ORIGINAL ARTICLE

Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

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ABSTRACT

BACKGROUND

Primary mediastinal B-cell lymphoma is a distinct subtype of diffuse large-B-cell lymphoma that is closely related to nodular sclerosing Hodgkin's lymphoma. Patients are usually young and present with large mediastinal masses. There is no standard treatment, but the inadequacy of immunochemotherapy alone has resulted in routine consolidation with mediastinal radiotherapy, which has potentially serious late effects. We aimed to develop a strategy that improves the rate of cure and obviates the need for radiotherapy.

METHODS

We conducted a single-group, phase 2, prospective study of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) and filgrastim without radiotherapy in 51 patients with untreated primary mediastinal B-cell lymphoma. We used results from a retrospective study of DA-EPOCH-R from another center to independently verify the outcomes.

RESULTS

The patients had a median age of 30 years (range, 19 to 52) and a median tumor diameter of 11 cm; 59% were women. During a median of 5 years of follow-up, the event-free survival rate was 93%, and the overall survival rate was 97%. Among the 16 patients who were involved in the retrospective analysis at another center, over a median of 3 years of follow-up, the event-free survival rate was 100%, and no patients received radiotherapy. No late morbidity or cardiac toxic effects were found in any patients. After follow-up ranging from 10 months to 14 years, all but 2 of the 51 patients (4%) who received DA-EPOCH-R alone were in complete remission. The 2 remaining patients received radiotherapy and were disease-free at follow-up.

CONCLUSIONS

Therapy with DA-EPOCH-R obviated the need for radiotherapy in patients with primary mediastinal B-cell lymphoma. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00001337.)

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Primary mediastinal B-cell lymphoma is a distinct pathogenetic subtype of diffuse large-B-cell lymphoma that arises in the thymus.[1,2] Although it comprises only 10% of cases of diffuse large-B-cell lymphoma, primary mediastinal B-cell lymphoma, which predominantly affects young women,[3] is aggressive and typically is manifested by a localized, bulky mediastinal mass, often with pleural and pericardial effusions. Less commonly, the disease involves extranodal sites, including the lung, kidneys, gastrointestinal organs, or brain.[4,5] This disease is clinically and biologically related to nodular sclerosing Hodgkin's lymphoma; the putative cell of origin for both conditions is a thymic B cell.[1,2]

The molecular features of primary mediastinal B-cell lymphoma, and its relationship to Hodgkin's lymphoma and other types of diffuse large-B-cell lymphoma, have been studied.[1,2,6-8] Most patients with primary mediastinal B-cell lymphoma have mutations in the B-cell lymphoma 6 gene (*BCL6*), usually along with somatic mutations in the immunoglobulin heavy-chain gene, suggesting late-stage germinal-center differentiation.[6,7] Unlike other types of diffuse large-B-cell lymphoma, primary mediastinal B-cell lymphoma involves defective immunoglobulin production despite the expression of the B-cell transcription factors OCT-2, BOB.1, and PU.1. More than half of patients with the disease also have amplification of the *REL* proto-oncogene and the *JAK2* tyrosine kinase gene, which frequently are found in patients with Hodgkin's lymphoma, suggesting that these diseases are related.[9,10] Furthermore, genes that are more highly expressed in primary mediastinal B-cell lymphoma than in other types of diffuse large-B-cell lymphoma are characteristically overexpressed in Hodgkin's lymphoma.[2]

Prospective studies in primary mediastinal B-cell lymphoma are few, which has led to conflicting findings and a lack of treatment standards.[11-14] Nonetheless, several observations have emerged from the literature. First, in most patients, adequate tumor control is not achieved with standard immunochemotherapy, necessitating routine mediastinal radiotherapy.[13-15] Second, even with radiotherapy, which is associated with serious late side effects, 20% of patients have disease progression.[11,13] Third, more aggressive chemotherapy is associated with an improved outcome.[12,13] Consistent with this observation, we found that the dose-intense chemotherapy regimen consisting of dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone (DA-EPOCH) had a favorable overall survival rate (79%) without consolidation radiotherapy in patients with primary mediastinal B-cell lymphoma.[16] On the basis of the hypothesis that rituximab may improve treatment, we undertook a phase 2, prospective study of DA-EPOCH plus rituximab (DA-EPOCH-R) to determine whether it would improve outcomes and obviate the need for radiotherapy.

