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REVIEW

Critical gaps in understanding treatment outcomes in adolescents and young adults with lymphoma: A review of current data

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Abstract

Adolescents and young adults (AYA) with lymphoma experience treatment-related effects in the short and long term that impact their quality of life and survivorship experience. The effort to improve outcomes for AYA lymphoma survivors requires understanding the available literature, identifying current knowledge deficits, designing better clinical trials incorporating the patient perspective, using novel tools to bridge data gaps and building survivorship guidelines that translate research to clinical practice. This review article summarizes the current state of lymphoma treatment-related outcomes in AYAs and provides future direction.

KEYWORDS
adolescents and young adults, adverse effects, lymphomas

1 | INTRODUCTION

Lymphoma is the most common malignancy in adolescents and young adults (AYA), defined as ages 15–39 years. Classic Hodgkin lymphoma (cHL, 42%) and diffuse large B-cell lymphoma (DLBCL,18%) as well as primary mediastinal large B-cell lymphoma (PMBCL) are the most common lymphoma subtypes affecting AYAs, and therefore, the most studied. These lymphomas are treated with curative intent, with 5-year relative survival rates of 94% for cHL and 79% for DLBCL in AYAs [1].

The clinical management of lymphoma involves balancing the risk of relapse against acute as well as late toxicity and quality of life impact (Figure 1). For AYAs with lymphoma, adverse effects (AEs) of treatment are particularly relevant because they have many decades of life after cancer diagnosis and treatment in which to experience them. In this article, we summarize the current evidence regarding short- and long-term toxicities from lymphoma treatment, and gaps in survivorship care guidelines for AYA lymphoma patients. We discuss the importance of aggregated data sources beyond therapeutic clinical trial data

FIGURE 1 Treatment of lymphomas in AYA: A balancing act.

and modeling as a novel tool of estimating toxicity risks and treatment effects. Through this review, we hope to provide a blueprint for future research with the goal of improving the outcomes of AYA patients with lymphoma.

1.1 | Treatment toxicity and tolerability in AYAs

While all patients with cancer can be affected by AEs of treatment, treatment toxicity can be of particularly impactful in the AYA population due to effects on life circumstances, such as school, employment, or relationships in this phase of life, as well as the potential for late toxicities occurring earlier in life, among a multitude of other factors. To understand these toxicities comprehensively, it requires broadening the scope of conventional AEs assessment [2]. The traditional approach of assessing and reporting AEs in clinical trials focuses on the safety of treatment, but fails to adequately characterize its tolerability, defined as "the degree to which symptomatic and nonsymptomatic AEs associated with the product's administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy [3]." By definition, evaluating treatment tolerability requires direct measurement of the impact of treatment on how a patient feels in addition to the impact on function [4]. Having the patient's lens of tolerability is particularly important given that what clinicians and patients perceive and are willing to accept as toxicity can be very disparate [5].

Many reports on the safety of novel therapies for lymphoma and other cancers include phrases, such as "the treatment was generally well tolerated," yet they have not incorporated the patient perspective on treatment tolerability, nor have they accounted for the time profile of AEs or the impact of chronic, low-grade AEs [6, 7]. A high burden of low-grade AEs may not produce a frank safety signal, but it can impact patients' ability to function and participate in instrumental activities of daily living. For example, while grade 2 neuropathy has not always been included in the conventional AE table that focuses on the incidence of grade 3 and 4 events only, but it limits instrumental activities like preparing meals or using the telephone. This type of AE affects any patient, but for AYA patients in school, in the early stages of their career, or involved in child rearing, the impact is magnified and can have long-term repercussions. This is especially relevant as treatment paradigms in lymphoma and other hematologic malignancies continue to change and include a broader range of mechanisms of action, different types of administration, and longer time frames of administration with toxicities that are different in time profile than conventional cytotoxic treatments [8–10].

Standardization involving the implementation and analysis of AE data and patient-reported outcomes (PROs) is a significant hurdle to understanding treatment tolerability in a rigorous, consensus manner. Multiple US-based and international consortia are tackling this challenge including the AYA PRO Task Force [11], the National Cancer Institute U01 Tolerability Consortium, the Patient-Reported Outcomes Tools (PROTEUS) Consortium, the Lancet Haematology Adverse Events Commission, and Setting International Standards of Patient-Reported Outcomes and Quality of Life endpoints in Cancer Clinical Trials (SISAQOL) [8, 10, 12]. Additionally, the US Food & Drug Administration and other regulatory agencies have prioritized several initiatives to improve tolerability evaluation and communication of tolerability data [13, 14]. Each of these efforts and ongoing research funding in this field will lead to better identification and understanding of treatment tolerability and improving the treatment experience for AYA patients with lymphoma.

