CODOX-M/IVAC-R *versus* DA-EPOCH-R in double-hit/triple-hit lymphoma patients aged 60 years or under

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Abstract

Intensified chemoimmunotherapy regimens are often used in young patients with double-hit and triple-hit lymphoma (DHL/THL) despite no survival benefit compared to R-CHOP. Favorable retrospective reports on the application of CODOX-M/IVAC-R are subject to selection bias as only young fit patients can tolerate this treatment. We conducted a retrospective analysis to investigate outcome differences between CODOX-M/IVAC-R and DA-EPOCH-R in DHL/THL patients aged 60 years or younger. One hundred and thirteen patients were identified; CODOX-M/IVAC-R (N=49) and DA-EPOCH-R (N=64). Eighty percent (39/49) achieved complete (CR) after completing CODOX-M/IVAC-R compared to 58% (37/64) with DA-EPOCH-R. The median follow-up was 5.3 years and 3.3 years for the CODOX-M/IVAC-R and DA-EPOCH-R group respectively. CODOX-M/IVAC-R demonstrated superior event-free survival (EFS) on univariate (hazard ratio [HR]=0.54, 95% confidence interval [CI]: 0.31-0.97) and multivariable analysis adjusted for age, *BCL* translocation (*BCL2 vs. BCL6 vs.* both), International Prognostic Index score and receipt of autologous stem cell transplant (adjusted HR [aHR]=0.52, 95% CI: 0.29-0.93); however there was no significant influence on OS (aHR=0.92, 95% CI: 0.46-1.84). The 1, 2 and 5 years EFS in the CODOX-M/IVAC-R group was 68.3%, 64.1% and 61.5%, respectively compared to 52.4%, 48.9% and 39.5%, respectively in the DA-EPOCH-R group. Primary refractory disease or relapse (R/R) occurred in 33% (16/49) of CODOX-M/IVAC-R and 54% (35/64) of DA-EPOCH-R recipients, and produced median OS of 10.3 months and 33.7 months, respectively, indicating poor outcomes in the CODOX-M/IVAC-R subgroup with R/R disease. More patients were able to receive subsequent salvage therapies in the DA-EPOCH-R group. No patients died of regimen toxicity and the rates of central nervous system relapse and therapy related hematologic neoplasms were similar in both groups.

Introduction

Patients with high-grade B-cell lymphoma (HGBL) including double-hit lymphoma (DHL) and triple-hit lymphoma (THL) have a more aggressive clinical presentation, shorter response to conventional R-CHOP therapy, and higher frequency of extra-nodal and central nervous system (CNS) involvement compared to patients with diffuse large B-cell lymphoma-not otherwise specified (DLBCL-NOS).[1-4] The median overall survival (OS) has been reported to range between 4.5 months to 34 months in various series.[1,5-8] However, the 2022 revision of the World Health Organization (WHO) classification of lymphoid neoplasms (WHO-HAEM5) has redefined the HGBL category such that it comprises only aggressive B-cell lymphomas that are genetically double-hit (DH) with dual *MYC* and *BCL2* rearrangements on fluorescence *in situ* hybridization (FISH) studies (MYC-BCL2 DHL) or triple-hit (TH) with rearrangements in *MYC, BCL2* and *BCL6* (MYC-BCL2-BCL6 THL).[9,10] In the WHO-HAEM5 classification, DHL with rearrangements in *MYC* and *BCL6* but lacking *BCL2* rearrangements (MYC-BCL6 DHL) are reclassified according to morphology as either DLBCL-NOS or HGBL-NOS mainly due to the heterogeneity in their gene expression and molecular profile compared to MYC-BCL2 DHL.[10-13] Additionally, it has been reported that prognosis of patients with MYC-BCL6 DHL may be better than those with MYC-BCL2 DHL.[8]

There is no standardized induction chemoimmunotherapy regimen for patients with DHL/THL. However, the associated poor outcomes have led to the utilization of intensified chemoimmunotherapy regimens despite the lack of prospective trials demonstrating survival benefit over conventional R-CHOP therapy in this subgroup of patients. Induction regimens that have been used include R-CHOP

with or without consolidative autologous stem cell transplant (ASCT) or the more intensive regimens such as DA-EPOCH-R, CODOX-M/IVAC-R, R-Hyper-CVAD and R-ACVBP.[14] The results of previous studies show conflicting results as to whether the more intensive regimens are better than standard R-CHOP.[1,14-16]

The use of hyper-fractionated alkylating agents and incorporating multiple agents that penetrate the CNS such as in the CODOX-M/IVAC-R regimen may have beneficial treatment outcomes in MYC-driven aggressive lymphomas. CODOX-M/IVAC-R is highly effective in the treatment of Burkitt lymphoma, but this comes with significant toxicity.[17-19] Some reports have documented favorable outcomes with this therapy in patients with HGBL.[20-22] In a retrospective study, CODOX-M/IVAC-R produced more favorable outcomes compared to R-CHOP and other intensified regimens (DA-EPOCH-R, R-Hyper-CVAD), with a statistically significant improvement in the 12 months event-free survival (EFS) in the 17 patients who received CODOX-M/IVAC-R compared to the 59 patients who received R-CHOP, DA-EPOCH-R and Hyper-CVAD (72% *vs*. 39%; *P*=0.04); this lost statistical significance after adjusting for age. A trend towards an improved OS (hazard ratio [HR]=0.37; 95% confidence interval [CI]: 0.11-1.23; *P*=0.10) was observed, although a selection bias may have played a role as most patients who received CODOX-M/IVAC-R were younger than 60 years.[22]

