

Review Article

Hodgkin Lymphoma in Children: A Review

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Received: May 30, 2014; **Accepted:** July 16, 2014;**Published:** November 03, 2014**Abstract**

Hodgkin Lymphoma (HL) with an incidence of 12.1 per million in individuals under 20 years of age, comprises 8.8% of all cancers in this age group. Since its clinical description in 1832, the disease has been stratified and classified into distinct subgroups. Various risk factors based on pathological and prognostic factors are known. While the etiology of the disease remains an enigma, various factors including Epstein-Barr virus (EBV), human herpes virus 6 (HHV6), cytomegalovirus (CMV), hepatitis C virus (HCV), and more recently, human immunodeficiency virus (HIV) have been implicated in the genesis of this disorder. Of these, the possible role of EBV has been best explored. The expression and upregulation of CD30, its intra and extracellular effect, as well as those of CD25 and their association with symptoms typical of HD has been probed. While no universally curative therapy has been identified, starting with radiation, various agents and combinations to successfully treat this disease have been developed. More recently, treatment combinations, and duration of therapy, have been tailored to match those of risk stratification, extent of the disease and prognostic factors. Understanding the biology and pathophysiology of HL, promises better and more specific treatments in the future.

Keywords: Hodgkin; Hodgkin's; Children; Lymphoma; Treatment; Etiology; EBV

Introduction

Hodgkin Lymphoma (HL) was first described in seven patients in 1832 by Dr. Thomas Hodgkin without the aid of a microscope [1]. It is of interest that when tissues from six of seven patients preserved and kept at the Gordon Museum of Guy's Hospital Medical School, London, were analyzed using established criteria for the disease, three cases, including a child, did not meet histological definitions of this disease [2]. The Reed Sternberg (R-S) cell, the malignant cell in HL was described by Carl Sternberg in 1898 and Dorothy Reed in 1902 [3,4]. Likewise, the treatment of the disease which first started with radiation therapy in 1902 [5] and nitrogen mustard in 1946 [6] has evolved to risk adapted combined modality chemotherapy with or without irradiation. This has greatly improved survival in this disease. This review will provide a brief synopsis of the disease, and its current treatments.

Epidemiology and Pathophysiology

Overall, the incidence of HL in the United States is approximately 2.7 cases per 100,000 people with a death rate of 0.4 cases per 100,000 [7]. It accounts for 5 to 8.8 percent of all childhood cancers. The annual incidence for individuals under age 20 years is 1 in 1.2 million. This increases to 1 in 3.2 million for adolescents age 15-19. There is a clear bimodal age distribution with an initial peak for the most part in adolescents and young adults aged 15-34 years of age. The second peak occurs in older adults over 55 years of age [8]. This bimodal distribution is not consistent throughout the world. For example, in Japan, the first peak seen in the developed countries is absent. The specific age distribution varies between the developed and developing world. HL is uncommon in children under 10 years of age in the developed world and it is rarely seen in children under five years old in the United States. In general, there is slight male overall

predominance in incidence of HL. For children under 10 years of age, males outnumber females by a ratio of 3-4:1. The male to female ratio evens in older children with a ratio of 1.3:1 in adolescent patients [8]. In economically disadvantaged countries, the initial peak tends to be younger with a higher incidence of disease in younger boys. It is notable that children and adolescents are more likely to have Nodular Sclerosing (NSHL), rather than other subgroups of HL [9].

In the United States the incidence of HL in childhood appears to increase with increasing family size and decreasing socioeconomic status. In contrast, in young adults, HL is associated with a higher socioeconomic status in industrialized countries. Familial HL represents approximately 4.5% of all cases. In monozygotic twins, during the adolescent and young adult period, there is a 99 fold increased risk of developing HL if one is diagnosed with this disease [10]. Siblings of patients with HL have a seven fold increased chance of developing this disorder [11].

