Pediatric Hodgkin Lymphoma: Making Progress

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Published online: 16 November 2013
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Abstract Hodgkin lymphoma (HL) is one of the more common cancers encountered among pediatric and adolescent patients; however, most HL occurs in adults, and children constitute only a small proportion of the total number of cases. Treatment outcomes for pediatric HL are excellent and current strategies focus on reduction of therapy-related toxicity while maintaining high survival. This has been achieved by identifying patient cohorts who are at a lower risk for relapse and can be successfully treated with reduced amounts of chemotherapeutic agents and radiation therapy. This identification has been assisted by better understanding of newer imaging modalities, in particular functional FDG–PET imaging. Patients who fail first-line therapy continue to have a chance of cure, and a variety of modalities are available for their treatment. New therapeutic agents, both traditional and biological, are under assessment.

Keywords Pediatrics · Hodgkin lymphoma · Treatment · Salvage therapy · Review

Introduction

Hodgkin lymphoma (HL) is one of the more common cancers encountered among pediatric and adolescent

patients; however, Hodgkins lymphoma in children constitutes only a small proportion of the total number of HL cases. Historically, diagnosis and treatment of childhood HL was based on the adult experience; it has, however, become evident that the therapeutic needs of the pediatric patient, and, indeed, the disease itself, may be somewhat different. This has led to a concerted effort by pediatric oncologists to specifically study pediatric HL to identify the best treatment options for these patients.

This review covers the epidemiology of HL, its geographic and chronological variability, particularly of the pathological subtypes, and how this may affect treatment outcomes. Current treatment strategies will be discussed, especially with regard to efforts to reduce the long-term toxicity of therapy. Treatment options for patients with recurrent or refractory HL are discussed.

Epidemiology of Hodgkin Lymphoma

There are significant geographical differences in the incidence of HL, with the highest incidence reported in North America and Europe. Age-specific incidence also varies between different geographic regions. In developed countries HL has a bimodal age-related distribution with an initial peak during early adulthood and a second peak during old age [1]. In many developing countries the earlier peak is shifted toward younger children, and the second peak is stunted. This is primarily a consequence of the greater incidence of mixed cellularity (MC) subtype HL in this age group [2]. The proportion of patients with MC-HL decreases among older children, adolescents, and young adults but increases again among the elderly. In all age groups the nodular sclerosis (NS) subtype predominates.

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It is believed that early exposure to Epstein–Barr virus (EBV) or possibly other common childhood exposure, as occurs in many resource-poor countries, may promote the development of MC-HL. With improved socio-economic conditions such exposure is delayed, resulting in a decline in HL among the youngest children. This change in HL age-related characteristics was demonstrated in a study of HL incidence patterns in Singapore over a 36-year period, when rapid development resulted in lifestyle changes [3]. There, age-related incidence has developed into one with the bimodal distribution described in industrialized countries. Such trends have also been described in other rapidly developing populations [4]. NS-HL is also associated with EBV although the proportion of samples expressing EBV-derived RNA (EBER) varies with age and race [5, 6]. In addition, epidemiological studies have demonstrated clustering and chronological relationships with EBV infections (infectious mononucleosis) [7, 8].

Diagnosis and Staging

Clinical Presentation

Patients with HL usually present with painless adenopathy of superficial lymph nodes. Because children may have concurrent upper respiratory infections, there is often a history of unsuccessful treatment with antibiotics. Lymphadenopathy most often involves the cervical region, although other sites can also be primarily involved. With more advanced mediastinal disease, patients may present with respiratory symptoms. Other signs and symptoms are related to specific sites of disease involvement and are often associated with dissemination. Patients may present with symptoms indicative of systemic involvement, for example fever, weight loss, and night sweats (B-symptoms), or may have other associated symptomatology, for example pruritus, which is not necessarily associated with systemic spread of the disease.

