Review Article

Current Strategies in the Treatment of Childhood Hodgkin's Disease

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Dramatic changes in the treatment of childhood Hodgkin's disease have taken place during the past three decades. Contemporary combined modality treatment regimens produce durable disease-free survival in 90 to 100% of patients with early disease and in 70 to 85% of patients with advanced disease. Studies using chemotherapy alone also report high survival rates, and current studies are few to highlight the superiority of chemo-radiotherapy vs. chemotherapy alone. After the prodigious improvement achieved in response and survival rates, current strategies aim at reducing late effects of therapy, reserving more aggressive treatment modalities for patients with high risk features.

Introduction

Hodgkin's disease (HD) represents about half of all childhood lymphomas, which are the third most common malignancies in children. Treatment modalities have varied from total nodal radiation therapy to combination chemo-radiotherapy, with significant improvement in survival rate throughout the last three decades.

Reviewing treatment of HD in childhood is not an easy task. However, such dramatic improvement in the prognosis of this disease has been achieved that HD is currently one of the most curable malignancies in children and adolescents. Therefore, most modern pediatric studies give a priority to limiting late effects of therapy. For instance, efficacy and toxicity of chemotherapy-alone protocols have been studied more recently in order to avoid late effects of radiotherapy while maintaining high cure rates. Optimal treatment strategy in children remains controversial, especially in cases of advanced disease. This detailed review of current treatment strategies in childhood HD will be beneficial for the readers of Indian Pediatrics for optimal management according to local facilities available, especially when specialised pediatric oncology centers are not easily reachable.

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Radiotherapy

Before the 1970s, children treated with high dose radiotherapy (RT) alone had a 10-year survival of only 11%. High relapse rate, solid second malignant neoplasms and fatal cardiac complications were responsible for such poor survival(1). Standard-dose extended-field radiotherapy was then used in combination with multi-agent chemotherapy to obtain better local tumor control. Adverse effects on musculo-skeletal development led to reduction of the radiation fields and of the radiation dose. Low-dose (15-25 Gy) involved-field radiotherapy (IFRT), first used in North American trials(2), is now widely accepted in all modern combined modality therapy protocols and should reduce the incidence of growth retardation, breast cancer and thyroid dysfunction. RT alone is very rarely a treatment alternative in childhood HD. In a recent trial conducted by the United Kingdom Children's Cancer Study Group,

stage I patients were treated with radiotherapy alone (35 Gy), with an unacceptable relapse rate of 30%, especially in mixed cellularity subtype(3). However, most cases were salvaged with conventional chemotherapy. Some North-American teams, such as Stanford(4) and the Pediatric Oncology Group (POG)(5), tend to treat stage IA lymphocyte predominant disease (LP) of the high neck with local irradiation alone. However, these very localised forms are particularly seen in young children, who run a greater risk of radiation-induced second malignancy and thyroid dysfunction. The French Society of Pediatric Oncology recently showed that no further therapy is required in LP HD children in complete remission after initial lymph node resection: among patients with complete lymph node excision, event-free survival was not significantly different between the group receiving additional treatment (involved-field radiotherapy, chemotherapy or combined modality) and the group receiving no further treatment. All patients who relapsed after simple adenectomy were salvaged with conventional chemotherapy(6).

Combination chemotherapy

Children with advanced HD who were treated with single agent chemotherapy prior to 1970 had a very poor survival. The combination of nitrogen mustard, vincristine, procarbazine and prednisolone (MOPP)(7) markedly improved the survival of HD in adults and in children. However, because of the high hematological toxicity of MOPP, as well as its induction of secondary acute myeloid leukemia (AML), azoospermia and ovarian dysfunction(8,9) the elaboration of alternative drug combinations became a major priority during the last decades.

Various hybrid combinations substituting nitrogen mustard or procarbazine with less toxic drugs were used in children, often in combination with radiotherapy, such as COPP, COMP, CVPP(10) or ChlVPP (3,11,12) regimens (*Table I*). Bone marrow suppression was less pronounced, and the observed risk of secondary leukemia or myelodysplastic syndrome proved lower than in MOPP regimen(8,9,13). The risk of infertility in boys, almost universal after 6MOPP cycles, is reduced when MOPP-derivate combinations are limited to three cycles(14,15). ChlVPP should be used with caution, because of its higher risk of gonadal toxicity, particularly in boys.

