



## ADOLESCENT AND YOUNG ADULT MALIGNANT HEMATOLOGY

# Management of aggressive B-cell NHLs in the AYA population: an adult vs pediatric perspective

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**The adolescents and young adult (AYA) population represent a group wherein mature B-cell lymphomas constitute a significant proportion of the overall malignancies that occur. Among these are aggressive B-cell non-Hodgkin lymphomas (NHLs), which are predominantly diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and Burkitt lymphoma. For the most part, there is remarkable divide in how pediatric/adolescent patients (under the age of 18 years) with lymphoma are treated vs their young adult counterparts, and molecular data are**

**lacking, especially in pediatric and AYA series. The outcome for AYA patients with cancers has historically been inferior to that of children or older adults, highlighting the necessity to focus on this population. This review discusses the pediatric vs adult perspective in terms of how these diseases are understood and approached and emphasizes the importance of collaborative efforts in both developing consensus for treatment of this population and planning future research endeavors. (Blood. 2018;132(4):369-375)**

## Introduction

Although diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL) make up the high proportion of aggressive B-cell non-Hodgkin lymphoma (NHL), their incidence and the distribution of NHL subtypes vary considerably across different age strata. While DLBCL constitutes 35% to 40% of all NHLs in adults, it is much less commonly seen in children. BL is a common NHL in children, it is uncommonly observed in adults and makes up <5% of all NHL. The breakdown into adult and pediatric lymphoma is not straightforward when it comes to these aggressive B-cell lymphomas, because the adolescents and young adult (AYA) population, defined by the National Cancer Institute as age from 15 years to 39 years, is particularly enriched in certain subtypes (Table 1). Historically, therapy selection (as well as treating physician) has been distinctly based on an age cutoff of typically 18 years, but if these lymphomas naturally occur on a narrow age spectrum that overlaps pediatrics and adults, should their management not be similar? In addition, pediatric and adult groups have approached the study of their biology differently, and directions with respect to novel approaches and treatment advances have varied between the 2 groups.

## Biology of aggressive B-cell NHL

### DLBCL

The biology of DLBCL has been much better studied in older adults because it typically occurs in people >60 years of age and is much more common with advancing age. Although this was once considered to be a single disease entity, distinct clinical and morphological variants are now recognized, and technologies such as gene expression profiling have revealed genetic heterogeneity.<sup>1</sup> Most cases can be divided into 1 of 2 molecular

subtypes depending on their cellular origin, which corresponds to a different stage of B-cell differentiation, a germinal center B-cell (GCB) subtype or an activated B-cell (ABC) subtype.<sup>2,3</sup> These subtypes are distinct in that they have completely different mechanisms of oncogenic activation. The ABC subtype is characterized by constitutive activation of the nuclear factor  $\kappa$ B (NF- $\kappa$ B) pathway in virtually all cases. Several genomic studies have identified a number of mutations and driver pathways that activate NF- $\kappa$ B in ABC DLBCL, and signaling through the BCR pathway particularly plays a critical role in lymphomagenesis. Approximately 20% of ABC DLBCL cases have mutations in the genes encoding the CD79a or CD79b subunits of the BCR, and MYD88 gain-of-function mutations occur in 40% of ABC DLBCL cases with 30% of cases harboring the L265P MYD88 mutation.<sup>4,5</sup> Activating mutations in the coiled domain of CARD11 occur in ~10% of cases.<sup>6</sup> In contrast to the ABC subtype, the GCB subtype frequently has a mutation involving *BCL2* in 30% of cases and involving *cMYC* in 10%.<sup>7</sup> As the age at diagnosis of DLBCL in older adults increases, the proportion of ABC cases relative to GCB also increases.<sup>8</sup>

In patients <30 years, it is rare to observe the ABC subtype, and it is rarely encountered in the pediatric population.<sup>9-11</sup> In a French-American-British (FAB) international study, 75% of cases had the GCB subtype.<sup>12</sup> Interestingly, in this study, a high proportion of cases had an *MYC* rearrangement (37% vs <10% in adult series), whereas translocations involving *BCL2* were infrequent. A recent large retrospective series of 67 patients with DLBCL (all <18 years) also demonstrated very low incidence of the ABC subtype. DLBCL cases that were diagnosed histopathologically were divided into nonmolecular Burkitt lymphoma or "intermediate," and ~80% were of GCB origin.<sup>10</sup> *MYC* and *BCL2* translocations were detected in 8% and 0% of cases, respectively. In comparison

