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Current role of high dose chemotherapy in the management of multiple myeloma

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In this issue of *Leukemia & Lymphoma*, Su and Sheng report a meta-analysis of 14 trials that compared autologous stem cell transplantation in multiple myeloma to novel agent-based consolidation. They conclude that stem cell transplantation significantly improved progression-free survival and response quality in the novel agent era. Is this data sufficient to lay to rest the argument as to whether stem cell transplantation remains standard of care in the era of novel agents? (1)

The quality of a meta-analysis is only as good as the constituent manuscripts included. Unfortunately, the heterogeneity among trials is large, limiting the value of combining the trials. Among the trials that randomized between transplant and lenalidomide-based consolidation therapy, there were 2421 patients. However, half of these patients belonged to a single trial [2], which has only been reported in abstract. All four trials involving lenalidomide and bortezomib suffer to some degree based on their design. In the Italian trials, the induction and the consolidation were lenalidomide-based and at no time in either arm were patients exposed to bortezomib, which does not reflect current practice where induction is VRD, VTD, VCD, and MPV (bortezomib-lenalidomide-dexamethasone; bortezomib-thalidomide- dexamethasone; cyclophosphamide-bortezomib-dexamethasone; melphalan-prednisone-bortezomib). Arguably, bortezomib is the single most active agent in the treatment of multiple myeloma, so a comparison of outcomes when this agent was never used is problematic.

In the Cavo trial, the consolidation represented VMP. VMP has historically been used in the transplant-ineligible population, and its value in a transplant-eligible population remains unclear. In other trials, the comparator arms constituted bortezomib-doxorubicin-dexamethasone with no novel agent exposure in the control arm or used doublet induction, which has been shown to be inferior to triplet induction [3]. As a consequence, the findings reported must be taken as not representing the final word. Nonetheless, there are a number of key findings in this article that argue that early autologous stem cell transplant should represent the standard of care for multiple myeloma. Depth of response was greater in the transplanted group. Depth of response assessed by ASO-PCR predicts outcome after stem cell transplantation [4]. Although survival has not been demonstrated to be superior in transplanted populations, progression-free survival is correlated with an increase of very good partial or better responses. Progression-free survival, from the patient's viewpoint, is time spent without myeloma [5]. Deeper responses increase the frequency of patients with

minimal residual disease (MRD) negativity, and this has been associated with superior survival. Minimal residual disease negativity is increased with early stem cell transplantation [6]. The trial of Attal and colleagues used triplet lenalidomide, bortezomib, and dexamethasone, which demonstrated a reduced relapse rate. Although this trial has not, as yet, demonstrated a survival advantage, given the median survival of myeloma now estimated at eight years for standard-risk patients, means that it will be some time before curve separation can be identified given the outstanding number of salvage regimens that exist [7].

The question of whether or not a transplant is as effective when done early as opposed to being done late has been argued vigorously because it has not been shown that there is a survival advantage for early transplant [8]. However, early stem cell transplant has a benefit of 1.96 quality-adjusted life years, which is 0.23 quality-adjusted life years more than delayed stem cell transplant, implying that early stem cell transplant is preferred [9]. Early on, I had been a strong proponent of the use of delayed stem cell transplantation [10]; but I have since changed my mind due to emerging data [11]. Although one may plan to offer patients the benefits of delayed high-dose chemotherapy, in reality, this does not always occur. In the published meta-analysis in this issue, 21% of patients receiving bortezomib-based triplets never receive their delayed transplant, and an astonishing 48% of patients never received salvage transplant in the alkylating agent plus lenalidomide subgroup. These findings are not surprising since many patients will relapse with aggressive disease or develop comorbidities that do not allow late transplantation to occur.

When we reviewed our own data on patients that had stem cells collected for salvage transplant, 11% of patients planned for delayed stem cell transplant were unable to undergo the transplant at the time of disease relapse. Therefore, discussion with a patient electing transplantation for a later date is somewhat disingenuous, since a significant proportion will never be able to undergo this life-saving procedure when they do relapse, and this actually leads to a survival disadvantage [12].

Although stem cell transplantation is an intense and aggressive procedure, with current delivery techniques, it should not be considered a treatment to be avoided. Advances in supportive care have now made it a routine ambulatory outpatient procedure [13]. In our own hands, the mortality of early transplantation has been reduced to 0.3%. This mortality includes patients who relapsed and died due to aggressive disease. The median hospital duration at Mayo Clinic is zero days, and only 25% of patients require a hospital stay of five days or greater. Outpatient transplantation with only a fraction being hospitalized makes this a therapy not to be avoided.

Quality of life is also impacted in a stem cell transplant population. Although during the first 60 days, quality of life is inferior, patients recover quickly, and mean scores on social and family wellbeing are significantly higher in a transplant group done as an outpatient compared with inpatients [14]. An improvement in health-related quality of life and pain on long-term follow-up has been noted [15].

The future holds greater promise. The recent publication of daratumumab in newly diagnosed untreated multiple myeloma is encouraging and suggests that four-drug induction of daratumumab-bortezomib-dexamethasone partnered with either thalidomide or lenalidomide or cyclophosphamide are on the horizon.

