

Review Article-I

Current Strategies in the Management of Pediatric Hodgkin's Lymphoma

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SUMMARY

Pediatric Hodgkin's lymphoma is currently one of the most curable childhood malignancies. Therapy is stratified based on disease stage and the presence of adverse prognostic factors. Optimal treatment strategy in pediatric remains controversial, especially in case of advanced disease. Risk-adapted combined modality therapy is the standard of care in favourable and unfavourable early disease. Chemotherapy-alone protocols are advocated by some groups, and show similar outcome, although isolated reports favour additional involved-field radiotherapy. Interim and post-therapy positron emission tomography (PET) is emerging as a tool to avoid radiation or to intensify therapy. Response-adapted therapy is a most effective new approach in order to decrease treatment related long-term toxicity while maintaining high cure rates.

INTRODUCTION

Hodgkin's lymphoma (HL) is a lymphoreticular malignancy characterized by a progressive painless enlargement of lymph nodes and defined by specific histo-pathological features. With the currently available treatment modalities (multiagent chemotherapy either alone or in conjunction with low-dose involved-field radiation therapy) and the use of risk-adapted therapy, over 90% of children diagnosed with HL are long-term survivors. Management designed to balance cure with the fewest effects of therapy continues to challenge pediatric oncologists.

Epidemiology

Incidence

With an incidence of 0.64 per 100,000 US children younger than 15 years, HL accounts for over half of all lymphomas, which are the third most common cancer in children after leukemias and brain tumours. HL is seen in 5% of cancers in US children younger than 15 and about 15% in adolescents 15–19 year of age.

Incidence of HL is roughly the same in Asians as in the US. Lower incidence rates have been reported for Japanese and Chinese than for Filipinos and Asian Indians, both in the US and in Asia.¹ Age-adjusted incidence of HL reported by Mumbai Cancer registry in about 1 per 100,000 population for men and 0.5 per 100,000 population for women. Among Indian children HL, is the fourth more common malignancy after acute lymphoblastic leukemia, brain tumours and retinoblastoma.

Age and sex distribution

In Western countries, HL has a bimodal distribution, with a rise in incidence in young adults (20 to 34 years) and in the elderly (55 to 74 years). In contrast, this bimodal distribution is not seen in developing countries, particularly Asia. A modest young-adult rate peak occurs for most US Asian subgroups (Chinese, Japanese, Filipinos, and Asian Indians) but not for any population in Asia.¹ Childhood HL occurs at a younger age in countries with limited resources as compared with Western countries. Most data from developing countries report a younger age at presentation, with a median age of 8-9 years against 12 years in industrialized countries. HL cases under the age of 5 years are seen in about 20 % of pediatric cases from developing countries vs. about 5% in Western countries.²

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Pediatric HL shows a slight male predominance in Western countries, with a male to female (M: F) ratio of about 1.5:1. However, male predominance is much higher in developing countries, M: F ratios being 2.5:1 to 8:1. This fact is partly explained by the higher proportion of cases under the age of 10 years, since males universally predominate in this age group (M: F ratio 4:1 to 8:1). Indian reports based on cancer registries show a higher M: F ratio in childhood HL as compared with all pediatric cancers, although the difference is not so striking in Mumbai (2.7:1 *vs.* 1.6:1)³ and Delhi (3.7:1 *vs.* 2:1)⁴ as in Bangalore (7.8:1 *vs.* 1.8:1)⁵ cancer registries.

Subtype distribution

Nodular sclerosis (NS) HL is mostly seen in teenagers, and accounts for the young adult peak seen in Western countries. Most cases of childhood HL are of NS subtype in developed countries, whereas in developing countries mixed cellularity (MC) is the commonest subtype, accounting for about 60% of the cases. MC is more common in children under the age of 10 years and in developing countries.^{2, 6}

Association with Epstein-Barr virus

Epstein-Barr virus (EBV) and tuberculosis, have been suggested an infectious cause. The role of EBV is supported by the presence of elevated antibodies to EBV before the onset of HL,⁷ the association between infectious mononucleosis and a increased risk of EBV positive HL in young adults,⁸ and the frequent presence of EBV genome and gene products in tumour cells, particularly in countries with limited resources.⁹ Around one third of all HL cases are EBV-associated in Western countries, 60 to 70% in the Far East and over two third in developing countries of Africa, America and Asia. EBV-association increases in the pediatric population, with reports of 40-50% in developed countries and 70-100% in developing countries. Two large Indian studies from Mumbai and Vellore report EBV association in 78 and 82% of all age HL, while two smaller studies from Chennai and Bangalore report 31% and 55% respectively. Ninety-six to 98% of pediatric cases from Mumbai, Vellore and Delhi have EBV genome detectable in tumour cells.⁹

