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Infusional etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone +/- rituximab as first-line therapy for aggressive non-Hodgkin lymphoma

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Abstract

Introduction—Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-EPOCH) was developed in an effort to overcome inadequate drug concentrations and to compensate for increased drug clearance. The goal of this study was to examine risk factors and outcomes in patients with aggressive non-Hodgkin lymphoma (aNHL) treated with DA-EPOCH.

Patients and Methods—We report 136 patients with previously untreated aNHL treated with infusional DA-EPOCH chemotherapy +/- rituximab from 2005-2013. Overall survival was estimated by Kaplan Meier methods. Univariate and multivariate logistic regression was used to determine factors associated with experiencing death, progression, or relapse at two years.

Results—The overall response rate was 82%. Relapse-free survival at 1, 3, and 5 years was 68%, 63%, and 52% with 95% CIs [0.59,0.85], [0.54,0.70], and [0.31,0.70], respectively. Patients with T-cell aNHL had increased risk of death, progression or relapse [OR:3.5, 95% CI: 1.4, 8.8] compared to those with B-cell aNHL. In multivariate analysis, current smoking, disease in the bone marrow and number of cycles completed were independent predictors of death or relapse.

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Conclusion—Our data suggests EPOCH+/-R is active in both B and T-cell aNHL. Toxicity did not significantly delay treatment or negatively impact outcomes. Dose adjustment by hematopoietic nadir had no impact on outcomes. The impact of smoking during chemotherapy should be further evaluated.

Keywords

dose-adjusted EPOCH protocol; antineoplastic combined chemotherapy protocols; smoking; patient outcomes; multivariate analysis

Introduction

Non-Hodgkin lymphoma (NHL) is the 7th most common malignancy in the United States; its incidence has been increasing by an annual average of 0.5% for the past decade. Aggressive NHL (aNHL) is defined by the National Cancer Institute as a type of lymphoma that grows and spreads quickly and has severe symptoms ¹. Standard treatment for aNHL usually includes cyclophosphamide, doxorubicin, vincristine and prednisone combined with Rituximab in B cell lymphomas and without Rituximab in T cell lymphoma ^{2, 3}. Despite improved outcomes, a significant proportion of patients with aNHL will require salvage therapy and ultimately die from the disease ⁴.

To improve this situation, several attempts at novel chemotherapy combinations, modified dosing schedules, and infusional rather than with bolus dosing have been reported. Etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) is an infusional regimen developed from *in vitro* studies showing that tumor cells are less resistant to prolonged low concentration exposure ⁵. Subsequent clinical trials with EPOCH showed individual variation in steady-state drug plasma concentrations, which led to a dose-adjustment strategy based on the hematopoietic nadir. This approach was shown to improve inadequate drug concentrations⁶. Dose-adjusted EPOCH (DA-EPOCH) has produced favorable outcomes in several phase II trials of untreated patients with large B cell lymphoma, primary mediastinal lymphoma, and HIV-related lymphomas ⁷⁻⁹. While previous studies have examined smoking as a risk factor for survival in NHL patients ¹⁰⁻¹², this modifiable risk factor has not been considered in terms of other patient outcomes and in a selection of patients with aNHL receiving DA-EPOCH.

Here, we describe our experience with 136 patients previously untreated for aNHL, who received infusional, dose-adjusted EPOCH chemotherapy with or without rituximab (EPOCH +/-R). The primary objectives of the study were to evaluate disease response, event-free survival, and toxicity associated with therapy. Secondary objectives were to examine outcomes by International Prognostic Index (IPI) score for aNHL ¹³ and smoking status.

Patients and Methods

Study Population

Consecutive patients were screened using the tumor registry at our academic comprehensive cancer center. Patients were included in the analysis if they were diagnosed with aNHL as

(defined by NCI criteria) and treated with infusional EPOCH +/-R as first-line therapy between January 1, 2005 and December 31, 2013. Chemotherapy was dose-adjusted based on the goal to achieve an absolute neutrophil count nadir of $0.5 \times 10^9/L$ or lower in the previous cycle, as described by Wilson et al⁶. Adjustments above the starting dose level applied to doxorubicin, etoposide and cyclophosphamide while dose adjustments below the starting dose level only applied to cyclophosphamide. All patients received growth factor with pegfilgrastim or filgrastim. Patients were excluded if EPOCH +/- R was not given as first-line therapy, or if they had one of the following diagnoses: indolent lymphoma except grade III follicular lymphoma, primary central nervous system lymphoma, mycosis fungoides, or primary cutaneous lymphomas not requiring therapy. The study was approved by the Wake Forest Health Sciences Institutional Review Board.

