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R-CHOP without Radiation in Frontline Management of Primary Mediastinal B-cell Lymphoma

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Abstract

Prior to the introduction of rituximab, primary mediastinal B-cell lymphoma (PMBCL) had high rates of treatment failure with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), prompting the use of consolidative mediastinal radiation or more intensive chemotherapy regimens. Cure rates improved dramatically with rituximab, but mediastinal radiation was still commonly employed with R-CHOP. We performed a retrospective review of patients treated with R-CHOP alone without radiation for PMBCL. Of 43 patients with PMBCL, 16 received R-CHOP alone. High risk factors included 56% with bulky disease, 75% with elevated LDH, 25% with SVC syndrome, and 13% with stage IV disease. Three-year progression-free survival (PFS) and overall survival (OS) were 93% and 100% respectively. These results suggest that R-CHOP alone has a high cure rate in PMBCL, while avoiding the side effects of mediastinal radiation.

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Disclosure of Interest

Disclosure forms provided by the authors are available with the full text of this article online.

Keywords

primary mediastinal B-cell lymphoma; PMBCL; diffuse large B-cell lymphoma; DLBCL; R-CHOP; non-Hodgkin lymphoma

Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a subtype of diffuse large B-cell lymphoma (DLBCL) that is thought to arise from thymic B cells and shares many characteristics with nodular sclerosis Hodgkin lymphoma [1]. PMBCL commonly presents with an isolated, bulky, mediastinal mass and disproportionately affects women in the third to fourth decade of life [1].

Low cure rates of approximately 50% with cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) chemotherapy led to the use of consolidative mediastinal radiation and/or more intensive chemotherapy regimens [2–4]. Despite dramatic improvements in response rates with the introduction of rituximab (R), R-CHOP was historically administered with consolidative radiation [5]. Given the long-term risks of mediastinal radiation in this predominantly young, female population, including cardiovascular disease and secondary breast cancer, many investigators favored radiation-sparing regimens, such as R-CHOP with time intensification or R-CHOP followed by R-ICE or autologous bone marrow transplant [6–8]. A study at the NCI demonstrated 93% event free survival and 97% overall survival at 5 years with a regimen of dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-R-EPOCH), with no patients receiving consolidative mediastinal radiation. Additionally, while 35% had residual FDG-PET activity greater than mediastinal blood pool at the end of treatment, the positive predictive value of this finding was only 17% [9]. Based on these phase II findings, many oncologists adopted this regimen for patients with PMBCL. The Phase III Alliance study comparing R-CHOP to DA-R-EPOCH demonstrated no improvement in progression-free survival (PFS) or overall survival (OS) in patients with DLBCL treated with DA-R-EPOCH. While subset analyses were not presented, it seems unlikely that the study will answer whether one regimen is favored for PMBCL specifically [10]. Limited data exist on R-CHOP without planned mediastinal radiation in PMBCL [11–12].

At Johns Hopkins Hospital, many patients with PMBCL are treated with R-CHOP without planned consolidative mediastinal radiation, providing a unique opportunity to evaluate the efficacy of this regimen. We undertook a retrospective comparison of PFS and OS among patients with PMBCL treated with R-CHOP or other chemotherapy regimens, with or without radiation.

Methods

Patients

Patients with biopsy proven PMBCL between 2000 and 2016 were identified through query of a database kept by the Pathology Department at Johns Hopkins Hospital. We excluded patients with previously treated disease, those treated without rituximab, and those whose

treatment was not directed through a Johns Hopkins oncologist. We collected baseline demographic and disease-specific characteristics from the electronic medical records. Evaluation of response was by CT or PET/CT using standard criteria. The study was approved by the Johns Hopkins University Institutional Review Board.

