

● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Gerrard et al, page 278

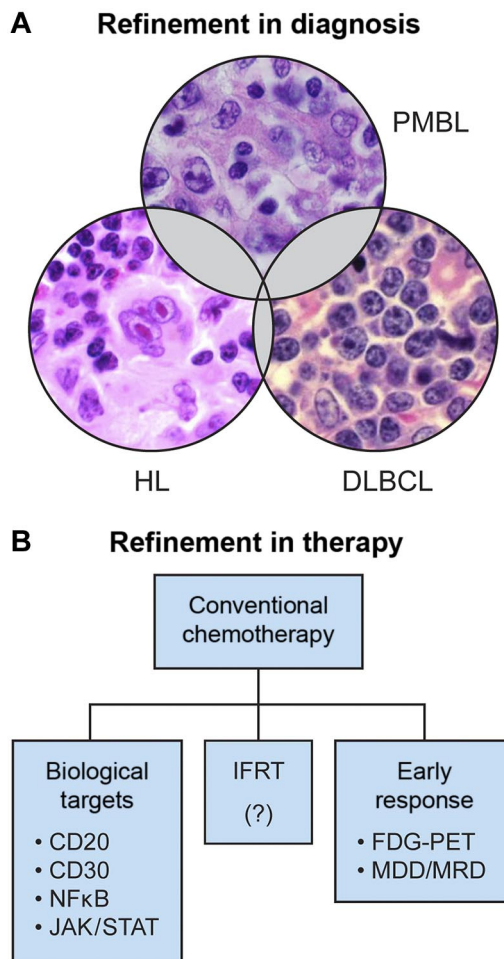
## Pediatric MBL: challenges remain

John T. Sandlund<sup>1</sup> and John Kim Choi<sup>1</sup> <sup>1</sup>ST JUDE CHILDREN'S RESEARCH HOSPITAL

In this issue of *Blood*, Gerrard et al report the outcome and histologic classification of children and adolescents with mediastinal large B-cell lymphoma (MLBL), and highlight the need for new treatment strategies.<sup>1</sup>

Improvement in the treatment outcome for children and adolescents with high-grade mature B-cell lymphomas (eg, Burkitt lymphoma [BL]; diffuse large B-cell lymphoma [DLBCL]) is one of the undisputed success stories in pediatric oncology.<sup>2-5</sup> However, in contrast to the other B-cell histologic subtypes, MBL remains a significant challenge. Despite receiving intensive multiagent chemotherapy, approximately one-third of children and adolescents have either recurrent or refractory disease. This point is clearly made by Gerrard and colleagues, who report a 5-year event-free survival (EFS) rate of 66% for stage III patients with MBL compared with 85% for those with stage III non-MLBL DLBCL, treated with the same regimen.<sup>1</sup> As the authors point out, there is clearly a need to consider a new paradigm in our therapeutic approach to this disease, particularly with respect to younger patients.

What strategies should be considered to improve outcome for children and adolescents with MBL? As Gerrard et al indicate, there are 2 general challenges that have to be addressed (see figure). First, there is clearly a need for refinement in establishing the accurate histologic diagnosis. Second, there is a need for refinement in therapeutic approach. The term mediastinal large B-cell lymphoma is somewhat nonspecific, referring to a spectrum of large B-cell lymphomas arising in the mediastinum. In the pediatric population, MBL may comprise primary mediastinal large B-cell lymphoma (PMBL), diffuse large B-cell lymphoma (DLBCL), and potentially "grey zone" lymphomas. In this regard, the distinction between PMBL and either Hodgkin lymphoma (HL) or DLBCL can be challenging in some cases; less frequently the distinction between HL and DLBCL is difficult (see figure). Gerrard and colleagues emphasize this dilemma and note that in some cases there was insufficient tissue available for the comprehensive immunophenotyping needed to distinguish between these subtypes in their retrospective review of pathology.<sup>1</sup> Does this



(A) Refinement in diagnosis. Among cases of MBL, the histologic distinction between PMBL, DLBCL and HL may be difficult. (B) Refinement in therapy may include the incorporation of novel biologic targeting agents, involved field radiation, and improved methods of measurement of early response to therapy. MBL indicates mediastinal large B-cell lymphoma; PMBL, primary mediastinal large B-cell lymphoma; HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; IFRT, involved field radiation therapy; MDD, minimal disseminated disease; and MRD, minimal residual disease.

matter? It does if biologic subsets have different responses to current therapy. Moreover, if therapy is to be enhanced by the addition of novel biologic “targeting” agents, one usually needs to know the target. More comprehensive and standardized immunophenotyping with immunohistochemistry panels and flow cytometric screening is required. Gene expression profiling studies may also be very helpful if done routinely. Improvement in therapeutic approach may be accomplished in a number of different ways, including the incorporation of novel targeting agents, involved field radiation therapy (IFRT) for poor responders, and treatment modifications based on early response to therapy. As these options are considered, it is important to take into account both the acute and late effects of therapy in the pediatric population. Side effects thought to be acceptable in an adult may be unacceptable in a child or adolescent.

