Myelodysplastic Syndrome After Autologous Transplant for Lymphoma

To the Editor:

Certain aspects of the article by Miller et al1 reporting myelodysplastic syndrome (MDS) after autologous stem cell transplant for lymphoma and the accompanying editorial by Stone2 deserve comment. Miller et al estimated the cumulative incidence of MDS as 14.5% at 5 years after autologous transplant for lymphoma using the method of Kaplan and Meier. The Kaplan-Meier analysis of these data may not be appropriate, because it assumes that the risk of MDS for censored patients after relapse or death would be the same as that for those patients followed beyond their time of censoring had they not been censored, an assumption that is untestable. Alternative analysis strategies not requiring such assumptions are available.3 We do not understand the authors’ choice of censoring patients at relapse after transplant. Although therapy after relapse may add to the MDS risk, so obviously may the therapies that patients receive before their high-dose therapy and stem cell rescue.

Assessment of MDS risk after transplantation for lymphoma that does not analyze Hodgkin’s disease (HD) and non-Hodgkin’s lymphoma (NHL) patients separately may obscure important risk factors. HD patients, treated initially and/or at first relapse with MOPP or MOPP-variants, are known to be at a significant risk for secondary MDS.4 However, as Dr Stone noted, standard therapies for the treatment of aggressive NHL are thought to carry little risk for secondary MDS.5 Therefore, although we agree with Dr Stone that much of the MDS diagnosed in HD patients can be attributed to prior exposure to alkylators (especially nitrogen mustard and/or chlorambucil) and procarbazine, another explanation is required for MDS in NHL patients. We have not identified an increased risk of MDS in NHL patients with the use of peripheral blood stem cells (PBSC) as the infusion product use for NHL patients. The risk is estimated to be zero for all NHL patients not receiving TBI and did not differ by rescue product in those receiving TBI (4/56 NHL patients receiving bone marrow vs 2/49 receiving PBSCs, P = .42). It is possible that the association between the risk of PBSCs and MDS risk seen by the authors resulted from their more frequent use of PBSCs following TBI containing preparatory regimens. In summary, we believe that the MDS risk after autologous transplant for NHL is primarily a result of cell damage caused by TBI and that this risk is absent following allogeneic transplant because of a “graft-versus-damaged host cells” effect which does not occur after autographs.

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REFERENCES


Response

We agree with Dr Anderson et al that the data may have been presented without censoring patients at relapse because they were still at risk of developing myelodysplastic syndrome (MDS) after transplant. In the initial draft of this manuscript we presented the incidence calculations in this manner. However, the change in presentation was made in response to the reviewers who felt that relapsed patients who required additional therapy obscured the statistical relevance of these findings. Without censoring at relapse, the Kaplan-Meier estimated incidence of MDS after autologous transplantation for lymphoma (n = 9) of all patients at risk (n = 206) between 1974 and 1993 would be 16.7% ± 12.6% at 5 years (the number of patients alive and at risk without MDS was 65 at 2 years and 41 at 4 years). The incidence was similar (P = .77) for patients with Hodgkin’s disease (HD) (4 of 66; 14.3% ± 14%) and non-Hodgkin’s lymphoma (NHL) (5 of 138; 19.3% ± 21%). These estimates do not differ from those published and do not alter any of our stated conclusions.

As mentioned by Drs Stone and Anderson et al, the therapy most implicated in induction of MDS in these complex patients is difficult to discern and we are unable to distinguish with precision the risk attributable to the preparative regimens from the confounding variables of other (nontransplant) radiation and chemotherapy. The association of MDS after therapy for HD is well described. For patients transplanted with NHL, it is intriguing that three of the four MDS patients who had received no prior radiation therapy and who were conditioned with cyclophosphamide (Cy) and total body irradiation (TBI) had earlier received only 6, 7, and 10 months of standard chemotherapy, which should carry only minimal risk of MDS. Yet these patients developed MDS at 8, 9, and 34 months after transplant (1.5, 1.8, and 4.8 years after the initial diagnosis of their NHL).
suggesting that the preparative regimen may have been the major contributor to the secondary MDS. However, the precise risk of Cy/TBI can only be addressed by an analysis including more patients or in a randomized trial compared with non-TBI conditioning. At our institution, all NHL patients regardless of stem cell source receive Cy/TBI unless they have received prior radiation which precludes TBI. Therefore, the independent risk of the preparative regimen cannot be assessed in our cohort of patients.

Also included in our original report (at the reviewer’s request), was the surprising apparently increased risk of MDS when peripheral blood stem cells (PBSC) (5 of 43 patients) were used as the infusion product compared with bone marrow harvest (4 of 156 patients). As mentioned in the discussion of the manuscript, this finding is inconclusive because the number of patients was small and reflects, in part, the assignment of higher-risk patients to PBSC collection (ie, those patients who had prior pelvic irradiation or had residual marrow involvement at the time of stem cell collection). Only formal comparative trials will determine if stem cell source contributes additional independent risk to the development of MDS. Lastly, the editorial by Dr Stone and comments by Dr Anderson et al further corroborate our findings that treatment-induced MDS is an important and frequent complication after potentially curative autologous transplantation for lymphoma and highlights therapeutic issues that should be addressed in clinical decision-making and in future clinical trials.

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