have the genetic background to drive disease relapse, an MRD-negative result despite a positive IFE should not be regarded as a false-negative result, since these patients have similar outcomes to those in complete response and those who are MRD-negative."

Bruno Paiva

#61 High-Dose Melphalan Significantly Increases Mutational Burden in Multiple Myeloma Cells at Relapse: Results from a Randomized Study in Multiple Myeloma

"These results describe a significant accumulation of mutations following high-dose melphalan in the transplant arm of the IFM 2009 clinical trial. Data suggest the need for reappraisal of the optimal use of high-dose melphalan in the era of novel agents and warrants some speculation – if a higher mutational burden is limiting the efficacy of salvage treatment upon relapse. If so, it could explain the similar overall survival despite increased PFS reported in patients receiving high-dose melphalan in this trial."

Bruno Paiva

Podcast: Should we still use high-dose melphalan in the era of novel agents?

The role of up-front autologous stem cell transplantation (auto-SCT) in obtaining measurable residual disease (MRD) negativity and long-term responses

#143 Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the IFM 2009 Trial

"The question about early *vs* delayed transplant has a solid answer, and ASCT should continue to be part of the up-front setting if the patient is transplant-eligible. The lack of OS benefit reported in the transplant arm is derived from the fact that over 80% of patients who did not undergo transplant up-front, received it at relapse."

María-Victoria Mateos

"This French study included 700 transplant-eligible patients and addressed the question: whether a delayed transplant yields similar results compared with a transplant given up-front. In short, the data confirm the hypothesis that a transplant given later during the treatment course, results in a similar survival outcome compared with a transplant given earlier on. But it's worthwhile to mention some issues: this strategy works well in young patients because they can easily receive a transplant 3–5 years after failure to first-line therapy. In older patients (still transplant-eligible) the window of opportunity for delayed transplant may be shorter. Hence, the classic philosophy of using transplants as first-line therapy still remains as the standard of care in Europe."

Heinz Ludwig

"The long-term results of this trial are very important for the current practice and support the continued use of stem cell transplants for the treatment of multiple myeloma. A significant progression-free survival advantage has been associated with the use of stem cell transplants as part of initial therapy of newly diagnosed myeloma. Even with a longer follow-up, of nearly 90 months, we still observe a similar overall survival suggesting that a delay in stem cell transplant to 1st relapse would be appropriate when taking into consideration patient preferences."

Shaji Kumar

VRd alone or followed by ASCT in NDMM: IFM 2009 long-term results

#141 Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized Forte Trial

#491 Impact of Minimal Residual Disease (MRD) By Multiparameter Flow Cytometry (MFC) and Next-Generation Sequencing (NGS) on Outcome: Results of Newly Diagnosed Transplant-Eligible Multiple Myeloma (MM) Patients Enrolled in the Forte Trial

"Lenalidomide (R) is a better partner for carfilzomib (K) than cyclophosphamide. High-dose therapy plus auto-SCT in the up-front setting after KRd, results in a longer PFS than KRd for 12 cycles without transplant. The addition of K to R as part of maintenance converts MRD-positive into MRD-negative, upgrading the quality of the response and leading to a longer PFS than a maintenance with R as single agent."

María-Victoria Mateos

"Even with an intensified induction therapy (here, 12 cycles of KRd), the addition of high-dose melphalan and auto-SCT significantly improved PFS in all subgroups of patients. In addition, an intensified maintenance using carfilzomib plus Len improved PFS compared with a Len monotherapy for maintenance."

Hermann Einsele

"This phase II randomized trial showed the huge activity of a second-generation triplet (KRd) followed by auto-SCT in newly diagnosed MM, in terms of attainment of MRD negativity and improving survival outcomes. Although KRd is not approved as a pre-auto-SCT induction regimen, the study clearly demonstrated that a PI+IMiD combination is the best compared with KCd, and that even in the novel agent era, the addition of auto-SCT is significantly preventing early relapse, particularly in high-risk patients. In my opinion, with this trial, the value of up-front auto-SCT is positively confirmed."

Elena Zamagni

"The FORTE trial is a gold mine for clinical myeloma research because it provides answers to pertinent questions. One of the questions raised in this abstract is whether MRD assessment by the two different techniques, namely NGS and NGF, yields similar results – which has been positively answered by the data presented. In addition, they show that the depth of response, namely MRD negativity, is enhanced during maintenance treatment with KRd compared with standard Rd. Furthermore, and this has been addressed before, it clearly shows that cyclophosphamide should be abandoned from induction regimens in the majority of patients, because the standard of care is combining IMiD with a PI and Dex, and in the near future, a monoclonal antibody. Another clear answer obtained from the FORTE trial is the confirmation that an autologous transplant cannot be abandoned at this point of time if optimizing the treatment outcome is the goal, both in standard- and high-risk patients."