**Table 1. Characteristics of aggressive B-cell lymphomas in the AYA population**

	BL		DLBCL		PMBCL	
	Pediatrics	Adults	Pediatrics	Adults	Pediatrics	Adults
NHL, %	50	2	15	40	3	4
Gender	M >> F	M >> F	M > F	M > F	M = F	F >> M
Cell of origin	GCB		Almost all GCB	GCB > ABC ABC ↑ with age	Thymic B cell	
Molecular features	All MYC rearranged, some differences reported			MYC-R 10%	No known differences	
Outcome	EFS > 90%	↓ with ↑ age	EFS > 90%	EFS 70%	EFS 70%	EFS > 85%

F, female; M, male.

with adult populations, molecular studies performed in pediatric populations are far fewer given the relative rarity of DLBCL in younger patients, and large-scale studies focused on the biology of DLBCL in the AYA population are critical to advance our understanding of this disease across the age continuum. Molecular features of DLBCL have not predicted outcome following standard pediatric regimens, and 1 study demonstrated that a significant proportion (31%) of pediatric DLBCL cases diagnosed histopathologically are reclassified as BL molecularly.<sup>11</sup>

Primary mediastinal B-cell lymphoma (PMBCL) is a particularly important entity to consider in the context of the AYA population because its incidence completely covers the spectrum of this age group, and it is a common lymphoma in AYAs: it constitutes 10% of all DLBCL, but almost all cases are in this AYA age range. Although it has been considered to be a subtype of DLBCL, it is now recognized as a distinct clinicopathologic entity by the World Health Organization Classification. In terms of its clinical presentation and molecular biology, it has much more in common with classic Hodgkin lymphoma (HL) than the GCB or ABC subtypes of DLBCL, and the role of the microenvironment is likely important.<sup>13</sup> Similar to the other subtypes of DLBCL, it is characterized by its own distinct mechanisms of oncogenic activation. Mediastinal B-cell lymphomas can be collectively considered a pathobiologic spectrum of diseases with PMBCL and nodular sclerosis HL at either ends of this, and “mediastinal gray-zone” lymphomas, that have histologic features of both nodular sclerosis HL and PMBCL, in between.<sup>14</sup> Both JAK-STAT and NF-κB pathways are critical for lymphomagenesis in this disease, and recently, many insights into the genetic alterations and perturbations in these pathways have been made. In addition, there is recognition that these lymphomas are “immune privileged” with the ability to avoid immune destruction.<sup>15</sup> PDL2 and PDL1 are critical target genes of chromosome 9p gains and amplifications that are found in >50% of PMBCL cases, supporting an important role of the microenvironment.<sup>16,17</sup> These genetic alterations are associated with phenotypic characteristics and are at play across this pathobiologic spectrum, providing evidence that these entities are molecularly related and likely derived from a common cellular origin (thymic B cell).<sup>18,19</sup> Biologic differences between pediatric and adult PMBCL have not been well studied. It is interesting that gene expression profiling of HL biopsy tissue correlates with treatment outcome in adults with classic HL, but when these predictors were looked at in a pediatric cohort, this was not the case, suggesting that pediatric

and adult HL may have biologic differences.<sup>20-22</sup> Given the shared biology of PMBCL and HL, similar studies in PMBCL and investigating potential biologic variants across the span of AYA patients would be of great interest.