1.2 | Using multisource data to characterize outcomes in HL after initial treatment

Thus far, most data on AYA clinical outcomes have come from clinical trials, which by design have limited follow-up, typically in the 5-year range. This leaves critical data gaps in post-trial morbidity, health-related quality of life, and functional outcomes, primarily in the 5- to > 15-year time period (Figure 2). Data from registries and healthcare utilization databases provide some additional information. However, because no one's data source is complete, diverse methodological approaches must be used and multidisciplinary partnerships are required to derive estimates of outcomes for AYAs. Individual data sources have strengths and weaknesses and, therefore, integrating these data is necessary. Use of validated PROs to assess toxicity across studies (eg, PRO-CTCAE and pediatric PRO-CTCAE) and similar self-reported measures for functional consequences and chronic health

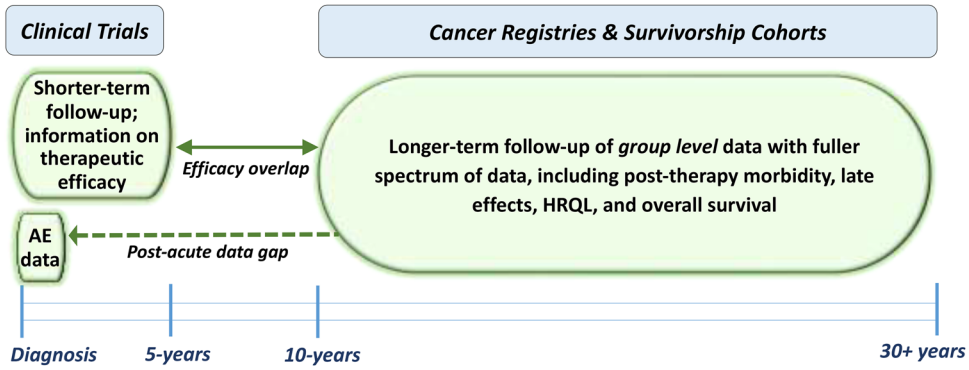

FIGURE 2 Data sources to study the continuun of care for Hodgkin lymphoma.

conditions over time are important for aggregation. The Children's Oncology Group (COG)-led, NCTN-wide protocol, AHOD2131 of early-stage Hodgkin lymphoma (cHL), plans to collect both short-term treatment tolerability and functional outcomes, as well as long-term follow-up of these critical outcomes over 12 years.

For the National Cancer Institute-funded AYA PRO initiative [11], the overarching concept is inclusion of study-specific symptom assessments, alongside targeted functional domains in clinical trials. The initiative has eight guiding principles: relevance to AYAs; prioritization of validated measures; stability of constructs across the age continuum; availability of measures without royalties and in multiple languages; adaptability to different cancer types and treatments; flexibility to measure different HRQoL domains and toxicities; and minimized burden on patients and sites. To date, this framework has been applied to five cross-NCTN Phase 3 trials, including two in lymphoma, in which both targeted symptoms and HRQoL domains are being collected.

In addition to collecting new data using these PROs, it is critical to continue using existing datasets and shared research aimed at using aggregated data to build predictive models for survival, measure the impact of alternative treatments and the impact of response-adapted imaging on survival over 5 years, and develop simulation models of late effects and long-term outcomes.