The ABVD combination regimen was developed in the mid-1970s, consisting of Adriamycin, bleomycin, vinblastine and dacarbazine(16). It presented neither hematological malignancies nor infertility, and was non-cross resistant to MOPP. Adult studies demonstrated that ABVD used alone or alternating with MOPP to enhance antineoplastic activity, provided results superior than with MOPP alone(17). The POG treated children with advanced disease with an alternating combination of MOPP and ABVD, which produced a complete response rate of 90% and a five-year EFS of 79%(18). However, ABVD is associated with a risk of cardiomyopathy and pulmonary dysfunction, especially in children(4,19-21). From then on till the 1990s, most childhood treatment regimens combined various numbers of cycles of ABVD and MOPP derivatives.

The use of hybrid chemotherapy protocols, in which two different chemo-therapy regimens are alternated, has the advantage of reducing cumulative doses of each agent and thus to limit the risk of long-term side effects. New combination cytotoxic regimens used by international study groups are anthracyclin - based and epipodophyllotoxin based: OPPA(15,22,) OEPA(10,15), VBVP(22),

TABLE I– *Combination chemotherapy protocols containing alylating agents used in HD (cycle to be repeated every 28 days).*

Protocol	Agents	Days	Dosage and route
COPP	Cyclophosphamide	1, 8	600 mg/m^2 i.v.
	Vincristine		1,8 1.5 mg/m^2 i.v.
	Procarbazine		1-14 100 mg/m^2 p.o.
	Prednisolone		1-14 40 mg/m^2 p.o.
COMP	Cyclophosphamide	1, 8	600 mg/m^2 i.v.
	Vincristine	1, 8	1.4 mg/m^2 i.v.
	Methotrexate	1, 8	40 mg/m^2 i.v.
	Prednisolone	1-14	40 mg/m^2 p.o.
CVPP	Cyclophosphamide	1, 8	600 mg/m^2 i.v.
	Vinblastine	1, 8	6 mg/m^2 i.v.
	Procarbazine	1-14	100 mg/m^2 p.o
	Prednisolone	1-14	40 mg/m^2 p.o.
ChlVPP	Chlorambucil	1-14	6 mg/m^2 p.o.
	Vinblastine	1, 8	6 mg/m^2 i.v.
	Procarbazine	1-14	100 mg/m^2 p.o.
	Prednisolone	1-14	30 mg/m^2 p.o.

VAMP(23), VEPA(24), EBO(25), and VEEP(26) (*Table II*). Etoposide-containing protocols present a higher risk of second malignancy, particularly acute myeloid leukemia, and are sometimes electively proposed to males, as males have a much higher risk of infertility following alkylating agents than females.

Combined modality therapy (CMT)

Donaldson *et al*.(27) at Stanford, using MOPP and low-dose radiation therapy, first introduced the concept of CMT for pediatric patients. For the last two decades, combined chemo-radiotherapy has been the treatment modality preferred in most studies on childhood HD, in order to optimise the risk/benefit ratio between cure rate and secondary effects(4,10,15,22-24,28,29) with 5-year overall survival rates greater than 95%, and 5-year EFS greater than 90% for all stages (*Table III*). Treatment outcome is particularly excellent in early stages, with overall survival rates of 97% or more(15,22,23).

Most investigators agree that patients with a mediastinal mass/thorax ratio greater than one third are best treated with combination modality therapy rather than chemotherapy or radiotherapy alone. The mediastinal mass/thorax ratio is calculated by measuring the size of the mediastinum at its widest diameter and the transthoracic widest diameter (just above the domes of the diaphragm). The radiation dose used in these cases varies between 25 Gy(4) and 35 Gy(3). However, association of ABVD and IFRT increase the risk of subclinical dysfunction of the heart, lungs and thyroid(4,30). In an Israeli study, children staged I and II received 4 to 6 courses of COPP alternating with ABVD, tailored according to clinical response: only cases with bulky mediastinal disease received mediastinal RT,

TABLE II–*Anthracyclin- and epipodophyllotoxin-based protocols used in HD (cycle to be repeated every 28 days)*