Heinz Ludwig

"These results are very important and continue to demonstrate the importance of induction therapy, stem cell transplant, as well as maintenance approaches in patients with newly diagnosed multiple myeloma. It highlights the importance of using a proteasome inhibitor and IMiD combination as part of the initial therapy prior to an autologous stem cell transplant. Even in the context of initial therapy with such a combination, a stem cell transplant appears to improve the depth of response and durability of response. Finally, there is evidence of improved progression-free survival with the dual maintenance compared with a single drug maintenance, particularly in those patients with high-risk disease, consistent with prior observations."

Shaji Kumar

The role of up-front auto-SCT in obtaining MRD negativity and long-term responses

#142 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

"This study confirms the role of auto-SCT in the up-front setting as better option than reserving it for the relapse, with superiority shown in terms of PFS as well as OS."

María-Victoria Mateos

"Auto-SCT, when compared with intensive standard therapy (VCD-VMP), improves not only PFS but also OS! In addition, in high-risk patients, tandem transplantation significantly improves PFS compared with single transplantation."

Hermann Einsele

"One of the most common questions that is asked in the clinic is: 'Doctor, do I still need to have a transplant?' – This study provided strong evidence in favor of answering 'Yes' to that question. The follow-up data provide further confirmation. Although the survival difference does not reach statistical significance, a further follow-up will be interesting."

Miles Prince

ASH 2020 discussion: The role of upfront transplant consolidation in the era of novel agents

The role of up-front auto-SCT in obtaining MRD negativity and long-term responses

Will outcomes improve by adding an anti-CD38?

#549 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

"The addition of a monoclonal antibody to triplets that are currently being used for the treatment of newly diagnosed, transplant-eligible patients, has been reported previously (in the CASSIOPEIA trial), demonstrating an improved progression-free survival. In the GRIFFIN trial, Dara has been added to VRd, consistent with the current practice. The trial demonstrates that with a longer follow-up, there is a continued improvement of the depth of response, which is more evident with the four-drug arm. There is no difference in the progression-free survival or overall survival at this time point; hence, a longer follow-up will be needed to demonstrate survival differences."

Shaji Kumar

Latest updates on Len-based triplets for patients with newly diagnosed MM, not eligible for auto-SCT

#551 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)

"Ixazomib is the only oral proteasome inhibitor that is currently available in the clinic. The use of ixazomib in combination with lenalidomide (Len) and dexamethasone (Dex) allows for the development of an all-oral induction therapy. In this phase III trial, the addition of ixazomib to Len and Dex (IRd) led to an increased progression-free survival by 13 months compared with Rd alone. Even though this difference did not meet the threshold for statistical significance, it is important to note that the median PFS at 35 months with IRd is very comparable with the one observed with bortezomib+Rd in the up-front setting."

Shaji Kumar

TOURMALINE-MM2 trial: Ixazomib with Rd versus Rd in newly diagnosed patients with MM

#2276 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

"For patients who are considered ineligible for a stem cell transplant, Dara in combination with Len and Dex is associated with a significantly improved progression-free survival, compared with using Len and Dex. The longer-term results of the trial with approximately a 4-year follow-up, demonstrate a consistent improvement in progression-free survival with a median that has not yet been reached, and projected to be closer to 55–60 months. Importantly, with a longer-term follow-up, it became clear that patients with high-risk disease also appeared to benefit from the addition of Dara. Finally, the improved PFS2 in the Dara-arm reflects the likelihood that this regimen will improve the overall survival. This regimen reflects the current standard of care for treating transplant-ineligible patients with NDMM."

Shaji Kumar

#412 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)

"Dara sc+Pd emerges as a new SOC in RRMM patients after at least one prior line; however, the population treated with one prior line was rather small in this trial. More evidence will be generated from its use in the real world."

María-Victoria Mateos

"This phase III randomized trial firstly demonstrated the efficacy and tolerability of Dara combined with pomalidomide (Pom) and Dex (Dara-Pd) in RRMM, and its superiority to Pd. Dara-Pd will soon become a standard of care for RRMM. With the progressively increasing percentage of Len-refractory patients after first-line therapy, the availability of Len-sparing triplets is of utmost importance, as well as availability of different Dara combinations. Unfortunately, only 10% of the patients enrolled in the trial were treated at first relapse after being Len-refractory; nevertheless, previous data showed the efficacy of Pom combinations, also in this setting."

Elena Zamagni

"CD38-directed antibodies, and particularly Dara, are a game changer. Whenever you add these antibodies to a standard doublet or triplet regimen, the outcome is in favor of the antibody–chemotherapy combination, which was also true in the APOLLO study in patients with at least one prior line of therapy. Dara+Pd resulted in higher response rates and significantly improved progression-free survival. These data are similar to the ICARIA study, which has already reported a similar benefit in adding isatuximab to Pom-Dex in relapsed/refractory myeloma. The APOLLO study has also shown the ease and excellent tolerance of administering Dara subcutaneously."