Diagnosis

Pathological diagnosis of HL requires an excisional biopsy, usually a complete lymph node. This is necessary not only for identification of the malignant cells but also for determination of nodal architecture, which helps to delineate the HL subtypes. HL is unique in that the malignant component comprises only a small minority of cells present within the mass; most of the tumor comprises of infiltrating normal immune cells, usually lymphocytes. As such, less inclusive biopsy specimens, for example as obtained by fine needle aspiration, may not be conclusive. The most recent WHO classification (2008) describes two histologically distinct

disease types of HL: nodular lymphocyte-predominant HL (LPHL) and classical HL (cHL). LPHL is relatively uncommon; approximately 5 % of all HL cases and almost 10 % in children and young adolescents, with a significant male preponderance [9]. The remaining cHL can be further sub-divided on a morphological basis into four subgroups: NS, MC, lymphocyte depleted, and lymphocyte rich.

Staging

Staging of patients with HL is based on the system proposed at the Ann Arbor Conference in 1971, with modifications made at the Cotswolds meeting in 1989 [10]. Staging involves appropriate imaging studies, to determine sites of involvement, and a detailed medical history to identify B-symptoms. For most patients, staging workup includes, at least, computerized tomography (CT) scans of clinically involved sites of the disease, usually the head and neck region, and of the chest, abdomen, and pelvis. Additional radiological studies (bone scans or MRI scans) are determined by symptomatology and clinical suspicion of disease involvement.

Over the past decade, the increased use of FDG–PET and PET–CT scans has transformed imaging of patients with HL. Although conventional clinical staging continues to be standard, several studies of adults and children have suggested that PET and PET–CT scans are better at delineating disease extent and should be used for initial staging [11–14]. PET–CT was more sensitive and at least as specific as conventional CT; it was able to identify additional lesions in significantly more patients, and was found to be especially useful in defining extranodal involvement and for planning radiation therapy (RT) fields. PET–CT scanning resulted in upstaging of the disease for 10–25 % of patients [12–14].

Bone marrow (BM) biopsies, usually bilateral, are indicated for patients with advanced disease (stages III and IV) and those with B-symptoms, but not in patients with radiological stage I or II disease. However, PET–CT is better at identifying BM and/or bone lesions. Studies of both adults and children have revealed higher sensitivity for detection of BM and bone involvement than conventional, blind BM biopsies (85–100 vs. 28–54 %) [15–17]. Such lesions are routinely patchy in their distribution and may not involve conventional sites for BM biopsies. A recent meta-analysis also confirmed these findings and reported that, although both are highly specific, combined sensitivity for BM biopsies was poorer than that for FDG–PET (39.4 vs. 94.5 %) and recommended initial use of FDG–PET for assessment of BM involvement [18]. On the basis of these findings, current recommendations state that PET–CT should be the imaging mode of choice for disease staging [19].

This is especially important because this is used for assessment of treatment response and thus an initial baseline study is mandated.

Treatment

Success in treating HL was achieved early in the era of anti-cancer therapy. High cure success was achieved by use of 30–50 Gy of RT for patients with localized disease. Toxicity of this therapy, particularly among children, was restrictive. Because of the early achievement of high cure rates HL is unique in that, for the past four decades, treatment strategy has focused on reduction of toxicity while maintaining efficacy. Effective chemotherapy regimens, for example MOPP, were developed and used in conjunction with RT to help reduce radiation dose, but also resulted in significant toxicity. Current strategies continue to focus on use of chemotherapy regimens with better toxicity profiles and further reduction in or elimination of RT.