Young patients with DHL/THL frequently receive one of the intensive chemoimmunotherapy regimens whereas patients over 60 years of age often receive R-CHOP. There are important differences between CODOX-M/IVAC-R and DA-EPOCH-R. CODOX-M/IVAC-R must be given in the hospital and even once discharged the patient needs to stay close to the treatment center. It does have the advantage of only four cycles of therapy. DA-EPOCH-R can be given as an outpatient with an infusion pump but patients often elect hospitalization; six cycles is the standard. Based on these facts and the prior highlighted reports demonstrating favorable outcomes with CODOX-M/IVAC-R but with the possibility of age-related selection bias; we aimed to study the outcome difference between patients who received CODOX-M/IVAC-R and individuals who received DA-EPOCH-R for treatment of DHL/THL in a larger cohort of patients who are 60 years or younger at diagnosis in an effort to mitigate age related selection bias.

Methods

This retrospective study received approval by the Mayo Clinic Institutional Review Board. Patient cases were identified through Epic electronic medical records chart review including individuals diagnosed with DHL/THL between July 15, 2010 and October 19, 2023 and received medical care at the Mayo Clinic. Over this period, selection between DA-EPOCH-R and CODOX-M/IVAC-R in young patients with DHL/THL was based on the preference of different Mayo physicians. DHL/THL cases were defined by morphology and FISH results. Morphology was determined by pathology report and could have features of HGBL, large B-cell lymphoma or in between. Stratification into DHL or THL relied on FISH results. DHL was defined genetically via FISH as having rearrangement of *MYC* along with *BCL2* (MYC-BCL2 DHL) or *BCL6* (MYC-BCL6 DHL). THL was defined as having rearrangement of *MYC* as well as *BCL2* and *BCL6* (MYC-BCL2-BCL6 THL). Inclusion criteria were patients who were 60 years old or younger at diagnosis of DHL/THL and either received CODOX-M/IVAC-R or DA-EPOCH-R for induction treatment. DHL/THL transformed from low-grade indolent B-cell lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) even if received prior lines of therapy for low-grade B-cell lymphoma were included. Patients with no available FISH reports in the chart were excluded. Cell of origin was determined by the Hans classifier.[23]

Medical records were also reviewed to obtain data on salvage treatment, development of therapy-related myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML), CNS relapse and cause of death.

Data were analyzed using 'R' statistical software, version 4.3.2. Quantitative discrete and continuous variables were described as a median and interquartile range; categorical variables were described as a number and percentage. Group comparisons were performed using Fischer's exact or χ^2 tests. Quantitative discrete variables were compared using the Wilcoxon rank-sum test.

Univariate and multivariate analyses of factors associated with survival were performed using the Cox proportional hazards regression model. *A priori* prespecified prognostic factors included in the model were age, receipt of consolidation with autologous stem cell transplantation, International Prognostic Index (IPI) for DLBCL and *BCL* translocation status (*BCL2 vs. BCL6 vs.* both). A two-side *P* value of <0.05 was considered statistically significant. EFS was defined as the time from diagnosis to progression, relapse, retreatment after initial chemotherapy, or death of any cause. OS was defined as the time from diagnosis to death of any cause or to last follow-up.

Results

Patient, therapy, and tumor characteristics

One hundred and thirteen patients were identified, 57% (64/113) were treated with DA-EPOCH-R and 43% (49/113) received CODOX-M/IVAC-R. The median number of administered DA-EPOCH-R cycles was six (interquartile range [IQR], 6-5). Fourteen percent (9/64) of the DA-EPOCH-R group did not complete intended therapy including eight patients who experienced disease progression while receiving treatment and one patient who stopped treatment

due to declining performance status. The median number of CODOX-M/IVAC-R cycles administered was four (IQR, 4-4). Four percent (2/49) of the CODOX-M/IVAC-R group did not complete intended treatment including one patient who had disease progression on treatment and one patient who stopped therapy due to treatment intolerance. Table 1 illustrates patient and disease characteristics in each treatment group. The percentage of patients with at least one comorbidity according to the Charlson Comorbidity Index (CCI) was similar between the DA-EPOCH-R and CODOX-M/IVAC-R groups (13% *vs*. 14%, respectively). The median CCI score (excluding age and a history of lymphoma) for the DA-EPOCH-R and CODOX-M/IVAC-R groups were both zero (IQR, 0-1). Two patients in the DA-EPOCH-R group and no patients in the CODOX-M/IVAC-R group had >1 comorbidity. Types of comorbidities were well balanced between the two groups, except for cardiac disease history (myocardial infarction or congestive heart failure) which was reported in four patients in the DA-EPOCH-R group but in none of the CODOX-M/IVAC-R group.