Methods

Study Conduct

The study was designed and the manuscript was written by the last author. All authors reviewed and approved the draft of the manuscript submitted for publication. All the authors vouch for the adherence of the study to the protocol (available with the full text of this article at NEJM.org) and for the completeness and accuracy of the data and analysis. The prospective study was approved by the institutional review board of the National Cancer Institute (NCI). All patients provided written informed consent. The retrospective analysis was approved by the institutional review board at Stanford University.

Filgrastim was provided to the NCI through an agreement with Amgen, which played no role in the study design, analysis, or data collection. No other commercial support was provided for the prospective study.

Prospective NCI Study

Patients

From November 1999 through August 2012, we prospectively enrolled 51 patients with untreated primary mediastinal B-cell lymphoma in an uncontrolled phase 2 study of DA-EPOCH-R. The primary study objectives were the rate of complete response, the rate of progression-free survival, and the toxicity of DA-EPOCH-R.

All eligible patients had not received any previous systemic chemotherapy, had adequate organ function, and had negative results on testing for the human immunodeficiency virus; among women with childbearing potential, a negative test for pregnancy was required. Any localized mediastinal masses (stage I) had to measure at least

5 cm in the greatest dimension. Evaluations included standard blood tests, whole-body computed tomography (CT), and bone marrow biopsy. Assessment of cardiac function, by means of echocardiography, and of central nervous system disease, with the use of CT or magnetic resonance imaging (MRI) and flow cytometry or cytologic analysis of cerebral spinal fluid, were performed if clinically indicated.

Study Therapy

Patients received chemotherapy consisting of DA-EPOCH-R with filgrastim for 6 to 8 cycles.[17,18] Disease sites were evaluated after cycles 4 and 6. Patients with a reduction of more than 20% in the greatest diameter of their tumor masses between cycles 4 and 6 received 8 cycles of treatment. Patients with a reduction of 20% or less between cycles 4 and 6 discontinued therapy after 6 cycles. The method of administering the DA-EPOCH-R is summarized in the Supplementary Appendix (available at NEJM.org).

We used standard criteria for tumor response to assess the study end points.[19,20] We used ^{18}F-fluorodeoxyglucose–positron-emission tomography–CT (FDG-PET-CT) after therapy to evaluate residual masses. Patients who had a maximum standardized uptake value greater than that of the mediastinal blood pool in the residual mediastinal mass underwent repeat scans at approximately 6-week intervals until normalization or stabilization. Mediastinal blood pool activity was defined as the maximum standardized uptake value over the great vessels and ranged from 1.5 to 2.5 in the study population. Tumor biopsy was performed as clinically indicated. Patients with evidence of thymic rebound underwent repeat CT at 6-week intervals until stabilization. All FDG-PET-CT scans were reviewed and scored by the same nuclear-medicine physician. No patients received radiation treatment during this prospective study.

INDEPENDENT, RETROSPECTIVE STANFORD STUDY

To provide an independent assessment of DA-EPOCH-R, we collaborated with investigators at Stanford University Medical Center who had begun to use DA-EPOCH-R in 2007 to treat primary mediastinal B-cell lymphoma.[21] They reviewed all charts from 2007 through 2012 and found 16 previously untreated patients who had been consecutively treated with DA-EPOCH-R; none required radiotherapy. NCI investigators confirmed the presence of primary mediastinal B-cell lymphoma in all 16 patients, according to the *WHO* [World Health Organization] *Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th edition.[3] Standard immunohistochemical studies were performed as indicated.[3,18]