This strategy therefore requires identification of risk-determining clinical variables that are then used for administration of risk-adapted therapy. Extent of disease, or stage, continues to be the strongest predictor of outcome and thus also determines intensity of treatment. While, broadly, stages I and II are regarded as low or limited stage, and stages III and IV as high or advanced stage, details of utilization of stage in risk stratification vary among clinical trials; this variability is detailed below and in Tables 1 and 2. Extent of disease involvement also includes local extra-lymphoid extension, tumor bulk or bulky disease, and distant non-lymphoid metastases which define stage IV. Other clinical features of prognostic value include histological subtype [20, 21], B-symptoms [20, 21, 22], bulky mediastinal involvement [23, 24], erythrocyte sedimentation rate [23], high leukocyte count [24], serum albumin level [23], and hemoglobin level [21, 24]. Similar to disease extent, use of these potentially prognostically relevant factors has been variable. Incorporation of these variables in a scoring system, similar to the International Prognostic Scoring (IPS) system used for adults, has been proposed [21, 24]. The Children's Oncology Group recently identified several risk-determining variables that could be developed into a scoring system, the childhood Hodgkin lymphoma international prognostic scoring (CHIPS) system [25]. This system assigns one point to each of four adverse prognostic features: stage IV disease, bulky mediastinal adenopathy, albumin <3.5 g/dl, and fever. An increasing patient score from zero to four correlated well with event-free survival. This proposed CHIPS requires prospective evaluation and validation in clinical trials before its general use.

Limited-Stage HL

The current therapeutic objective for patients with limited stage HL is toxicity reduction while maintaining overall survival (OS) at more than 90 %. Chemotherapy protocols have focused on elimination or reduction of alkylating agents and anthracyclines. However these reductions must be balanced with reductions in RT if efficacy is not to be reduced.

Children's Cancer Group (CCG) study 5942 tested elimination of RT for HL patients treated with COPP/ABV [22]. Limited stage patients who achieved a radiological complete response (CR) after four cycles of chemotherapy were randomized to receive either RT or no further therapy. This study reported significantly better event-free survival (EFS) with RT (92.1 vs. 82.9 %). However, patients who relapsed without first-line RT could be salvaged without requiring aggressive therapy or stem cell transplantation (SCT), resulting in no difference in OS. Longer follow-up of this cohort of patients has shown the persistence of these results [20]. This 8 % difference in EFS has raised questions regarding the number of patients who must be irradiated to prevent a single relapse.

Elimination of RT for patients with limited stage HL has also been studied by others [26, 27, 28, 29]. These studies tested response-based RT assignment rather than randomization. Patients who achieved a radiological CR after chemotherapy did not receive RT. Although chemotherapy regimens, timing of assessment and the methodology of evaluation differed between studies, a subset of patients (20–57 %) did not receive RT yet had outcomes (PFS/EFS and OS) similar to those who received it. The Children's Oncology Group (COG), in their study AHOD0431, further refined early response assessment by performing functional imaging (PET scan) after a single cycle of chemotherapy; this strategy proved better at identifying patients who did not require RT than the end of chemotherapy response evaluation [27].

The COG P9426 study among lower-risk HL patients focused on chemotherapy restriction as a means of treatment reduction, with all patients receiving involved-field RT (IFRT; 25.5 Gy) [30]. Patients achieving a radiological CR after two cycles of DBVE chemotherapy received only RT; those with a partial response continued on to receive a total of four cycles, followed by RT. Forty-five percent of the patients were eligible for therapy reduction and there were no differences in EFS or OS between the two groups. EFS for the stage III patients enrolled in this study was lower (69.8 %) than that for patients with stages I and II (91.7 and 85.6 %); those who relapsed could be salvaged, however, equalizing OS.

These studies have demonstrated that further reductions in treatment can be achieved for patients with low-risk HL.

Table 1 Treatment details and outcomes for clinical trials for patients with limited stage HL