Protocol	Agents	Days	Dosage and route
ABVD	Doxorubicin (Adriamycin)	1, 15	25 mg/m^2 i.v.
	Bleomycin	1, 15	10 U/m^2 i.v.
	Vinblastine	1, 15	6 mg/m^2 i.v.
	Dacarbazine (DTIC)	1, 15	375 mg/m^2 i.v.
OPPA	Vincristine (Oncovin)	1, 8, 15	1.5 mg/m^2 i.v.
	Procarbazine	1-15	100 mg/m^2 p.o.
	Prednisolone	1-15	60 mg/m^2 p.o.
	Doxorubicin (Adriamycin)	1, 15	40 mg/m^2 i.v.
OEPA	Vincristine (Oncovin)	1, 8, 15	1.5 mg/m^2 i.v.
	Etoposide	3-6	125 mg/m^2 i.v.
	Prednisolone	1-15	60 mg/m^2 p.o.
	Doxorubicin (Adriamycin)	1, 15	40 mg/m^2 i.v.
VAMP	Vinblastine	1, 15	6 mg/m^2 i.v.
	Doxorubicin (Adriamycin)	1, 15	25 mg/m^2 i.v.
	Methotrexate	1, 15	20 mg/m^2 i.v.
	Prednisolone	1-14	40 mg/m^2 p.o.
VBVP (repeat cycle every 21 days)	Vinblastine	1, 8	6 mg/m^2 i.v.
	Bleomycin	1	10 U/m^2 i.v.
	Etoposide	1-5	100 mg/m^2 i.v.
	Prednisolone	1-8	40 mg/m^2 p.o.
EBO	Epirubicin		70 mg/m^2 i.v.
	Bleomycin		10 U/m^2 i.v.
	Vincristine (Oncovin)		1.5 mg/m^2 i.v.

and long-term morbidity was found mainly in patients receiving RT(31).

Many groups give IFRT to all initial sites of bulky disease, even when complete remission is obtained after chemotherapy(28,29). Bulky disease in children is defined as any tumor with a diameter greater than 6 cm, or a mediastinal mass exceeding one third of the maximum thoracic width. Some study groups successfully reduce morbidity with a radiation dose depending on the degree of response to induction chemotherapy(22,23,28). Residual disease after completing chemotherapy should be treated by radiotherapy. However, persistence of a mediastinal mass after treatment with chemotherapy alone does not always require additional RT, as it does not correlate with a higher risk of recurrence: subsequent chest radiographs examinations show a slower regression of the mediastinal mass as compared with what is seen in CMT(32).

Chemotherapy alone versus CMT

Certain groups have a tendency to use chemotherapy alone(11,25,26,33-38) (*Table IV*), particularly in younger children, so as to avoid long-term sequelae due to radiotherapy, especially premature epiphyseal fusion, and secondary solid tumors in radiation fields or adjacent to radiation fields(39). Indeed, long-term follow-up of patients treated for HD in childhood shows a 18.5-fold increased risk of

TABLE III– *Results of combined modality regimens in childhood HD.*

Author	Country, year	N	Stage	Chemotherapy	RT	OS	EFS/PFS
Vecchi(28)	Italy, 1993	215	1 - IA, IIA, no bulky med 2 - Bulky med, IB, IIB, IIIB, IIIS, 3 - IIIB, IV	- 3 ABVD + IFRT - 3 MOPP / 3 ABVD + IFRT - 3 MOPP / 3 ABVD + EFRT+ 2 MOPP / 2 ABVD	IFRT, 20-40 Gy acc. to age and response	7y 86%	7y EFS 82% 1 - 95% 2 - 81% 3 - 60%
Hunger(4)	USA (Stanford), 1994	57	I-II 40% III-IV 60%	3 MOPP / 3 ABVD + IFRT	IFRT 15-25 Gy	10y OS 96% I-III: 100% IV: OS 85% P<0.02	10 y EFS 93% I-III: 100% IV 69% P<0.0005
Sackman-Muriel(10)	Argentina, 1997	64 24	1- Intermediate 2- Unfavorable	1- CRT 3 CVPP+IFRT+ 3 CVPP vs. 3 AOEP+IFRT+ 3 AOEP 2- 3 CCOPP/3 CAPTe + RT			80 mo EFS 1- 87% vs. 67% (p=0.04) 2- 83%
Shankar(3)	UK (UKCCG), 1997	331	I-II 68% III-IV 32%	-IFRT alone (IA) -6 to 10 ChlVPP ± RT for bulky mediastinal disease	Mediastinum 35Gy	10y I-II 92% III 84% IV 71%	10y PFS I 70%, II 85% III 73%, IV 38%
Schellon(15)	Germany-Austria, 1999	578	I-IIA 47% IIB-IIIA 22% IIIB-IV 31%	- 2 OEPA or OPPA (I-IIA) - + 2 COPP (IIB-IIIA) - + 4 COPP (IIIB-IV)	IFRT	5y 98%	5y EFS 91%
Landman-Parker(22)	France (SFOP), 2000	202	I-II	4 VBVP + IFRT (20 or 40 Gy) ± OPPA according to response	IFRT		5y OS 97% 5y EFS 91%
Hamilton (29)	USA (Philadelphia) 2001	29	I-IIA IIB-III IV	- 4 COPP/ABV - 6 COPP/ABV - 8 COPP/ABV	IFRT to bulky areas 20 Gy	5y 93%	5-y 82%
Donaldson (23)	USA (Stanford), 2002	110	I-II non bulky	4 VAMP + IFRT	IFRT 15-25 Gy acc. to response	5y 99%	5y 93%
Friedman (24)	USA (St Jude)	56	I-II bulky 46% III-IV 54%	6 VEPA + IFRT	IFRT 15-25 Gy	5y 81%	5y 68% I 100%, II 79% III 70%, IV 50%

