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RESEARCH LETTER

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TO THE EDITOR:

Prognostic factors for adult patients with Burkitt lymphoma treated with dose-adjusted EPOCH-R

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Burkitt lymphoma (BL) is a highly aggressive B-cell lymphoma characterized by high tumor proliferation and frequent involvement of the bone marrow (BM) and/or central nervous system (CNS).[1] It commonly affects children and adolescents, and >90% of pediatric patients are cured with highly dose-intensive chemotherapy, including patients with high-risk features such as leukemic disease or CNS involvement.[2-5] Highly dose-intensive chemotherapy is also effective in adults, but the clinical outcomes are worse overall, in part, because of poor treatment tolerance and/or potentially worse tumor biology than that in younger patients.[6,7] The pharmacodynamically adjusted regimen dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) was developed to overcome the adverse effects of high tumor proliferation through continuous low-dose administration.[8,9] Prospective studies have confirmed high efficacy and tolerance in adults with BL.[10,11] Recent genomic studies identified distinct genetic and epigenetic BL subtypes associated with disparate clinical outcomes, and both pediatric and adult BL share common pathobiology.[12] Thus, it remains unclear whether the prognostic effect of age is related to poor treatment tolerance, high-risk biology, or their combination.[13]

Disease-related factors including CNS involvement and tumor burden are also associated with poor outcomes.[13,14] Recently, a multicenter retrospective study reported clinical results from 633 adult patients who were treated with 3 common BL regimens.[15] From this data set, the BL International Prognostic Index (BL-IPI) was developed, which stratified patients into risk categories based on 4 factors: age ≥ 40 years, an Eastern Cooperative Oncology Group (ECOG) performance status ≥2, serum lactate dehydrogenase (LDH) levels > 3 times the upper limit of normal (ULN), and CNS involvement.[16] Patients with low-risk (no risk factor), intermediate-risk (1 risk factor), and high-risk (≥2 risk factors) disease had differences in 3-year progression-free survival of 92%, 72%, and 53%, respectively, in the derivation cohort and 96%, 82%, and 63%, respectively, in the validation cohort.

Herein, we analyze the prognostic utility of the BL-IPI in adult patients with untreated BL in a multicenter prospective trial (NCI 9177) of risk-adapted DA-EPOCH-R, in which treatment tolerance was not a major issue (the trial was clinically registered at www.clinicaltrials.gov as #NCT01092182).

NCI 9177 was a multicenter study of DA-EPOCH-R for patients with untreated BL aged ≥18 years with any HIV status.[11] Treatment was risk adapted based on baseline prognostic factors independent of age. Patients with low-risk disease received 3 cycles without CNS prophylaxis. Patients with high-risk disease

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Data are available on request from the corresponding author, Mark Roschewski (mark.roschewski@nih.gov).

