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The Combination of Monoclonal Antibodies and Conventional Chemotherapy for Children with Malignant Lymphoma: Opportunities and Challenges

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Introduction

The improvement in treatment outcome for children with high grade B-cell lymphomas is largely the result of refinements in intensive contemporary risk-based therapy. (1–3) The prognosis for patients who relapse after being treated with such intensive primary therapy is generally poor and active salvage regimens are clearly needed. Specifically, these regimens could include new active cytotoxic agents, antibodies, and small molecule inhibitors - ideally in combinations with synergistic activity and non-overlapping toxicity.

Regimen summary

Griffin et al. have described in this issue of *Pediatric Blood & Cancer* a novel salvage regimen (RICE) which features both a dose intensification of the ICE regimen (ifosfamide, carboplatin and etoposide) as well as incorporation of the anti-CD20 antibody, Rituximab(4). The use of ICE is based on the activity of this combination in pediatric NHL reported by Kung et al., although its activity against specific histologic subtypes was not described in the initial report. (5) Rituximab was incorporated because of its activity against other mature B-cell neoplasms and reports of improvements in treatment outcome in patients receiving this agent. For example, Rituximab combined with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) resulted a superior outcome compared to CHOP alone in adult patients with diffuse large B-cell lymphoma.(6,7) Similar survival advantages have been reported with its use in adults with follicular lymphoma.(8) Rituximab is likely to be active in patients with Burkitt lymphoma; however, there are relatively little direct clinical data to support this. As Griffin points out, there have been case reports of Rituximab's activity in children with relapsed Burkitt lymphoma/leukemia and mediastinal large B-cell lymphoma. (9,10) Additionally, the authors of a study done at MD Anderson in adults with Burkitt lymphoma treated with Rituximab combined with Hyper-CVAD suggested an improvement in outcome compared to historical controls treated with Hyper-CVAD alone. (11)

Griffin et al. report an encouraging treatment response and outcome for this high risk group of patients when treated with RICE. Therefore, RICE represents an active salvage regimen which should be considered in patients with recurrent high grade B-cell lymphoma and will likely serve as a standard to which other salvage regimens for children with high grade B-cell lymphoma are compared.

Although it is likely that Rituximab contributed to the response and outcome reported, the lack of a Rituximab randomization or an upfront window component in the study design

makes it difficult to definitively establish Rituximab's role in treatment outcome with the RICE regimen. Nevertheless, the documentation of the activity and safety of this multi-agent regimen in children with recurrent or refractory high grade B-cell lymphoma is noteworthy.

Future opportunities and challenges in the use of monoclonal antibodies

1) Establishing the activity and safety of new antibodies

Antibodies that have been shown to be active in adult hematopoietic malignancies have naturally sparked interest in their potential use in children. As these agents are explored in clinical trials, investigators and families need to be cognizant of not only the potential benefits, but also the potential risks which could include the reactivation of viral infections(12) or in very rare cases, the potential development of a second malignancy(13). In this regard, Griffin and co-investigators screened patients for hepatitis B carrier status to reduce the chance of putting carriers at risk for reactivation.

The activity and toxicity of forthcoming monoclonal antibodies should be determined in children, both as a single agent and in combination with established cytotoxic agents. There may be additive or synergistic activity when the antibody is used in combination with chemotherapy. Additionally, there may be a different scope and/or degree of toxicity encountered when the antibody is combined with chemotherapy as compared to toxicity associated with either the antibody or chemotherapy alone.

The authors have established an important model for the combination of active conventional cytotoxic agents with an active monoclonal antibody, on which future regimens will certainly build. For example, the development of a new anti-CD30 antibody(14), which has been shown to be active in adults with anaplastic large cell lymphoma (ALCL),(15) is currently being evaluated in a 4 week single agent window phase and subsequently in combination with ICE (same doses as used in Griffin's study) in children with ALCL in first or second relapse.

2) Improvement in frontline treatment outcome

Active immunotherapeutic agents will not only be helpful for children with high risk recurrent disease, but may also be considered for incorporation into treatment regimens for newly diagnosed patients. In this regard, the Children's Oncology Group is piloting studies which incorporate Rituximab into LMB-96 therapy(1). Preliminary results of the combination of LMB-96 Group B chemotherapy and Rituximab are promising, with excellent outcome and tolerability (Dr. Stanton Goldman, personal communication)(16). The Berlin-Frankfurt-Munster (BFM) consortia is currently conducting a trial in which newly diagnosed patients with high grade B-cell lymphomas non-randomly receive Rituximab in an upfront window before starting conventional chemotherapy (Prof. Dr. Alfred Reiter, personal communication). The two aforementioned trials will provide both feasibility data and in the case of the BFM trial, single agent Rituximab activity data; however, randomized trials should be considered to more clearly establish the therapeutic role of Rituximab in the context of conventional aggressive B-cell lymphoma chemotherapy. One of the major challenges, however, in the development of a randomized trial pertains to the statistical aspects of the study design. Can enough patients be accrued to demonstrate a significantly improved outcome with the use of Rituximab? An international study may be required.

3) Reduction of concerning late effects in current therapies

The goals of incorporating novel immunotherapeutic agents into primary treatment regimens for children with hematopoietic malignancies include both that of improving disease free

survival as well as potentially reducing or eliminating the incorporation of agents with worrisome late effects. For example, the increased risk for cardiotoxicity and infertility associated with high cumulative doses of anthracyclines and alkylators, respectively, may be reduced if antibody therapy can be safely substituted for these agents. Several challenges exist with respect to design of these trials. From a statistical standpoint, it may be very difficult to accrue enough patients to demonstrate in a randomized trial that these substitutions can be safely made in patients who have an excellent prognosis when treated with conventional therapy. Another challenge pertains to the risk:benefit ratio. Specifically, for highly curable patients whose prognosis becomes very poor in the setting of recurrent disease, the potential benefit of reducing chemotherapy associated late effects must be carefully weighed against the potential risk of reducing survival.

Conclusions

Exciting opportunities to improve treatment outcomes for children with hematopoietic malignancies through the incorporation of monoclonal antibodies into existing chemotherapy regimens lie ahead for pediatric oncologists. The study by Griffin et al. is important not only because of the activity and toxicity data provided, but also because of the paradigm change it represents. Children deserve the opportunity to receive novel targeted therapies, whose activity and safety is studied in prospective clinical trials.

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