Ref.	Protocol	Years of enrollment	Definition of risk	N	Treatment		OS	EFS
					Chemotherapy	Radiotherapy		
Nachmann et al. [22] Wolden et al. [20•]	CCG5942	1995–1998	Stage IA, IB, IIA without adverse features ^a and complete response post chemotherapy	207	COPP/ABV×4	If CR post chemotherapy randomized to 21 Gy IFRT (<i>n</i> = 94) or no RT (<i>n</i> = 113)	100 % 89.1 %	<i>p</i> = 0.001
Tebbi et al. [30]	P9426	1996–2000	IA, IIA, IIIA ₁	255	Response-based assignment DBVE×2; <i>n</i> = 103 DBVE×4; <i>n</i> = 144	All patients received IFRT (25.5 Gy)	96.8 % 96.2 %	<i>p</i> = 0.82 <i>p</i> = 0.78 85.8 %
Dorff et al. [26•]	GPOH-HD95	1995–2001	TG1 = IA, IB, IIA	328	OEPA/OPPA×2	Response based assignment; CR = no RT PR = 20–35 Gy based on volume of residual	96.3 % 98.8 % 97.3 %	85.4 %; 88.2 % ^b 93.2 % ^b 86.7 % ^b
Metzger et al. [28]	VAMP	2000–2009	IA, IIA non-bulky, no extranodal extension, <3 nodal regions.	88	VAMP×4	Response based assignment ^c ; CR after 2 cycles = no RT (<i>n</i> = 47) PR after 2 cycles = 25.5 Gy IFRT (<i>n</i> = 41)	100 %	88.5 %; 89.4 % 87.5 % <i>p</i> = 0.61
Mauz-Korholz et al. [29•]	GPOH-HD2002	2002–2005	TG1 = IA, IB, IIA	195	OE ^a PA/OPPA×2	Response based assignment; CR = no RT PR = 20–35 Gy based on volume of residual	99.5 %	92 % 93.2 % 91.7 % <i>p</i> = 0.74
Keller et al. [27]	AHOD-0431	2006–2008	IA, IIA non-bulky	287	AVPC×3	Response based assignment ^c ; CR after 3 cycles = no RT PR after 3 cycles = 21 Gy IFRT	100 %	80 % 88 % <i>p</i> = 0.11

^a Adverse features included hilar lymphadenopathy, involvement of four or more nodal regions, mediastinal tumor ≥1/3 of chest diameter, bulky disease >10 cm^b Progression-free survival (PFS) at 10 years^c Response assessment based on functional imaging with FDG-PET scan

However it is difficult to extrapolate these findings to formulate a general rule. First, the definition of “lower-risk” or “limited-stage” differed between the studies (details are given in Table 1) and thus comparability of the studies is limited. Results for a particular protocol are restricted to LR patients as defined in that protocol. The chemotherapy protocol used is also important in determining RT restriction. In the three studies which tested this, CR after two cycles of chemotherapy varied from 20 to 57 %, revealing that the ability of a particular regimen to compensate for RT elimination may differ. It is, though, encouraging that further treatment reduction is a possibility, but how this affects long term toxicity requires further follow-up of these cohorts.

Advanced-Stage HL

The treatment strategy for patients with HL beyond the limited stage follows the same principles of restricting toxicity while trying to maintain survival. Combined modality therapy has been successfully used to treat advanced-stage HL, but the requirement for more intensive chemotherapy and a wider field for radiation results in the potential for more toxicity. As for limited stage HL, current clinical trials for more advanced-stage HL have attempted to reduce this potential for toxicity by utilizing different methodologies. Table 2 provides details of recently reported treatment strategies for advanced-stage HL. Similar to the strategy for limited-stage disease, randomized assignment of radiation therapy was tested in CCG5942 for patients who had achieved a CR with chemotherapy; however, the different EFS seen for the limited-stage disease was not demonstrated here, possibly as a result of more intensive chemotherapy [20•]. In a subsequent COG study, which also randomized a subset of patients to receive RT, there was also no benefit discernible for RT; patients with a rapid early response (RER) to chemotherapy who then achieved a CR had an EFS of 87.9 % with IFRT compared to 85.4 % without ($p = 0.07$). [31] In this study, all slow early-responding (SER) patients received IFRT, but were randomized to extra chemotherapy (two additional cycles of DECA); this additional chemotherapy failed to improve EFS, except for those patients who were documented as SER by PET imaging. Other studies have assigned RT on the basis of chemotherapy response. Using escalated-BEACOPP as the induction regimen COG investigators were able to successfully eliminate RT for girls achieving CR; boys received 21 Gy IFRT as a compromise for reduction of procarbazine administration [32]. Others have used the Stanford V chemotherapy regimen with a radiation dose based on an interim evaluation of response, with excellent OS [33]. The German (GPOH-HD95) clinical trial, which

also tested the elimination of RT for patients who achieved CR after two cycles of OPPA/OEPA, resulted in a significantly worse outcome for their intermediate-risk (TG2) patients who did not receive RT ($p < 0.001$) but not in their high-risk group (TG3) [26•]. This difference in the ability to limit RT between the trials could be because of the higher treatment intensity of the BEACOPP and Stanford V induction regimens compared with OPPA/OEPA. Chemotherapy intensification and use of consolidation RT for patients in CR in their subsequent trial (GPOH-HD2002) eliminated the poorer outcome for their TG2 patients.