UKCCG: United Kingdom Children's Cancer Group. SFOP: French Society of Pediatric Oncology. ChlVPP: chlorambucil, vinblastine, procarbazine, prednisolone. OEPA: vincristine, etoposide, prednisolone, doxorubicin. OPPA: vincristine, procarbazine, prednisolone, doxorubicin. CCOPP: CCNU, vincristine, procarbazine, prednisolone. CAPTe: cyclophosphamide, doxorubicin, prednisolone, teniposide. VBVP: vinblastine, bleomycin, etoposide, prednisolone. RT: radiotherapy. IFRT: involved-field RT. LD: low-dose. TNI: total nodal irradiation. EFRT: extended-field RT. CR: complete remission. n.a.: information not available. OS: overall survival. EFS: event-free survival. PFS: progression-free survival.

developing a second malignant neoplasm, mainly radiation-associated solid tumors (breast and thyroid cancers)(40).

Treatment results of MOPP hybrid alone in children with early stage disease showed DFS or EFS rates of about 90%, with equivalent results when 3 or 6 CVPP cycles were administered(10). Even stages I to IV treated with either MOPP or ChlVPP chemotherapy alone in Australia had a 10-year failure-free survival of 94%(11). However, when the UKCCG treated stage IB to IV disease without bulky mediastinal mass with 6 to 10 ChlVPP, 10-year progression-free survival was 73% for stage III and only 38% for stage IV(3). Alternating 6 cycles of CVPP and 6 cycles of EBO in stage IIIB and IV children from Costa Rica provided a 4-year relapse-free survival of 92%(25). Six cycles of ABVD alone were administered to all stages in the Netherlands, but a high proportion of relapse led the authors to use MOPP/ABVD instead(34).

In Madras, treatment of all stages with 6 to 8 cycles of COPP/ABV hybrid alone (62% were stage III or IV) provided a 5-year relapse-free survival of 86%, and only 5% of patients received IFRT because of residual disease(36). Kapoor, *et al.*, from Bombay, reported a 7-year overall and event-free survival of 73% and 64% respectively after treatment with either COPP or ABVD or COPP/ABVD (37% of stage III or IV)(37). In Delhi, All India Institute of Medical Sciences treated 148 children stage I to IV with 8 alternating cycles of COPP/ABVD, with a 5-year EFS of 88%(38).

The role of adjuvant radiotherapy in advanced stage cases that show complete response to chemotherapy remains controversial. In a retrospective study on 43 children with stage IV disease treated with chemotherapy alone (MOPP or MOPP/ABVD) or with chemoradiotherapy, a difference was seen only when B symptoms were present (stage IV B). Failure from progression rate was significantly higher in the group that received additional radiotherapy for partial remission after chemotherapy and/or initial bulky thoracic disease as compared with the group that received chemotherapy alone(41).