Therapy outcomes

The percentage of patients who achieved complete remission (CR) on end of treatment (EOT) positron emission

Table1. Patient and disease characteristics in each treatment group.

Characteristic	Therapy			
	Overall N=113[1]	DA-R-EPOCH N=64[1]	R-CODOX-M/IVAC-R N=49[1]	*P*[2]
Age in years, median (IQR)	54 (44-57)	55 (46-57)	53 (44-57)	0.4
Female	61 (54)	30 (47)	31 (63)	0.08
ECOG 0-1 2 Unknown	 107 (96) 5 (4.5) 1	 62 (97) 2 (3.1) 0	 45 (94) 3 (6.3) 1	0.6
IPI 0-1 2 3-4	 27 (24) 50 (44) 36 (32)	 21 (33) 27 (42) 16 (25)	 6 (12) 23 (47) 20 (41)	0.027
Extra-nodal disease >1 extra-nodal site	89 (79) 40 (35)	48 (75) 21 (33)	41 (84) 19 (39)	0.3 0.5
Bone marrow involvement	12 (11)	7 (11)	5 (10)	>0.9
DHL *versus* THL DHL THL	 82 (73) 31 (27)	 49 (77) 15 (23)	 33 (67) 16 (33)	0.3
Translocations *MYC-BCL2* *MYC-BCL6* *MYC-BCL2-BCL6*	 66 (58) 16 (14) 31 (27)	 40 (63) 9 (14) 15 (23)	 26 (53) 7 (14) 16 (33)	0.5
Stage I/II III/IV	 17 (15) 96 (85)	 14 (22) 50 (78)	 3 (6.1) 46 (94)	0.020
Immunophenotype (Hans algorithm) GCB Non-GCB Unknown	 104 (95) 5 (4.6) 4	 62 (98) 1 (1.6) 1	 42 (91) 4 (8.7) 3	0.2
De novo versus transformed De novo Transformed	 84 (74) 29 (26)	 46 (72) 18 (28)	 38 (78) 11 (22)	0.5
ASCT consolidation	22 (19)	11 (17)	11 (22)	0.5

[1]Median (IQR), N (%). [2]Wilcoxon rank sum test; Pearson's χ^2 test; IQR: interquartile range; Fisher's exact test. ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; DHL: double-hit lymphoma; THL: triple-hit lymphoma; GCB: germinal center B cell; ASCT: autologous stem cell transplant.

tomography-computed tomography scan (PET-CT) in the CODOX-M/IVAC-R group and DA-EPOCH-R group was 80% (39/49) and 58% (37/64) respectively. The median follow-up time was 5.3 and 3.3 years for the CODOX-M/IVAC-R and DA-EPOCH-R group respectively. CODOX-M/IVAC-R was associated with superior EFS on univariate (HR=0.54; 95% CI: 0.31-0.97) and multivariable analysis adjusted for age, *BCL* translocation status (*BCL2 vs. BCL6 vs.* both), IPI and receipt of consolidation ASCT (adjusted HR [aHR]=0.52; 95% CI: 0.29-0.93). However, there was no significant association with OS (aHR=0.92; 95% CI: 0.46-1.84). The EFS for the CODOX-M/IVAC-R group at 1, 2 and 5 years was 68.3%, 64.1% and 61.5%, respectively compared to 52.4%, 48.9% and 39.5%, respectively in the DA-EPOCH-R group (*P*=0.035) (Figure 1).

In light of the WHO22-HAEM5 classification,[10] we examined whether the 16 patients with MYC-BCL6 DHL have more favorable outcomes with either therapy. On univariate analysis compared to DHL patients with *BCL2* rearrangements, patients with BCL6-DHL had comparable EFS (HR=0.69; 95% CI: 0.29-1.65; *P*=0.41) and OS (HR=1.06; 95% CI: 0.40-2.81; *P*=0.92). These results were unchanged when adjusting for the treatment received; EFS (aHR=0.70; 95% CI: 0.30-0.95; *P*=0.41) and OS (aHR=1.06; 95% CI: 0.40-2.84; *P*=0.90). When analysis was restricted to only patients with a MYC-BCL6 rearrangement (N=16), there was no significant difference in EFS (*P*=0.2) or OS (*P*=0.22) between the two treatment groups on univariate Cox proportional hazards modeling. We also evaluated whether transformed DHL/THL patients had more favorable outcomes with either therapy. On univariate analysis, transformed DHL/THL was associated with comparable outcomes to *de novo* disease in EFS (HR=1.37; 95% CI: 0.76-2.50; *P*=0.30) and OS (HR=1.37; 95% CI: 0.66-2.84; *P*=0.41). On multivariable analysis adjusted for treatment received, transformed disease had similar results again: EFS (HR=1.30; 95% CI: 0.72-2.37; *P*=0.38) and OS (HR=1.36; 95% CI: 0.65-2.84; *P*=0.42).

