

LETTER TO THE EDITOR

Conditioning regimens for ALL allografts

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In reply to the comments of Marks *et al.* regarding our recent publication,¹ we provide the following clarification.

We are aware of the large Center for International Blood and Marrow Transplant Research (CIBMTR) study for adult and pediatric acute lymphoblastic leukemia (ALL) examining different doses of total body irradiation (TBI) along with cyclophosphamide or etoposide (VP16) as conditioning regimens.² However, our study was submitted before their publication and therefore their larger study was not cited in our reference list. We appreciate the comments from Dr Marks highlighting some subtle issues regarding this very important subject. In the CIBMTR study that looked only at sibling allografting, there was an advantage for recipients of higher dose of TBI (≥ 13 Gy) or recipients of VP16 compared to cyclophosphamide in advanced disease. In agreement with the CIBMTR results, in our study there was a trend towards more relapse for children conditioned with cyclophosphamide receiving matched sibling allografts compared to VP16 (65 vs 41%, $P=0.2$) with a comparable probability of acute and chronic graft-versus-host disease (GVHD), Tables 2 and 3.¹ Nonetheless, for unrelated allografts recipients, the effect was the opposite with less relapse and more probability for acute and chronic GVHD in the cyclophosphamide group compared to the VP16 group resulting in better 3-year event-free survival for the cyclophosphamide group compared to the VP16 group (64 vs 49%), Tables 2 and 3.¹ It is difficult to extract conclusions from nonsignificant values. However, these trends may suggest that there are subtle differences between the two most commonly used conditioning regimens for ALL and perhaps we should consider studying the effect of different conditioning regimens depending on disease stage and donor source, and not to use a uniform regimen for all patients. VP16 is well known for its antileukemic effect, and when utilizing sibling donors there is less GVHD/graft-versus-leukemia (GVL) effect, therefore, VP16 may be of choice in this scenario particularly in advanced disease. On the other hand, cyclophosphamide is well known for its immunosuppressant effect and may be of choice when utilizing unrelated donors to enhance engraftment and maximize

GVHD/GVL effect from the unrelated graft. We agree that the CIBMTR study is larger and there was an opportunity to examine the effect of different TBI doses on outcome both in children and adults but our smaller pediatric only study has its own merits. In particular, it is a single institution study where there is uniform stem cell and radiation technology, donor selection including human leukocyte antigen typing, GVHD prophylaxis and treatment and supportive care compared to the CIBMTR study where eligible cases came from 111 reporting teams with a trend towards center effect ($P=0.07$) and almost all recipients of VP16 and TBI (≥ 13 Gy) came from one center. In addition, with this more intensive conditioning regimen, transplant-related mortality was the least in that particular center. Finally, we agree that to address the issue of which is the best conditioning regimen for pediatric and adult ALL, a randomized trial is warranted as suggested at the end of the CIBMTR study. We have to acknowledge, that both VP16 and cyclophosphamide along with TBI were used for the last 20 years as conditioning regimens for ALL with somewhat stable outcome and both have not improved survival significantly over the years. It is probably worthwhile investigating new novel agents in the conditioning regimens especially for those with advanced disease.

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- 2 Marks DI, Forman SJ, Blume KG, Perez WS, Weisdorf DJ, Keating A *et al.* A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. *Biol Blood Marrow Transplant* 2006; 12: 438–453.