Reply to M. Hertzberg et al

Hertzberg et al¹ commented on our report of etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) in Burkitt lymphoma (BL).² The diagnosis of BL is relatively straight forward because of its readily identifiable histology and immunophenotype and the *MYC* translocation, which is optional in the WHO diagnostic criteria.³ Among 65 centrally reviewed pathology reports from our study, four patient cases (6%) did not have confirmation of a *MYC* translocation but had a classic histologic appearance, with Ki67 > 95% and *BCL2* negative. Thus, it is highly unlikely that our series included a large number of misdiagnosed cases, as suggested by the authors. In contrast, the authors present an inaccurate description of the published literature to support their concern. The first reference cited was described as a report using central pathology review, but it is actually a letter to the editor on a retrospective series of 145 patients with BL, Burkitt leukemia, or high-grade B-cell lymphomas that focuses on the poor outcomes of relapsed disease and does not address pathologic review.⁴ The second citation asserts that the rate of reproducibility of BL diagnosis is 53%, but the study is mischaracterized.⁵ In fact, the retrospective study of 1,378 cases of lymphoma diagnosed three decades ago included only 10 patient cases of BL, which were all confirmed on secondary review. The series also included 29 patient cases originally diagnosed as “high-grade B-cell, Burkitt-like lymphoma,” which had an agreement rate of 53% with secondary pathology review and which are no longer recognized diagnoses. In contrast, an accurate estimate according to contemporary diagnostic criteria comes from a study of 260 adult patients, which confirmed BL in 90% of cases on central pathology review.⁶ Finally, it is notable that the GMALL study, which the authors cite for comparison with our results, included Burkitt-like lymphoma and atypical Burkitt lymphoma, many pathological characteristics of which are not consistent with BL, as well as Burkitt leukemia.⁷

The authors raise concerns related to the definition of high risk used in our study. There are no universally accepted definitions of disease risk in BL, making cross-comparisons difficult. We used a definition based on stage, lactate dehydrogenase level, performance status, and mass size, similar to other studies.⁸ The percentages of patients with high risk according to the International Prognostic Index in our and the GMALL studies were similar: 45% and

51%, respectively. When comparing results of the DA-EPOCH-R and GMALL studies, the authors noted

5-year outcomes of 81.5% (event-free survival) and 90% (overall survival [OS]), respectively, for patients with an IPI of 0-2, suggesting that DA-EPOCH-R was less effective. However, the GMALL study included pediatric patients where among patients age 16-25 years versus > 25 years, the OS was 90% versus 62%-64%, respectively, indicating a major influence of age on outcome. Importantly, the percent of patients > 55 years old in the DA-EPOCH-R study was 42% compared with only 27% in the GMALL study—for which the progression-free survival was 60%. It is notable that the authors make no mention of the equivalent efficacy of DA-EPOCH-R across age groups and ignore the notable adverse effect of age in the GMALL study. It is also troubling that the authors did not compare the outcomes of patients with high-risk IPI scores, for which DA-EPOCH-R showed an event-free survival rate of 88.2% and OS of 92.1% (W. Wilson, personal communication, August 2020) compared with an OS of 75% in the GMALL study. The suggestion that patients with CNS/bone marrow disease fared better in the GMALL study is also problematic, as the outcomes of 58.6% (event-free survival with DA-EPOCH-R) versus 67% (OS with GMALL) are within the confidence intervals and all patients with CNS disease in GMALL received radiotherapy. We point out these selective and inaccurate comparisons by the authors to emphasize the pitfalls of comparing greatly disparate trials and the importance of careful and thoughtful analyses.

We believe that a strong argument in favor of DA-EPOCH-R over dose-intensive regimens is its risk-benefit in adult BL. Oddly, the authors imply that this may be untrue, because only “82% completed the full protocol.”¹ In actuality, only five patients (5%) with high-risk disease stopped DA-EPOCH-R early because of toxicity. One patient with low-risk disease abbreviated therapy because of toxicity. The notion that various regimens are equally tolerable lacks credibility. Indeed, the toxicity profile of any regimen is associated with age and performance status of the patient, which is why toxicity was separately reported for patients younger than 55 years in the GMALL study—but not in the DA-EPOCH-R study.⁹ Thus, we stand by our findings that DA-EPOCH-R compares favorably to more intensive regimens, but we recognize that improved therapeutic strategies are needed for adults with CSF involvement as well as careful consideration of treatment choices when treating highly curable diseases.

However, we would like to emphasize that mischaracterizations and inappropriate comparisons of trials are of no service to patients or the medical community.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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