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Transplantation for Myeloma — Now or Later?

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The outlook for patients with multiple myeloma has improved dramatically during the past two decades. The median overall survival is now more than 6 years, as compared with an overall survival of 3 to 4 years during the era of treatment with alkylating agents and anthracyclines.[1] This progress resulted from the introduction of new classes of agents (immunomodulatory drugs, proteasome inhibitors, and more recently, monoclonal antibodies) and the intensification of therapy with autologous stem-cell transplantation, as well as incremental improvements that are attributable to refinements of drugs within these same therapeutic classes.

Following the pioneering efforts of Dr. Bart Barlogie,[2,3] multiple randomized trials showed that autologous stem-cell transplantation was associated with improvements in progression-free and overall survival,[4–6] and transplantation is now a recommended consolidation therapy for most medically fit patients up to 70 years of age. With the use of mobilized peripheral-blood stem cells, the duration of severe cytopenias is less than 2 weeks, and transplant-related mortality is approximately 1%. Indeed, at many centers, the entire procedure is done in the outpatient setting.

So, why would it be necessary to conduct another randomized trial in which transplantation is compared with other therapies? The combination of immunomodulatory drugs and proteasome inhibitors is associated with high response rates similar to those achieved with transplantation, whereas previous trials had used less effective chemotherapy regimens as comparators.[7] The Intergroupe Francophone du Myélome (IFM) 2009 trial, which is the latest in a series of influential transplantation studies from the IFM,[4,5,8] therefore addresses a current and clinically relevant question, which contrasts somewhat with the less clinically relevant designs of some randomized trials that were aimed at the approval of newer agents for patients with more advanced myeloma. The results of the IFM 2009 trial are reported by Attal et al. in this issue of the *Journal*.[9]

In the IFM 2009 trial, the planned treatments were realistic. Approximately 90% of patients in the two treatment groups completed the assigned induction therapy with three cycles of RVD (lenalidomide, bortezomib, and dexamethasone) and then consolidation therapy with either five additional cycles of RVD (in the RVD-alone group) or high-dose chemotherapy plus stem-cell transplantation followed by two additional cycles of RVD (in the transplantation group). Patients in both groups received maintenance therapy with

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lenalidomide for 1 year. Salvage transplantation was recommended at the time of disease progression, and remarkably, 136 of the 207 patients in the RVD-alone group who had disease progression underwent the specified transplantation. The cumulative incidence of disease progression at 4 years was lower in the transplantation group than in the RVD-alone group (approximately 49% vs. 65%), and 59% of patients in the transplantation group versus 48% in the RVD-alone group achieved a complete response.

A question remains as to whether all patients with multiple myeloma should undergo immediate autologous stem-cell transplantation, since the use of delayed transplantation resulted in similar overall survival, with some patients not needing transplantation to date. The observed lack of a survival benefit for early transplantation was consistent with previous results that suggested salvage transplantation is an equalizer in this regard.[10] It is notable that patients in whom minimal residual disease was not detected by means of flow cytometry (which has a sensitivity of 10^{-4}) had better outcomes than those in whom minimal residual disease was detected; however, 50% of the patients in whom minimal residual disease was not detected have had progression to date. More sensitive tests for minimal residual disease may prove to be more discriminating. With no suggestion of a plateau on the progression-free survival curves, it appears that even in combination with the most effective induction and maintenance therapies, autologous stem-cell transplantation is not a curative therapy for multiple myeloma.

Transplantation also had some consequences. Four cases of acute myeloid leukemia occurred in the transplantation group versus one in the control group, and the incidence of acute myeloid leukemia is likely to increase, since therapy-related acute myeloid leukemia–myelodysplastic syndrome continues to occur up to 10 years after transplantation. It is likely that maintenance lenalidomide also contributes to the risk of this disease.

The overall cost of treatment is also a consideration. The price of 1 year of maintenance lenalidomide is more than $120,000 in the United States; it is perhaps lower in other countries with more thoughtful and competitive pricing programs but is still formidable. An ongoing U.S. trial (ClinicalTrials.gov number,) that was prospectively planned as a companion to the IFM 2009 trial has a nearly identical design, except that maintenance lenalidomide is being administered until myeloma progression. The combined results of the two trials will be of interest, particularly within biologically defined risk groups and among patients in whom minimal residual disease is not detected. The added “value” of extended maintenance therapy will be dubious unless an improvement in overall survival is established. Given the prices of the new drugs, the price of transplantation, which was once considered to be prohibitively expensive, now represents a relatively small part of the overall monetary cost of the treatment program.

In summary, transplantation resulted in a deeper and longer initial treatment response than did a nontransplantation approach. However, the benefits of transplantation were more modest than some might have hoped, and it did not appear to be curative. While some questions about initial therapy remain unanswered, we owe a big “merci” to the IFM investigators for the important issues addressed in this study.

References

1. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2014; 28: 1122–8. [PubMed: 24157580]
2. Barlogie B, Hall R, Zander A, Dicke K, Alexanian R. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. Blood 1986; 67: 1298–301. [PubMed: 3516252]
3. Jagannath S, Vesole DH, Glenn L, Crowley J, Barlogie B. Low-risk intensive therapy for multiple myeloma with combined autologous bone marrow and blood stem cell support. Blood 1992; 80: 1666–72. [PubMed: 1391937]
4. Attal M, Harousseau J-L, Stoppa A-M, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996; 335: 91–7. [PubMed: 8649495]
5. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m^2 melphalan and 8 Gy total body irradiation plus 140 mg/m^2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. Blood 2002; 99: 731–5. [PubMed: 11806971]
6. Child JA, Morgan GJ, Davies FE, et al. High-dose chemo-therapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003; 348: 1875–83. [PubMed: 12736280]
7. 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; 389: 519–27. [PubMed: 28017406]
8. Attal M, Harousseau J-L, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003; 349: 2495–502. [PubMed: 14695409]
9. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med 2017; 376: 1311–20. [PubMed: 28379796]
10. Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood 1998; 92: 3131–6. [PubMed: 9787148]