The exact cause of HL is unknown. Etiology appears to vary with age at diagnosis and geographical location [12]. Risk factors that have been associated with HL in the past are lowered immunity, breast feeding, hair dyes, pesticides, workplace chemicals, alcohol, smoking, and obesity. Studies have suggested an infectious etiology for development of HL. HL is more common in human immunodeficiency virus (HIV) infected patients [13-16]. Epstein-Barr virus (EBV) has been implicated as a cause of HL, by both epidemiological studies and elevated titers. This hypothesis has been supported by in situ hybridization revealing evidence of EBV genomes in R-S cells [17,18]. Furthermore, several cases of HL following serologically proven primary EBV virus infection have been reported. In Boston-Worcester case control studies, adult patients with a history of EBV infection had a higher titer of antibodies against the capsid antigen than controls [19]. Nevertheless, there is only a threefold increase in

the incidence of HL in patients with prior history of mononucleosis [20,21]. It is hypothesized that multiple co-factors including age at infection by EBV may be involved. Due to these associations, there appears to be a genetic and environmental trigger for the disease. Approximately 30% of HL cases are positive for the EBV virus with a higher prevalence of EBV DNA in the R-S cells of children 14 years of age or younger than in young adults. Also, EBV associated HL varies by ethnicity and race affecting 93% of Asians, 86% of Hispanics, 46% of Whites and 17% of African American children with HL. There is evidence of the EBV genome in R-S cells [12]. Because of this, there is some evidence to suggest that in EBV-positive HL, the EBV encoding genes may play a role in preventing apoptosis, possibly through nuclear factor kappa-B (NF- κ B). EBV latent membrane protein-1 (LMP-1) is a protein expressed on the surface of EBV infected cells. It is noted in varying levels among the different histologic subtypes of HL. This membrane protein mimics an activated CD40 receptor, which in turn activates the anti-apoptotic NF- κ B. NF- κ B is a protein complex that controls transcription of DNA and is found in almost all animal cell types. It is involved in various cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL and bacterial or viral antigens. Kappa light chains are critical components of immunoglobulin and NF- κ B plays a key role in regulating the immune response to infection. Incorrect regulation of NF- κ B has been linked to various cancers, inflammatory and autoimmune diseases, septic shock and improper immune development. NF- κ B also participates in cytokine production and cell survival. The five members of the mammalian NF- κ B family are p65 (RelA), RelB, c-Rel, p50/p105 (NF- κ B1), and p52/p100 (NF- κ B2). These proteins exist in unstimulated cells as either homo- or heterodimers bound to the Inhibitor of kappa B (I κ B) family of proteins. I κ B inhibits NF- κ B by binding and blocking NF- κ B from translocating to the nucleus, thereby maintaining NF- κ B in an inactive state. I κ B kinase (IKK) phosphorylates I κ B thereby disassociating I κ B from NF- κ B and allowing NF- κ B to migrate to the nucleus to activate multiple genes [22,23].

The CD30 molecule is a membrane glycoprotein that belongs to the tumor necrosis factor superfamily. The extracellular domain of this receptor molecule binds to CD30 ligand, while the intracellular portion signals to modulate a variety of cytokines such as IL-13 directly or IL-6 through activation of NF- κ B [24]. Elevated serum levels of soluble CD30 have been reported in advanced stage HL, with the presence of B symptoms and in cases with poor outcome. CD25 (IL-2 receptor) which is expressed by R-S cells, is also associated with advanced disease and is a harbinger of poor outcome. Both CD30 and CD25 can be targeted for immune therapy in appropriate patients. Elevated expression of CD30 (and CD40) by R-S cells may result in activation of NF- κ B and c-Jun N-terminal kinase pathways which regulate proliferation of R-S cells, secretion of various cytokines and expression of adhesion molecules, resulting in more aggressive disease [25-28].

In HL, there appears to be a T-cell mediated immune deficiency that may be a potential predisposing factor to the development of HL. This T-cell immune deficiency has been described even in the early stage disease. Patients with HL tend to develop opportunistic infections. Over 25% of patients with HL will develop herpes zoster re-infection (shingles) and there is a high incidence of fungal and

mycobacterial infections. These immune defects may persist even after therapy. It is unclear if this is due to the treatment regimens for HL or due to the disease itself.

