Published in final edited form as:

Leuk Lymphoma. 2018 February ; 59(2): 505–508. doi:10.1080/10428194.2017.1339882.

***MYC* gene rearrangement in diffuse large B-cell lymphoma does not confer a worse prognosis following dose-adjusted EPOCH-R**

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Diffuse large B-cell lymphomas (DLBCL) are a molecularly and clinically heterogeneous group of diseases. Specific molecular events such as *MYC* rearrangement (*MYC*-R), which occurs in a number of B-cell lymphomas including DLBCL and high-grade B-cell lymphoma not otherwise specified (NOS), is associated with a worse prognosis [1–5]. In several retrospective studies, the presence of a *MYC*-R alone termed ‘single-hit’ or in combination with a BCL2 or BCL6 translocation termed ‘double-hit’ were associated with significantly lower 2-year survivals ranging from 35 to 59% following standard R-CHOP chemotherapy [6–8]. However, patients with *MYC*-R tumors who receive more intensive chemotherapy appear to have a significantly improved progression-free survival (PFS) compared to those who receive R-CHOP chemotherapy [9,10]. Thus, we hypothesized that the dose-intense dose-adjusted etopo-side, prednisone, vincristine, cyclophosphamide and doxorubicin with rituximab (DA-EPOCH-R) regimen would produce similar outcomes in patients with and without *MYC*-R [11–13]. It is also noteworthy that DA-EPOCH-R is highly effective in Burkitt lymphoma, which harbors *MYC*-R and requires dose intensive treatment [14].

We performed a retrospective analysis of newly diagnosed patients with DLBCL enrolled on one of two phase II studies of DA-EPOCH-R between June 1999 and April 2016 ([ClinicalTrials.gov](https://clinicaltrials.gov) NCT00001337 and NCT00006436) [11,15]. Among 161 patients enrolled, 85 (53%) patients had available tissue for analysis of *MYC*-R. The majority of the cases were referred from outside institutions and repeat biopsy was not required, limiting the

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Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at <https://doi.org/10.1080/10428194.2017.1339882>.

amount of available tissue for analysis. *MYC*-R was assessed by fluorescence *in situ* hybridization (FISH) using a breakapart probe and was scored as positive if greater than 10% of the nuclei were rearranged [16].

Eligibility criteria for the phase II studies included *de novo* DLBCL, no prior treatment, age >18 years, ECOG 0–4, adequate organ function unless due to disease, and stage I–IV disease. Eligibility assessments included standard laboratory tests, whole-body CT scans, and history and physical. Patients were provided written informed consent in accordance with the Declaration of Helsinki, and the studies were approved by the institutional review board.

Among the 85 patients assessed by FISH for *MYC*-R, 13 (15%) were positive and 72 (85%) were negative for a rearrangement. The clinical characteristics of all patients included a median age 50 years (range 9–90), stage III/IV disease in 78%, elevated lactate dehydrogenase (LDH) in 62%, high-intermediate/high-risk disease in 43%, and HIV infection in 39% (Table 1). There were only three (4%) patients with stage I disease, all of whom were HIV positive. In the HIV patients, anti-retroviral therapy was either suspended or among treatment naïve patients, not initiated until completion of chemotherapy. A comparison of clinical characteristics between patients with and without a *MYC*-R was performed (Table 1). The association of *MYC*-R with age was determined by an exact Wilcoxon rank-sum test. The association between *MYC*-R and a set of dichotomous parameters was determined by Fisher's exact test while the association of *MYC*-R with the international prognostic index was treated as an ordered categorical parameter and determined using an exact Cochran–Armitage test for trend. As shown in Table 1, there was no significant difference in these clinical characteristics.

We also compared outcomes among patients with and without *MYC*-R. Overall survival (OS) was determined from the on-study date until date of death or last follow-up. Time to progression (TTP) was determined from on-study date until the date of progression or last follow-up; patients who died without progression had their follow-up censored at the date of death. PFS was determined from the on-study date until the date of progression, or death if no progression occurred, or last follow-up; both progressions and deaths were considered as events. The probability of survival, TTP, or PFS was determined by the Kaplan–Meier method. The statistical significance of the difference between a pair of Kaplan–Meier curves was determined by a log-rank test. All *p* values are two-tailed and presented without any adjustment for multiple comparisons. With a median potential follow-up of 11.7 years, the 5-year OS probability was 73.6%, TTP was 74.1%, and PFS was 64.5% for all 85 patients in the study (Figure 1(A–C)). When outcomes were analyzed according to the presence or absence of *MYC*-R, there were no significant differences overall, with 5-year OS of 63.5 versus 75.3% (*p* = .89), TTP of 68.6 versus 74.8% (*p* = .87), and PFS of 57.1 versus 65.5% (*p* = .85), respectively (Figure 1(D–F)). There were 13 deaths unrelated to lymphoma, which included five secondary malignancies, one HIV complication, one complication from drugs, one sepsis, one subdural bleed, one radiation induced dementia, one unknown, one stroke and one liver failure.