Comparison of results between trials is again hampered by the variability in the definition of risk strata and, as with protocols for limited-stage disease, the results are relevant solely to patients who conform to that particular risk criterion. Developing strategies for toxicity reduction is more difficult for this group of patients and must focus narrowly on specific cohorts. For example, the COG59704 trial restricted RT in girls, who are at higher risk of developing second malignancies, but limited the procarbazine dose for boys, for whom sterility is a greater concern [32]. Whether these maneuvers will eventually result in long-term toxicity reduction requires longer follow-up.

Nodular Lymphocyte-Predominant HL

Although earlier trials had included patients with LPHL with the cHL patients, there is clearly a difference in their presentation and outcome [1]. Patients with LPHL present with limited-stage disease (usually stage I or II) and rarely have B-symptoms [9]. Treatment outcomes for these patients were found to be at least as good as those for low-risk cHL [34–36], and may have been a consequence of the predominantly low-stage presentation for these patients and their chemosensitivity. To minimize treatment-related toxicity, several groups have studied the outcome for limited-stage (usually IA) LPHL patients who receive no further therapy after complete surgical resection [37–39]. Although incidence of relapse was higher than expected, these patients could be salvaged successfully without intensive therapy, resulting in high OS. Also, because relapses in LPHL occur late, these patients were older at the time they received salvage therapy and could, therefore, potentially be at lower risk of some toxic effect, particularly those related to growth. Alternatively, and for patients who could not be resected, lower-intensity chemotherapy with or without radiation has been shown to be effective [40]. However, because LPHL behaves as an indolent lymphoma, very long term follow-up is required for these patients, who remain at risk of relapse and of progression to non-Hodgkin Lymphoma (NHL).

Table 2 Treatment details and outcomes of clinical trials for patients with advanced stage Hodgkin Lymphoma

Ref.	Protocol	Years of enrollment	Definition of risk	N	Treatment		OS	EFS
					Chemotherapy	Radiotherapy		
Nachmann et al. [22]	CCG-5942	1995–1998	G2 = IA, IB, IIA ^a , IIB, IIIA, IIIB	225	COPP/ABV×6	If CR post CT randomized to 21 Gy IFRT or no RT		84 % 78 %
Wolden et al. [20•]			G3 = IVA, IVB	66	COPP/ABV + CHOP + HDARAC/Etopx2			88.5 % 79.9 %
Dorffel et al. [26•]	GPOH-HD95	1995–2001	TG2 = IA _E , IB _E , IIA _E , IIB, IIIA	256	OEPA/OPPAx2 + COPPx2	Response based assignment; CR = no RT PR = 20–35 Gy based on volume of residual	97.7 % 98.1 %	$p = 0.308$ $p < 0.001$
			TG3 = IIIB, IVA, IVB, IIB _E , IIIA _E , IIIB _E	341	OEPA/OPPAx2 + COPPx4		100 % 95.3 %	$p = 0.099$ $p = 0.259$
Kelly et al. [32]	CCG-59704	1999–2001	IIB and IIBB with bulky disease, IVA, IVB	98	BEACOPP×4; if CR: girls COPP-ABV×4 boys ABVD×2 + IFRT if no CR; BEACOPP × 4 + IFRT	Response based assignment; If CR: girls = no RT boys = 21 Gy if no CR 21–35 Gy	97 %	94 %
Mauz-Korholz et al. [29•]	GPOH-HD2002	2002–2005	TG2 = IA _E , IB _E , IIA _E , IIB, IIIA	139	OE ^a PA/ OPPA×2 + COPDAC/ COPP×2	CR = 20 Gy PR = 20–35 Gy based on volume of residual	98.5 %	88.3 %
			TG3 = IIIB, IVA, IVB, IIB _E , IIIA _E , IIIB _E	239	OE ^a PA/ OPPA×2 + COPDAC/ COPP×4		94.9 %	86.9 %
Friedman et al. [31]	AHOD-0031		IA, IIA bulky disease IB, IIB, IIIA, IVA	1,712	ABVE-PC×2; If RER/CR: ABVE-PC × 2 if SER: ABVE-PCx2 or DECAx2 + ABVE-PCx2	RER ^c patients randomized to ± IFRT SER ^c patients 21 Gy IFRT	All 98.2 %	All 85.6 % RER/CR 87.9 % vs. 85.4 %; $p = 0.07$ SER 75.6 % vs. 80.2 %; NS
Metzger et al. [33]	Stanford V	2002–2011	IIB, IIIB, IVA, IVB	141	Stanford V×12 weeks	Response ^c after 8 weeks CR = 15 Gy no CR = 25.5 Gy	97 %	79 %