Heinz Ludwig

"The results of this phase III trial clearly demonstrate the advantage of adding Dara in patients with relapsed MM. This trial provides important information on what's been previously observed for isatuximab in combination with Pom-Dex, in a similar patient population. The results clearly highlight the utility of this regimen in patients who are refractory to Len at the time of relapse, which is quite common given the widespread use of Len in the up-front setting, as maintenance."

Shaji Kumar

APOLLO trial results: Addition of daratumumab to pomalidomide + dexamethasone in relapsed/refractory multiple myeloma

#726 Selinexor in Combination with Pomalidomide and Dexamethasone (SPd) for Treatment of Patients with Relapsed Refractory Multiple Myeloma (RRMM)

"Although the results are preliminary, the addition of Selinexor (Sel) to Pom-Dex in heavily pretreated myeloma patients is encouraging, with a greater efficacy than that observed for Pom-Dex or Sel-Dex combinations. The use of weekly Sel did not affect the efficacy but significantly improved its tolerability."

María-Victoria Mateos

"Sel clearly has a place in patients who have failed a PI and Len. We are all a little hesitant to add Pom-Dex alone in patients that are Len-refractory. This study is very valuable in demonstrating that adding Sel to Pom is not only safe but also likely more effective. Although this is not a randomized comparison, the comparison with historical data is quite compelling."

Miles Prince

"Sel is different from all other myeloma drugs because it impacts on the export of proteins (tumor suppressor and oncogenes); hence, it shows a different mode of activity. Combining Sel with other drugs raises hope for improvement of anti-myeloma efficacy with acceptable tolerance. In fact, this has been shown in abstract #726, where Sel was combined with Pom-Dex, resulting in a significant benefit of the triplet combination over the standard doublet therapy (Pom-Dex) in relapsed/refractory myeloma."

Heinz Ludwig

"Sel has recently been approved for use in combination with Dex or with bortezomib and Dex in patients with relapsed disease. Unlike many of the other new therapies, Sel is an oral therapy that allows for the development of all-oral combination regimens. Sel with Pom-Dex shows activity in relapsed and refractory disease, suggesting that this combination can be of value in earlier lines of therapy in Len-refractory disease."

Shaji Kumar

"Sel+Pom+Dex reported good data, but for a phase III study, I would compare SPd with Carfilzomib+Pd."

Nina Shah

Selinexor in combination with bortezomib and dexamethasone approved for relapsed/refractory multiple myeloma

#725 Part 1 Results of a Dose Finding Study of Belantamab Mafodotin (GSK2857916) in Combination with Pomalidomide (POM) and Dexamethasone (DEX) for the Treatment of Relapsed/Refractory Multiple Myeloma (RRMM)

“The initial results with belantamab clearly show that this antibody–drug conjugate targeting BCMA is effective in RRMM that has stopped responding to the current standard-of-care agents. The results from this trial demonstrate that it can also be safely combined with Pom, providing an option for use as a triplet in earlier lines of therapy, even in patients who are relapsing on Len-containing regimens.”

Shaji Kumar

“Belamaf+Pom+Dex combination with some split dosing (Day 1 and 8, every 4 weeks) reported keratopathy still in ~70% of cases. There was an overall response rate of 82% and a median PFS NR yet in the 2.5 mg/kg arm. This is a very effective combination, so now that we have better efficacy, we need to play around with dose and schedule to minimize toxicities.”

Nina Shah

The European Commission approves belantamab mafodotin for the treatment of patients with RRMM

Adding cyclophosphamide to improve outcomes of approved triplet combinations for RRMM

#415 Randomized Phase 2 Study of Weekly Carfilzomib 70 Mg/m2 and Dexamethasone Plus/Minus Cyclophosphamide in Relapsed and/or Refractory Multiple Myeloma (RRMM) Patients (GEM-KyCyDex)

"I believe this study will be immediately practice-changing, especially in countries where the combination PI+IMiDs is not easily available. This study showed that cyclophosphamide added to 70 mg/m^2 carfilzomib+Dex (Kd) weekly in RRMM patients, after 1–3 prior lines, prolonged PFS compared with Kd; particularly in the Len-refractory population. The administration of K at a dose of 70 mg/m^2 weekly was safe and more convenient, and overall, the toxicity profile was manageable in both arms."

Miles Prince

"KyCyDex with weekly carfilzomib in RRMM resulted in better results than Kd alone, especially in Len-refractory patients. This is not a groundbreaking study, but practice informing/adding. I personally use this combination, and probably need to be more courageous with the 70 mg/m^2 weekly dosing."

Nina Shah

#413 A Randomized Phase II, Open Label, Study of Daratumumab, Weekly Low-Dose Oral Dexamethasone and Cyclophosphamide with or without Pomalidomide in Patients with Relapsed and Refractory Multiple Myeloma

"This study is exploring how to bring quadruplet combinations to the second-line of therapy."

Nina Shah

"These two abstracts (#413 and #415) confirm, once more, how cyclophosphamide can be combined with Pom-Dex plus Dara or carfilzomib and increase the efficacy, confirming also its potential immunomodulatory effect."

María-Victoria Mateos

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