Etiology

Role of EBV

The association of EBV with a large subset of HL cases is believed to be causal because of the monoclonal origin of EBV genome within tumour cells, suggesting that monoclonal proliferation of the neoplastic clone takes place after EBV infection. In vitro studies have revealed that EBV oncogene products latent membrane protein (LMP)-2 and LMP1 mimic 2 cell surface signals, antigen binding by surface immunoglobulins¹⁰ and CD40 ligand induction¹¹ respectively, thereby leading to the inappropriate survival of a B lymphocyte otherwise bound to undergo apoptotic death. However, EBV might only act as a cofactor, and the physiopathology of non EBV-associated cases remains unclear. Molecular studies have shown no evidence for the presence of other lymphotropic herpesviruses within Reed-Sternberg cells, such as cytomegalovirus, human herpes virus (HHV) 6, HHV-7 and HHV-8.¹² The significance of torquetenovirus (TT virus) detection in more than 30% of NS HL tumour cells, with frequent co-infection with EBV, remains unclear.¹³

The proportion of EBV-associated HL in any population is greater in early childhood (<10 years) and in older adults (>50 years), male sex and mixed cellularity subtype. A four-disease model of HL has been proposed, which divides the disease into 4 subgroups on the basis of age, EBV association, and age of exposure to EBV.¹² This model recognizes a single non EBV-associated group and 3 EBV-associated subgroups. The EBV-negative HL group accounts for the major part of the young adult incidence peak observed in developed countries. EBV-positive subgroups include a childhood group (<15 years, incidence peak below 10 years of age), accounting for almost all cases of HL in early childhood, with higher incidence in developing countries and usually MC subtype; a young adult group (15 to 34 years), which is associated with delayed exposure to EBV, is more prevalent in developed countries and usually of NS subtype; and an older adult group, which affects over half the cases occurring over 55 years of age, usually of MC subtype, and is

likely to be related to EBV reactivation events resulting from loss of the normal balance between latent EBV infection and host immunity.

Genetic predisposition

Rare cases of familial HL have been reported, mostly in adults.¹⁴ There is an increased risk in young adult twins and first-degree relatives ranging from 3- to 7-fold. Yet evidence for a genetic predisposition to HL is difficult to disentangle from the effects of shared environment, such as a common exposure to the same etiologic agent. Various data suggest that the HLA-class II region is associated with susceptibility to HL, and specifically DPB1*0301.¹⁵ Since susceptibility and resistance to infections are partly controlled by HLA class II genes, the increased frequency of DPB1*0301 in HL may be associated with susceptibility to an infectious agent involved in the etiology.

Immune deficiency

Pre-existing immunodeficiency, either congenital or acquired, increases the risk of developing HL. The increased incidence of HL in AIDS is approximately 3- to 10-fold. A large population-based adult study has recently shown that personal or family history of certain autoimmune conditions, including rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, and immune thrombocytopenic purpura, is strongly associated with increased risk of HL.¹⁶

Pathology

Lymph nodes involved by HL show a partial or total replacement of nodal architecture by an inflammatory infiltrate containing Reed-Sternberg (RS) cells or their mononuclear variants, Hodgkin's cells. Characteristic RS cells are binucleate or multinucleate giant cells, with prominent nucleoli and abundant cytoplasm.

The current WHO classification of HL includes two biologically and clinically distinct entities: nodular lymphocyte predominance HL (NLPHL) and classical HL, which includes MC, NS, lymphocyte depletion (LD) and lymphocyte-rich classical HL (LRCHL).¹⁷ Subtyping should be done prior to therapy, since chemotherapy and/or radiotherapy induce a LD pattern.

Hodgkin's and RS (H-RS) cells of classical HL are typically CD15 positive, CD30 positive and leukocyte common antigen (CD45) negative, while T cell and B-cell-associated antigens are usually negative. MC is characterized by a mixed cellular background comprising plasma cells, eosinophils, histiocytes and small lymphocytes. NS subtype is characterized by the presence of sclerosis, rare diagnostic RS cells and lacunar variants of RS cells. LD subtype of HL is rarely seen in children and is characterized by the presence of numerous H-RS cells and few lymphocytes, some eosinophils, plasma cells, neutrophils, diffuse fibrosis and necrosis. LRCHL shows H-RS cells in a cellular background comprising numerous lymphocytes, but no neutrophils and eosinophils.