We undertook this retrospective analysis to determine if *MYC*-R was associated with a worse prognosis following DA-EPOCH-R as a prelude to the development of a prospective study of DA-EPOCH-R in *MYC*-R DLBCL. While this data is limited by the retrospective study design, it was performed in an unselected population of patients with DLBCL enrolled on two prospective studies of DA-EPOCH-R, and has a mature median potential follow-up of 11.7 years. To confirm there was no sample acquisition bias, since tissue was only present for analysis on 53% of patients, we compared our patients to patients on the Phase II study of DA-EPOCH-R in untreated DLBCL [11]. There was no difference between patient characteristics in our retrospective data compared to the prospective study (data not shown). The presence of a *MYC*-R in 15% of our patients is similar to other studies [3,17,18]. In the present analysis, we observed no difference in OS, TTP or PFS among patients with and without a *MYC*-R, suggesting that unlike R-CHOP, DA-EPOCH-R may overcome the adverse effects of *MYC*-R patients. It is noteworthy that the clinical characteristics of patients with *MYC*-R were similar to those without a rearrangement in our series. However, a difference between the groups may be obscured by the relatively poor clinical characteristics of both groups, which likely reflects the inclusion of HIV positive DLBCL. Interestingly, one series has reported that *MYC* negative patients are more likely to have elevated LDH and IPI 3–5 [18]. Several retrospective studies suggest that dose intensive treatments are more effective than R-CHOP. In a retrospective analysis of double-hit DLBCL treated with DA-EPOCH-R, R-Hyper CVAD, R-CODOXMVAC or R-CHOP, the dose-intensive regimens all produced significantly better PFS compared to R-CHOP with no differences among the dose intensive regimens [10]. There seems to be a range of older patients more likely to receive R-CHOP or DA-EPOCH-R, potentially biasing their use in poorer prognosis patients. In a retrospective study of double-hit lymphomas from MD Anderson, patients who received DA-EPOCH-R had a better EFS compared to patients who received R-Hyper-CVAD/MA or R-CHOP [9]. Unfortunately, we were unable to probe for *BCL2* rearrangements secondary to inadequate tissue. While we recognize this is a limitation of our study, multiple series have shown that from 30 to 74% of *MYC*-R patients also harbor a *BCL2* rearrangement [17,19], which suggests a reasonable proportion of patients in our study harbored double hits. Furthermore, a number of studies have not found that a second translocation in addition to *MYC*-R significantly impacts the prognosis [17,20]. Based on the results of our retrospective analysis and supported by the aforementioned studies, we instituted a prospective multicenter study of DA-EPOCH-R in *MYC*-R DLBCL, which recently completed accrual.

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Figure 1.

Kaplan–Meier curves of outcomes for all patients reported at 5 years [95% confidence interval (CI) range]. (A) OS for all patients 73.6% (61.4–82.5). (B) TTP for all patients 74.1% (62.3–82.7). (C) PFS for all patients 64.5% (52.4–74.3). (D) OS in *MYC* rearranged 63.5% (23.8–86.6) versus *MYC* negative 75.3% (62.6–84.2) $p = .89$. (E) TTP in *MYC* rearranged 68.6% (30.5–88.7) versus *MYC* negative 74.8% (62.0–83.8) $p = .87$. (F) PFS in *MYC* rearranged 57.1% (21.7–81.5) versus *MYC* negative 65.5% (52.6–75.7) $p = .85$.

Table 1.

Patient characteristics in all patients, MYC-R, and MYC negative.

Characteristic	All patients (N = 85)	MYC-R (N = 13)	MYC negative (N = 72)	p Value ^a
Age				
Median	50	52	49	.34
Range	9–90	36–77	9–90	
International prognostic index (IPI), n (%)				
Low (0–1)	27 (32)	5 (38)	22 (31)	1.00
Low-intermediate (2)	21 (25)	2 (15)	19 (26)	
Intermediate-high (3)	23 (27)	3 (23)	20 (28)	
High (4–5)	14 (16)	3 (23)	11 (15)	
Sex, n (%)				
Male	60 (71)	11 (85)	49 (68)	.33
Female	25 (29)	2 (15)	23 (32)	
Elevated LDH, n (%)				
<ULN	32 (38)	8 (62)	24 (33)	.067
>ULN	53 (62)	5 (38)	48 (67)	
ECOG, n (%)				
0–1	60 (71)	10 (77)	50 (69)	.75
>2	25 (29)	3 (23)	22 (31)	
Extranodal involvement, n (%)				
0–1 sites	55 (65)	8 (62)	47 (65)	.76
>2 sites	30 (35)	5 (38)	25 (35)	
Stage, n (%)				
I/II	19 (22)	3 (23)	16 (22)	1.00
III/IV	66 (78)	10 (77)	56 (78)	
HIV status, n (%)				
Positive	33 (39)	4 (31)	29 (40)	.76
Negative	52 (61)	9 (69)	43 (60)	

^aRepresents comparison between MYC-R and MYC negative patients.