Clinical Presentation

HL typically presents with the development of non-tender enlarged lymph nodes. These nodes are often asymmetric, painless and non-adherent to the skin. They tend to have a rubbery consistency and are often matted together. The neck and supraclavicular area is involved in approximately 75% of cases. A mediastinal mass may be found in 60% of cases. Other areas of involvement are the abdomen, liver and spleen which may present in 25% of cases. HL spreads contiguously through the lymphatic system. The most common sites for extra-nodal disease include the bone marrow in approximately 5% of cases [29]. Bone, liver, lung, pericardium and pleura can also be involved. Patients may also experience systemic symptoms designated as B symptoms. These B symptoms may occur in 30% of patients and consist of the triad of fever, drenching night sweats and unexplained weight loss of greater than or equal to 10% of body weight. Other systemic symptoms of HL may include fatigue, weakness, and pruritus. Pain at the site of the disease involvement after alcohol consumption is a rare symptom of HL. Symptoms associated with a mediastinal mass are cough, chest pain, shortness of breath and vena cava syndrome. Other presenting symptoms include abdominal pain, bowel disturbance, ascites and bone pain.

Diagnosis is normally achieved through biopsy. The R-S cells are the minority of the cells within the tumor sample with biopsy often showing many reactive lymphocytes surrounding these cells. Often, fine needle aspiration does not give sufficient sample for a definitive diagnosis, thus excisional biopsy is the preferred method. Histologically, the R-S cell has a classic appearance of a binucleated cell with a prominent nucleolus however variations exist. These cells appear to derive from a pre-apoptotic B-cell of germinal center origin [30]. The R-S cell is normally surrounded by a reactive background of eosinophils, lymphocytes and plasma cells. Examination of the lymph node may reveal fibrosis of the tissue architecture. According to the most recent WHO classification in 2008, HL is divided into two major subtypes – the nodular lymphocyte predominant HL (LPHL) which comprises approximately 5% of all HL and the classical HL (cHL). Classical HL is further divided into subgroups which include nodular sclerosis (NS) HL comprising approximately 70% of all cases, mixed cellularity (MC) amounting to about 20% of patients and lymphocyte depleted HL comprising 5% of all cases [31].

The classical HL, despite its B-cell origin, does not exhibit B lymphocyte cell markers such as CD19, CD20 and CD45. Instead, it tends to be CD30 and CD15 positive. As stated above, evidence of EBV clonal genes or EBV proteins such as LMP-1 has been described in various subgroups of classical HL. Evidence of EBV is found in approximately 75% of mixed cellularity and 50% of lymphocyte depleted cases. Evidence of EBV can also be found in 10-40% of the nodular-sclerosing subgroup [12]. In contrast to classical HL, nodular lymphocyte-predominant HL exhibits B-lymphocyte markers. Thus some consider this category not to be a part of HL.

Workup

Common laboratory tests initially performed in the workup of

HL include complete blood count (CBC), sedimentation rate (ESR), liver function tests, albumin, kidney function tests and lactate dehydrogenase (LDH). Chest x-ray is typically performed in the workup for enlarged lymph nodes in search of a mediastinal mass. Staging was previously performed through laparotomy and entailed splenectomy, liver biopsy, and retroperitoneal lymph node biopsies. With advancement in imaging studies, laparotomy is no longer a part of routine staging. Computed tomography (CT) scan of the chest, abdomen and pelvis are routinely performed for staging. Functional radiographical imaging is increasingly utilized. Gallium scans and more recently fluorodeoxyglucose positron emission tomography (FDG-PET) scan with or without CT (PET CT) is increasingly used as functional imaging for both staging and therapy response [32-35]. Bilateral bone marrow aspirate and biopsy is can be performed in patients with stage III or IV disease and/or with B symptoms. Recently, there is some evidence to show that PET-CT may be superior in detecting bone marrow disease and PET-CT often times finds lesions not detected by either CT or by blind bone marrow biopsy. Because of this, PET-CT is now recommended for all patients in initial staging.

While other staging systems are available, staging is still largely based on the proceedings of the Ann Arbor conference of 1971 and then the Cotswald Conference in 1989. Stage I is involvement of a single lymph node region (I) or of a single extra lymphatic organ or site (I_E). Stage II is Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extra-lymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (II_E). Stage III has involvement of lymph node regions on both sides of the diaphragm (III) which may be accompanied by involvement of the spleen (III_S) or by localized involvement of an extra-lymphatic organ or site (III_E) or both (III_{SE}). Stage IV is diffuse or disseminated involvement of one or more extra lymphatic organs or tissues with or without associated lymph node involvement. The presence or absence of B symptoms is denoted as A or B at the end of the stage with “A” being the absence and “B” the presence of B symptoms. B symptoms denote higher risk disease (Table 2) [36,37].