**BL**

BL cases harbor an *MYC* translocation, which is typically at 8q24 and results in deregulation of the *MYC* gene.<sup>7,23</sup> In most (>80%) cases, the translocation partner for *MYC* is the immunoglobulin heavy chain locus on chromosome 14; in other cases, there is involvement of κ and λ light chain loci on chromosomes 2 and 22. Recent genomic studies have identified novel mutations in addition to *MYC* in nonendemic BL cases.<sup>24-27</sup> Approximately 70% of cases have mutations in *TCF3* or its negative regulator *ID3*, which encodes a protein that blocks *TCF3* action. In addition, ~38% of nonendemic cases harbor a mutation in *CCND3*; this is activated by *TCF3* and encodes cyclin D3, which is responsible for cell-cycle progression. Several studies have looked for molecular differences between pediatric and adult BL with varying results.<sup>11,28-30</sup> One study evaluated patterns of genetic aberrations in 24 cases of BL (11 adults and 13 children). The study specifically looked at copy number variations, copy-neutral loss of heterozygosity (CN-LOH), and mutations in *TP53*, *CDKN2A*, *ID3*, *TCF3*, and *CCND3*.<sup>30</sup> Significant differences in genetic anomalies were found between adults and children with more frequent 13q amplifications, 7q gains, and 5q CN-LOH in young patients, whereas 17p and 18q CN-LOH were only detected in adults; *ID3* mutations were found in all adult samples but only in 42% of childhood cases, for example. Other studies have also demonstrated age-related genomic differences.<sup>29</sup> Regarding prognosis, the prognostic impact of secondary chromosomal abnormalities in pediatric and adult high-stage BL was looked at in another study, and although chromosome 22q and 13q aberrations were associated with a poor prognosis in pediatrics, chromosome 17 aberrations were associated with adverse risk in adults.<sup>31</sup> As novel molecular insights into BL continue to be appreciated, it will be interesting to do further comparative biology studies in pediatrics vs adults and investigate this across the AYA spectrum.

**Pediatric vs adult therapeutic approaches**  
**DLBCL and BL**

The paradigms for management of BL and DLBCL are distinct in pediatrics vs adults, and it is important to note that unlike in the case of adults, both DLBCL and BL are treated similarly in

**Table 2. Selected studies in pediatric aggressive B-cell lymphomas**

Trial	No.	Histology	Age, y	Stage	Regimen	EFS
Woessmann <sup>33</sup> (BFM-95)	505	BL/DLBCL	Median 9.3	All stages	BFM95	89% @ 3 y
Gerrard <sup>34</sup> (FAB/LMB96)	132	BL/DLBCL	Median 10	I-II	COPAD	98.3% @ 4 y
Minard-Colin <sup>36</sup> (Inter-B-NHL)	310	BL/DLBCL (and B-ALL)	All <18	III-IV	LMB-96 + R	94.2% @ 1 y
					LMB-96	81.5% @ 1 y
Gerrard <sup>51</sup> (FAB/LMB96)	42	PMBCL	Median 16	III	FAB LMB 96	66% @ 5 y

B-ALL, B-cell acute lymphoblastic leukemia; EFS, event-free survival.

pediatrics. The outcome for pediatric patients with both BL and DLBCL (excluding the subtype PMBCL) is excellent with similar aggressive regimens being used (Table 2). Early strategies in childhood aggressive B-cell lymphoma were modeled on approaches using short-duration, dose-intensive, multiagent regimens. The current standard approaches are based on modifications of 2 cooperative group trials (Lymphomes Malins B [LMB]-96 and Berlin-Frankfurt-Munster [BFM]-95), where both BL and DLBCL cases were included.<sup>32-34</sup> Other than for a small proportion of patients with localized disease, the treatment backbones emphasize the importance of central nervous system–directed therapy, including high-dose methotrexate. The outcomes with these approaches have been excellent with EFS and overall survival (OS) >90% in early stage patients and >80% in patients with advanced stage disease. Following a feasibility pilot study performed by the Children’s Oncology Group adding rituximab to the LMB-96 chemotherapy backbone, an international intergroup randomized, phase 3 trial was conducted for children with high-grade mature B-cell lymphomas (including BL and DLBCL).<sup>35,36</sup> Patients with high-risk disease were randomized to receive rituximab, and the first interim analysis of the study demonstrated a survival advantage (1 year EFS of 94% vs 81%) in the rituximab group leading to cessation of the randomization and suggesting that all pediatric patients with aggressive, mature B-cell lymphomas should receive the monoclonal antibody.<sup>36</sup>