Twenty-two percent (N=11/49) of CODOX-M/IVAC-R and 17%

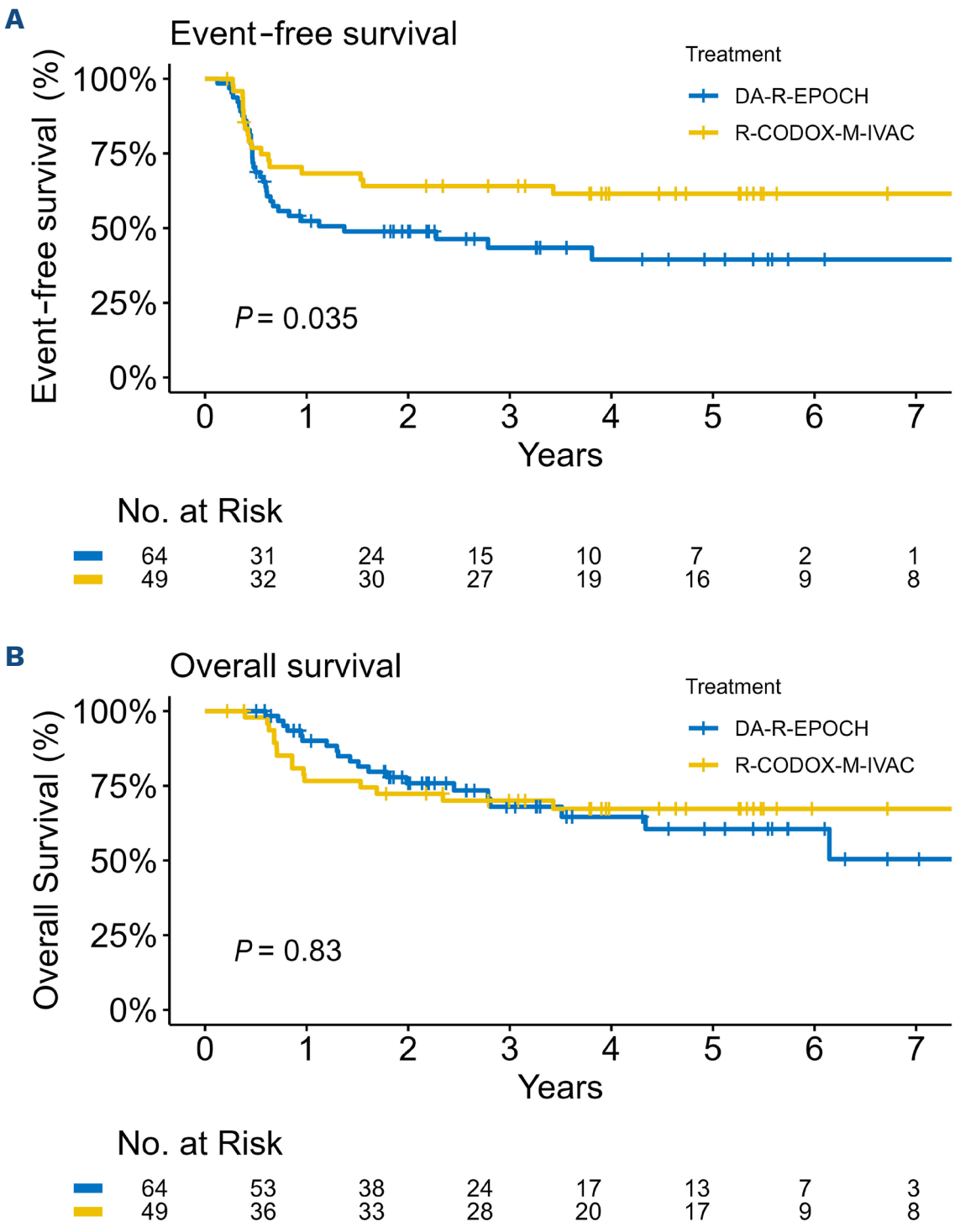

Figure 1. Comparison of outcomes based on frontline treatment regimens in patients with double-hit lymphoma or triple-hit lymphoma who are ≤60 years old. (A) Event-free survival stratified by treatment regimen, comparing CODOX-M/IVAC-R and DA-EPOCH-R. (B) Overall survival stratified by treatment regimen, comparing CODOX-M/IVAC-R and DA-EPOCH-R.

(11/64) of DA-EPOCH-R patients received ASCT consolidation after induction therapy. ASCT produced superior EFS compared to no ASCT on univariate (HR=0.30; 95% CI=0.14-1.13; *P*=0.011) and multivariable analysis adjusted for age, treatment and BCL translocation status (aHR=0.28; 95% CI=0.11-0.70; *P*=0.0069). However, ASCT was used almost exclusively in patients who attained a CR following induction (except for 1 patient who obtained a PR) and when the effect of ASCT was restricted to patients who had obtained a CR following induction therapy, there was no significant difference observed in EFS (HR=0.69; 95% CI: 0.23-2.13; *P*=0.52) and OS (HR=1.3; 95% CI: 0.38-4.45; *P*=0.68).