In adults, other markers of poor prognosis include an ESR of greater than 50mm/h, a hemoglobin concentration of less than 10.5 g/Ld., a WBC count less than 15,000/lug, absolute lymphocyte count less than 600/lug, and an Albumin level of less than 4 g/Ld. In children, marker of poor prognosis used in clinical trials include stage IV disease, large mediastinal adenopathy, a mediastinal mass greater than one third of internal thoracic diameter, albumin less than 3.5 g/Ld., the presence of fever, age, bulky disease which includes a node or nodal aggregate of greater than 6cm [38].

Treatment

The treatment of HL has significantly changed during the past three decades. Originally, early stage HL was treated with extended field radiation therapy which included not only the clinically involved nodes but also the adjacent, clinically uninvolved nodes. This was able to achieve cure in certain low stage patients. In the 1960s, the chemotherapy regimen MOPP was developed consisting of nitrogen mustard, vincristine (oncovin), prednisolone and procarbazine. The combination of this regimen with radiation therapy led to the

cure of the majority of advanced stage patients with HL. This was followed in the 1970s by ABVD which consisted of adriamycin, bleomycin, vinblastine and dacarbazine. ABVD had similar survival to MOPP with less toxicity. Acute complications of therapy included myelosuppression, nausea, alopecia, mucositis, and infections. The 1970s also explored the use of bone marrow/stem cell transplant which continues to be used in relapsed or refractory HL (Table 1).

Unfortunately, the success from early treatments followed the development of long term side effects. Late complications of the above therapies included second malignancy at the radiation sites including breast and lung cancers and there is also an increased risk of secondary leukemia and non-HL. Various other late effects of therapy for HL have included endocrine disorders such as hypothyroidism after irradiation to the neck, restrictive pericarditis and pulmonary fibrosis following radiation to the chest or the use of bleomycin. Anthracyclines can produce early or late occurring cardiac myopathy. Infertility is a secondary effect of alkylating agents. In pediatric patients, musculoskeletal growth retardation has been noted following radiation therapy.

Treatment of low risk disease

Due to the success of early treatments in HL, the emphasis of treatment in clinical trials has begun to shift toward the reduction of side effects. In the 1990s, various studies by the Children’s Oncology Group (COG) (studies 9226, 9426 and 9427) and the German Collaborative Group introduced the use of prognostic factors and risk grouping. COG studies used a back bone of ABVD but replaced dacarbazine for etoposide and vincristine for vinblastine (DBVE) [39]. During these studies, surgical staging was omitted in favor of radiographical staging. Radiation dose and fields were likewise reduced. Involved field radiation (IFRT) was used which decreased the radiation field to encompass only the clinically involved regions such as the mediastinum and the low-supraclavicular fields. Chemotherapy regimens began to reduce the cumulative dose to achieve lower rates of long term side effects. With COG 9426 for low risk patients defined as stages I, IIA, and IIIA, patients were treated with an initial two cycles of DBVE and then assessed for response. Those in complete response received IFRT and those with partial response went on to receive two additional cycles of DBVE and IFRT. During conduct of these studies, LPHL patients were excluded. Eight year event free survival (EFS) and overall survival (OS) were 86.3% and 96.5% respectively [40]. This study showed that decreasing the dose in low risk patients based on response led to no difference in

Table 1: Major Regimens Used for Treatment of Hodgkin Lymphoma.

Low Risk Disease (IA, IIA, no bulky disease or B symptoms)
DBVE x 2-4 courses + IFRT
VAMP x 4 courses +/- IFRT
COPP/ABV x 4 courses +/- IFRT
OEPA (males) or OPPA (Females) x 2 courses +/- IFRT
Intermediate Risk Disease (IA, IIA not classified as low risk, IIIA, IVA)
DBVE-PC x 3-5 courses + IFRT
COPP/ABV x 6 courses +/- IFRT
OEPA/OPPA x 2 courses + COPDAC/COPP x 2 courses + IFRT (20-35Gy)
High Risk Disease (IIIB, IVB)
DBVE-PC x 3-5 courses + IFRT
BEACOPP x 4-8 courses + ABVD/COPP-ABV x 2-4 courses +/- IFRT
OEPA/OPPA x 2 courses + COPP/COPDAC x 4 courses + IFRT

The number of courses of chemotherapy and IFRT dose depends on response to treatment in risk adapted regimens.