Regarding the treatment of DLBCL in young adults who would meet the definition of AYA, there really have been no dedicated prospective studies performed in this specific age group (except in PMBCL, which is discussed in “PMBCL”). Studies in the adult population have typically used 60 years as a cutoff for young vs elderly patients. In adults, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) is the standard backbone used, and the most significant advance in therapeutics has been the addition of rituximab to CHOP, which showed a significant survival advantage in older (>60 years) and younger (<60 years) adults.<sup>37</sup> Many attempts have been made to intensify CHOP or add etoposide to it (eg, R-CHOP-14 [every 14 days], R-CHOEP [rituximab, cyclophosphamide, vincristine, etoposide, prednisone], DA-EPOCH-R [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab]), but as of yet, the only regimen to improve on R-CHOP has been R-ACVBP (rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone).<sup>38-42</sup> Interestingly, this was in a study of younger patients <60 years, suggesting that therapy intensification may have a role in younger adult patients.<sup>41</sup> The median age of patients was 47 years and 48 years (R-ACVBP and R-CHOP,

respectively) with both arms, including patients ranging upwards from 18 years. The study only included patients with an age-adjusted international prognostic score (IPI) of 0 to 1, but leaves open the question that younger adults (including the AYA population) may benefit from more intensive approaches than R-CHOP. R-ACVBP was associated with significantly more toxicity and would likely not be well tolerated in patients over the age of 60 years, the group in which most new cases occur. Interestingly, unlike in the case with pediatrics, methotrexate has not been a standard drug in adult DLBCL regimens, as 1 early pivotal study that compared a methotrexate-containing combination (m-BACOD [methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone]) did not demonstrate superiority to CHOP but resulted in more toxicity.<sup>43</sup> Several recently completed and ongoing studies have added targeted agents to R-CHOP in an attempt to augment curability in clinical and molecular inferior prognostic groups, and results of some of these should be available soon. One of the biggest challenges in designing adult DLBCL randomized trials is deciding which subgroups to include and target and if that should be driven by clinical characteristics (such as IPI score) or molecular factors (such as overexpression of MYC/BCL2 or cell of origin) or a combination of both? There is a need to move beyond an age cutoff of 60 years and perform prospective studies in the AYA population to assess if this group has a similar outcome to other adults and specifically evaluate if treatments other than R-CHOP are superior in this group.

Unlike the case with pediatrics, in adults, the approaches to BL vs DLBCL are distinct for the most part (Table 3). Adult BL treatment has typically contained multiple chemotherapy agents given in alternating cycles that are of short duration, and methotrexate has typically been incorporated. A commonly used regimen is CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine) with rituximab, or HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) with rituximab, and these are associated with high CR rates but high toxicity also.<sup>44-46</sup> A large prospective German trial assessed the outcome of 363 patients with BL/leukemia following six 5-day chemotherapy cycles with high-dose methotrexate, high-dose cytosine arabinoside, cyclophosphamide, etoposide, ifosfamide, corticosteroids, and triple intrathecal therapy.<sup>47</sup> The overall 5-year survival was 80% with significant differences between adolescents, adults, and elderly patients (OS rate of 90%, 84%, and 62%, respectively). The benefit of adding rituximab to chemotherapy was demonstrated in another

**Table 3. Selected published studies in adult aggressive B-cell lymphomas**

Trial	No.	Histology	Median age, y (range)	Stage (%)	Regimen	EFS
Mead <sup>46</sup>	52	Burkitt	35 (15-60)	III-IV (61%)	CODOX-M/IVAC	65% @ 2 y
Hoelzer <sup>47</sup>	363	Burkitt	42 (16-85)	III-IV (71%)	GMALL-B-ALL/NHL	75% @ 5 y (PFS)
		B-ALL				
Ribrag <sup>48</sup>	260	Burkitt	39% < 40 y	III-IV (62%)	LMB vs	62%
					LMB-R	75%
Dunleavy <sup>49</sup>	30	Burkitt	33 (15-88)	III-IV (67%)	DA-EPOCH-R	95% @ 7y (FFP)
					SC-EPOCH-RR	100% @ 6 y (FFP)
Recher <sup>41</sup>	379	DLBCL	47 (18-60)	III-IV (55%)	R-CHOP	73% @ 3 y (PFS)
					R-ACVBP	87% @ 3y (PFS)
Cunningham <sup>38</sup>	1080	DLBCL	61 (18-88)	III-IV (62%)	R-CHOP-14	75% @ 2 y (PFS)
					R-CHOP-21	75% @ 2 y (PFS)
Wilson <sup>40</sup>	72	DLBCL	50 (19-85)		DA-EPOCH-R	79% @ 5 y (PFS)
Rieger <sup>55</sup>	87	PMBCL	36 (27-43)	All aa IPI 0-1	R-CHOP	78% @ 3 y
Dunleavy <sup>52</sup>	51	PMBCL	30 (19-52)	All stages	DA-EPOCH-R	93% @ 5 y
Giulino-Roth <sup>54</sup>	156	PMBCL	31 (9-70)	All stages	DA-EPOCH-R	86% @ 23 mo

