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Reply to N.-K.V. Cheung et al

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The randomized trial reported by Matthay et al¹ used event-free survival (EFS) as the primary end point, which has been sustained as significant even in an unplanned later long-term follow-up: 5-year EFS for autologous bone marrow transplant (ABMT), 30%; chemotherapy consolidation, 19% ($P = .04$).^{1,2} Although overall survival (OS) was not statistically significant, in the analysis of all four randomized arms, 5-year OS for ABMT with isotretinoin was higher than both non-ABMT arms ($P = .054$; Fig 4B¹), even though this was an unplanned analysis for these subgroups.¹ As noted by Cheung et al,³ the only two additional randomized trials showed a significant advantage for ABMT over conventional chemotherapy.^{4,5} It is noteworthy that the Children's Cancer Group trial used an intensive chemotherapy comparison arm to ABMT with similar hospitalization days, death related to toxicity rate, and second malignancy, and still showed a significant advantage in EFS for the ABMT arm.²

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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As with any reported randomized trial, new therapies emerge, and it is possible that in the future a superior induction therapy incorporating new biologic agents will supersede the need for the myeloablative chemotherapy with hematopoietic stem-cell transplant (HSCT) that is the current standard. The most recent published results from the Children's Oncology Group (COG) with deletion of the use of total-body irradiation and use of autologous peripheral blood stem cells rather than bone marrow reported 5-year EFS 38% from diagnosis (OS: 50%).⁶ Thus, the EFS and OS for children with high-risk neuroblastoma enrolled on COG trials continue to show improvement correlated with the incorporation of HSCT. The randomized trial adding anti-GD2 antibody for therapy of minimal residual disease then further significantly improved the EFS of patients undergoing transplant compared with the use of isotretinoin alone. Longer follow-up is needed to determine effect on OS.

As Cheung et al³ noted, delaying time to relapse (EFS) is important if long-term quality of life is improved and late toxicities are lessened; otherwise, overall survival is the ultimate goal. New approaches with targeted therapy not available when this study was done have made delay of mortality possible, though often this requires multiple hospitalizations, travel to centers with available treatments, adverse effects, and ultimately death.

It is true that EFS is a surrogate end point but was agreed on as a valid primary end point in multiple cooperative trials as a result of the long follow-up required for overall survival (OS) and on the basis of inevitable later mortality from recurrent tumor or second malignancy. Using EFS as the primary end point allows for more efficient study designs in a rare orphan disease, where a minimum of 5 years' accrual is sufficient to produce enough patients and events to answer the primary objective; however, this still requires a large EFS difference. For OS, more patients would be required to observe enough deaths, such that 10 years of accrual might be necessary to answer an OS question. Attaining a better EFS also will obviate the need for including rescue therapy, which entails more treatment with more late effects and usually ultimate demise, as there are few children with neuroblastoma who are cured of their relapsed disease.

Disease monitoring on a regular basis is necessary to determine EFS, whereas for OS all that is needed is a death date. However, in the trials reported from the COG, patients were monitored with regular I-123-metaiodobenzylguanidine scan and computed tomography scans and urinary catecholamines (every 3 months for 2 years, then every 6 months for 2 years, then every year for 2 years) for 6 years from completion of therapy. A comprehensive panel of testing for late effects (cardiac, pulmonary, neurologic, endocrine, immunologic, second malignancy) was recommended. Therefore, it is unlikely that there was any bias toward more monitoring of the group randomly assigned to no transplant.

In summary, constant re-examination of what is standard of care is required, given the rapidly evolving therapeutic landscape. Most importantly, only carefully designed randomized trials can answer this question. These have established to date that high-dose therapy with HSCT, followed by therapy for minimal residual disease with isotretinoin and anti-GD2 antibody, have provided the best outcome for children with high-risk neuroblastoma, and the international consensus remains that this strategy improves EFS.⁷

However, it is also clear that ongoing intense research efforts in the immunogenomics of neuroblastoma may lead to novel therapies with significant impacts on outcome. Continuing to improve EFS with incorporation of new, more specific treatments will be the key to fewer long-term sequelae and ultimately better survival and quality of life.⁸

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