Acta Scientific Pharmaceutical Sciences

Volume 2 Issue 2 February 2018

Clinical Review

First-Line Therapy in the Transplant Candidate Multiple Myeloma Patient: Short Clinical Review

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Received: December 29, 2017; **Published:** January 19, 2018

Abstract

The current therapeutic paradigm for the transplant recipient in multiple myeloma needs to be continuously updated. It will be clarified if it actually defines the standard of care stating the unmet needs as well. With the dual purpose of treating a symptomatic disease and obtaining a maximized depth of response autologous stem cell support (ASCT) is the backbone of young multiple myeloma patient approach. This manuscript provides a real-life oriented strategy, needed for a patient centered clinical practice

Keywords: Transplant; Multiple Myeloma; Autologous Stem Cell Support (ASCT)

Goals of a new agent-based induction therapy in multiple myeloma: an overview

A severe and high-quality response (CR) in order to promptly reverse serious complications such as renal failure and hypercalcemia, ameliorate symptoms, reduce tumor burden and bone-marrow (BM) plasma cells (PCs) infiltration, enabling a successful collection of PBSCs during ASCT and finally improve post-ASCT outcomes [1-3].

Progression free survival (PFS) is strongly correlated to ASCT [4]. It has long been known that the achievement of high-quality response after induction therapy deeply impacts the prognosis. In a multicenter prospective randomized open label controlled phase III trial in newly diagnosed multiple myeloma (NDMM) patients, the use of chemotherapeutic agents with a different mode of action was able to improve response rates, both in pre-and post-transplantation, with an achievement of an improved PFS [5]. Induction therapy should be effective, as suboptimal induction therapy, with only IMIDs (Thalidomide or Lenalidomide) in combination with dexamethasone and cyclophosphamide, may be inadequate. In fact, patients who had a lower or equal response to partial remission (PR) were randomized to receive a second rescue induction, including a proteasome inhibitor, achieved a PFS from 28 to 48 months for patients treated with VCD (HR 0.50) with 38% response improvement with VGPR and VCDs. (CR) of 65% for patients receiving VCD vs 38% for those who went straight to transplant [5].It is beyond question that the choice of therapy should be optimal. It has been shown that an optimal induction therapy practicable is three-drug therapy, including a proteasome inhibitor. Indeed, a number of randomized studies have demonstrated that these therapeutic combinations (VTD/VRD, VCD, PAD) are capable of inducing high quality responses (VGPR or better) in about 60% of cases and CRs around 35% of cases [6]. VCD is less toxic than PAD: SAEs, 24% vs 32.7% (p = .04); VCD is associated with a higher incidence of hematologic toxicities grade 3/4 compared with VTD. Remarkably VTD is associated with a higher incidence of peripheral neuropathy grade 3/4 as compared with VCD: 7.7 vs 2.9% (p = .05) [7]. At the moment, therefore, the VTD and VCD regimes are the most used regimes in Europe. The possibility of inserting the first-generation immunomodulatory agent is replaced by lenalidomide. Response rates are equally high, like complete remissions, but the toxicity profile is definitely better [8]. The success of drug combinations in elderly subjects has led to testing the dominant role of ASCT as upfront therapy. Two clinical studies with median follow up of 31.6 and 43.5 months respectively [8,9] showed that ASCT should remain a standard of care.

Furthermore, it was investigated in a formal manner if only one or two transplants were needed [9]. The double auto-transplant option was also used before the approval of new drugs. The randomized upfront application of double vs single transplantation confers about 30% reduction in risk of progression or death (HR 0.70), considering all patients, this reduction is reduced to about 50% if we consider the carriers of disease with high-risk cytogenetics [10]. The IMWG consensus on treatment of high-risk cytogenetics stated that a newly diagnosed patient with high-risk cytogenetics should be treated with a combination of PI + lenalidomide or pomalidomide + dexamethasone, HDT + double ASCT. Moreover thalidomide does not overcome the adverse effect of t (4; 14), t (14; 16), t (14; 20) and del (17) or del (17p) and gain (1q) in transplant-eligible patients [11]. Also ESMO guidelines recommend an induction with 3-drug regimen, 200 mg/m2 melphalan followed by ASCT and a maintenance [12]. Remarkably, the goal of treatment in MM is obtaining the best and sustained response. Furthermore phase II and III studies have shown that consolidation with VTD, a short-term therapy administered after ASCT, upgraded to CR by 30% and in other study VRD led to an upgrade between 36 and 38% [9,13]. We cannot conclude much, because the studies carried out so far have differences in the induction patterns used (VCD, VRD, VTD) and in the duration of the induction therapy, which varies in the various studies.