Three prospective randomised multicentric studies have been conducted so far in children with HD to compare CMT and chemotherapy alone, by the POG(42) and the Children's Cancer Group (CCG)(43,44). The two first ones have not shown any statistical superiority of CMT, even though OS and EFS were higher in the CMT groups (*Table V*). The POG study compared the addition of low-dose total nodal irradiation *vs.* no irradiation after receiving 4 MOPP / 4 ABVD for stage IIB-IV. The 5 year EFS was 80% for the CMT group vs. 79% for chemotherapy alone, while 5-year overall survival (OS) was higher in the group that did not receive radiotherapy: 96% vs. 87% (P = 0.97)(42). Hutchinson, *et al.* (CCG) randomised 111 stage III and IV patients to either 6 MOPP/6 ABVD or 6 ABVD plus low dose regional radiotherapy, with a 4-year EFS of 87% vs. 77% (P=0.09)(43). Though none of these two trials prove the superiority of either CMT or chemotherapy alone for the treatment of children with advanced disease, low-dose radiation seems to improve their outcome. The most recent randomised control trial from the CCG gave a risk-adapted combination chemotherapy to 829 patients staged I to IV, and randomised those with complete response for either low-dose IFRT or no further treatment. As-treated analysis showed higher 3-year EFS for the group that received additional radiotherapy (93% vs 85%, P = 0.002)(44).

An important drawback in multiagent chemotherapy-alone regimens is acute

TABLE IV–*Results of chemotherapy alone regimens in childhood HD.*

Author	Country	N	Stage	Chemotherapy	OS	EFS / FFS
Ekert(11)	Australia, 1988	53	I-II 72% III-IV 28%	6-12 MOPP or ChlVPP	94% at a median FU of 45 months	FFS 92% at a median FU of 45 months
Lobo-Sanahuja(25)	Costa Rica, 1994	86	I-IIIA IIIB-IV	3-6 CVPP 6 CVPP / 6 EBO	5y - 100% - 81%	5y RFS - 90% - 60%
Baez(33)	Nicaragua, 1997	48	I-II 42% III-IV 58%	6 to 10 COPP or COPP/ABV hybrid		I-IIIA: 3y 100% IIIB-IV: 3y 74.9%
Van den Berg(35)	Netherlands, 1997	21	I-II 71% III-IV 29%	3 MOPP / 3 ABVD		EFS 90% (median FU 61 months)
Sackman-Muriel(10)	Argentina, 1997	26	favorable	RCT: 3 CVPP vs. 6 CVPP		80 months EFS 86% vs. 88%
Arya(38)	India (AIIMS), 2004	148	I-II 55% III-IV 45%	4 COPP / 4 ABVD	5y 92%	5y 88% I: 100%. II: 93% III: 83%. IV: 50%

RCT: randomised controlled trial. RT: radiotherapy. OS: overall survival. EFS: event-free survival. FFS: failure-free survival. RFS: relapse-free survival. AIIMS: All India Institute of Medical Sciences.

TABLE V–*Randomised controlled trials comparing chemotherapy alone vs. combined modality therapy in childhood HD.*

Author	Country/year	N	Stage	Chemotherapy	RT	OS	EFS
Weiner (42)	USA (POG), 1997	179	IIB-IV	- 4 MOPP/ 4 ABVD or - 4 MOPP/ 4 ABVD + LD TNI	±LD TNI	5y OS: 96% (CT) vs. 87%(CMT)	5y EFS: 79% (CT) vs. 80% (CMT)
Hutchinson(43)	USA (CCG), 1998	111	III-IV	- 6 MOPP / 6 ABVD or - 6 ABVD + LD-EFRT	±LD-EFRT	4y OS: 84% (CT) vs. 90% (CMT)	4y EFS: 77% (CT) vs. 87% (CMT)
Nachman(44)	USA (CCG), 2002	829	I-IV	- I-II favourable: 4 COPP/ABV - I-II unfavourable, III: 6 - IV: 2 (cycle A / B / C)*	Randomisation after CR: ±LD-IFRT	3y OS: 99% (CT) vs. 98% (CMT)	3y EFS: 85% (CT) vs. 93%(CMT), p=0.002