GMALL, German acute lymphoblastic leukemia group.

study that randomly allocated 260 patients to rituximab or no rituximab, with an LMB chemotherapy backbone.<sup>48</sup> With a median follow-up of 38 months, 3-year EFS was superior in the arm that received rituximab (75% vs 62%). Increased age was significantly associated with an inferior outcome. Therefore, although these approaches are very effective in younger adults with the disease, toxicity is a big challenge in adults. This is particularly the case in older and immunosuppressed people, where outcomes observed in pediatric BL have not been achieved. Many attempts have been made to deintensify therapy with the goal of maintaining high cure rates with less toxicity, but mostly, these have been unsuccessful in adults. In a single-center study, the DA-EPOCH-R regimen was associated with excellent outcomes and relatively low toxicity, and recently, these results were confirmed in a multicenter study of 113 patients.<sup>40,49,50</sup> Interestingly, patients with low-risk disease received no central nervous system prophylaxis and only 3 cycles of therapy. Over the past few years, a randomized study of DA-EPOCH-R vs R-CODOX-M/IVAC has been ongoing in Europe.

### PMBCL

Unlike the other aggressive mature B-cell NHLs where the outcome is excellent in pediatrics following LMB-based approaches, this has not been the case with PMBCL, and the optimal treatment of this subtype remains controversial. In the LMB-96 study, the group with PMBCL had a 5-year EFS of just 66%, which was significantly inferior to the outcome of DLBCL (EFS 85%).<sup>51</sup> This is much worse than the outcome in adults with PMBCL following approaches such as the DA-EPOCH-R regimen.<sup>52</sup> In an attempt to improve on the outcome of this subgroup, the same international intergroup conducted a phase 2 study of DA-EPOCH-R in PMBCL

patients under the age of 18 years. Early analysis of the study (47 patients accrued) at a median follow-up of 27 months demonstrated an EFS and OS of 72% and 82%, respectively.<sup>53</sup> Of note, in this study, 40% of patients received 1 cycle of the COP (cyclophosphamide, vincristine, and prednisone) regimen before receiving the study regimen. A recently published multicenter study looked at the “real-world” outcome of the regimen in 156 PMBCL patients from 24 centers.<sup>54</sup> In 38 pediatric patients, at a median follow-up of 23 months, EFS and OS were 81% and 91%, respectively. It should be noted that in this latter study, 15% of patients received mediastinal radiation.

Although historically approached in adults like DLBCL, PMBCL is now recognized as a distinct clinicopathologic entity, and the median age at diagnosis in adults is ~30 years, which is different from other DLBCLs. Early studies in adult PMBCL suggested that dose intensity was an important factor in curing the disease, and this led to the investigation of many approaches that were more intensive than R-CHOP. Although R-CHOP has been effective in early stage disease, radiation was given to the majority of patients, and in the few studies that have looked at advanced stage patients, their outcome was poor.<sup>55,56</sup> One of the biggest challenges in developing curative strategies for this disease is overcoming the (historical) empiric use of mediastinal radiation, because the AYA population is particularly prone to very serious late effects. Single-arm studies with approaches like DA-EPOCH-R without radiation have demonstrated very high cure rates, and this and similar regimens have been adapted by many.<sup>52</sup> The earlier mentioned “real-world” experience of the regimen in 156 adult and pediatric patients demonstrated no difference in outcome among pediatric and adult groups.<sup>54</sup>