In contrast to classical HL, the tumour cells of NLPHL, also called lymphocytic-histiocytic (L&H) cells or "popcorn cells", are characterized by a complete or nearly complete B cell phenotype, CD45 positivity, while CD15 and CD30 are negative. L&H cells are multinucleate giant cells with large nuclei and scant cytoplasm. NLPHL has a distinct clinical behavior, with an early stage at presentation, a late median time to recurrence and a low mortality rate as compared with classical HL.¹⁸

In all NLPHL and more than 90% of classical HL, tumour cells have rearranged immunoglobulin heavy-chain variable genes, suggesting a monoclonal B lymphocyte origin.¹⁹ Clonal somatic hypermutation of the immunoglobulin heavy-chain variable genes indicates a derivation from preapoptotic germinal center B cells.²⁰

Clinical presentation

The most common presentation of HL in children is a painless cervical or supraclavicular lymphadenopathy, usually unilateral, firm and rubbery, which may become fluctuant over time. Inguinal and axillary lymphadenopathy is uncommonly the first presenting sign. Mediastinal lymphadenopathy is seen in more than half the patients and is more commonly found in NS subtype. Primary disease in a subdiaphragmatic site occurs in only about 3% of cases.

HL arises in lymphoid tissue and spreads to adjacent lymph node areas. Hematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow, or brain, and is usually associated with systemic (B) symptoms. B symptoms include unexplained persistent fever (above 38°C or 100.4°F), night sweats, weight loss $\geq 10\%$ of body weight in the previous six months.

Patients in developing countries have more of advanced disease (>50%) bulky disease (50%) and 'B' symptoms (40-50%) at initial presentation.² In Western countries, three fourth of newly diagnosed children have early disease

accurate staging is of fundamental importance. Staging is universally done according to the revised Ann Arbor staging system (Table 2).²¹

Although not part of staging investigations, 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET-CT), wherever available, has been used successfully in the diagnosis, staging, monitoring of response to therapy, and surveillance of adult HL. It offers the double advantage of being not only anatomical but also functional study, with lower radiation exposure as compared with computerized tomography (CT) scan. The International Harmonization Project recommends the use of FDG-PET scan in

Table 1. Recommended workup for Clinical Staging

Measurement of palpable lymph nodes, liver, and spleen
Complete blood count, ESR
Liver function tests, Serum Alkaline phosphatase (SAP)
Chest radiograph
Chest contrast enhanced computerized tomography (CECT)
Neck CECT, if high cervical nodes palpable
Abdominal CECT or MRI
Bone marrow biopsy except in stage IA
Bone scan, if elevated SAP level and/or bone pain

at presentation (stage I-II) and only one fourth of the patients have advanced (stage III-IV) disease. The cause for such differences remains unknown. It might be related to a delay in reporting to the hospital, or to a more aggressive nature of the disease, or to an altered host immune response resulting in more aggressive clinical features.

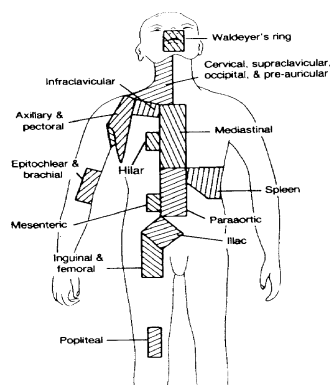
Staging

Clinical staging has since long replaced pathological staging. It is based on involvement of lymph node regions as shown in Fig. 1. Risk-adapted therapy being the standard of care,

the initial staging of HL adult patients and post-treatment assessment of residual disease.²² It is particularly accurate for the assessment of spleen, mediastinum and abdominal lymph nodes. However, the role of PET and PET combined with CT is less clearly defined in the management of pediatric malignancies, particularly HL,²³ in which published studies include a limited number of subjects, often mixtures of HL and non Hodgkin's lymphomas. PET is likely to change initial staging - mostly upstaging - in 15-20% of the patients.^{24, 25}

Table 2. Cotswolds revision of Ann Arbor staging classification and Annotations to stage definition²¹