Table 2: Examples of Recent Risk Groups Currently Used by Cooperative Groups.

Group	Risk Factors	Low Risk	Intermediate/ Early Unfavorable Risk	High Risk
COG		IA/IIA - no bulk or extranodal (E) disease	IA with Bulk, IE, IB IIA with bulk IIE IIIA IVA	IIIB IVB
GMPS		IA/B, IIA	IIB IIIEA IIIB	IIEB IIIEA/B, IIIB IVA/B
St. Jude/ Stanford/Dana Farber	Categorized as favorable or unfavorable risk by IPS	IA/IIA no bulk	IA bulk, IB IIA bulk, IIB III IV	

COG = Children's Oncology Group

GMPS = German Multicenter Pediatric Studies

event free survival or overall survival. P9425 showed similar results for risk stratification using a DBVE + prednisone and cyclophosphamide (DBVE-PC) in advanced stage patients [41].

Similarly Children's Cancer Group (CCG) protocol CCG5942 explored the question of whether or not complete responders to chemotherapy required radiation therapy as compared to chemotherapy alone by randomizing them to receive or not receive IFRT. 10 year EFS and OS was 91% and 83% for those treated with IFRT vs. no radiation, though the OS was 97% vs. 96% respectively showing a higher relapse rate for those not treated but no difference once second line therapy was employed [42].

Donaldson et al. was able to demonstrate excellent results without the use of alkylating agents by employing four cycles of vinblastine, doxorubicin, methotrexate and prednisone (VAMP) plus IFRT. Patients who achieved a CR with two cycles of VAMP had 5 and 10 year EFS of 100% and 95% and patients with nodular lymphocyte predominant histology had 100% EFS. Excluding patients with lymphocyte predominant HL, patients with classical HL had 5 and 10 year EFS of 86% and 85.4%, which is more in line with other studies [43].

The German Collaborative Group in a series of studies (85, 90, 95 and 2002) attempted to decrease toxicity by using different chemotherapies depending on sex (i.e. avoiding procarbazine in boys) and through response based reductions in chemotherapy and radiation therapy. In low risk patients (stage IA, IB or IIA), a regimen of vincristine, etoposide, prednisone and adriamycin (OEPA) in males or vincristine, procarbazine, prednisone, and adriamycin (OPPA) in females were added. Patients who achieved a CR did not receive IFRT while those with non-CR received IFRT. This group had and overall EFS in low stage patients of 92%. EFS of patients without IFRT, was 93% and EFS was 92% for those who did receive IFRT. This data did not include LPHL [44].

More recently, AHOD0431 designed a study to determine the prognostic implication of PET imaging after one cycle of chemotherapy. This study used three cycles of doxorubicin, vincristine, prednisone and cyclophosphamide (AVPC) and then evaluated response with a CR defined as at least 80% reduction in

nodal size and PET or gallium scan negativity. Those patients with a PET negative after one cycle had noticeably improved EFS as compared to those patients who did not in both the group of patients who achieved CR after three cycles and for those who did not [45]. Thus, early response may indicate a better prognosis.

It is not possible to directly compare the above reported regimens since each trial defined low risk patients differently. However, all of these studies highlight the importance of risk adaptive therapy in identifying those patients that can avoid extra toxicity from those who benefit from increased treatment.

LPHL represents a distinct subset of low stage HL which has a particularly good prognosis. Several trials were performed that evaluated no treatment following surgical resection in limited stage LPHL [43,46-50]. Patients had excellent OS despite a high relapse rate. This was due to a high salvage rate without intensive chemotherapy. For patients with limited stage LPHL that were not eligible for primary resection, reduced intensity chemotherapy with or without radiation was effective [51,52].

Treatment of advanced stage disease

Much like in the treatment of low risk disease, the treatment of advanced stage disease has also benefited from trials to reduce the toxicity of conventional treatment. Recent trials have decreased the radiation exposure depending on treatment response. CCG5942, while showing a statistically significant difference in EFS for low stage HL, did not show a significant difference in EFS or OS in advanced stage patients who did or did not receive IFRT. It is difficult to conclude whether or not the more intensive chemotherapy allowed for the omission of IFRT or if this was a due to small numbers in the trial [42]. As a comparison, the German trial GPOH-HD95, revealed significantly decreased EFS in advanced stage patients if they received chemotherapy alone [53]. Due to this finding, in the followup trial to GPOH-HD95, GPOH-HD-2002, chemotherapy was intensified and all patients received RT. These changes eliminated the previous poor response [44]. Unfortunately, due to the small numbers and difference in chemotherapy between the German cooperative group and COG trials, it is difficult to make direct comparisons between studies.