OTHER COMPARATIVE DATA

To provide a long-term assessment of the DA-EPOCH platform, we reviewed the pathological data for all patients from our phase 2 study of DA-EPOCH in patients with diffuse large-B-cell lymphoma, which also did not permit radiotherapy, and identified 18 patients with primary mediastinal B-cell lymphoma.[16]

STATISTICAL ANALYSIS

We calculated the duration of overall survival from the date of enrollment until the time of death or last follow-up. The duration of event-free survival was calculated from the date of enrollment until the date of progression, radiotherapy, discovery of a second mass, or time of last follow-up. We used the Kaplan–Meier method to determine the probability of overall or event-free survival.[22] Patients' characteristics were compared by means of Fisher's exact test for dichotomous variables and by means of the Wilcoxon rank-sum test for continuous variables. All P values are two-tailed. The median follow-up was calculated from the date of enrollment through November 2012, the date of the most recent update.

RESULTS

BASELINE CHARACTERISTICS AND CLINICAL OUTCOMES

The 51 patients enrolled in the NCI phase 2 prospective study had a median age of 30 years (range, 19 to 52) and a median tumor diameter of 11 cm; 59% were women (Table 1). Indicators of advanced disease included bulky tumor with a greatest diameter of 10 cm or more (in 65% of patients), an elevated lactate dehydrogenase level (in 78%), and stage IV disease (in 29%).

The 16 patients identified in the retrospective Stanford study had baseline characteristics similar to those of our 51 patients (Table 1) except for a significantly lower frequency of extranodal

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Prospective NCI Cohort (N=51)	Retrospective Stanford Cohort (N=16)	P Value between Study Cohorts
Female sex — no. (%)	30 (59)	9 (56)	1.00
Age — yr			0.04
Median	30	33	
Range	19–52	23–68	
Bulky tumor, ≥10 cm			0.57
Patients — no. (%)	33 (65)	9 (56)	
Maximal diameter range — cm	5–18	7–18	
Stage IV disease — no. (%)	15 (29)	7 (44)	0.36
Elevated lactate dehydrogenase level — no. (%)	40 (78)	11 (69)	0.51
Extranodal site — no. (%)	27 (53)	3 (19)	0.02
Pleural effusion — no. (%)	24 (47)	10 (62)	0.39
CD20+ malignant cells — no. (%)	51 (100)	16 (100)	1.00
BCL6+ malignant cells — no. (%)	33/37 (89)	ND	ND

* BCL6 denotes the B-cell lymphoma 6 protein, NCI National Cancer Institute, and ND not done.

disease and significantly older age; 56% of patients had bulky disease, and 44% of patients had stage IV disease.

At a median follow-up of 63 months (range, 3 to 156), the event-free survival rate in the prospective NCI study was 93% (95% confidence interval [CI], 81 to 98), and the overall survival rate was 97% (95% CI, 81 to 99) (Fig. 1A and 1B). Three patients had evidence of disease after DA-EPOCH-R treatment; two had persistent focal disease, as detected on FDG-PET-CT, and one had disease progression. Two of these patients underwent mediastinal radiotherapy, and one was observed after excisional biopsy. All three patients became disease-free. One later died from acute myeloid leukemia, while still in remission from his primary mediastinal B-cell lymphoma.

In the retrospective Stanford cohort, over a median follow-up of 37 months (range, 5 to 53), 100% of patients (95% CI, 79 to 100) were alive and event-free (Fig. 1C and 1D).

Finally, we assessed the outcome for 18 patients with primary mediastinal B-cell lymphoma who were enrolled in our phase 2 study of DA-EPOCH.[16] These patients had baseline characteristics similar to those in the prospective DA-EPOCH-R study (data not shown). Over a median follow-up of 16 years, the event-free and overall survival rates were 67% (95% CI, 44 to 84) and 78% (95% CI, 55 to 91), respectively. No cardiac failure or second tumors were observed.