In conclusion, early stem cell transplantation produces deeper responses, a higher rate of complete responses, and longer progression-free survival. Even without a survival advantage, the improved quality of life, the ability to perform the procedure as an outpatient, and the fact that salvage transplants are not done in up to 48% of patients argues that the standard of care remains early autologous stem cell transplantation and that delayed autologous stem cell transplantation as a clinical choice should be limited to participants in clinical trials. Not offering early autologous stem cell transplantation to transplant-eligible patients does not meet the standard of care, in my opinion.

References

1. Su B, Sheng Z “Autologous transplantation versus novel agent-based therapy for newly diagnosed multiple myeloma.” *Leukemia & Lymphoma* 2018. Publisher needs to insert volume and page numbers when this goes to press).
2. Cavo M, Hájek R, Pantani L, et al. Autologous Stem Cell Transplantation Versus Bortezomib-Melphalan-Prednisone for Newly Diagnosed Multiple Myeloma: Second Interim Analysis of the Phase 3 EMN02/HO95 Study. *Blood*. 2017;130(Suppl 1):397–397. [PubMed: 28576879]
3. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017 2 4;389(10068):519–527. doi: 10.1016/S0140-6736(16)31594-X. PubMed PMID: 28017406; PubMed Central PMCID: PMCPMC5546834. [PubMed: 28017406]
4. Putkonen M, Kairisto V, Juvonen V, et al. Depth of response assessed by quantitative ASO-PCR predicts the outcome after stem cell transplantation in multiple myeloma. *Eur J Haematol*. 2010 11;85(5):416–23. doi: 10.1111/j.1600-0609.2010.01510.x. PubMed PMID: 20722702. [PubMed: 20722702]
5. Mangal N, Salem AH, Menon RM, et al. Use of depth of response to predict progression-free survival in relapsed or refractory multiple myeloma: Evaluation of results from 102 clinical trials. *Hematol Oncol*. 2018 4 19. doi: 10.1002/hon.2514. PubMed PMID: 29672885.
6. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-analysis. *JAMA Oncol*. 2017 1 1;3(1):28–35. doi: 10.1001/jamaoncol.2016.3160. PubMed PMID: 27632282; PubMed Central PMCID: PMCPMC5943640. [PubMed: 27632282]
7. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med*. 2017 4 6;376(14):1311–1320. doi: 10.1056/NEJMoa1611750. PubMed PMID: 28379796. [PubMed: 28379796]
8. Dunavin NC, Wei L, Elder P, et al. Early versus delayed autologous stem cell transplant in patients receiving novel therapies for multiple myeloma. *Leuk Lymphoma*. 2013 8;54(8):1658–64. doi: 10.3109/10428194.2012.751528. PubMed PMID: 23194056; PubMed Central PMCID: PMCPMC3769940. [PubMed: 23194056]
9. Pandya C, Hashmi S, Khera N, et al. Cost-effectiveness analysis of early vs. late autologous stem cell transplantation in multiple myeloma. *Clin Transplant*. 2014 10;28(10):1084–91. doi: 10.1111/ctr.12421. PubMed PMID: 25040732. [PubMed: 25040732]
10. Gertz MA, Lacy MQ, Inwards DJ, et al. Delayed stem cell transplantation for the management of relapsed or refractory multiple myeloma. *Bone Marrow Transplant*. 2000 7;26(1):45–50. doi: 10.1038/sj.bmt.1702445. PubMed PMID: 10918404. [PubMed: 10918404]

11. Kumar SK, Lacy MQ, Dispenzieri A, et al. Early versus delayed autologous transplantation after immunomodulatory agents-based induction therapy in patients with newly diagnosed multiple myeloma. *Cancer*. 2012 3 15;118(6):1585–92. doi: 10.1002/cncr.26422. PubMed PMID: 22009602; PubMed Central PMCID: PMC3262884. [PubMed: 22009602]
12. Kansagra A, Gonsalves WI, Gertz MA, et al. Analysis of Clinical Factors and Outcomes Associated with Nonuse of Collected Peripheral Blood Stem Cells for Autologous Stem Cell Transplants in Transplant-Eligible Patients with Multiple Myeloma. *Biol Blood Marrow Transplant*. 2018 4 12. doi: 10.1016/j.bbmt.2018.04.007. PubMed PMID: 29656139.
13. Khouri J, Majhail NS. Advances in delivery of ambulatory autologous stem cell transplantation for multiple myeloma. *Curr Opin Support Palliat Care*. 2017 12;11(4):361–365. doi: 10.1097/SPC.0000000000000305. PubMed PMID: 28922292. [PubMed: 28922292]
14. Martino M, Ciavarella S, De Summa S, et al. A Comparative Assessment of Quality of Life in Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation Through an Outpatient and Inpatient Model. *Biol Blood Marrow Transplant*. 2018 3;24(3):608–613. doi: 10.1016/j.bbmt.2017.09.021. PubMed PMID: 29032271. [PubMed: 29032271]
15. Chakraborty R, Hamilton BK, Hashmi SK, et al. Health-Related Quality of Life after Autologous Stem Cell Transplantation for Multiple Myeloma. *Biol Blood Marrow Transplant*. 2018 4 4. doi: 10.1016/j.bbmt.2018.03.027. PubMed PMID: 29626515.