Using a different initial chemotherapy regimen, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC) in intermediate group patients, the recent COG study AHOD0031 was able to show that early response to chemotherapy appears to improve outcome. Patients with rapid early response (RER) as determined with PET scan after two cycles of chemotherapy and CR after four cycles of chemotherapy had similar EFS whether or not they received IFRT (88%vs 85%) [54].

Early dose intensification with subsequent de-escalation based on response was attempted in trials as well. Following four cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP), COG investigators assessed for rapid response. For those patients achieving rapid response, reduced therapy was continued. Females were spared RT and males, while receiving IFRT, had dose reductions on procarbazine. There was a five year EFS of 94% with OS 97% [55]. In another trial, a multi-institutional group evaluated 12 weeks of

Stanford V (prednisone, vinblastine, doxorubicin, nitrogen mustard, etoposide, vincristine, and bleomycin) on unfavorable risk HL with a reduced IFRT dose to rapid responders. This trial yielded EFS and OS of 79% and 97% respectively [56].

Salvage therapy for relapsed/refractory disease

Failure of therapy occurs in approximately 10% of low risk and 20-25% of high risk patients. Despite this, most patients can still be salvaged with second line therapies or high dose chemotherapy followed by stem cell transplant. Determinants of prognosis for relapsed patients is the length of time passed from remission to relapse, stage at relapse, B symptoms, LDH level, type of initial therapy and response to salvage therapy [57-63]. Second line therapy consists of either standard dose chemotherapy (SDCT), high dose chemotherapy (HDCT) with or without autologous stem cell transplant (ASCT). For patients refractory to chemotherapy/radiation therapy, allogeneic stem cell transplant is also used. Those patients that have a late relapse or low stage disease can often times be treated with SDCT with or without radiation [57,62,64]. A recent pediatric phase II trial demonstrated efficacy of gemcitabine and vinorelbine in relapsed/refractory HL and found a measurable response rate of 76% with very good response rate or CR noted in 68% of patients [65]. Bendamustine is an alkylating agent that has demonstrated response in HL [66-69]. For patients with early relapse or with refractory disease, HDCT with ASCT is an option. Disease-free survival rates between 40-70% following HDCT with ASCT have been reported [60,62-64,70]. For those who fail HDCT with ASCT, allogeneic stem cell transplant is an option as well. OS is approximately 45% at five years in these patients [59].

In an effort to reduce toxicity, various trials of non-chemotherapeutic treatment modalities have been completed or are underway. Rituximab is used both as primary and relapse therapy in HL [71]. Brentuximab-Vedotin is an anti-CD30 monoclonal antibody with an attached anti-tubulin agent that has activity against HL in adults [72,73]. There are various trials in pediatric and adult patients for this agent. Another class of new agents that has been tested in adults with HL is the histone deacetylase inhibitors. EBV directed cytotoxic t-cells have been used in EBV positive HL [74] and there are currently trials underway with anti-CD30 chimeric antigen receptor (CAR) T-cells and other cell surface targets [75-77].

Conclusion

The treatment of HL has significantly improved with excellent survival even for those patients with advanced stage disease. The acknowledgement of LPHL as a distinct subtype of HL has resulted in a population of patients that can be treated with surgery alone or with minimal chemotherapy. Recent trials have demonstrated that it is possible to identify patients that benefit from reduced treatment by assessing for response to therapy and either decreasing the cumulative chemotherapy dose or by eliminating radiation. Radiation fields have been reduced as well. Using this approach, survival continues to be excellent while toxicity is reduced. New treatment options designed to specifically target the R-S cell are increasingly becoming available. Despite these advancements and improvements in salvage therapy, long term side effects continue to persist. Further studies into the pathophysiology and genetics of HL should unlock new therapies to continue to improve the survival and reduce short and long term side

effects of therapy in children with HL.

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