Outcomes for patients with refractory/relapsed disease

Thirty-three percent (16/49) of the CODOX-M/IVAC-R patients had refractory or relapsed (R/R) disease. This included patients who did not have a CR on EOT PET-CT (10/49 including 9 with refractory disease and 1 with partial

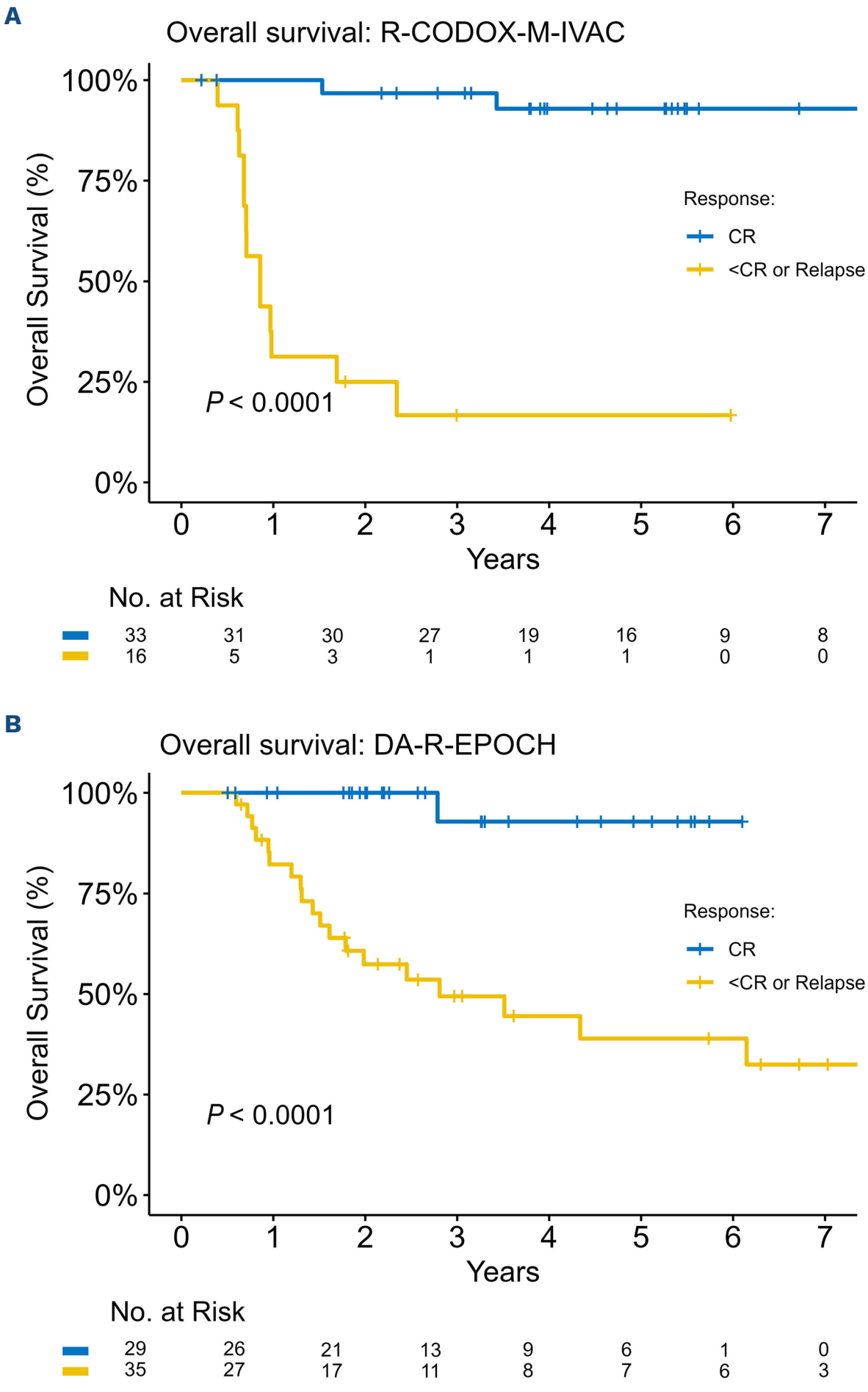

Figure 2. Overall survival is compared between patients who achieved sustained complete remission after induction treatment and those with relapsed/refractory disease. (A) Patients treated with CODOX-M/IVAC-R. (B) Patients treated with DA-EPOCH-R. CR: complete remission.

response) or who had relapsed disease (6/49, 12%). The percentage of patients with R/R disease in the DA-EPOCH-R group was 54% (35/64) including 42% (27/64) who did not achieve CR on EOT PET-CT (22 refractory, 3 partial response [PR], 1 stable disease, 1 undocumented response) and 13% (8/64) who relapsed later. The median OS for the patients who had R/R disease after receiving CODOX-M/IVAC-R was 10.3 months compared to 33.7 months in the R/R DA-EPOCH-R group (Figure 2). More patients in the DA-EPOCH-R with R/R disease were able to receive salvage therapy and proceed to undergo ASCT, allogeneic stem cell transplant and/or receive chimeric antigen receptor (CAR) T cells. (Figure 3).