1.3 | Postacute complications of lymphoma treatments

There is substantial research on long-term outcomes after cHL, with a focus on late AEs of treatment, particularly with alkylators and extended field radiotherapy, with consequential secondary malignancies and cardiac toxicity. Less is known about postacute (<10 years) outcomes, especially in the more modern treatment setting. A recent population-based study aimed to identify cause-specific mortality among patients with cHL who had been treated since 2000 [15]. In an assessment of over 20,000 individuals in US population-based cancer registries, patients between 20 and 74 years with stage I/II (early) or III/IV (advanced) cHL, who were treated with initial chemotherapy during 2000–2015 (follow-up through 2016) were assessed and mortality risk calculated to understand disease-specific death burden. Overall, noncancer standardized mortality ratios were increased 2.4-fold (95% CI, 2.2 to 2.6; observed) and 1.6-fold (95% CI, 1.4 to 1.7) for advanced- and early-stage cHL, respectively. The highest noncancer excess absolute risk (EAR) after advanced-stage cHL was for heart disease (EAR, 15.1; SMR, 2.1), infections (EAR, 10.6; SMR, 3.9), interstitial lung disease (ILD; EAR, 9.7; SMR, 22.1), and AEs related to medications or drugs (EAR, 7.4; SMR, 5.0). For early-stage cHL, the highest EAR was for heart disease (EAR, 6.6; SMR, 1.7), ILD (EAR, 3.7; SMR, 13.1), and infections (EAR, 3.1; SMR, 2.2). These types of data are important because they can inform post-treatment clinical follow-up care in real-world practice to guide efforts to reduce mortality after cHL. Future work could include how to identify the patients at the highest risk for these types of events. Importantly, the follow-up time frame in this study is postacute, and longer follow-up data are needed to determine long-term risks for patients treated over the last two decades.

The impact of treatment on fertility is a particular concern among AYA patients. But despite evidence that discussion of fertility issues, with appropriate specialist referral, can substantially reduce patient anxiety and postdecision regret [16], fertility concerns are typically discussed in less than half of treatment disclosures [17]. For patients with HL, the transition away from radiation- and alkylator-based treatment to ABVD has led to a significant reduction in the risk of treatment-related ovarian failure and infertility. A survey of 460 women treated on European Organization for Research and Treatment of Cancer and Groupe d'Et'tude des Lymphomes de l'Adulte trials between 1964 and 2004 reported a linear decrease in risk of premature ovarian failure (POF) with decreasing alkylator dose, and no increase in the risk of POF following treatment with ABVD [18]. A study of 449 female HL survivors in Swedish cancer registries found no differences in childbirth rates between ABVD-treated patients who were 3–7 years post-treatment and age-matched population comparators [19], and similarly, a study of female HL survivors treated who attempted pregnancy following ABVD treatment, reported a 12-month pregnancy rate of 70%, not significantly different than control subjects [20]. Similarly, AVD brentuximab vedotin (BV) does not appear to impact pregnancy rates [21].

For high-risk HL and PMBCL, however, alkylator-containing regimens continue to be used by some centers. For example, Demeestere

et al, found that following six cycles of BEACOPP escalated 46.1% of females experienced POF and 96.3% of males were azoospermic. By contrast, when PET was used after two cycles of BEACOPP escalated to transition rapid responders to ABVD, 14.5% of females experienced POF and 33.3% of males were azoospermic [22]. Similarly, a study of female survivors treated with dose-adjusted R-EPOCH for PMBCL found that at 1-year follow-up, 14 of 19 (74%) patients were menstruating, and 6 (43%) of these patients delivered healthy children [23]. However, there was a significant decline in anti-Muellerian hormone levels that, for most patients, did not recover 10–18 months post-treatment, and so while young patients are not routinely rendered infertile by this regimen, there will be some women who experience significant fertility impairment, especially those who are 35 years of age or more. Similarly, R-CHOP which is used in DLBCL and in some cases of PMBCL, can also be associated with infertility [24]. Considering male survivors with cHL or DLBCL, a recent systematic review found that 83 and 78% of patients post-ABVD and R-CHOP had normospermia. Azospermia occurs in 0–8% post-ABVD but increases to 90–100% post-eBEACOPP [25]. These data highlight the importance of having a detailed discussion including preservation options, at the time of diagnosis.

1.4 | Long-term complications of lymphoma treatment: Impact of old and new therapies

The US population-based study highlights the increased risk of death and the scope of effects that can occur using standard chemotherapy and reduced radiotherapy fields and dose in the more modern treatment era. A population-based study from BC Cancer evaluated the risk of relapse of cHL at event free time points and found the risk of relapse is less than 5% in those that are event free at 2 years, however, the risk of death due to other causes, including treatment effects, continues to rise. Further, survival did not normalize to the general population even for those who were event free at 5 years, suggesting lingering effects [26]. Similar potential risks exist with aggressive lymphomas, especially PMBCL, which may also affect AYAs.