Statistical analysis

Overall response rate (ORR) was defined as the proportion of patients with complete (CR) or partial response (PR) after the initial treatment regimen. PFS was defined from the initiation of the treatment to the first occurrence of disease progression or death, whichever occurred first. Patients who did not experience disease progression or death were censored at the date of last follow up. Descriptive statistics were used for patient characteristics by treatment groups. ORR and Kaplan-Meier estimates for PFS were reported. The treatment differences in PFS were assessed by Cox proportional hazard model where the hazard ratio (HR) and its 95% confidence interval (CI) were reported. In the intention-to-treat cohort for patients who received R-CHOP upfront without planned radiation, two clinical endpoints were considered. One was event-free survival (EFS) that considered patients with radiation or treatment escalation as treatment-failure event along with progression or death, whichever occurred first. The other alternative endpoint was PFS, defined as before, but now with censoring of patients at the date of radiation or escalation treatment. Kaplan-Meier estimates of the three year EFS and PFS in the upfront R-CHOP treatment cohort were reported.

Results

Forty-three patients were diagnosed with PMBCL and treated with chemotherapy and rituximab at our institution between 2000 and 2016. Patient and disease characteristics are summarized in Table 1. As expected, patients tended to be young (median age 36) and female (51%). High risk factors included elevated lactate dehydrogenase (LDH) in 67%, pericardial effusion in 40%, bulky disease in 47%, and superior vena cava (SVC) syndrome on presentation in 21%.

The ORR for the entire cohort was 98% (74% CR). Sixteen patients received R-CHOP alone without radiation or any additional upfront treatment and ten received R-CHOP plus consolidative mediastinal radiation. Among sixteen patients treated with R-CHOP alone, 25% had low (0), 44% had intermediate (1), and 31% had high risk (2–3) age-adjusted IPI (aaIPI) scores. aaIPI scores were 20% low, 50% intermediate, and 30% high risk for the 10 patients treated with R-CHOP plus radiation. ORR was 94% (75% CR) for the R-CHOP alone group. At the end of R-CHOP plus radiation, ORR was 100% (80% CR). Three-year PFS was 93% (95% CI: 82–100%) and OS was 100% in patients treated with R-CHOP alone, compared to 100% and 100% respectively with R-CHOP plus radiation (p=0.85 for PFS, Table 2). No deaths occurred in the R-CHOP alone group. One patient died in the radiation group 5.7 years after treatment as a result of a primitive neuroectodermal tumor in the right axilla.

Three of the sixteen R-CHOP alone patients had residual PET activity greater than blood pool on end of treatment imaging. None received additional treatment and there were no incidents of progression. Of the ten patients treated with R-CHOP plus radiation, seven had

planned radiation and three had radiation based on residual PET activity on end of treatment imaging. None of these patients had disease recurrence. The patients who received planned radiation tended to be treated earlier (median year of treatment 2004) compared with those who received R-CHOP alone (median year of treatment 2010). An additional seven patients treated from 2003 to 2006 as part of a clinical trial received 2–3 cycles of R-CHOP followed by R-ESHAP or R-ICE and autologous bone marrow transplant, based on residual activity on mid-treatment PET. Another patient received consolidation with cytarabine and etoposide under a pediatric regimen, and was excluded from subgroup analysis.

By intention-to-treat analysis, we grouped all 26 patients who received R-CHOP upfront without planned radiation, including patients who received radiation due to PR on end of treatment imaging (12%) and patients who underwent treatment escalation as part of a clinic trial based on mid-treatment PET (27%). The three year EFS for intention-to-treat R-CHOP alone was 57% (95% CI: 41–80%) and the three year PFS was 94% (95% CI: 84–100%) when censoring patients with radiation or treatment escalation at the date of radiation or treatment escalation (Table 2).

Nine patients received DA-R-EPOCH and none received consolidative radiation. The ORR and CR rates were 100% and 89% respectively. These patients tended to be treated more recently, from 2011–2016. Follow up data are limited by the recent adoption of this regimen at Johns Hopkins, but three of the nine patients (33%) had disease progression within two years of treatment.

Discussion

Consensus for the optimal treatment of PMBCL is lacking. The ideal regimen would eliminate the need for radiation as well as limit chemotherapy exposure to avoid long-term risk of cardiovascular disease and secondary malignancies in this predominantly young population. Impressive outcomes of greater than 90% PFS with DA-R-EPOCH without radiation are encouraging, but there is no phase III data comparing it to R-CHOP.