POG: Pediatric Oncology Group. CCG: Children's Cancer Group. * Cycle A: Cytarabine, Etoposide. Cycle B: COPP/ABVD. Cycle C: COAP (cyclophosphamide, vincristine, doxorubicin, prednisolone). RT: radiotherapy. IFRT: involved-field RT. LD: low-dose. TNI: total nodal irradiation. EFRT: extended-field RT. CT: chemotherapy alone. CMT: combined modality therapy. OS: overall survival. EFS: event-free survival.

complications related to myelosuppression and long-term organ toxicity-cardiac, pulmonary, gonadal and secondary leukemia. Protocols with MOPP chemotherapy (or derivatives) alone use higher cumulative doses of alkylating agents than CMT, and are associated with an increased risk of infertility and a higher cumulative risk of leukemia (7.9%) at 15 years after chemotherapy alone than after CMT (3.4%), as shown by the Late Effects Study Group(9). Regimens alternating ABVD with MOPP-equivalent regimens improve disease control and reduce the cumulative dose of alkylating agents, but increase the risk of long-term cardio-pulmonary toxicity. However, this risk is reduced when no radiotherapy is given to the mediastinum. Other hybrid chemotherapy programs decrease exposure to alkylating agents, anthracyclines and bleomycin, without totally eliminating their late effects. Follow-up of chemotherapy-alone studies is still too short to fully appreciate the late effects.

Risk-adapted therapy

Various clinical and laboratory features have been identified as poor prognostic factors in children with HD, and lead to more aggressive therapy in a particular subset of patients. They are related to tumor burden and tumor spread, B symptoms, response to therapy, biology and host factors. The major distinction made in risk-adapted therapy trials is related to the extension of the disease. Thus initial work-up of the patients should include a complete history and careful physical examination, along with the minimum following investigations for proper evaluation of disease extension: complete hemogram with Westergren erythrocyte sedimentation rate, upright postero-anterior chest *X*-ray, contrast-enhanced computerised tomography of the chest, abdomen and pelvis, and bone marrow biopsy.

Treatment of early stage disease

Early stage disease (I to IIA for most authors) presents excellent results with either CMT or chemotherapy alone, with DFS or EFS in excess of 90%. An exception is worth mentioning: in a recent Australian trial attempting to reduce treatment toxicity, treatment with 5 to 6 VEEP cycles alone showed 35% of treatment failure in stage I(26). Localised disease with unfavorable features, such as bulky presentation or more than two involved areas, is controlled with a more aggressive treatment than localised favorable disease(10,24). Various study groups assign stage IIB and IIIA, or stage IIB and III disease to an intermediary group, in view of administering an intermediary number of chemotherapy cycles as compared with early and advanced disease(23,29).

Treatment of advanced stage disease

Advanced disease (III to IV) requires more aggressive therapy. Subsequent trials from international study groups have obtained increasing overall and disease-free survival rates, especially by increasing the dose intensity of treatment. Contemporary CMT trials report 5-year EFS rates greater than 80% in advanced disease. ChlVPP chemotherapy and RT to bulky or residual disease provide a 10-year progression-free survival (PFS) or EFS of only 38% to 49% in stage IV(3,12). Hybrid regimens using ABVD/ABV alternating with MOPP/COPP provide disease control in about 75% of stage IIB-IV patients without RT(33) but stage IV patients do poorly with such conventional therapy, whether additional IFRT is administered or not: Vecchi, *et al.* reported a 7-year progression-free survival of 41% in stage IV patients treated with MOPP/ABVD and extended field RT(28). Some chemotherapy regimens such as VEPA plus low-dose IFRT, though adequate

for early stage disease with unfavorable features, have proven unsatisfactory for advanced stage patients, with a 5-year EFS of 49.5% in stage IV(24).

The CCG evaluated a dose-intensive regimen in stage IV patients, consisting of cytarabin and etoposide, in conjunction with standard chemotherapy, with further randomisation for additional RT after complete remission, obtaining a 3-year EFS of 83%(44). Dose-intensified chemotherapy protocols, such as Stanford V (nitrogen mustard, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisolone)(45) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) along with G-CSF(46) improved the outcome of adults with advanced HD with acceptable toxicity. The first attempt to treat children with stage IIB, IIIB or IV with four doses of escalated BEACOPP as induction therapy demonstrated its feasibility and good tolerance in children(47). Rapid early responders further received either 4 cycles of COPP/ABV (girls) or 2 ABVD plus IFRT (boys), while slow early responders received four more BEACOPP cycles plus IFRT. Early results show a significant improvement in EFS (98% at a median follow-up of 6 months)(47), but further follow-up is necessary to evaluate effective-ness and long-term toxicity of dose-intensive chemotherapy in children.