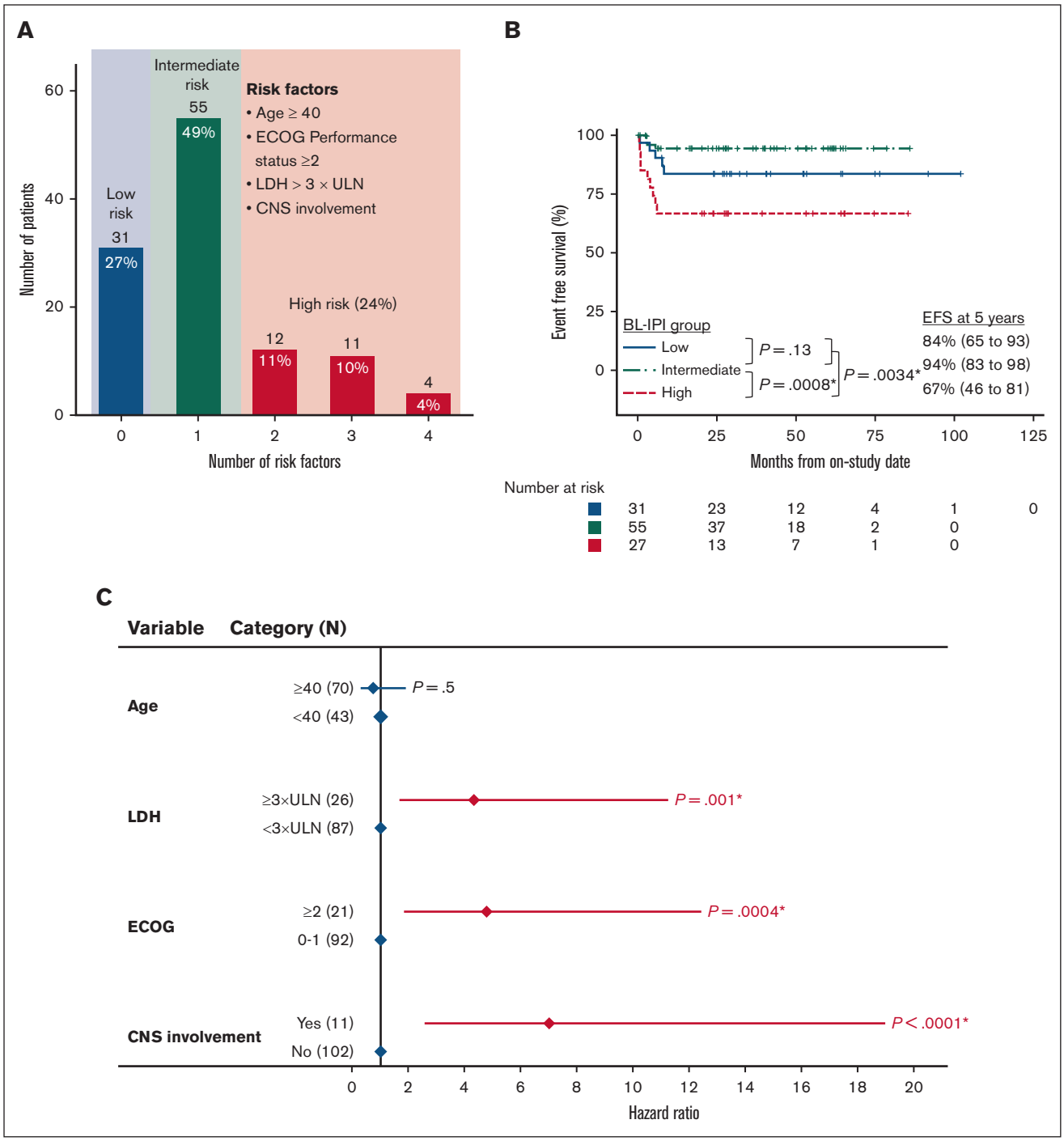

Figure 1. Prognostic impact of BL-IPI risk groups and individual components applied to the DA-EPOCH-R cohort. (A) Distribution of study population between BL-IPI risk groups. (B) Comparison of Kaplan-Meier estimates of EFS of patients in each BL-IPI risk group. (C) Forest plot depicting the prognostic impact of each BL-IPI component on EFS. The diamonds depict HRs, and straight lines depict 95% CIs; *$P < .05$.

received 6 cycles along with either prophylactic intrathecal therapy or an intensified intrathecal therapy schedule for active CNS disease.

Event-free survival (EFS) was calculated from study entry until progression, documented active disease, death, or last follow-up. Overall survival was calculated from study entry to death from any cause or last follow-up. Kaplan-Meier estimation and log-rank tests were used to determine the prognostic utility of the BL-IPI components.

The study was approved by local institutional review boards of participating institutions, and all patients signed informed consent forms.

In total, 113 patients were enrolled, including 15 (13%) considered at low-risk based on protocol-specified criteria. Median patient age was 49 years (range, 18-86 years) and the BM and/or cerebrospinal fluid was involved in 29 (26%) patients. At a median

A

Group	K-M	BL-IPI group	CNS/BM/PB	N	5-year EFS %(95% CI)	*P*-value
1	——	Low/Int	Negative	76 (67)	93% (84-97)	1 vs 2: .45 1 vs 3: .025* 1 vs 4: <.0001* 2 vs 3: .10 2 vs 4: .026* 3 vs 4: .25
2	- - -	High	Negative	8 (7)	100%	
3	—·—	Low/Int	Positive	10 (9)	70% (33-89)	
4	— —	High	Positive	19 (17)	53% (29-72)	