Here we present a cohort of patients with PMBCL treated with R-CHOP without planned radiation. We present the results using both intention-to-treat (ITT) and as-treated approaches. In the ITT analyses, the unplanned addition of radiation and/or escalation was considered in two different ways: as a treatment failure or as censoring. However, seven of these patients had therapy escalation based on mid-treatment PET, which is not a reliable indicator of the ultimate effectiveness of therapy. In addition, even end of treatment PET in PMBCL has a low positive predictive value. Based on previous studies of PET in PMBCL, most of these patients with PR would have ultimately been cured without further treatment [9]. Therefore, it would be conservative to consider those receiving radiation and/or escalation as failures. A reasonable alternative would be to censor the patients at the date of radiation or treatment escalation for PFS endpoint in ITT analysis. In addition to these two ITT analyses, we also presented results of as-treated analysis. This separates patients who received R-CHOP alone from those who received any other upfront therapy.

The three-year PFS in the R-CHOP alone as-treated group was 93%, with seemingly no benefit to adding radiation. These outcomes are similar to that seen in the prospective phase II study of DA-R-EPOCH. Recent multi-center retrospective data on DA-R-EPOCH in PMBCL indicates a more modest 85.9% estimated 3 year EFS [14]. In fact, the high PFS rate in the NIH cohort treated with DA-R-EPOCH is likely due in part to a policy of reimaging patients with a positive PET scan every six weeks rather than categorizing these patients upfront as treatment failures. Residual mass on CT or PET has been shown to be a poor predictor of ongoing disease activity and long-term response in PMBCL [15]. Eighteen of the fifty-one patients in the NIH cohort had residual PET activity greater than mediastinal blood pool and only three progressed [9]. Our study also included patients treated with DA-R-EPOCH. Due to the recent adoption of this regimen at our institution, this is only a small number of patients with limited follow up. This limits our ability to directly compare the regimens.

Our data on the use of radiation with R-CHOP is consistent with a recent multicenter retrospective review by Shah et al. comparing R-CHOP to DA-R-EPOCH. Despite a lower CR rate for R-CHOP, there was no difference in OS or PFS at two years. Patients receiving DA-R-EPOCH had higher rates of infection, neutropenic fever, and hospitalization for acute toxicities. Of those treated with R-CHOP, 59% received consolidative mediastinal radiation. At two years, there was no significant difference in PFS or OS by radiation status. In addition, radiation status was not correlated with response to initial chemotherapy [12]. In our study, there were sixteen patients treated with R-CHOP without radiation. One had SD, three had PR and twelve had CR. Of those with CR, PFS was 100% at 36 months. By ITT analysis, there were six patients with PR after a full course of R-CHOP alone. Three received radiation and three received no additional therapy. PFS for this group was also 100% at 36 months.

Our results support withholding radiation from patients with PMBCL treated with R-CHOP who achieve complete response to initial chemotherapy, since none of these patients had disease recurrence in our study. By ITT analysis, this comprised the majority of the patients treated with a complete course of R-CHOP in our study. There were six patients who received mediastinal radiation despite a CR after R-CHOP. These patients were treated from 2001–2005, when R-CHOP without radiation for PMBCL had not yet become common at our institution.

The decision of whether to use radiation in those treated with R-CHOP who have partial response to initial R-CHOP is less clear. In our study, three of six patients who achieved PR received radiation, and none had disease recurrence. End of treatment PET has poor positive predictive value in PMBCL. In the prospective study of DA-R-EPOCH by Dunleavy et al., eighteen of the fifty-one patients had residual PET activity greater than mediastinal blood pool at the end of treatment. These patients were observed with serial PET scans and only three ultimately had disease progression. This strategy of observation for positive end of treatment PET in PMBCL has not yet been prospectively evaluated for frontline R-CHOP but seems warranted based on the available data.

Seven patients in our study received more aggressive therapy as part of a prospective clinical trial after lack of complete metabolic response following 2–3 cycles of R-CHOP. There was one relapse in this group. While it is possible that the patients had more aggressive disease and responses may have been worse with R-CHOP alone, none of the patients underwent biopsy to confirm refractory disease. In addition, residual PET activity on mid-treatment imaging is of questionable significance, especially in light of poor predictive value of end of treatment PET in PMBCL.