Maintenance therapy is applied for a prolonged period of time with the goal of prevent cancer progression [14]. Continuous cytoreduction of clonal population, eliminating the minimal residual disease (MRD), obtains a sustained suppression of disease burden, prolonging the duration of response and improving long-term outcome. On the other hand, maintenance should not select the treatment of clones and avoid the impact on the quality of life (QoL). These features represented a problem especially with thalidomide which involved six randomized trials [15], because although being an advantage in PFS, it costed several limits. Remarkably, the onset of resistant clones in high-risk diseases was emphasized, with a detrimental effect on the OS and a worsen QoL. The ideal drug, therefore, appeared to be lenalidomide, on which several randomized trials were performed, showing an advantage in terms of OS [16]. Many patients benefit from the above drug, but there is a warning for high-risk patients. In this subset of subjects we have a doubt that lenalidomide is effective in prolonging the OS [16]. In this subgroup the role of bortezomib-maintenance was studied, with a survival advantage for del (17p) [17,18]. At the moment this strategy is controversial. The first possibility to improve the outcome can be offered by in the strategy of including the newest

agents. Indeed, the inclusion of carfilzomib and ixazomib, or the use of anti-CD38 moAb (daratumumab) and anti-SLAMF7 (elotuzumab), could play an important role [12]. Phase II studies incorporating carfilzomib plus IMIDs as induction and consolidation therapy have shown an improvement in complete remissions and sCR after transplantation, also in terms of MRD. The results are promising, but it is mandatory to consider safety [19-21]. These results, although preliminary, were partly confirmed by other authors, who showed a rate of VGPR equal to 74% [22]. A further strategy is offered by ixazomib, which at the expense of a less pronounced response, offering a better toxicity profile, is able to apply for a more long-term therapy, with a consolidation and maintenance [23].

Conclusions

We can conclude that 3 -drug combinations are recommended induction regimens, newer combinations along the whole treatment sequence, including induction regimen and post-ASCT therapy (Figure 1). ASCT should remain as standard of care 2018. Moreover tandem transplant is undoubtedly useful, particularly in high risk patients.

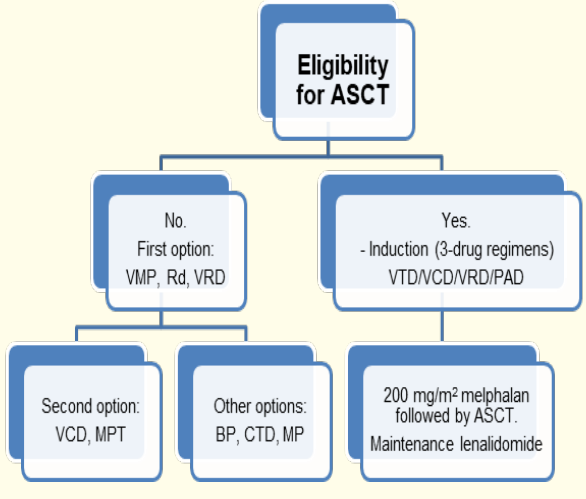

Figure 1. Guidelines: frontline therapy. Modified from ref [12]. BP, bendamustine-prednisone; ESMO, MP, melphalan-prednisone; MPT, melphalan-prednisone-thalidomide. See text for other abbreviations.

Acknowledgements

We thank Mary Victoria Pragnell, BA from the School of Medicine and Surgery, University of Bari for linguistic editing.

Bibliography

1. Cavo Michele., *et al*. "International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation". *Blood* 117.23 (2011): 6063-6073.

2. Cavo Michele., *et al*. "Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma". *Blood* 120.1 (2012): 9-19.

3. Ludwig Heinz., *et al*. "European perspective on multiple myeloma treatment strategies in 2014". *The Oncologist* 19.8 (2014): 829-844.

4. Moreau Philippe., *et al*. "Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial". *Blood* 117.11 (2011): 3041-3044.