## Current challenges in AYA aggressive B-cell NHL

The obvious big question is, At what point should a pediatric patient (<18 years) become an adult patient (>18 years) with respect to receiving curative therapy for aggressive B-cell lymphoma? Are there young adults with DLBCL who would benefit from methotrexate-containing or more intensive regimens, and if yes, how can they be identified? Are there pediatric patients with BL and DLBCL who do not require methotrexate (other than very low-risk patients who do not currently receive it) in whom therapy could be scaled back with no impact on cure and a reduction in long-term toxicities? Does PMBCL in pediatrics have distinct biologic characteristics that could explain an inferior outcome, and should it be approached differently than PMBCL in other AYA patients? How heterogeneous are the pharmacokinetics of drug metabolism and patients' changing organ-specific physiology across this age range, and how much of an impact could that have on the curative treatment of aggressive lymphoma? How do long-term complications differ according to these various regimens, and what regimens or approaches are less cardiotoxic long term? Does the administration of infusional vs bolus doxorubicin (as in the DA-EPOCH-R regimen) mitigate the risk of cardiotoxicity? These are some of the pertinent questions that need to be asked in an attempt to optimize therapy further in these AYA patients, and therefore, trials focused on the treatment and biology of aggressive B-cell NHL need to span the entire age spectrum of AYAs. This group of patients has many other unique challenges that are not lymphoma specific but need to be considered and anticipated in the context of administering therapy: these include many potential psychosocial, emotional, fertility, and financial obstacles and issues in this age group.

## Novel approaches and strategies

Improved understanding of the biology of aggressive B-cell AYA lymphomas is critical to improving their therapeutic outcome. To date, most of the biologic studies that have evaluated prognostic factors in the context of clinical outcome in these diseases have been performed in adult populations, and it is critical that pediatric and AYA populations are a high priority for future studies. So far, many novel molecular findings have paved the way for the development of new approaches. This is particularly true in PMBCL, where deregulated receptor signaling, targetable surface markers, and the PDL axis are all potentially targetable by select strategies.<sup>19</sup> Although not as active as in relapsed HL, which is clinically and biologically similar, a recent study demonstrated good response rates using immunological checkpoint inhibitors in heavily pretreated adult patients with relapsed/refractory PMBCL, suggesting that this class of drugs may have a role in the upfront setting in some pediatric/AYA patients who currently do not have optimal outcomes with standard approaches.<sup>57</sup> Inhibitors of the JAK/STAT pathway are interesting to think about. There has been much recent excitement over the use of anti-CD19 chimeric antigen

receptor (CAR)-T-cell platforms in DLBCL, and early studies suggest particularly good activity in relapsed/refractory PMBCL.<sup>58-60</sup> Based on activity in ALL, developing anti-CD19 CAR-T-cell therapy in BL may be an interesting therapeutic strategy. There are also many other targets for CAR-T cells that are potentially promising.

Novel genomic findings in BL, such as *TCF3*, *ID3*, and *CCND3*, are a good rationale for investigating agents such as PI3 kinase inhibitors and inhibitors of *CDK6* in this disease. The challenge with drug development in BL, particularly in children in Western countries, is that the outcomes are so excellent with standard approaches that the scope for testing new ones is limited.

## Conclusions and future directions

In moving the field of AYA aggressive B-cell lymphomas forward, better collaborations between pediatric and adult hematologists/oncologists and researchers are needed, and it is critical that certain historical therapeutic approaches and paradigms of management be reevaluated and challenged in the context of recent advances in the field. The study of AYA lymphomas provides an excellent opportunity for collaborations between the 2 groups with a potential for high impact. Key goals should be the identification of BL, DLBCL, and PMBCL patients, across the span of the AYA population, who currently have suboptimal outcomes and the implementation of subsequent investigative studies to determine the biologic, clinical, epidemiological, and social root causes of this. Historically, the proportion of AYA cancer patients on clinical trials has been exceedingly low, and this may explain why there has been far less improvement in overall cancer-specific survival among AYAs compared with young children and older adults.<sup>61</sup> Survival outcomes for patients with DLBCL, BL, and PMBCL with comparisons to other age groups need to be further studied in the AYA population. In the future, innovative trials in the arena of aggressive B-cell NHL need to span the entire AYA population with the goal of further augmenting cures in these lymphomas.

## Authorship

Contribution: K.D. and T.G.G. contributed to the writing of the manuscript.

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## Footnote

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