The role of additional RT in stage III or IV disease remains controversial. In a meta-analysis of chemotherapy vs CMT adult trials, the International Database on Hodgkin's Disease Overview Study Group showed that adjuvant radiotherapy presents no survival advantage, though better local tumor control is obtained(48).

Adverse prognostic factors

A prognostic model for adults with advanced HD has been developed by the international collaborative study, based on the following adverse factors: age of 45 or more, stage IV disease, male sex, leukocyte count = 15,000/μL or more, lymphocyte count <800/μL or <8% of the white cell count, serum albumin < 4 g/dL and hemoglobin (Hb) < 10.5 g/dL(49).

Most publications on treatment results in childhood HD have identified various prognostic factors. Age is significant only at univariate level: Italian children aged 7 or more had a poorer outcome than younger children, as the incidence of stage IV disease, bulky mediastinal mass(50), B symptoms and lymphocyte depletion histology was higher in this age group(28). Independent risk factors revealed by multivariate analysis on childhood HD include male sex, as male children do worst than females when the same treatment protocol is used(18,50); B symptoms(15, 28,50); stage IV as compared with stage II and III(18,28,43) or for another author stage IIB, IIIB or IV(51); a greater number of nodal regions involved, presence of a bulky mediastinal mass(28,42,50); enlarged liver size at diagnosis(43); Hb <10.5 g/dL(22) or 11 g/dL(50); raised ESR(43); total leukocyte count >13,500/μL(50). The presence of two or more of the following biologic findings is also an independent factor predictive of poor outcome: ESR (40 mm/hr, fibrinogen > 5g/L, leukocytosis>12,000/mm3 and/or neutrophil count >70%, (α^2-globulin >10g/L and albumin <3.5g/dL(22). Response to induction chemotherapy is predictive of final outcome(24,42) and should guide consolidation therapy accordingly: results of response-adapted therapy are very encouraging in early stage disease(22). Lymphocyte-predominant histology is associated with favorable

Key Messages

- Childhood Hodgkin's disease is curable in over 90% of early stages and in 50 to 70% of advanced stages.
- The choice between chemotherapy alone protocols and chemo-radiotherapy is guided by the desired balance between cure and long-term effects of therapy.

outcome(52) while nodular sclerosis, particularly type 2, has a negative impact on EFS(15,22,23,53).

The Argentine Group for Treatment of Acute Leukemia (GATLA) defined a valuable prognostic index in children and adults HD patients, based on age, number of constitutional symptoms, stage and number of regions involved, and defining 3 groups: favorable, intermediate and unfavorable(54). Selective treatment of all stage Argentinean children according to this prognostic index provided an EFS of 81% at 6.7 years for the whole cohort(10). Such prognostic scores should be developed in childhood HD, so as to guide therapeutic alternatives in the context of risk-adapted therapy.

Treatment of relapsed or refractory disease

Most relapses occur within the first three years, although relapses as late as ten years or more from diagnosis are seen. Patients with early relapse (within a year from initial remission), multiple relapses or progressive disease on first line therapy respond poorly to conventional salvage therapy and require high dose chemotherapy with agents such as ifosfamide, epirubicin, etoposide, cisplatin, melphalan and stem cell transplantation. This approach provides OS rates of 30 to 50%(55,56). Forty to 50% of late relapses can be treated with combined modality therapy, with a high risk of treatment related morbidity. Cooperative group investigations are required to assess prognostic factors in relapsed disease, as previously done in adults(57).

Conclusion

Treatment results of childhood Hodgkin's disease have enjoyed considerable progress over the years, with excellent achievements in early stage favourable disease, enabling the use of fewer cycles of cytotoxic chemotherapy and elimination or reduction of drugs responsible for late sequelae. Additional low-dose involved field radiotherapy after complete response to first line chemotherapy is the best strategy for many groups, while others prefer chemotherapy alone protocols. More efforts are still required in order to improve long-term survival in unfavorable and advanced disease as well as relapsed cases. Decision-making for the management of pediatric HD should be guided by the relative risks and benefits associated with treatment regimens.

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