The event-free and overall survival rates were greater with the addition of rituximab in the NCI prospective cohort than in the cohort of 18 patients who received DA-EPOCH alone (P=0.007 and P=0.01, respectively). This finding suggests that the addition of rituximab may account for the improvement and is consistent with other reports.[11]

FDG-PET-CT FINDINGS

To identify DA-EPOCH-R treatment failures early, the 36 patients who were found to have residual mediastinal masses in the prospective study underwent FDG-PET-CT in order to optimize curative radiotherapy. Half the patients had a maximum standardized uptake value that was no more than the value in the mediastinal blood pool, which represents the upper limit of the normal range of uptake (Table 2). The other half had a maximum standardized uptake value that was more than the value in the mediastinal blood pool. Although diffuse or focal uptake within the residual tumor mass that is higher than that in

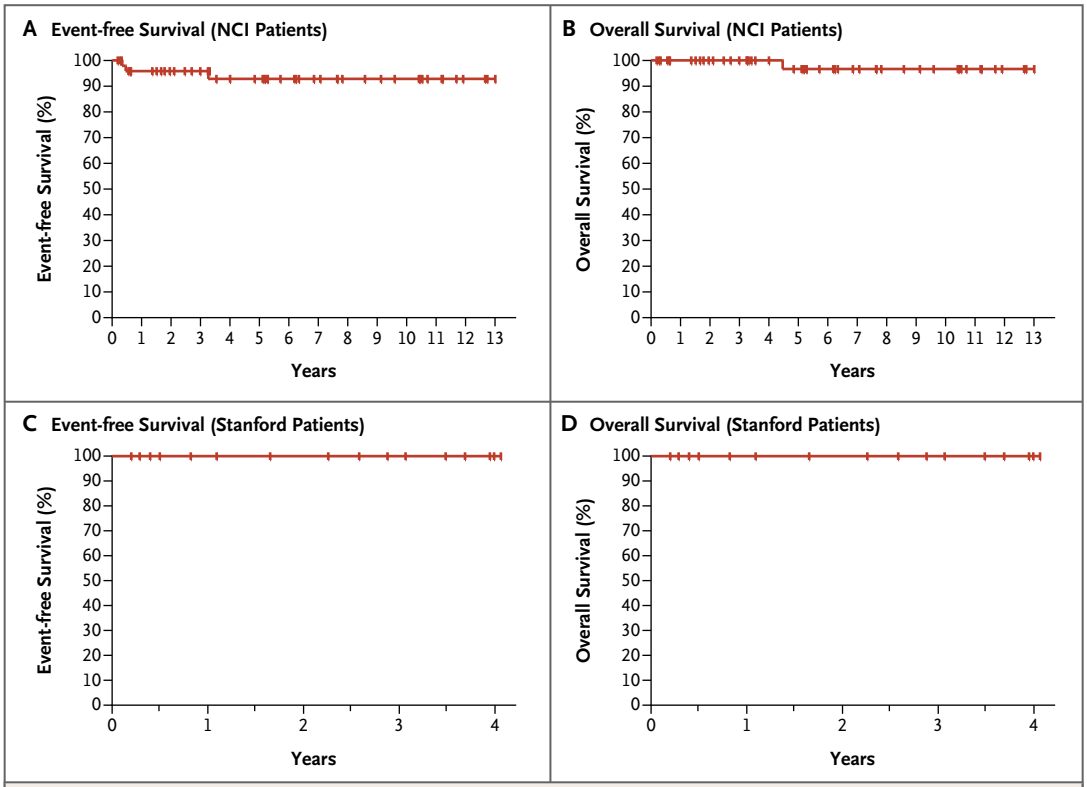

Figure 1. Kaplan–Meier Estimates of Event-free and Overall Survival of Patients with Primary Mediastinal B-Cell Lymphoma Receiving DA-EPOCH-R, According to Study Group.