Stage	Definition
I	Involvement of a single lymph node (LN) region (I) or of a single extranodal organ or site (IE)
II	Involvement of two or more LN regions, on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more LN region on the same side of the diaphragm (IIE)
III	Involvement of LN 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 extralymphatic organ (III E) or both (IIISE)
IV	Noncontiguous involvement of one or more extralymphatic site with or without LN involvement
Annotation	Definition
A	No B symptoms
B	At least one of the following within the last 6 months: <ul style="list-style-type: none"> a. Weight loss >10% b. Unexplained persistent or recurrent fever c. Drenching night sweats
X	Bulky disease (≥ 6 cm in diameter or mass > 1/3 of mediastinal) diameter
E	Extension to a single extralymphatic organ adjacent to a known involved site

**Fig. 1: Anatomic definition of separate lymph node regions (from Hudson and Donaldson)⁴⁰****Prognostic factors**

Various clinical and laboratory features have been identified as poor prognostic factors in children with HL, and these patients need more aggressive therapy. They are related to tumour

burden and tumour spread, constitutional symptoms, response to therapy, biology and host factors (Table 3).²⁶⁻²⁸

An international prognostic score for advanced HL, including serum albumin, hemoglobin, sex, age, stage IV disease, total leukocyte count and lymphocyte count, is widely utilized for adult patients. Stanford - Dana Faber - St Jude consortium treated 328 children with chemotherapy adapted to stage and bulky disease.²⁸ The authors devised a prognostic index, assigning a score of 1 for each of the 5 independent risk factors for inferior disease-free survival: male sex; stage IIB, IIIB, and IV disease; bulky mediastinal disease; total leukocyte count >13,500 /cmm; and hemoglobin <11.0 g/dL. The index was able to predict response to initial chemotherapy, overall survival (OS) and disease-free survival.²⁸

Early response to induction chemotherapy is highly predictive of final outcome and has been used successfully in early favourable disease to reduce overall treatment intensity for good responders to initial chemotherapy.²⁷ The impact of the EBV status on the prognosis of HL patients remains controversial, several authors reporting a favorable outcome, while 2 studies found a poorer outcome in older patients.²⁹

for all stages, with similar survival results. Long-term surveillance of survivors might show a benefit of chemotherapy alone in terms of treatment-related morbidity, even at the cost of a possible decrease in EFS. The latter approach, however, confers risks of late effects associated with higher cumulative doses of anthracyclines, alkylating agents, and bleomycin, particularly cardiac, gonadal and pulmonary toxicity and

Table 3. Independent poor prognostic factors in pediatric HL from various studies (from SDS, SFOP, GHSG)²⁶⁻²⁸

Risk factors	
Tumour burden	Bulky disease Bulky mediastinal disease ≥3 nodal regions involved
Tumour spread	Advanced disease (stage III-IV or IIB-IV or IIB, IIIB, IV)*
Symptoms	B symptoms
Response to therapy	<70% response to 2 induction cycles
Biology	Hb ≥ 10.5 g/dL (or < 11 g/dL)* ESR ≥ 40 mm TLC ≥ 12,000 /cmm (or > 13,500 /cmm)* Serum albumin < 3.5g/dl CD15-negative classical HL Nodular Sclerosis type-2
Host factors	Male sex

Notes. SDS: Stanford -Dana Faber-St Jude. SFOP: French Society of Pediatric Oncology. GHSG: German Hodgkin's Study Group. *Depending on the study. Hb: hemoglobin. ESR: erythrocyte sedimentation rate at 1st hour. TLC: total leukocyte count.

Treatment of Pediatric HL

Treatment approaches

Numerous trials for childhood HL support the efficacy of combined-modality therapy, in which low-dose (15-25 Gy) involved-field radiotherapy (IFRT) is used. Results of combined chemo-radiotherapy show 5-year OS rates greater than 95%, and 5-year event-free survival (EFS) greater than 90% for all stages.

However, the desire to avoid long-term adverse events, particularly radiation-associated solid tumours,³⁰ has motivated continued investigation of chemotherapy-alone

secondary myeloid leukemia. The use of hybrid chemotherapy protocols, in which two different chemotherapy regimens are alternated, has the advantage of reducing cumulative doses of each agent and thus of limiting the risk of long-term side effects.