Prior lines of therapy in patients with transformed disease

Among the 18 patients with transformed disease who received DA-EPOCH-R, 39% (N=7) had previously undergone treatment for indolent B-cell lymphoma. Of these, five patients had received one prior line of therapy (4 with bendamustine + rituximab and 1 with rituximab alone), while two had undergone four lines of therapy each. One of these two patients had received rituximab, CVP chemotherapy, ibritumomab tiuxetan, and bendamustine plus rituximab (BR), and the other patient had received chlorambucil + prednisone, CVP-R, radiation, and BR.

In the CODOX-M/IVAC-R group, 11 patients had transformed disease, with 55% (N=6) having received prior therapy for indolent B-cell lymphoma. Of these six, five had received one line of therapy (3 with BR, 1 with CHOP chemotherapy, and 1 with radiation alone), and one had received two lines of therapy (ABVD chemotherapy and RICE chemoimmunotherapy followed by ASCT consolidation).

Therapy-related hematologic neoplasm, central nervous system relapse and cause of death

None of the patients who received CODOX-M/IVAC-R or DA-EPOCH-R died of regimen related toxicity, excluding one

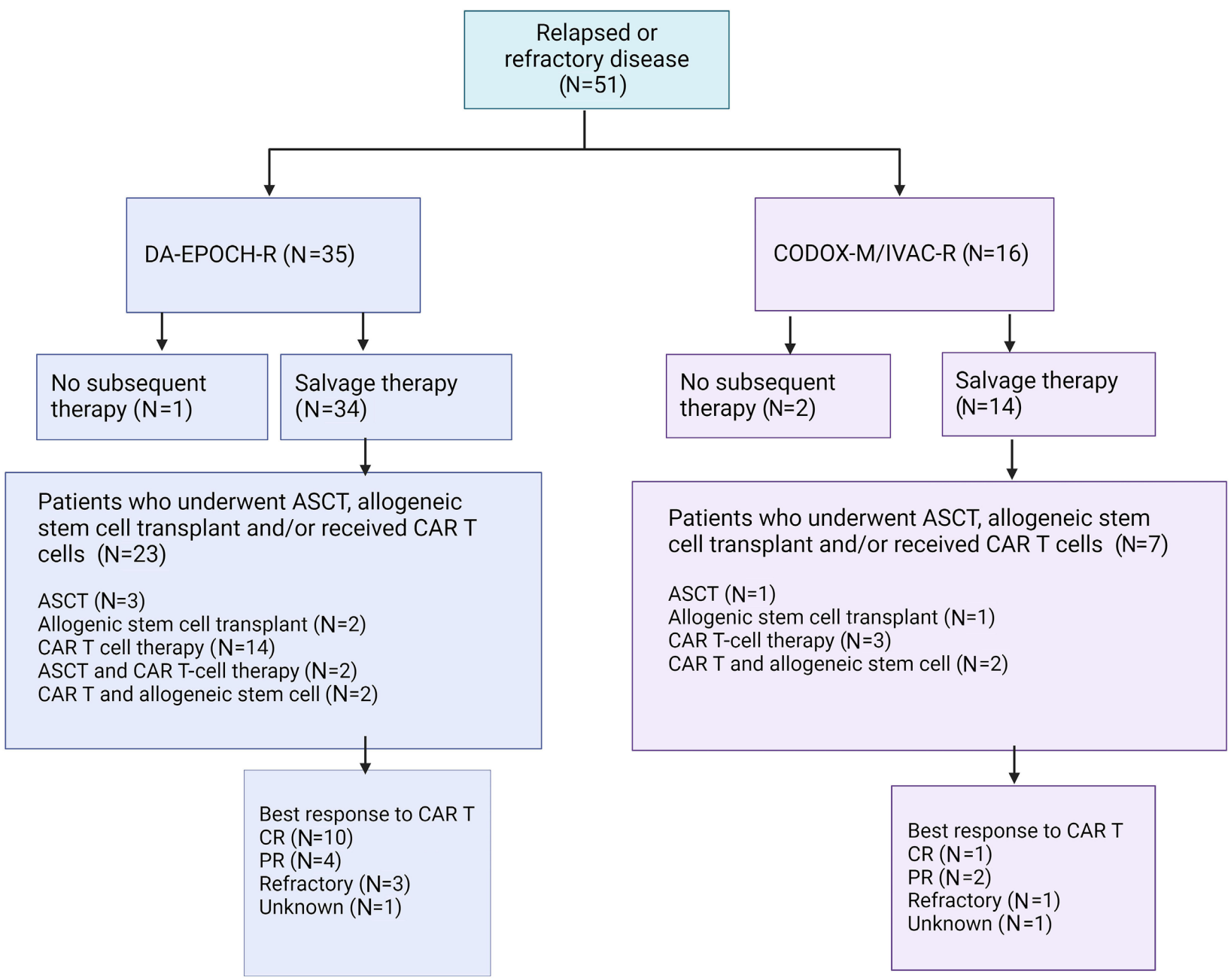

Figure 3. The number of patients who experienced refractory/relapsed disease within each of the DA-EPOCH-R and CODOX-M/IVAC-R groups and received subsequent therapy including individuals who underwent autologous stem cell transplant, allogeneic stem cell transplant and/or received CAR T cells. ASCT: autologous stem cell transplant; CAR: chimeric antigen receptor.

patient who died of therapy-related AML in the CODOX-M/IVAC-R group.