Data Collection

Study data were collected and managed using the REDCap database system¹⁴. The medical record was reviewed for the age, diagnosis, date of diagnosis, disease stage, HIV status, IPI score, smoking status, date of chemotherapy initiation and completion and number of chemotherapy cycles completed, response achieved and whether salvage therapy was required. Vincristine was considered dose-capped if given as a fixed total dose of 2 mg. BMI was calculated using pre-treatment weight in kilograms divided by height in centimeters. Therapy toxicity was defined as an event leading to dose reduction, interruption, or discontinuation of therapy; or unplanned hospitalization or death attributed to EPOCH +/-R. Chemotherapy delay was defined as 28 or more days between the previous and subsequent chemotherapy cycle. Disease response to therapy was defined as described by Cheson et al¹⁵.

Statistical Analysis

Means and standard deviations for continuous variables and frequencies and percentages for categorical variables were used to summarize the data, unless otherwise noted. Overall survival was estimated by Kaplan Meier methods. We tested for differences in overall survival by IPI risk (low risk vs. low intermediate risk vs. high intermediate risk vs. high risk) using the log-rank test. To determine factors associated with experiencing an event (death, progression, or relapse) at two years, univariate and multivariate logistic regression was used. Covariates included in the multivariate model were selected using backward elimination. Possible adjustment variables were sex, race, disease in bone marrow, B or T cell disease, HIV infection, dose adjusted by nadir, number of cycles completed, delay of cycle, complications during treatment, number of hospitalizations, further chemotherapy regimens, transplant, BMI, cardiac ejection fraction prior to treatment, weight used to calculate dose, vincristine dose capped, smoking, IPI risk, and disease subtype. All analyses were conducted in SAS Version 9.4 (Cary, NC), and p values less than 0.05 were considered significant.

Results

A total of 138 patients met the inclusion criteria. Patient demographics and risk factors are presented in Table 1. One patient with mantle cell lymphoma and one patient with

plasmablastic lymphoma were excluded because EPOCH +/- R was not given as first line therapy, resulting in 136 patients eligible for analysis, 24 of which had T-cell lymphoma. Treatment characteristics and outcomes for the full study population as well as the T-cell subset are presented in Table 2. The median duration of follow-up was 27 months. Ten patients died within 30 days of completing treatment. Sixty-seven patients were dose-adjusted (13 of T-cell patients); 36 were dose-adjusted below level 1 (10 T-cell patients) and 31 were adjusted above level 1 (3 T-cell patients). Sixty-six patients (10 T-cell patients) remained at dose level 1 for the duration of their therapy. Thirty-seven percent of patients had at least one cycle of therapy delayed. For patients who experienced a delay, 20 were delayed because of hematologic toxicity, specifically neutropenia (n=13) and thrombocytopenia (n=5). The overall response rate was 82% (79% in T-cell patients), with 76 B cell and 14 T cell lymphoma patients achieving a complete response and 16 B cell and 5 T cell lymphoma patients achieving a partial response.

Using Kaplan Meier estimates, relapse-free survival at 1, 2, 3, and 5 years was 68%, 64%, 63%, and 52%; 95% confidence intervals (CIs) [0.59,0.85], [0.55,0.71], [0.54,0.70], and [0.31,0.70], respectively. Overall survival was significantly different by IPI score (p=0.0003, Figure 1). From univariate logistic regression models predicting death, progression, or relapse at two years, patients with T cell NHL had increased risk of an event [OR:3.5, 95% CI(1.4, 8.8)] compared to B-cell NHL. Age, sex, race, BMI, HIV status, stage at diagnosis, dose adjustment, delay of chemotherapy, number of unplanned hospitalizations, hematologic or non-hematologic toxicity, treatment complications, and stem cell transplantation were not significantly associated with risk of an event in univariate or multivariate analyses. In multivariate analysis, current smoking (p=0.02), disease in the bone marrow at diagnosis (p=0.001), number of cycles completed (p=0.0003), and receipt of subsequent chemotherapy (p=0.003) were independent predictors of death, progression or relapse (Table 3).

Discussion

In this study, we observed that EPOCH was active in both B and T cell lymphomas and that current smoking was an independent predictor of death or relapse. In addition, disease in the bone marrow at diagnosis was associated with adverse outcomes.