A few randomized controlled trials (RCT) have compared CMT and chemotherapy-alone in pediatric HL. Two RCTs from the Pediatric Oncology Group and the Children's Cancer Group (CCG) did not find any significant benefit for radiation therapy. In the only pediatric trial showing statistical superiority of CMT, the CCG gave a risk-adapted combination chemotherapy

Table 4. Treatment protocols in pediatric HL

	Early favorable disease	Early unfavorable disease	Advanced disease
SFOP ²⁷	4 VBVP - Good response (>70%): + IFRT 20 Gy - - Poor response: + 1 or 2 OPPA + 20 or 40 Gy		6 alternating MOPP/ABVD Good response: IFRT 20 Gy - Poor response: IFRT 40 Gy
GHSG ²⁶	2 OPPA or OEPA	2 OPPA or OEPA + 2 COPP {CR: no IFRT; good PR (>75%): IFRT 20 Gy; PR<75%: IFRT 30 Gy}	2 OPPA or OEPA + 4 COPP
SDS ^{28, 36}	4 VAMP + IFRT (15Gy or 25 Gy)*	6 alternating VAMP/COP + IFRT (15 or 25 Gy)*	6 alternating VAMP / COP + IFRT (15 or 25 Gy)*
CCG ³¹	4 COPP/ABV ± IFRT (21 Gy)	6 COPP/ABV ± IFRT (21 Gy)	2 (Ara-C-VP16 + COPP/ABV+COAP) ± IFRT (21 Gy)
COG ³⁷	4 DEVB + 25.5 Gy		

Notes. SFOP: French Society of Pediatric Oncology. GHSG: German Hodgkin's Study Group. SDS: Stanford -Dana Faber-St Jude. CCG: Children's Cancer Group. COG: Children's Oncology Group. CR: complete response. PR: partial response. Ara-C: cytarabine. VP-16: etoposide.

* 15Gy if CR after 2 cycles, otherwise 25 Gy.

to children staged I to IV, and randomized those with complete response for either low-dose IFRT or no further treatment. The group that received additional radiotherapy had significantly higher 3-year EFS (93% vs. 85%, $p = 0.002$).³¹ Similarly, Laskar et al from India randomized 179 patients with HL (including 83 children) staged I-IV who achieved complete response after 6 cycles of ABVD to receive either observation or consolidation radiation. The EFS was significantly better in the CMT arm for the study population as a whole, with significant benefit for patients younger than 15 years, patients with B symptoms, patients with bulky disease, and patients in advanced stages (III-IV).³² The latest pediatric RCT, from the Children's Oncology Group (COG), shows that 6 courses of chemotherapy alone (alternating MOPP/ABVD) could achieve the same outcome than 4 courses of chemotherapy followed by IFRT in pediatric patients with asymptomatic low-stage and intermediate-stage HL.³³

Most investigators agree that patients with bulky mediastinal disease are best treated with CMT rather than chemotherapy alone. Bulky disease at diagnosis might require higher radiation doses only in case of insufficient remission. There are no published randomized

controlled trials comparing additional radiotherapy vs. no further treatment in patients with initial bulky disease and negative post-treatment PET.

A few adult studies highlight the predictive value of interim PET, after the first few cycles of chemotherapy.³⁴ Its value to assess early response is the object of an on-going European HL childhood study, aiming to minimize therapy and related late effects. PET might prove a powerful tool to limit the use of radiotherapy to patients with persisting FDG activity after induction therapy.

It is common practice to consider radiotherapy to a residual mass of uncertain significance at the end of treatment with radiotherapy. However, standard imaging tests such as CT scan do not accurately differentiate between a benign fibrotic mass and residual tumour, and only 20% of these patients will eventually relapse. Wherever available, PET imaging has shown a very high negative predictive value (80 to 90%) for the assessment of residual disease in adults. Thus, post-chemotherapy PET could reduce the indications of radiotherapy, since a negative PET scan practically excludes residual disease and further relapse. Its positive predictive value is lower,

about 50 to 65%.²⁴ The German Hodgkin Study Group recently reported 275 adults with advanced HL. PET-negative patients assessed as partial responders by CT scan were not given additional radiotherapy and had a prognosis similar to those in complete remission, contrasting with high progression/relapse rates in partial responders with PET-positive residual disease, in spite of additional radiotherapy.³⁵

Risk-adapted therapy

In recent years, children with HL are grouped on the basis of risk factors and risk-adapted therapy is the standard of care. Most commonly accepted definition of risk group is based on stage, B symptoms, and tumour burden. Early favorable disease, or low risk HL, includes stage I-II non bulky, with no B symptoms and less than 3 nodal sites involved. Early unfavorable disease, or intermediate risk HL, includes stage I-II with one or more unfavorable features (bulky disease, B symptoms, 3 or more nodal sites involved). Advanced disease includes stages III and IV for most study groups.