There are various novel targeting agents that can be considered. The incorporation of anti-CD20 antibodies into conventional cytotoxic therapy has improved outcome for adults with CD20<sup>+</sup> lymphomas. Among adults with PMBL, the addition of rituximab to dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DA-EPOCH-R) produced a superior outcome compared with that achieved with DA-EPOCH without rituximab.<sup>6</sup> This encouraging result has prompted international investigators to pilot this approach in children and adolescents with PMBL (NCT01516580). Of some concern with this strategy, however, is the potentially high total cumulative anthracycline dosage that patients may receive if dosage escalation is needed; close long-term follow-up will be required in these patients to determine the degree of late cardiotoxicity associated with this regimen in young patients. CD30 is frequently detected in PMBL, and is therefore another immunotherapeutic target for which antibody or antibody–drug conjugates may have a therapeutic role.<sup>7</sup> Gerrard et al point out in their discussion that NFκB and JAK/STAT pathways are other potential targets.

The incorporation of IFRT is another modality that may improve outcome, particularly with respect to local control. Its use in adults is somewhat controversial and generally considered for patients with poor early response or residual disease at the end of induction. Its use in children would have to be weighed against the associated RT-related risks, including

cardiotoxicity and second malignancies (eg, breast cancer in young females).

A final strategy for improved outcomes is a more routine and accurate method for determining early response to therapy. Poor responders may be candidates for novel agents or further intensification of therapy, which may include hematopoietic stem cell transplantation. What will be the best method for determining early response in children and adolescents with MLBL? The use of functional imaging with fluorodeoxyglucose positron emission tomography (FDG-PET) is certainly one consideration, as is now commonly used in adults. In the study by Gerrard and colleagues, FDG-PET was not required and results for those who may have had this imaging were not reported.<sup>1</sup> In the context of a research study, the effectiveness of treatment modifications based on FDG-PET findings should be investigated in future trials. Early response to therapy may also be determined through recent advances in the development of technology to measure minimal disseminated disease (MDD) and minimal residual disease (MRD).<sup>8–10</sup> In this regard, flow cytometric measurement of the level of MDD in children with lymphoblastic lymphoma has prognostic significance and is the basis for clinical trials at both St Jude Children’s Research Hospital and the Children’s Oncology Group. The feasibility and prognostic significance of MDD/MRD as determined by PCR in children with high grade mature B-cell lymphomas has also been described.<sup>9,10</sup>

Although challenges remain in our approach to the management of MLBL in the pediatric and adolescent population, there are clearly exciting opportunities for advancement. Determining the impact of refinements in both establishing the accurate histologic diagnosis and in therapeutic approach will require large multicenter and international trials.

*Conflict-of-interest disclosure: J.T.S. received institutional and salary support from Seattle Genetics. The remaining author declares no competing financial interests.* ■

## REFERENCES

- Gerrard M, Waxman IM, Sposto R, et al. Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. *Blood*. 2013;121(2):278–285.
- Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. *Blood*. 2007;109(7):2736–2743.
- Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. *Blood*. 2007;109(7):2773–2780.
- Woessmann W, Seidemann K, Mann G, et al. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. *Blood*. 2005;105(3):948–958.
- Meinhardt A, Burkhardt B, Zimmermann M, et al. Phase II window study on rituximab in newly diagnosed pediatric mature B-cell non-Hodgkin’s lymphoma and Burkitt leukemia. *J Clin Oncol*. 2010;28(19):3115–3121.
- Dunleavy K, Pittaluga S, Janik J, et al. Primary mediastinal large B-cell lymphoma (PMBL) outcome may be significantly improved by the addition of rituximab to dose-adjusted (DA)-EPOCH and obviates the need for radiation: results from a retrospective study of 44 patients [abstract]. *Blood (ASH Annual Meeting Abstracts)*. 2006;108(11). Abstract 209.
- Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin’s lymphoma. *J Clin Oncol*. 2012;30(18):2183–2189.
- Coustan-Smith E, Sandlund JT, Perkins SL, et al. Minimal disseminated disease in childhood T-cell lymphoblastic lymphoma: a report from the children’s oncology group. *J Clin Oncol*. 2009;27(21):3533–3539.
- Shiramizu B, Goldman S, Kusao I, et al. Minimal disease assessment in the treatment of children and adolescents with intermediate-risk (Stage III/IV) B-cell non-Hodgkin lymphoma: a children’s oncology group report. *Br J Haematol*. 2011;153(6):758–763.
- Mussolin L, Pillon M, d’Amore ES, et al. Minimal disseminated disease in high-risk Burkitt’s lymphoma identifies patients with different prognosis. *J Clin Oncol*. 2011;29(13):1779–1784.

## ● ● ● IMMUNOBIOLOGY

Comment on Dovedi et al, page 251

# A shot in the arm for radiotherapy

Paul Greaves<sup>1</sup> and John G. Gribben<sup>1</sup> <sup>1</sup>BARTS CANCER INSTITUTE

In this issue of *Blood*, Dovedi et al demonstrate convincing evidence for the therapeutic efficacy of a new systemic immunostimulatory agent, the toll-like receptor-7 (TLR7) agonist R848, to augment radiotherapy-induced anticancer immunity.<sup>1</sup>