^a With adverse features including hilar lymphadenopathy, involvement of four or more nodal regions, mediastinal tumor $\geq 1/3$ of chest diameter, bulky disease >10 cm^b Progression-free survival (PFS) at 10 years^c Response assessment based on functional imaging with FDG–PET scan

Response Assessment and Follow-up

Early response to chemotherapy has been shown to be a strong predictor of outcome for adult and pediatric patients with HL. Studies have shown that complete radiological response after 1–3 cycles of chemotherapy (usually two cycles) selects for a subgroup of patients with an excellent outcome [41–43]. On the other hand, patients with radiologically determined residual disease at this point had a significantly worse outcome. Because of the slow regression of HL masses with therapy, traditional radiological studies have limited ability to identify residual lesions which may, in fact, be negative for malignancy (CRu status); because of its high specificity (>90 %) and negative predictive value (>90 %), functional imaging with FDG–PET has to a large extent eliminated this category. Interim FDG–PET (iPET) has replaced conventional imaging for assessment of this early treatment response. Clinical trials have studied the utility of iPET in treatment modification based on early response by reduction in therapy (and hence potential for toxicity) for patients who are iPET-negative and intensification of therapy for those who are iPET-positive [28, 31]. Unfortunately, the relatively low sensitivity (50–75 %) of iPET and its high false-positivity limits the unequivocal identification of patients who would benefit from this therapy modification. A recent meta-analysis has also confirmed the equivocal ability of iPET in predicting outcome [44]. There are ongoing attempts to standardize FDG–PET reporting, but criteria for “positivity” may have to be dependent on the objective of the therapy. Currently, while iPET-negativity can predict a good outcome on standard therapy, use of iPET in treatment modification (either reduction or intensification) should be restricted to clinical trials.

The utility of CT scans and PET–CT during post-therapy surveillance has been questioned. These imaging studies utilize ionizing radiation and potentially augment toxicity that the patients have encountered during their therapy. Recent studies have noted the low yield of these imaging modalities in identifying HL relapses and have recommended limiting their routine use [45–47]. Our own practice for the past several years has been to use plain chest radiograph, abdominal ultrasound, and complete physical examination at follow-up visits for our patients. Those with suspicious findings are then selectively subjected to appropriate confirmatory studies.

Salvage Therapy for Relapsed/Refractory Hodgkin Lymphoma

Although the outcome of first-line therapy for pediatric HL is excellent, a proportion of patients will fail therapy (10 % in low-risk and 20–25 % in high-risk). However, as these patients continue to have the potential for cure, all should

receive salvage therapy. No “standard” or “best” salvage therapy guidelines are currently available for pediatric patients. Physicians have the option to treat patients either with standard-dose chemotherapy (SDCT) or with high-dose chemotherapy (HDCT) and/or autologous stem cell transplant (ASCT). To date there are no head-to-head comparisons of these modalities for children, and most treating physicians base the choice on risk assessment.