CMT is the standard of care in early favorable disease, using 4 cycles of chemotherapy (4 VAMP, 4 ABVD, 2 OPPA/OEPA + 2 VBVP or 4 DBVE) and additional low-dose (15-25 Gy) IFRT (Table 4).^{26-27, 36-37} Children who achieve a complete response after 2 cycles are safely given a lower dose (15 Gy) of IFRT than those with a partial response (25 Gy).^{36, 38} Such approaches lead to 5 year OS and EFS rates greater than 97% and 95%.

Early unfavorable disease is usually treated with 4 to 6 cycles of alkylating agent or anthracyclin-based chemotherapy and IFRT (20-25 Gy). Children with advanced disease are treated with more aggressive therapy. Western trials report cure rates of 75-85% in advanced stage. Nevertheless, stage IV patients do poorly with conventional therapy. The COG has shown the feasibility and efficacy of dose-intensive chemotherapy with 4 escalated BEACOPP as induction therapy.³⁹ Rapid early responders further received either 4 cycles of COPP/ABV (girls) or 2 ABVD plus IFRT (boys), while slow early responders received 4 more BEACOPP cycles plus IFRT. The CCG has obtained 83% 3-year EFS in children with stage IV treated with a dose-intensive regimen consisting of 2 cycles

each of cytarabin/etoposide, COPP/ABV and COAP chemotherapy.³¹

Treatment of Nodular Lymphocyte Predominant HL

NLPHL commonly presents at an early stage, without B symptoms or bulky disease, and has an excellent prognosis, leading to less aggressive therapeutic approaches. In early favorable NLPHL, limited or no therapy after complete surgical resection is the standard of care for most authors, to reduced adverse effects. Although the adult treatment paradigm advocates radiotherapy for NLPHL, children do well with chemotherapy alone. Small non-randomized European and US studies have shown that treatment of localized NLPHL with surgery alone is a reasonable approach.⁴⁰⁻⁴² Such observational strategy remains experimental and should be appropriately assessed in randomized controlled trials. About 30% of children with complete remission and all patients with residual disease after initial surgery are likely to develop recurrences. Such relapses usually show the same stage as initial disease and are easily salvaged with conventional chemotherapy. Thus partial remission following excisional biopsy should lead to either brief chemotherapy or second look surgery.

Early unfavorable and advanced NLPHL shows similar outcomes as classical HL and should be treated with the same treatment protocols.¹⁸

Relapsed and refractory disease

Time to progression or relapse is the strongest prognostic factor in adults and children with treatment failure.⁴³ Other prognostic factors include B symptoms, extranodal disease and advanced stage at the time of relapse. Early relapse occurs within 12 months from the end of therapy, late relapse beyond 12 months. Very late relapses, more than 5 years and upto 10 years, are mainly seen in NLPHL. The German Pediatric Oncology Group reports 10-year disease-free survival (DFS) and OS of 86% and 90%, respectively in children with late relapse, while those with early relapse had 10-year DFS and OS of 55% and 78%, respectively. Children

progressing on treatment or until 3 months after completion of therapy had the worst outcome, with 10-year DFS and OS of 41% and 51%, respectively.

Late relapses after low-dose therapy can generally be salvaged with standard chemotherapy and radiotherapy (Fig.2). Patients with early relapse, multiple relapses or primary progressive disease respond poorly to conventional salvage therapy and require aggressive second line chemoradiotherapy followed by autologous hematopoietic stem cell transplantation (HSCT). Salvage combination regimens include ICE (ifosfamide, carboplatin,

dose chemoradiotherapy alone. Myeloablative therapy followed by HSCT leads to 5-year EFS greater than 60% in children with primary refractory disease or relapse.⁴⁷ Non myeloablative is less toxic and recommended for patients receiving allogeneic HSCT following relapse after autologous transplant. The most commonly used preparative regimens for HSCT are BEAM (carmustine, etoposide, cytarabine, melphalan) and thiotepa-etoposide combined with either cyclophosphamide, carboplatin, or melphalan. HSCT is not recommended for children with an atopic history, who have a high