EPOCH is a regimen that was developed at the National Cancer Institute based on *in vitro* studies showing that tumor cells may exhibit less resistance with prolonged low-concentration exposure to chemotherapy as compared to brief, high concentration exposure¹⁶. The regimen has demonstrated safety and activity in high-risk patients with diffuse large B cell lymphoma¹⁷. DA-EPOCH was developed in an effort to overcome inadequate drug concentrations and to compensate for increased drug clearance. The dynamic dose adjustment schedule may be an improved treatment strategy¹⁸; however, we did not find differences in outcomes based on dose adjustment above or below dose level one.

Among the patients in our series, the overall response rate was 82%. Among patients with T cell NHL, the response rate was 79%, although T cell histology was still associated with death, progression, or relapse at 2 years. Peng et al reported a response rate of 85% among

previously untreated patients with peripheral T cell lymphoma and concluded that EPOCH was effective and well-tolerated in that population ¹⁹.

In a phase II study evaluating the DA-EPOCH regimen in previously untreated patients with diffuse large B cell lymphoma, 5-year progression-free and overall survival rates were 79% and 80%, respectively; however, in patients with the highest IPI scores, these rates dropped to 47% and 37%, respectively ²⁰. Our study supports the finding of outcome differences based on IPI score. In our study, bone marrow involvement of disease was associated with adverse outcomes. This finding is consistent with published literature because marrow involvement is indicative of Ann Arbor stage IV disease and has known prognostic and therapeutic implications.

We also found that current smoking was associated with adverse outcomes. It has been suggested that cigarette smoking is associated with an increased risk of developing lymphoma ²¹. While previous studies have considered smoking as a risk factor for survival in NHL patients ¹⁰⁻¹², we demonstrate that current smoking is associated with adverse outcomes in aggressive NHL. It has been suggested that nicotine may negatively impact the chemosensitivity of tumor cells against antineoplastic drugs in other malignancies²².

Our study has several limitations. We retrospectively evaluated a heterogeneous population of patients with aggressive lymphomas at a single medical center, and our study population may not be representative of the general aggressive lymphoma population. We included all patients who received at least one cycle of EPOCH, and our outcomes are comparable to published literature. Another limitation is that patients were considered dose-adjusted if medications were adjusted above or below dose level one. It is possible that some patients experienced a hematopoietic nadir at dose level one and did not require dose adjustment; however, such patients could not be distinguished from patients that were maintained at dose level one at the discretion of the physician. In addition, our institution has shown a preference towards dose capping vincristine at a maximum total dose of 2 mg; this approach has been recommended for CHOP regimens, but has not been routinely recommended for EPOCH regimens. We are awaiting the results of CALGB 50303 that compares the outcomes of R-CHOP versus R-EPOCH regimens in previously untreated patients with DLBCL.

Conclusion

Our findings show that EPOCH is active in aggressive B and T cell lymphomas. We found that cigarette use during EPOCH therapy may negatively treatment outcomes. The impacts of dose adjustment and smoking during the EPOCH regimen should be further evaluated.

Acknowledgments

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Clinical Practice Points

This study provides support for the use of EPOCH in both T and B cell malignancies. It is hypothesis generating for the role of dose adjustment in EPOCH chemotherapy. Current smoking was identified as an independent negative prognostic indicator and should be further evaluated in prospective clinical trials

Figure 1.
Overall survival from date of diagnosis by International Prognostic Index.

Table 1
Patient characteristics and risk factors at diagnosis of the study population (N=136) and the subset of T-cell lymphoma patients (n=24)

Variables	All patients		T-cell patients only	
	n	% or mean (IQR)	n	% or mean (IQR)
Age		57.5 (46.8,69.1)		51.0 (35.3,61.8)
Gender				
Male	86	63.2	18	75.0
Female	50	36.8	6	25.0
Race				
White	101	74.3	11	45.8
Black	26	19.1	11	45.8
Asian	2	1.5	0	0
Unknown	7	5.2	2	8.3
Type				
B cell	112	82.4	0	0.0
T cell	24	17.7	24	100.0
Sub-type				
Diffuse large B cell lymphoma	82	60.3	--	--
Mantle cell lymphoma	9	6.6	--	--
Follicular grade 3 or chronic lymphocytic leukemia-transformed lymphoma	9	6.6	--	--
Mediastinal large B cell lymphoma	4	2.9	--	--
Other B-cell lymphomas	8	5.9		
ALK- anaplastic large cell lymphoma	6	4.4	6	25.0
ALK+ anaplastic large cell lymphoma	6	4.4	6	25.0
Peripheral T cell lymphoma	6	4.4	6	25.0
Angioimmunoblastic lymphoma	3	2.2	3	12.5
Other T-cell lymphomas	3	2.2	3	12.5
Stage				
1	16	11.8	3	12.5
2	18	13.2	4	16.7
3	27	19.9	5	20.8
4	75	55.1	12	20
IPI Risk				
Low	31	22.8	8	33.3
Low intermediate	41	30.2	3	12.5
High intermediate	43	31.6	8	33.3
High	21	15.4	5	20.8
Disease in bone marrow				