There are some limitations pertaining to our observational data. Due to the small sample size and small number of events, adjustment for confounding was not feasible. Patients treated with DA-R-EPOCH had shorter median follow up. While choice of regimen was most dependent on treatment era and treating oncologist, the observational nature of the data and lack of adjustment suggests a possibility of selection bias. Although our study is limited by its small size, it represents one of the largest cohorts of patients treated with R-CHOP alone. In comparison, the multicenter study by Shah et al. comparing R-CHOP and DA-R-EPOCH in PMBCL contained 21 patients treated with R-CHOP alone without radiation [12]. The findings of this study were similar to our own, with 88% 2 year PFS for patients treated with R-CHOP without radiation. There was no statistical difference in PFS or OS between those treated with R-CHOP alone and those treated with R-CHOP plus radiation or DA-R-EPOCH. 59% of the patients treated with R-CHOP were treated with radiation [12].

The promising results of this and other retrospective analyses, along with the emerging data on the lack of benefit with DA-R-EPOCH over R-CHOP in DLBCL, should prompt a larger observational study of R-CHOP without radiation in the treatment of primary mediastinal B-cell lymphoma.

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Table 1.

Patient Characteristics by Treatment Status

	Overall* (n=43)	R-CHOP + radiation (n=10)	R-CHOP alone (n=16)	R-CHOP with escalation (n=7)	DA-R-EPOCH (n=9)
Median Follow-up (mon)	35.8	46.6	42.7	97.4	13.8
Age at Dx					
median(range)	36 (14,60)	40.5 (19,60)	36 (23,52)	41 (21,44)	33 (14,51)
Gender Female – n(%)					
	22 (51.2)	2 (20)	11 (68.8)	5 (71.4)	3(33.3)
Stage at Dx - n(%)					
III-IV	9 (20.9)	1(10)	3 (18.8)	4 (57.1)	1 (11.1)
LDH High **					
	29 (67.4)	8 (80)	12 (75)	5 (71.4)	3 (33.3)
ECOG PS – n(%)					
2–4	5 (11.6)	2 (20)	2 (12.5)	1 (14.3)	0
Age-adjusted IPI					
0	13 (30)	2 (20)	4 (25)	0	6 (66.7)
1	18 (42)	5 (50)	7 (43.8)	4 (57.1)	2 (22.2)
2	12 (28)	3 (30)	5 (31.2)	3 (42.9)	1 (11.1)
3	0	0	0	0	0
Pericardial effusion – n(%)					
	17 (39.5)	3 (30)	8 (50)	1 (14.3)	4 (44.4)
Pleural effusion - n(%)					
	13 (30.2)	4 (40)	3 (18.8)	2 (28.6)	4 (44.4)
Bulky-n(%)					
>10cm	20 (46.5)	5 (50)	9 (56.3)	3 (42.9)	3 (33.3)
SVC syndrome-n(%)					
	9 (20.9)	3 (30)	4 (25)	1 (14.3)	1 (11.1)

*One patient with RCHOP+HIDAC was not listed in the next following columns

**LDH high = LDH above the upper limit of normal

Table 2.

Results of clinical outcomes by treatment type

	n (%)	events	3yr PFS Prob	HR (95%CI)	p-value
Entire Cohort	43 (100)	6	0.89(0.80–1.00)	-	-
As-Treated Group *					
RCHOP + radiation	10 (23)	1	1	Reference	-
RCHOP alone	16 (37)	1	0.93(0.82–1.00)	0.77(0.05–12.43)	0.85
RCHOP escalation	7 (16)	1	1	0.90(0.06–14.56)	0.94
DA-R-EPOCH	9 (21)	3	0.51(0.21–1.00)	12.71(0.81–199.95)	0.07
ITT RCHOP Cohort	**n (%)**	**events**	**3-yr EFS/PFS Prob**		
EFS	26 (100)	11	0.57 (0.41–0.80)		
PFS	26 (100)	1	0.94 (0.84–1.00)		

Abbreviations: PFS: Progression-Free Survival; EFS: Event-Free Survival; ITT: Intention-to-Treat; yr: year; Prob: Probability, HR: Hazard Ratio

*One patient with RCHOP+HIDAC was not listed