K-M = Kaplan-Meier curve, BL-IPI = Burkitt Lymphoma International Prognostic Index, CNS/BM/PB = central nervous system, bone marrow, or peripheral blood involvement, EFS = event free survival
*Statistically significant

B

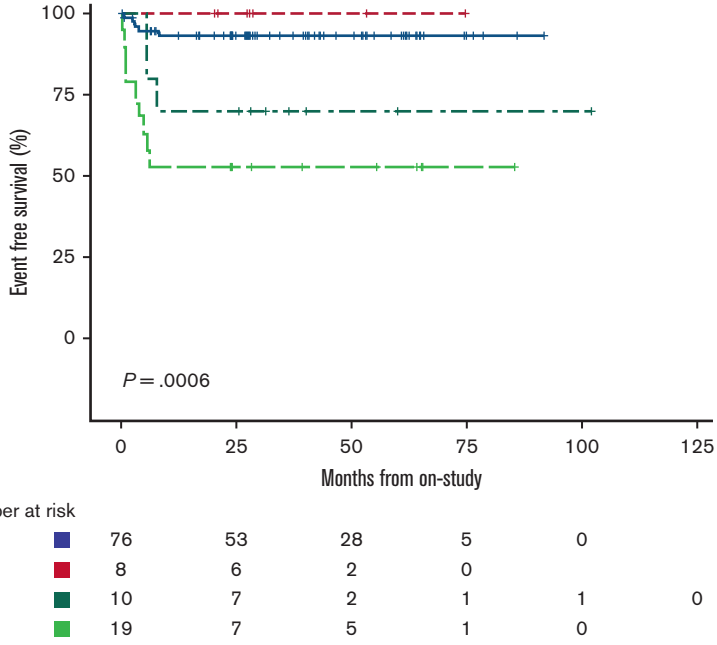

Figure 2. Prognostic impact of CNS, BM, or peripheral blood involvement within BL-IPI risk groups. (A) Kaplan-Meier estimates of 5-year EFS and (B) Kaplan-Meier survival curves divided by BL-IPI risk group and CNS, BM, and/or peripheral blood involvement.

follow-up of 58.7 months, the 4-year EFS and overall survival for all patients were 84.5% and 87.0%, respectively.[11] Applying the BL-IPI model, 31 (27%) patients were at low risk, 55 (49%) were at intermediate risk, and 27 (24%) were at high risk (Figure 1A). Based on BL-IPI, no difference was noted in the 5-year EFS between patients with low-risk and those with intermediate-risk disease: 83.6% (95% confidence interval [CI], 65-93) vs 94.2% (95% CI, 83-98; $P = .13$), but high-risk BL-IPI predicted a worse 5-year EFS of 66.7% (95% CI, 46-81) compared with 90.3% (95% CI, 82-93; $P = .003$) in combined groups of patients with low/intermediate-risk disease (Figure 1B).

Individual components of the BL-IPI were analyzed for prognostic impact by univariate analysis (Figure 1C). Notably, the 5-year EFS was similar for patients aged ≥40 years (n = 70) vs <40 years (n = 43) at 86.7% (95% CI, 76-93) vs 81.1% (95% CI, 66-90; hazard ratio [HR], 0.7; $P = .50$). Interestingly, of the 15 patients who were considered at low risk based on protocol-specified criteria and received only 3 cycles of chemotherapy; 12 (80%) would have been considered to be at intermediate risk based on BL-IPI because of age >40 years. The 5-year EFS for these patients was 100%. Patients with serum LDH levels ≥ 3 × ULN (n = 26) had an inferior 5-year EFS compared with those with serum LDH levels < 3 × ULN (n = 87): 65.4% (95% CI, 44-80) vs 90.4% (95% CI, 82-95; HR, 4.4; $P = .001$). Similarly, patients with an ECOG performance status ≥ 2 (n = 21) had an inferior 5-year EFS compared with those with an ECOG performance status of 0 or 1 (n = 92): 61.9% (95% CI, 38-79) vs 89.8% (95% CI, 81-95; HR, 4.8; $P = .0004$), and patients with CNS involvement (n = 11) had a markedly inferior 5-year EFS compared with those without CNS involvement (n = 102): 45.5% (95% CI, 17-71) compared with 88.8% (95% CI, 81-94; HR, 7.0; $P = .0001$).

