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The Bottom Line

Think Twice: Doubling Back to Tandem Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma with Extramedullary Disease

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The advent of high-dose therapy with autologous stem cell transplantation (ASCT) heralded improved progression-free (PFS) and overall survival (OS) along with increased depths of response, and now, 3 decades after its arrival for multiple myeloma, the optimal utilization of this tool continues to be refined. In newly diagnosed transplant eligible patients, high-dose melphalan (MEL) continues to play an additive role in combination with highly active triplet regimens as recently demonstrated in the phase 3 FORTE trial. In the carfilzomib, lenalidomide, dexamethasone (KRd) for 12 cycles followed by lenalidomide maintenance arm, early relapse at <18 months from randomization was 17% compared with 8% in the KRd induction plus MEL 200-mg/m^2 and KRd consolidation arm (P = .015). Importantly, the benefit of KRD + ASCT was most pronounced in Revised-International Staging System stage II/III patients [1].

Raising dose intensity through use of double or tandem transplantation with high-dose melphalan was introduced before the era of novel agents, and several phase 3 studies demonstrated a PFS benefit and some an OS benefit, especially in patients achieving less than very good partial response (VGPR) after the first transplant [2]. Two contemporary phase 3 studies evaluating the role of tandem transplantation with high-dose melphalan following induction therapy reached differing conclusions, and uncertainty remains regarding which groups of patients benefit from tandem transplantation in an era of highly active induction regimens such as bortezomib/lenalidomide/dexamethasone (VRd) or KRd. The EMN02/HO95 study reported that double transplant compared with single transplant with MEL 200 mg/m^2 resulted in significant prolongation of 3-year PFS at 73% versus 64% (hazard ratio [HR], 0.7; P = .04) and 3-year OS at 89% versus 82% (HR, 0.52; P = .011) [3]. In contrast, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0702 trial found that tandem ASCT or consolidation following induction and a single transplant with MEL 200 mg/m^2 provided no additional PFS or OS benefit [4]. Subgroup analyses from studies evaluating tandem transplantation suggest high-risk subgroups, including patients failing to achieve ≥VGPR after single autologous stem cell transplant (ASCT1), International Staging System (ISS) stage II/III, and high-risk cytogenetics, may benefit most from tandem transplantation. From the pooled analysis of phase 3 studies using induction with bortezomib/thalidomide/dexamethasone (VTd) or bortezomib/doxorubicin/dexamethasone with prespecified randomization to single or double transplantation, Cavo et al. [5] reported improved PFS and OS with double transplantation. In a high-risk group with ISS stage II/III, high-risk cytogenetics, and failure to achieve CR after ASCT1, median PFS was 35 months with tandem autologous stem cell transplant (ASCT2) compared to 14 months with ASCT1 (HR, 0.45, P = .008) and 10-year OS probability was 26% in the ASCT2 group compared with 6% with ASCT1 (HR, 0.44; P = .025).

Gagelman and colleagues [6] in this issue describe the baseline characteristics and cytogenetic risk profile of 488 newly diagnosed patients with multiple myeloma from the European Group for Blood and Marrow Transplantation registry with extramedullary disease (EMD) and evaluate the role of single and double transplantation as well as autologous/allogeneic transplant. Forty-one percent of the patients harbored high-risk cytogenetic abnormalities at diagnosis, comprised primarily of del17p. Tandem transplantation was associated with prolonged 4-year PFS of 45% in high-risk cytogenetics patients compared with 22% with single ASCT, as well as improved 4-year OS of 84% versus 41% in the single ASCT patients (P< .001). In the tandem ASCT and auto/allo treatment arms, high-risk and standard-risk cytogenetics patients experienced equivalent PFS and OS at 4 years, whereas in the single-transplant arm, 4-year OS and PFS were significantly lower in the high-risk cytogenetics group. PFS and OS outcomes in the auto/allo group were not significantly differently from the auto/auto group, but the limited sample size in the auto/allo group (n = 31) requires caution in interpreting the role of this therapy from these data. Several limitations of the study should be noted, including the absence

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of data on maintenance therapy, salvage treatment, or details on induction therapy beyond whether bortezomib was used or not (73% versus 27%, respectively). Future prospective studies would benefit from minimal residual disease (MRD) and positron emission tomography/computed tomography assessments to gain additional response information following single or double transplantation or autologous/allogeneic transplantation.

The authors in this analysis provide evidence supporting the use of tandem transplantation based on improved survival outcomes in this challenging but growing cohort of high-risk newly diagnosed patients with myeloma with EMD. Despite improved outcomes with tandem compared with single ASCT with MEL 200 mg/m^2, 55% of these patients relapsed by 4 years, demonstrating the need for further optimization of therapy. PFS in this population improved over time, from 33% before 2009 to 49% after 2012, likely reflective of progress in induction and maintenance strategies over time. The addition of daratumumab to the current induction regimens of VTd in the phase 3 CASSIOPEIA trial, VRd in the phase 2 GRIFFIN study, or KRd in the phase 1b MMY1001 resulted in increased depth of response and MRD negativity rates of 50% to 63% postconsolidation [7]. Further investigation is needed to determine if MRD negativity retains its prognostic significance in extramedullary disease or can be used for risk stratification of MRD-positive patients with EMD. Additionally, modification of the standard MEL 200-mg/m^2 conditioning regimen is being explored, including busulfan plus melphalan, which resulted in the prolongation of median PFS to 64.7 months compared with 43.5 months in the MEL 200-mg/m^2 group (HR, 0.53; $P = .022$), although rates of grade 2 to 3 mucositis were significantly higher in the experimental arm. Whether tandem autologous transplantation will continue to provide benefit in this high-risk population with EMD in an era of highly active induction regimens, cellular therapeutics, and effective maintenance therapy is an open question, but Gagelmann and colleagues [6] have provided evidence that outcomes with tandem transplant are superior to standard induction and a single transplant alone and should be weighed as an option factoring in patient and disease characteristics, trial availability, and access to active triplet and quadruplet induction regimens.

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