The DA-EPOCH-R included intrathecal chemotherapy for CNS disease prophylaxis, however, 13% (8/64) received additional high-dose methotrexate (HDMTX) for CNS prophylaxis. CNS relapses occurred in 4.7% (3/64) of patients who received DA-EPOCH-R; all of whom died of disease. One patient treated with DA-EPOCH-R had CNS disease at initial diagnosis. All three patients with CNS relapses received prior intrathecal chemotherapy for CNS prophylaxis and one also received HDMTX. Among the 31% (20/64) of patients who died in the DA-EPOCH-R group, 17 patients died of lymphoma progression while three died of other causes including one patient who died of lung cancer, one patient died of COVID 19 pneumonia, and one patient died of progressive multifocal leukoencephalopathy. The incidence of developing therapy-related hematologic neoplasm (AML/MDS) was 4.7% (3/64) in the DA-EPOCH-R arm.

Fifteen patients (30.6%) died in the CODOX-M/IVAC-R group. Four of the 15 patients died of causes unrelated to lymphoma including one patient died of CAR T-cell therapy-related complications (despite achieving response), one died of an unrelated neurological syndrome, one died of allogeneic stem cell transplant complications and one patient died of therapy-related AML. Four percent (2/49) developed CNS relapse without having CNS disease at initial diagnosis. One patient treated with CODOX-M/IVAC-R had CNS disease at initial diagnosis, did not respond to treatment and was palliated. In addition, 4.1% (2/49) developed therapy-related AML/MDS.

Discussion

There is currently no standard induction regimen choice for treatment of patients with DHL/THL. The results of previous studies show conflicting results as to whether the more intensive regimens are better than standard R-CHOP. A large retrospective study (N=129) by Oki *et al*. showed more favorable outcomes in DHL/THL patients treated with intensive treatment regimens compared to R-CHOP.[16] Petrich *et al*. showed a superior median progression-free survival (PFS) in patients who underwent induction treatment with DA-EPOCH-R (*P*=0.0463), R-Hyper-CVAD (*P*=0.001) and CODOX-M/IVAC-R (*P*=0.036) compared to R-CHOP however no survival benefit was observed.[1] In the systematic meta-analysis by Howlett *et al*. there was reduced risk of progression with DA-EPOCH-R compared to R-CHOP (relative risk reduction of 34%; *P*=0·032) with no OS benefit.[15] In a prospective phase II study that involved 24 patients with DHL treated with DA-EPOCH-R, the 4-year OS rate after a median follow-up of 55.6 months was 82% in the DHL/THL group, higher than historical data.[24] However, real-world studies of DHL patients treated with DA-EPOCH-R showed inferior survival outcomes compared to the data from the prospective phase II study.[25-27] Additionally, the role of consolidation with ASCT after an intensive chemoimmunotherapy regimen has shown benefit only if R-CHOP is the upfront regimen.[28]

Some reports have documented favorable outcomes with CODOX-M/IVAC-R in patients with HGBL.[20-22] Sun *et al*. reported on 25 patients who received CODOX-M/IVAC-R including 16 patients who had subsequent consolidation with ASCT. The 2-year PFS and 2-year OS in these 16 patients were 60% and 82% respectively.[21] A single-center series demonstrated favorable outcomes when using CODOX-M/IVAC-R for treatment of DHL/THL compared to R-CHOP and intensive regimens including DA-EPOCH-R and R-Hyper CVAD.[22] However, the CODOX-M/IVAC-R sample size was limited (N=17). Additionally, the possibility of age-related selection bias leading to superior outcomes in the CODOX-M/IVAC-R was acknowledged in the report as most of the patients (12/17) who received CODOX-M/IVAC-R were 60 years old or younger at diagnosis compared to the DA-EPOCH-R group who only had three patients aged 60 years or younger.

Our findings in a large sample size limited to young DHL/THL patients revealed that despite an improved EFS in patients who received CODOX-M/IVAC-R, there was no difference in OS between patients treated with CODOX-M/IVAC-R and individuals who received DA-EPOCH-R. A possible attribution to these findings may be explained by other results we demonstrated in which higher proportion of patients in the DA-EPOCH-R group who had R/R after induction treatment were able to undergo salvage chemotherapy and proceed with subsequent ASCT, receive CAR T cells and/or undergo allogeneic stem cell transplantation. The rates of treatment-related mortality were low, with only one patient dying of a therapy-related myeloid neoplasm during follow-up. In general, both groups were well balanced in terms of age and performance status however patients in the CODOX-M/IVAC-R group tended to have higher IPI scores and stage. EFS remained superior in the CODOX-M/IVAC-R group on multivariate analysis after adjusting for IPI and stage.