DA-EPOCH-R was administered to 51 patients in a prospective trial at the National Cancer Institute (NCI), and to 16 patients in a retrospective trial at Stanford University. In the prospective NCI cohort, the event-free survival rate was 93% (Panel A) and the overall survival rate was 97% (Panel B) at a median follow-up of 63 months. In the retrospective Stanford cohort, the event-free and overall survival rates were both 100% (Panel C and Panel D, respectively) at a median follow-up of 37 months.

the mediastinal blood pool has been considered indicative of lymphoma,[20] among these 18 patients, only 3 (with maximum standardized uptake values of 5.9, 10.2, and 14.5) were found to have residual lymphoma. Thus, FDG-PET-CT had a positive predictive value of 17% and a negative predictive value of 100%.

Among the 15 patients with a maximum standardized uptake value greater than that in the mediastinal blood pool who did not have disease, 10 underwent repeat FDG-PET-CT; the other 5 did not undergo additional screening, because their initial FDG-PET-CT scans were interpreted as unlikely to represent disease. The 10 patients underwent 1 to 6 additional FDG-PET-CT scans (total, 26); all the findings were interpreted as false positive results on the basis of stabilization or improvement of the maximum standardized uptake value. None of the 10 patients had a recurrence of lymphoma during follow-up.

Three patients underwent post-treatment biopsy. One, with a maximum standardized uptake value of 5.9, had a viable tumor of less than 1 cm in area. Owing to the uncertain importance of this finding, the patient was followed for 7 years without treatment, and the tumor did not recur during follow-up. Two patients, with maximum standardized uptake values of 4.6 and 6.4, had negative biopsy results and no tumor recurrence during 6 years of follow-up.

In two patients, treatment failed but repeat biopsy was not performed. One patient had disease progression on CT during treatment, and the other had a post-treatment maximum standardized uptake value that increased from 10.2 to 19, consistent with disease progression.

Table 2. FDG-PET-CT Findings after DA-EPOCH-R Therapy in the Prospective NCI Cohort.*

Lymphoma Status	Maximum Standardized Uptake Value				FDG-PET-CT Performance
	≤Value in Mediastinal Blood Pool (N=18)	>Value in Mediastinal Blood Pool (N=18)			
		total	value <5	value ≥5	
					percent
No disease (no. of patients)	18	15	12	3	
Disease recurrence (no. of patients)	0	3	0	3	
Sensitivity					100
Specificity					54
Positive predictive value					17
Negative predictive value					100

* Shown are values for 36 patients with residual mediastinal masses in the prospective NCI study after treatment. The maximum standardized uptake value is the amount of ^{18}F-fluorodeoxyglucose that is taken up by tumor tissue as seen on positron-emission tomography–computed tomography (FDG-PET-CT). Mediastinal blood pool activity was defined as the maximum standardized uptake value over the great vessels and ranged from 1.5 to 2.5 in the study population. A maximum standardized uptake value that is lower than the value in the mediastinal blood pool typically indicates the likelihood of no disease, and a value that is higher typically indicates the likelihood of disease. The three patients who were found to have actual residual disease had maximum standardized uptake values of 5.9, 10.2, and 14.5.

DOSE AND TOXICITY OF DA-EPOCH-R IN THE NCI STUDY

In the NCI study, 90% of patients received six cycles, and 10% received eight cycles, of DA-EPOCH-R. More than half the 51 patients had an escalation to at least dose level 4, representing a 73% increase over dose level 1; 6% of patients did not have a dose escalation. More than half the patients received 69 mg of doxorubicin per square meter of body-surface area for at least one cycle and cumulative doses of 345 to 507 mg per square meter. To assess cardiac toxic effects, ejection fractions were measured in 42 patients. All had normal ejection fractions up to 10 years after treatment (Fig. 2). There was no significant relationship between the ejection fraction and the length of time since treatment (P=0.30) or between the ejection fraction and the cumulative doxorubicin dose (P=0.20), and no significant interaction between the dose and time interval (P=0.40).