Studies are emerging investigating the impact of reduced field radiotherapy in the modern treatment area on secondary complications. One study demonstrated that two to four cycles of ABVD followed by limited field radiotherapy in early-stage HL are still associated with a greater risk of cardiovascular (primarily venous thromboembolism) and respiratory disease (primarily asthma), with a trend to increased solid tumors (HR = 1.5) compared to matched controls [27]. Although informative, as follow-up remains short (median 16 years) for these longer-term complications, and it was not specifically in the AYA population.

Overall, there has been a shift away from routine use of radiotherapy with the integration of PET in risk-adapted approaches [28, 29], but in some instances the tradeoff is the use of more intensive chemotherapy, which may also rarely have long-term sequelae such as rare treatment-related-myeloid malignancies and gonadotoxicity with regimens like BEACOPP or DA-EPOCHR, as described. Further, there is more limited information on the long-term morbidity effects as well as the impact on HRQL of these therapies.

Beyond traditional chemotherapy and radiotherapy, over the last 25 years, there has been exciting progress in the scope of treatment options in lymphomas. Rituximab was first approved in relapsed or refractory B-cell lymphomas in 1997 and subsequently changed the landscape of therapy across B-cell lymphomas in combination with chemotherapy. There has been a steady flow of new treatments since then, including the anti-CD30 antibody drug conjugate BV [30, 31] and PD1 inhibitor checkpoint therapy in cHL, and more recently, cellular therapies including CART-cell and bispecific antibody therapy primarily in relapsed or refractory aggressive B-cell lymphomas. However, for many of these treatments, the long-term safety and impact on quality of life, have not been extensively evaluated.

As an example, 5-year follow-up of AYA patients on the ECHELON-1 trial demonstrated that although in most patients BV-induced peripheral neuropathy improves or resolves over time, approximately one-fourth still had any grade of neuropathy, 7% of which was grade 2, which by definition does impact function [32]. Similar data in the real-world setting, where monitoring may not be as vigilant, has not yet been reported. PD1-inhibitor checkpoint therapies have very high efficacy in relapsed or refractory cHL and are being explored in combination with chemotherapy earlier in therapy. T-cell activation can induce immune-related adverse events (irAEs), which may be severe in 10–15% and rarely life threatening. Industry trials are typically expected to follow for irAEs for 100 days after the last dose and, thus, long-term toxicities may not be reported [33, 34]. A longer-term study (but still only > 3 months) in melanoma patients demonstrated "chronic" irAEs in 43% of patients, and this and other studies have noted that endocrine and rhematologic side-effects tend to be permanent [35]. There are potential impacts on fertility and while there is limited information, the prospect of moving away from alkylator-containing regimens for high-risk HL, for example, offers hope that patients may have a better chance of emerging with their fertility intact [36, 37]. Profound B-cell depletion can occur with CART-cell and bispecific antibody therapy with still limited information on the duration of immunosuppression and the risk of long-term of infections [38]. All B-cell depleting therapies impact vaccine response which remains a relevant concern with COVID19 infections still reported.

Real-world studies that collect long-term data are needed to capture the full scope of downstream effects (Table 1). In addition to observational studies, known dose-risk relationships for long-used components of treatment (radiation, anthracyclines, and alkylating agents) can be applied to contemporary protocol exposures to model the risk of late toxicity and quantify the potential benefits of different protocol modifications. For example, when agent-specific models of cardiac toxicity developed in long-term childhood survivors are applied to the COG trial exposures, the predicted 30-year cumulative incidence of severe or fatal cardiac disease is predicted to decline from 9.6% for patients treated with the standard arm of the AHOD0031 trial (accrual 2002–2009), to 6.3% for those treated in the recent S1826 trial (accrual 2019–2022) [39]. Much of this reduction in long-term cardiac toxicity arises from the reduced use of mediastinal

TABLE 1 Long-term complications in AYA lymphoma survivors: past, present, and future.