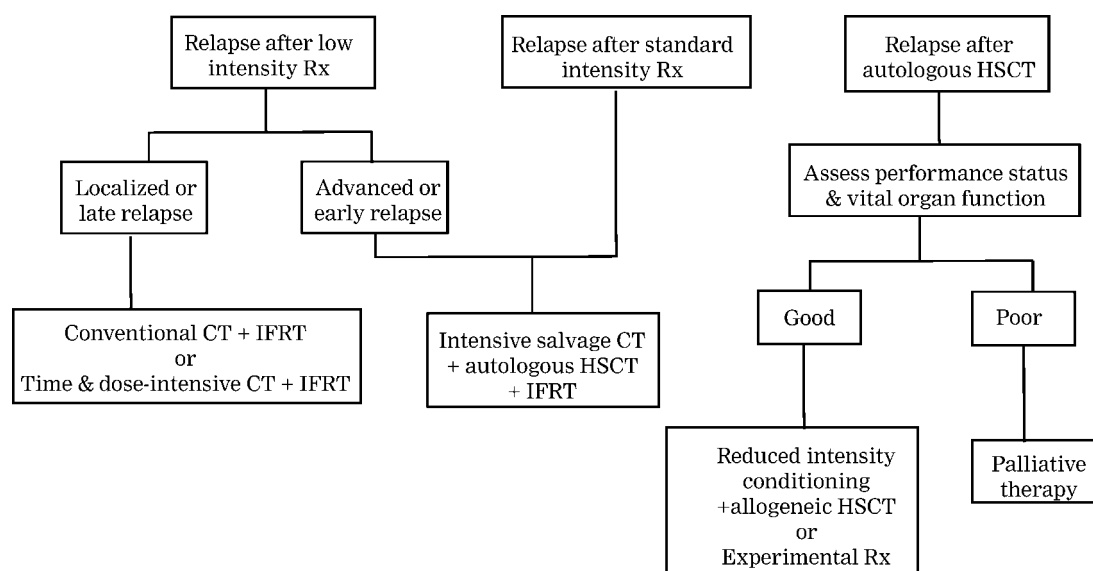


Fig. 2. Management of relapsed Hodgkin's Lymphoma

Rx: therapy. Low intensity Rx: up to 4 chemotherapy cycles and IFRT, or 6 cycles of chemotherapy alone.

Standard-intensity Rx: 6 cycles of chemotherapy + IFRT, or 8 cycles of chemotherapy alone.

Time & dose-intensive CT: escalated BEACOPP and Stanford V regimens.

CT: chemotherapy. IFRT: involved-field radiotherapy.

etoposide),⁴⁴ DECA (dexamethasone, etoposide, cisplatin, cytarabine),⁴⁵ Gemcitabin/vinorelbine,⁴⁶ and IEP (ifosfamide, etoposide, prednisolone)-ABVD-COPP.⁴³ Low-dose IFRT to sites of recurrent disease is administered if these sites have not been previously irradiated. Survival lower than 50% is achieved with high

incidence of idiopathic diffuse pulmonary toxicity after transplantation.

Experimental therapies

Phase II trials with novel therapies are underway in adults and children. The anti-CD20 antibody Rituximab may be useful for children

with NLPHL and CD20+ classical HL. Rituximab has also been advocated in CD20 negative classical HL, since most cases have a B-cell derivation. Interim results of the use of Rituximab in addition to ABVD in the treatment of adults with classical HL have shown improvement in the survival of high-risk patients.⁴⁸ The presence of EBV antigens in EBV-positive tumour cells can be used as a target for new therapeutic strategies, particularly immunotherapy. The use of autologous EBV-specific cytotoxic T lymphocytes has proven particularly effective in patients with recurrent or refractory EBV-associated disease.⁴⁹ Pre-clinical studies also try to develop a LMP1 epitope-based vaccination designed to control EBV-associated malignancies.

Conclusion

Epidemiological features of childhood HL vary greatly among countries with different socio-economic level. Current challenges include earlier diagnosis in countries with limited resources and improving survival at the cost of minimal late complications. Accurate staging is a key to facilitating risk-adapted therapy. Treatment results of pediatric HL have enjoyed considerable progress over the years, with excellent achievements in early stage favourable disease. Efforts are still required to improve long-term survival in unfavorable and advanced disease, refractory disease and relapsed cases. The accurate definition of risk groups to segregate low-, intermediate-, and high-risk groups on the basis of a prognostic score promises for future advances in pediatric Hodgkin's lymphoma.

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