5. Graham H Jackson., *et al*. "Response Adapted Induction Treatment Improves Outcomes for Myeloma Patients; Results of the Phase III Myeloma XI Study". *Blood* 128.22 (2016): 244.

6. Sonneveld Pieter., *et al*. "Bortezomib-based versus non-bortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials". *Journal of Clinical Oncology* 31.26 (2013): 3279-3287.

7. Moreau Philippe., *et al*. "VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial". *Blood* 127.21 (2016): 2569-2574.

8. Attal Michel., *et al*. "Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma". *New England Journal of Medicine* 376.14 (2017): 1311-1320.

9. Stadtmauer Edward A., *et al*. "Comparison of autologous hematopoietic cell transplant (autoHCT), bortezomib, lenalidomide (Len) and dexamethasone (RVD) consolidation with len maintenance (ACM), tandem autohct with len maintenance (TAM) and autohct with len maintenance (AM) for up-front treatment of patients with multiple myeloma (MM): primary results from the randomized phase III trial of the blood and marrow transplant clinical trials network (BMT CTN 0702-StaMINA Trial)". ASH 2016 Annual Meeting Abstract LBA-1 (2016).

10. Cavo Michele., *et al*. "Upfront autologous stem cell transplantation (ASCT) versus novel agent-based therapy for multiple myeloma (MM): A randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM trial)". *Journal of Clinical Oncology* 34.15 (2016): 8000.

11. Sonneveld Pieter., *et al*. "Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group". *Blood* 127.24 (2016): 2955-2962.

12. Moreau P., *et al*. "Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Annals of Oncology* 28.4 (2017): 52-61.

13. Sonneveld Pieter., *et al*. "Consolidation followed by maintenance therapy versus maintenance alone in newly diagnosed, transplant eligible patients with multiple myeloma (MM): a randomized phase 3 Study of the European Myeloma Network (EMN02/HO95 MM Trial)". *Blood* 128.22 (2016): 242.

14. Ludwig Heinz., *et al*. "IMWG consensus on maintenance therapy in multiple myeloma". *Blood* 119.13 (2012): 3003-3015.

15. Kagoya Yuki., *et al*. "Thalidomide maintenance therapy for patients with multiple myeloma: meta-analysis". *Leukemia Research* 36.8 (2012): 1016-1021.

16. McCarthy Philip L., *et al*. "Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis". *Journal of Clinical Oncology* 35.29 (2017): 3279-3289.

17. Neben Kai., *et al*. "Administration of bortezomib before and after autologous stem-cell transplantation improves outcome in multiple myeloma patients with deletion 17p". *Blood* 119.4 (2012): 940-948.

18. Nooka AK., *et al*. "Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients". *Leukemia* 28.3 (2014): 690-693.

19. Zimmerman Todd., *et al*. "Final results of a phase 2 trial of extended treatment (tx) with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (KRd) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM)". *Blood* 128.22 (2016): 675.

20. Roussel Murielle., *et al*. "Frontline therapy with carfilzomib, lenalidomide, and dexamethasone (KRd) induction followed by autologous stem cell transplantation, KRd consolidation and lenalidomide maintenance in newly diagnosed multiple myeloma (NDMM) patients: primary results of the Intergroupe Francophone Du MyéLome (IFM) Krd phase II study". ASH 2016 Annual Meeting Abstract 1142 (2016).

21. Wester Ruth., *et al*. "Phase 2 study of carfilzomib, thalidomide, and low-dose dexamethasone as induction/consolidation in newly diagnosed, transplant eligible patients with multiple myeloma, the carthadex trial". *Blood* 128.22 (2016): 1141.

22. Gay Francesca Maria., *et al*. "Carfilzomib-lenalidomide-dexamethasone (KRd) vs carfilzomib-cyclophosphamide-dexamethasone (KCd) induction: Planned interim analysis of the randomized FORTE trial in newly diagnosed multiple myeloma (NDMM)". Journal of Clinical Oncology 35.15 (2017): 8003.

23. Moreau Philippe., *et al*. "Ixazomib-lenalidomide-dexamethasone (IRd) combination before and after autologous stem cell transplantation (ASCT) followed by ixazomib maintenance in patients with newly diagnosed multiple myeloma (NDMM): a phase 2 study from the intergroupe francophone du myélome (IFM)" (2017).

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