Toxicity was assessed during the administration of all 294 cycles of DA-EPOCH-R. The targeted absolute neutrophil count of less than 500 cells per cubic milliliter occurred during 50% of cycles. Thrombocytopenia (<25,000 platelets per cubic millimeter) occurred during 6% of cycles, and hospitalization for fever and neutropenia occurred during 13% of cycles. Nonhematopoietic toxic effects were similar to those that have been reported previously.[17,18] One patient died from acute myeloid leukemia while in remission from his primary mediastinal B-cell lymphoma, 49 months after treatment. Owing to the unexpected severe neutropenia during treatment in this patient, we looked for a germline telomerase mutation, which is associated with chemotherapy intolerance and myeloid leukemia.[23] Telomere shortening (length, 2.5 SD below the mean) and a heterozygous mutation for the telomerase reverse transcriptase gene (*TERT*) codon Ala1062Thr were identified.

DISCUSSION

The use of DA-EPOCH-R obviated the need for radiotherapy in all but 2 of 51 patients (4%) with primary mediastinal B-cell lymphoma in a prospective cohort, and no patients had recurring disease over a median follow-up of more than 5 years (maximum, >13). Furthermore, in an independent retrospective cohort, treatment with DA-EPOCH-R in patients with primary mediastinal B-cell lymphoma resulted in an event-free survival rate of 100%.

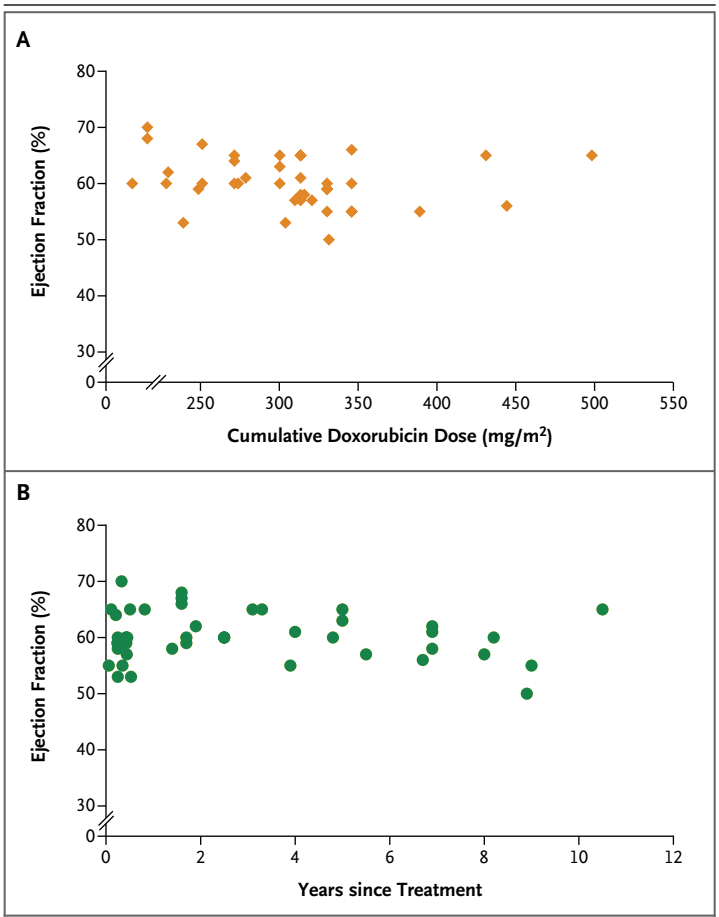

Figure 2. Cardiac Ejection Fraction after Treatment with DA-EPOCH-R in 42 Patients in the Prospective NCI Cohort.

Patients' ejection fractions are shown according to the cumulative dose of doxorubicin they received (Panel A) and the years since they underwent treatment (Panel B). Cardiac echocardiography was performed in 42 available patients, beginning in 2009. There was no significant difference in ejection fraction over dose or time, nor was there a significant interaction between dose or timing of treatment and the ejection fraction (P=0.30 and P=0.20, respectively).