Several risk-determining variables have been used, the most important of which remains time to relapse [48, 49]; primary refractory disease results in the worst outcome, and patients who relapse more than one year after completion of therapy are believed to be at lower risk. Other risk-determining variables include stage at relapse, B-symptoms, LDH level, type of first-line therapy and most importantly, response to salvage chemotherapy [48–54]. Patients with low-stage, late relapses tend to do well with SDCT with or without IFRT, achieving survival rates of in excess of 80 % [48, 53, 55]. There are numerous effective protocols available but no formal comparisons between these protocols have been made. The choice of protocol depends on the first-line therapy the patient received, with non-cross resistant agents used for salvage.

The combination of two new agents, gemcitabine and venorelbine, with or without additional drugs, has been found to be effective for adult patients. Promising results were obtained in a pediatric phase II study of this combination—measurable responses for 76 % of patients and CR/VGPR for 68 % [56]. Bendamustine, an agent known for many years, has recently received attention for its efficacy in achieving responses in HL. Bendamustine is an alkylating agent with a mechanism of action distinct from traditional alkylators. Although no pediatric studies have been reported, early trials have shown significant benefit for heavily pre-treated adult patients, with overall response of 50–58 % and CR for 29–33 % of patients [57–59]. Most importantly, in two of these cohorts 13 patients out of a total of 75 were able to undergo allogeneic SCT (alloSCT).

Although no randomized clinical trials have compared SDCT with HDCT/ASCT, most would opt for the latter for patients with refractory disease or early relapse. Although response to pre-ASCT chemotherapy and disease status at time of ASCT have been shown to be highly prognostic, most studies have failed to show any benefit of HDCT/ASCT over SDCT, except for patients with highly chemoresistant disease (refractory or multiple relapses). Disease-free survival for this group of patients is reported to be between 40 and 70 % [51, 53–55, 60]. A review of experience at our institution revealed a five-year estimated OS from SCT of 61.6 % ($n = 29$; 27 ASCT and 2 alloSCT), with an EFS of 57.9 %. Patients who had persistent and/or progressive disease at the end of first-line therapy or relapsed after <6 months off therapy had a worse OS and EFS than those who relapsed later (OS 42.9 vs.

75.3 %, $p = 0.047$ (Taron–Ware); EFS 41.7 vs. 60.8 %, $p = 0.052$ (Taron–Ware); unpublished data).

The potential for an immune mediated graft-versus-lymphoma effect has raised interest in alloSCT for treatment of high-risk relapsed/refractory HL. The only series reports progression-free survival of 30 % at five years, with OS of 45 % [50]. Reduced intensity conditioning was associated with more relapses than myeloablative conditioning, and the fairly high non-relapse mortality (23 %) was no different for the two conditioning modalities.

Because of the long-term toxicity associated with traditional HL therapy, immune-mediated strategies are being tested. The use of EBV-directed autologous cytotoxic T-lymphocytes has led to promising results for patients with EBV-positive HL [61]. Other epitopes as targets for the CTLs are being identified for those patients with HL who are EBV-negative [62]. Brentuximab-vendotin, an anti-CD30 monoclonal antibody conjugated with a potent anti-tubulin agent, was found to have excellent activity against HL [63]. This agent is currently undergoing clinical trials among adult and pediatric patients.

Conclusions

HL is a highly treatable malignancy with current strategies for therapy in children focusing on reduction of the toxic effects of therapy. Although different approaches have been used for toxicity reduction, dose-reduction or elimination of radiation has been given major attention. Because of these different strategies one must be careful to not extrapolate results from one protocol to others, because radiation reduction has to be balanced with appropriate chemotherapy intensity. Standardization of risk classification and response evaluation would benefit inter-trial comparisons. Curative options are also available for patients who fail first-line therapy, and new therapeutic modalities are under development which may result in further improvements in quality of life for these children

Disclosure Asim F. Belgaumi and Amani A. Al-Kofide declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by either of the authors.

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