We previously reported that patients in NCI 9177 with BM, peripheral blood, and/or CNS (BM/CNS) involvement had inferior

outcomes: the 4-year EFS for patients with no involvement of the cerebrospinal fluid or BM (n = 69) vs that for those with involvement of either (n = 29) was 92.4% (95% CI, 83-97) vs 58.6% (95% CI, 39-74; $P = 001$), respectively.[11] Herein, we analyzed these risk factors within the BL-IPI risk groups. Twenty-nine (26%) patients had BM/CNS involvement, including 19 (70%) who were at high risk and 10 (30%) who were at low or intermediate risk based on BL-IPI (Figure 2A). Specifically, BM or peripheral blood involvement was observed in 3 (10%), 7 (13%), and 16 (59%) patients in the low-, intermediate-, and high-risk BL-IPI groups, respectively. All 11 patients with CNS involvement were categorized as being at high risk by the BL-IPI. Patients with BM/CNS involvement who were at high risk based on the BL-IPI had a markedly worse 5-year EFS than those without involvement: 52.6% (95% CI, 29-72) compared with 100% ($P = .03$; Figure 2B). Notably, among low-/intermediate-risk disease, BM/CNS involvement was an adverse prognostic factor, with a 5-year EFS of 70.0% (95% CI, 33-89) compared with 93.0% (95% CI, 84-97; $P = .03$) in patients without BM/CNS involved.

Dose-adjusted EPOCH-R is included in National Comprehensive Cancer Network guidelines for untreated BL and has become a preferred regimen at many institutions. We have demonstrated that the BL-IPI is prognostic in a prospective clinical trial of DA-EPOCH-R and could be used for risk stratification in future studies. Patients with low- or intermediate-risk disease based on the BL-IPI had an excellent 5-year EFS of 90.3% when treated with DA-EPOCH-R, whereas those with high-risk disease had a 5-year EFS of only 66.7%. Notably, patients at high risk per the BL-IPI comprised only 24% of our cohort, compared with nearly 50% of the patients included in the original BL-IPI analysis. These data suggest that the patient population in this clinical trial does not represent the full spectrum of the disease in adults. Although the BL-IPI model was prognostic overall as well as for the individual factors of LDH, ECOG PS of $\geq$2, and CNS involvement, the lack of prognostic value of age $\geq$40 with the DA-EPOCH-R regimen suggests that when treatment tolerance is moderated, age is not associated with high-risk disease biology. In this way, age may only carry prognostic information for patients who are treated with other highly dose-intensive regimens but not DA-EPOCH-R.

Our data also suggest that the other components of the BL-IPI such as LDH level, ECOG performance status, and, especially, CNS involvement are highly prognostic with the use of DA-EPOCH-R. Indeed, with the composite risk factor of BM and/or CNS involvement, we were able to further risk stratify patients within BL-IPI categories. These data are important when considering which adult patients with BL should be prioritized for novel treatment approaches. In NCI 9177, patients without BM/CNS involvement made up 70% of the protocol-specified high-risk cohort and had a 5-year EFS of 92%. It will be difficult to improve upon these outcomes. Conversely, patients with BM/CNS involvement had a 5-year EFS of only 59%, with many of the events related to early toxic death often on the first cycle despite the relatively good treatment tolerance of DA-EPOCH-R. Taken together, these data suggest that further intensification of standard chemotherapy regimens in those with BM/CNS involvement may not improve outcomes because it will also further increase the risk of treatment-related toxicity, particularly in older patients with an impaired performance status. In summary, adult patients with BL that should be considered high-risk for treatment failure should be extended beyond the BL-IPI and include all patients with CNS involvement. These patients should be prioritized for novel treatment approaches including PI3K pathway inhibitors, chimeric antigen receptor T-cell therapy, and other forms of immunotherapy.

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