Potential long-term complications of lymphoma treatment	Modern approaches to minimize risk of complications	Novel therapies with unknown long-term toxicities
• Cardiovascular disease • Pulmonary complications • Secondary cancers • Dental issues • Endocrinopathy • Musculoskeletal, eg Avascular necrosis • Neuropathy • Infection risk • Diminished vaccine response • Immune-related adverse events • Ocular toxicity, eg, cataracts • Fertility • Sexual dysfunction • Psychosocial • QOL • Anxiety/depression • Financial toxicity	• Radiotherapy: extended vs reduced fields • PET-adapted treatments • Moving away from frontline dose-intensive regimens and autologous stem cell transplant, except for specific indications • Decreased use of allogeneic stem cell transplant for lymphoma due to available novel therapies	• Checkpoint inhibitors • Antibodies: Obinutuzumab, Tafasitamab, bispecific antibodies • CART-cell therapy • Antibody drug conjugates: Brentuximab vedotin, polatuzumab vedotin, loncastuximab teserine • Immunomodulatory, and targeted agents: lenalidomide, BTKi, BCL2i, etc.

radiation therapy and the increasing use of dexrazoxane among children enrolled in COG HL trials [40]. Moreover, further increasing the use of dexrazoxane was predicted to produce a greater additional reduction in cardiotoxicity than reducing the doxorubicin dose from 300 to 200 mg/m^2, an important finding given that dose reduction could be associated with an increased relapse risk.

Finally, an underappreciated but very important impact of lymphoma in the AYA age group is altered mental health and diminished HRQL [41, 42]. An increased risk of suicide was reported in HL European patients, far exceeding that of the general population [43]. The 2020 report of the German Hodgkin Study Group also described persistent fatigue among cHL survivors [41].

1.5 | Survivorship guidelines for AYA lymphoma

There are 89,000 new cancers in AYA patients in the US every year. When developing survivorship guidelines, challenges include heterogeneity of cancer types and treatments as well as the wide range of patient ages. There are no evidence-based AYA specific guidelines available, and most often, guidelines are extrapolated from childhood cancer survivors and adult cancer survivors. There are two existing AYA consensus guidelines: the COG Long-Term Follow-up Guidelines (COG LTFU) and the National Comprehensive Cancer Network (NCCN AYA) guidelines [44, 45]. These two sets of guidelines disagree on the link between treatment exposures and late effects, which populations should be screened, the screening tests to be used, and the time interval of testing. Specific examples of this include differences in recommendations for screening for cardiac toxicity, breast cancer, and neurocognitive deficits.

Variation in guideline-recommended follow-up arises largely as a result of limited evidence to definitively support specific screening and management practices for survivors. Clinical trials to compare different follow-up practices have been logistically very challenging (or impossible) to execute, and in these circumstances, investigators have used multistate health models to evaluate different follow-up strategies for childhood cancer survivors including echocardiographic screening [46], breast cancer surveillance [47], and colonoscopic screening [48] for high-risk survivors. These methods not only help to provide quantitative evidence to support guideline recommendations, but also can serve to identify the most significant knowledge gaps for future research needed to create less speculative recommendations for follow-up.

There is a need for standardized, independent platforms for data collection and to educate patients on the need for follow-up care. In addition to surveillance for late effects, recommendations for physical activity and lifestyle behaviors (diet, tobacco use, etc.) are important as these have a tremendous impact on lymphoma survivor well-being. A panel of patient advocates should be included when developing a reporting system and guidelines for patients. Other challenges noted with existing guidelines are that observer bias may be at play: if patients are not being screened, late events will not be identified and will be underreported. Addressing these two issues will be important because it will be relevant for developing and measuring the effectiveness of surveillance recommendations.

In summary, despite significant progress in therapeutics for the treatment of lymphoma in AYAs, there remain significant deficiencies in our understanding of short- and long-term toxicities, patient experience, and impact of lymphoma therapies on different aspects of quality of life. There is a critical need for AYA-focused survivorship care guidelines and the application of PROs, as well as novel research methodology, such as multisource data aggregation and modeling to overcome the limitations of clinical trial data, especially for NHL (see Table 2).

TABLE 2 Critical research questions and next steps.

Research gaps/critical research questions	Next steps
- Data on outcomes of NHL in AYAs - Treatment toxicities, PRO, HRQL data specifically in AYA patients and with newer lymphoma therapies - Mechanisms to collect long-term morbidity data beyond the usual limited clinical trial duration of follow-up - Tools to identify AYA patients at higher risk of postacute and long-term complications and interventions to reduce risk	- Clinical trials designed for AYA lymphoma need to improve • Longer follow-up of morbidities • Need to report lower-grade toxicity to determine tolerability • Integration of PROs and HRQL measures - Development of multisource databases, data modeling to study toxicity and late effects - Harmonization of AYA survivorship care guidelines

AUTHOR CONTRIBUTIONS

All authors contributed to the writing and revision of the manuscript.

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DATA AVAILABILITY STATEMENT

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