Editorial

A bridge over troubled water—Extending induction for high-risk neuroblastoma patients with poor end-of-induction response

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Although the intensification of therapy, including induction,[1] consolidation,[2,3] and postconsolidation,[4] has advanced the cure rate of patients with high-risk neuroblastoma, approximately half of these patients die of the disease.[3] Despite these therapeutic advances, patients who have a poor end-of-induction (EOI) response still have a poor prognosis. Pinto and colleagues[5] performed a retrospective analysis evaluating more than 1200 patients from 4 consecutive Children's Oncology Group (COG) high-risk neuroblastoma trials (A3973, ANBL02P1, ANBL0532, and ANBL12P1). In their analysis, an EOI response less than a partial response (PR) was associated with significantly lower 3-year event-free survival (21% vs 54%; $P < .0001$) and 3-year overall survival (46% vs 73%; $P < .0001$). Although these data provided valuable insight into the prognosis of patients with a poor EOI response, the field has been plagued by a paucity of data describing the clinical courses of poor EOI responders, including subsequently administered treatments. Furthermore, little is known about patients enrolled in clinical trials who discontinue the protocol therapy because of a poor EOI response and/or receive therapy outside a clinical trial.

Understanding the clinical course of patients with a poor EOI response is especially critical in the modern era of targeted therapy[6,7] and successful chemoimmunotherapy.[1,8,9] ^{131}I-metaiodobenzylguanidine (MIBG) with or without chemotherapy has demonstrated an objective response rate of approximately 15% to 30% in patients with recurrent or refractory (RR) disease.[6] More recently, chemoimmunotherapy using a combination of an anti-GD2 monoclonal antibody and different chemoimmunotherapeutic regimens in the RR neuroblastoma population has demonstrated the most robust response rates to date.[8,9] In the largest study (ANBL1221), patients with RR neuroblastoma who were randomized to treatment with dinutuximab, irinotecan, and temozolomide had an objective response rate (PR or better) of 53%.[10] The trial expanded accrual to better evaluate the response rate and toxicity profile of this combination. In the combined chemoimmunotherapy cohorts, a 41.5% response rate was observed; this included a 32.3% response rate for patients with refractory or progressive disease.[9] The results of this trial led to a shift in clinical practice to administer dinutuximab, irinotecan, and temozolomide as a standard of care for patients with refractory disease with the goal of "getting them back on track" and proceeding to tandem autologous stem cell transplantation (ASCT), albeit without data demonstrating that this improves outcomes.

In their article titled "Efficacy of Post-Induction Therapy for High-Risk Neuroblastoma Patients With End-Induction Residual Disease," Desai and colleagues[11] retrospectively assess the clinical course and outcomes of patients treated at 6 large pediatric centers who had an EOI response of PR or worse. Specifically, they evaluated patients with EOI residual disease who received "bridge therapy" before receiving consolidation (high-dose chemotherapy followed by ASCT) and compared them with a group of patients who did not receive bridge therapy. Bridge therapy most often included chemoimmunotherapy or MIBG therapy.

For Desai et al's analysis,[11] the patients were divided into 3 cohorts: 1) no bridge therapy before ASCT, 2) bridge therapy before ASCT, and 3) bridge therapy without ASCT. Not surprisingly, the groups were skewed, with a higher percentage of patients who received bridge therapy having had a worse EOI response in comparison with cohort 1 patients

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A subset of patients with high-risk neuroblastoma who have a poor end-of-induction response may benefit from receiving chemoimmunotherapy as bridge therapy before consolidation. Prospective studies evaluating this therapeutic approach and improved identification of biomarkers of response are warranted.

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(who did not receive bridge therapy). Interestingly, although Pinto et al's data would suggest that cohorts 2 and 3 should, therefore, have had worse outcomes because of the disproportionate number of patients with an EOI response worse than a PR, Desai et al demonstrated that patients in cohort 2, who received bridge therapy before consolidation, had outcomes similar to those of the patients in cohort 1. Furthermore, those patients who were able to achieve a metastatic complete response (CR) had a statistically significant improvement in outcomes in comparison with those with EOI metastatic stable disease who did not receive bridge therapy. This suggests that a subset of patients may benefit from additional therapy before ASCT with the goal of achieving an improved metastatic response before consolidation.

It is difficult to draw significant conclusions from the patients included in cohort 3, who received bridge therapy but did not undergo ASCT. As the ANBL0532 study demonstrated, some patients with high-risk neuroblastoma who had an EOI response of PR or worse ultimately had improved outcomes related to ASCT.[3] Thus, it is not entirely surprising that the patients included in cohort 3, who did not receive ASCT, had inferior outcomes in comparison with cohorts 1 and 2. However, a small subset of patients treated in cohort 3 who achieved a metastatic CR after bridge therapy remained alive as of their last follow-up. This highlights the necessity of further evaluating data from multi-institutional and cooperative group trials to better identify which patients with high-risk disease may achieve excellent outcomes without the need for ASCT. This is a critical question that the field will need to address in the future.[12] Furthermore, it highlights the need for the identification of better biomarkers of response in neuroblastoma assessments.

Prior studies from North American and European cooperative groups have analyzed the prognostic value of EOI Curie scores and concluded that patients with EOI Curie scores >2 and International Society of Paediatric Oncology European Neuroblastoma Group MIBG skeletal scores >3 have inferior outcomes.[13,14] However, nearly all of the patients included in these prior analyses were treated without postconsolidation immunotherapy. Thus, the optimal EOI Curie cut point in the context of modern high-risk neuroblastoma therapy remains unknown. Desai and colleagues[11] did not provide data on EOI Curie scores; rather, they analyzed patients with the International Neuroblastoma Response Criteria (INRC).[15] Although their data are compelling, we caution clinicians against continuing to treat patients until they achieve a metastatic CR without additional prospective studies to validate this approach. The Desai dataset included very few patients (7%) with EOI stable disease, so it is not clear that the "metastatic CR bar" can be applied to all patients with an EOI response worse than a PR. This approach may delay consolidation and/or could lead to overtreatment and increased toxicity without additional improvements in outcomes. Future prospective studies analyzing the overall INRC response, including individual INRC response components (metastatic soft tissue and bone, primary site, and bone marrow response), and EOI Curie scores in a modern cohort of patients with high-risk neuroblastoma are needed.

Despite extensive efforts to identify biomarkers of response to guide therapeutic changes, the neuroblastoma community still lacks a robust method for identifying which patients are likely to fail treatment and, importantly, which patients can potentially be salvaged. Known variables, including age, stage, *MYCN* amplification, and segmental chromosomal aberrations, are prognostic and are included in risk classification.[16] However, unlike the evaluation of minimal residual disease in the treatment of acute lymphoblastic leukemia,[17,18] less is known about molecular biomarkers of neuroblastoma response to guide real-time treatment modification. Although preliminary data for candidate biomarkers such as telomere maintenance mechanisms, circulating tumor DNA, and circulating GD2 suggest that these factors are important, further study of these biomarkers in the context of modern high-risk neuroblastoma therapy is needed before they can be incorporated.[19–21] Future studies should evaluate whether these biomarkers can be used as standalone predictors of outcome and/or used in combination with other clinical factors and response.

Desai and colleagues[11] provide strong retrospective data that support the need to evaluate bridge therapy using chemoimmunotherapy in future studies for patients who experience a poor EOI response to standard induction chemotherapy. These studies should be designed in a way that keeps patients who receive bridge therapy on study. Furthermore, prospective studies should implement detailed data collection tools to better evaluate patients who come off protocol therapy so that outcomes for this patient population can be accurately described in the future.

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