Although CODOX-M/IVAC-R is known for its high toxicity rates; there were no treatment-related deaths in our CODOX-M/IVAC-R group, except for one late death secondary to a therapy-related myeloid neoplasm. In the phase II UK NCRI trial evaluating CODOX-M/IVAC-R in high-risk DLBCL patients, treatment was well tolerated. However, the five deaths attributed to treatment toxicity primarily occurred among patients aged ≥50 years with ECOG PS of 3.[20] Thirteen patients aged >60 years were among the participants in the trial. In our study, none of the patients in the CODOX-M/IVAC-R group had an ECOG PS of ≥3, and only two patients aged ≥50 years had ECOG PS of 2. Therefore, it is possible that this difference in patent characteristics along with the younger patient population in our study

could have contributed to the lower treatment mortality rate we observed. Although comorbidities were infrequent and generally balanced between the treatment groups, there was a notable difference in cardiac disease history reported in the DA-EPOCH-R group. Additionally, no patients in the CODOX-M/IVAC-R group had more than one comorbidity. Thus, we cannot exclude the possibility that the favorable comorbidity profile along with the absence of cardiac disease history in the CODOX-M/IVAC-R group may have attributed to the better EFS and absence of treatment-related deaths in the CODOX-M/IVAC-R group. Despite the CODOX-M/IVAC-R regimen having agents that can penetrate the CNS, the rate of CNS relapse was similar between the DA-EPOHC-R and CODOX-M-IVAC-R groups. However, it is worth mentioning that a higher percentage of patients in the CODOX-M/IVAC-R group had a high-risk CNS IPI score (10% *vs*. 3%) and intermediate-risk CNS IPI score (76% *vs*. 66%) compared to the DA-EPOCH-R group. A strength of this study is that it comprises a large number of patients who received CODOX-M/IVAC-R and a relatively large number of patients with DHL/THL whom are 60 years old or younger, thus mitigating selection bias related to age. Additionally, we included only patients whose FISH and pathology reports were available for our review. The limitations of this study lie in its retrospective nature. Although this study is not a randomized trial, selection between DA-EPOCH-R and CODOX-M/IVAC-R in young patients with DHL/THL and proceeding with ASCT consolidation was based on the preference of different Mayo clinic physicians. As discussed earlier, both groups were similar in age, performance status and CCI scores; however, the more prominent history of cardiac disease in the DA-EPOCH-R group cannot be ruled out as a source of selection bias for this regimen. Another limitation was that not all FISH and pathology studies were centrally reviewed at our institute. Some FISH studies were performed outside our institute and in some cases, there was inadequate tissue to perform a complete FISH probe analysis. Although our cohort of patients who are 60 years old or younger may be larger than the ones published previously, it is still inadequate to draw definitive conclusions especially on small sub analysis groups such as patients who had MYC-BCL6 DHL or patients who had transformed disease. However, we did not identify a difference in clinical outcome based on MYC-BCL6 or transformed disease status.

In conclusion, we found no difference in OS between young patients with DHL/THL who underwent induction treatment with DA-EPOCH-R and those treated with CODOX-M/IVAC-R. However, the CODOX-M/IVAC-R group had an improved EFS, higher CR rate and no increased treatment-related mortality compared to the DA-EPOCH-R group. Patients who have R/R disease after induction treatment with DA-EPOCH-R were more able to receive salvage treatment with ASCT, CAR T-cell therapy and allogeneic stem cell transplantation. In light of this, some patients may elect to pursue treatment with CODOX-M/IVAC-R in a well monitored hospitalized setting with careful monitoring for toxicity as this may potentially spare them receiving subsequent therapies in the future. Prospective and larger cohort studies will be required to further investigate these findings. Furthermore, it will be important to look into whether incorporating novel targeted and immunotherapy agents currently being investigated in clinical trials for first-line treatment of large B-cell lymphoma could replace the need for using intensified regimens in high-risk patients including those with DHL/THL.

Disclosures

JM discloses consulting for Pharmacyclics/Abbvie, Bayer, Gilead/Kite, Beigene, Pfizer, Janssen, Celgene/BMS, Kyowa, Alexion, Fosunkite, Seattle Genetics, Karyopharm, Aurobindo, Verastem, Genmab, Genzyme, Genentech/Roche, ADC Therapeutics, Epizyme, Beigene, Novartis, Morphosys/Incyte, MEI, TG Therapeutics, AstraZeneca and Eli Lilly; research funding from Bayer, Gilead/Kite, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, Millennium, Novartis and Beigene; honoraria from Targeted Oncology, OncView, Curio, Genzyme and Physicians' Education Resource. All other authors have no conflicts of interest to disclose.

Contributions

GSN and SAAY contributed to the conception, design and analysis of the study and prepared the first draft of the manuscript. MJR contributed to data analysis. SAAY contributed to data collection and all authors contributed to data interpretation, provided critical and insightful comments, and approved the final manuscript.

Data-sharing statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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