Variables	All patients		T-cell patients only	
	n	% or mean (IQR)	n	% or mean (IQR)
No biopsy done	10	7.5	0	0.0
Yes	27	20.2	5	20.8
No	97	72.4	19	79.2
HIV status				
Positive	10	7.3	1	4.2
Negative	73	53.7	16	66.7
Unknown	53	39.0	7	29.8
Smoking				
Never smoker	63	46.3	11	45.8
Former smoker	37	27.2	4	16.7
Current smoker	36	26.4	9	37.5
Body mass index		28.6 (23.4,31.9)		29.8 (22.2,34.2)

N: number of patients; IQR: interquartile range; ALK: anaplastic lymphoma kinase; IPI: International Prognostic Index

Table 2
Treatment characteristics and outcomes of the study population (N=136) and the subset of T-cell lymphoma patients (n=24)

Variable	All patients		T-cell patients only	
	n	%	n	%
Dose adjusted by nadir				
No	66	48.5	10	41.7
Yes	67	49.3	13	54.2
Unknown	3	2.2	1	4.1
Adjustment below dose level 1				
No	31	46.3	3	23.1
Yes	36	53.7	10	76.9
Vincristine dose-capped				
No	19	14.0	6	25.0
Yes	111	81.6	17	70.9
Unknown	6	4.4	1	4.1
Number of cycles completed				
1	16	11.8	3	12.5
2	11	8.1	2	8.3
3	5	3.7	0	0.0
4	11	8.1	5	20.8
5	8	5.9	2	8.3
6	75	55.2	11	45.8
7	1	0.7	1	4.2
8	9	6.6	0	0.0
Number of cycles delayed				
0	84	61.8	17	70.8
1	36	26.5	5	20.8
2	10	7.4	0	0
3	3	2.2	0	0
5	1	0.7	1	4.2
Unknown	2	1.4	1	4.2
Number of hospitalizations				
0	76	55.9	17	70.8
1	40	29.4	5	20.8
2	13	9.6	1	4.2
Unknown	7	5.1	1	4.2
Best response				
Complete	90	66.2	14	58.3

Variable	All patients		T-cell patients only	
	n	%	n	%
Partial	21	15.4	5	20.8
Stable disease	2	1.5	0	0
Relapsed disease or progression	15	11.0	3	12.5
Unknown	8	5.6	2	8.3
Receipt of subsequent chemotherapy				
No	91	66.9	9	37.5
Yes	44	32.3	15	62.5
Unknown	1	0.8	0	0
Receipt of stem cell transplant				
No	115	84.6	11	45.8
Yes	21	15.4	13	54.2
Type of transplant				
Autologous	18	85.7	11	84.6
Reduced-intensity allogeneic	2	9.5	1	7.7
Haploidentical	1	4.8	1	7.7

Table 3
Logistic regression analysis^a for odds of death, progression, or relapse at 2 years

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Disease in bone marrow	Yes	5.0	2.1,13.0	0.0004	10.4	2.5,43.5
	No	Ref		Ref		0.0013*
	No biopsy done	2.6	0.7,9.7	0.1562	10.5	1.6,71.2
Type	B-Cell	Ref		--		0.016*
	T-Cell	3.5	1.4,8.8	0.0072*		
Number of cycles completed	0.6	0.5,0.7	<.0001*	0.6	0.5,0.8	0.0003*
Receipt of subsequent chemotherapy	No	Ref		Ref		
	Yes	7.1	3.2,15.9	<.0001*	6.1	1.9,19.8
Vincristine dose capped	No	Ref		--		0.0027*
Smoking	Yes	1.4	0.5,3.8	0.5529		
	Never smoker	Ref		Ref		
	Former smoker	1.2	0.5,2.8	0.7434	0.3	0.1,1.3
Smoking	Current smoker	2.9	1.2,6.7	0.0142*	4.9	1.3,19.0
						0.0223*
IPI risk	Low	Ref		--		
	Low intermediate	0.9	0.3,2.5	0.8527		
	High intermediate	3.4	1.1,10.9	0.0379*		
	High	1.2	0.5,3.3	0.7027		

OR: odds ratio; CI: confidence interval; IPI: International Prognostic Index

d_p Covariates included in the multivariate model were selected using backward elimination (criteria to stay in the model was set at 0.2).

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