Despite the limitations of the phase 2 study and the retrospective study, these findings suggest that DA-EPOCH-R is a therapeutic advance for this type of lymphoma. Our results suggest that rituximab significantly improves the outcome of chemotherapy in patients with primary mediastinal B-cell lymphoma.

The toxicity of DA-EPOCH-R was similar to that reported previously.[16] The use of neutrophil-based dose adjustment maximized the delivered dose and limited the incidence of fever and neutropenia to 13% of the cycles. The infusional schedule of doxorubicin allowed for the delivery of high maximal and cumulative doses of doxorubicin without clinically significant cardiac toxic effects.[24,25]

We used post-treatment FDG-PET-CT to identify patients who had persistent disease and a possible need for radiotherapy. Unlike the high clinical accuracy of FDG-PET-CT in other aggressive lymphomas,[20] we found the technique to have a poor positive predictive value in primary mediastinal B-cell lymphoma. We frequently observed residual mediastinal masses that continued to shrink for 6 months, suggesting that inflammatory cells might account for the FDG uptake. These findings indicate that FDG-PET-CT uptake alone is not accurate for determining the presence of disease in these patients.

There is no established standard treatment for primary mediastinal B-cell lymphoma. Although R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) has become a de facto standard, it is not universally accepted.[11,12] Most strategies also incorporate consolidation radiotherapy to overcome the inadequacy of immunochemotherapy, although some observers have questioned its routine use.[12,26] The most accurate assessment of R-CHOP and radiotherapy is a subgroup analysis of patients with primary mediastinal B-cell lymphoma in the Mabthera International Trial Group study of R-CHOP–based treatment.[11] Among 44 patients, 73% received radiotherapy, with an event-free survival rate of 78% at 34 months.[11] These results indicate that patients who receive R-CHOP–based treatment, most of whom are young women, may have serious long-term consequences of radiotherapy, including second tumors and the acceleration of atherosclerosis and anthracycline-mediated cardiac damage.[27]

Current standard therapy is also inadequate for children with primary mediastinal B-cell lymphoma. In a recent subgroup analysis in the FAB/LMB96 international study, the event-free and overall survival rates were 66% and 73%, respectively, among children receiving a multiagent pediatric regimen.[28]

Retrospective studies have long suggested that patients with primary mediastinal B-cell lymphoma have improved outcomes with the receipt of regimens of increased dose intensity.[13] Dose intensity appears to be important in treating

Hodgkin's lymphoma, a closely related disease.[29] Indeed, outcomes associated with the use of DA-EPOCH-R may well be related to dose intensity as well as the continuous infusion schedule.[30] DA-EPOCH therapy involves the administration of pharmacodynamic doses to normalize drug exposure among patients and maximizes the rate of administration. DA-EPOCH may also more effectively modulate the expression of *BCL6*,[7] which encodes a key germinal-center B-cell transcription factor that suppresses genes involved in lymphocyte activation, differentiation, cell-cycle arrest (p21 and p27Kip1), and response to DNA damage (p53 and *ATR*) and that is expressed by most primary mediastinal B-cell lymphomas (Table 1).[31] The inhibition of topoisomerase II also leads to down-regulation of *BCL6* expression, suggesting that regimens directed against topoisomerase II may have increased efficacy in treating primary mediastinal B-cell lymphoma. In this regard, DA-EPOCH-R was designed to inhibit topoisomerase II by including two topoisomerase II inhibitors, etoposide and doxorubicin, and maximizing topoisomerase II inhibition by way of extended drug exposure.[16]

In conclusion, our results indicate that DA-EPOCH-R had a high cure rate and obviated the need for radiotherapy in patients with primary mediastinal B-cell lymphoma. To provide confirmatory evidence, an international trial of DA-EPOCH-R in children with primary mediastinal B-cell lymphoma has been initiated (ClinicalTrials.gov number, NCT01516567).

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