Indian J Pediatr (May 2017) 84(5):371–381
DOI 10.1007/s12098-017-2304-6

REVIEW ARTICLE

Management of Hodgkins Lymphoma: ICMR Consensus Document

Venkatraman Radhakrishnan[1] · Gauri Kapoor[2] · Brijesh Arora[3] · Deepak Bansal[4] · Tushar Vora[3] · Maya Prasad[3] · Girish Chinnaswamy[3] · Siddharth Laskar[5] · Sandeep Agarwala[6] · Tanvir Kaur[7] · G. K. Rath[8] · Sameer Bakhshi[9]

Received: 3 December 2016 / Accepted: 30 January 2017 / Published online: 30 March 2017

Abstract Pediatric Hodgkins lymphoma is a highly curable disease even in the developing world. Current treatment paradigms follow a risk and response based approach. The goal is to minimise treatment related short and long-term toxicity while maintaining excellent survival. A confirmed histopathological diagnosis and full staging work-up are essential prior to embarking on treatment and guidelines for these are provided in the text. All patients require combination chemotherapy while radiotherapy is usually reserved for a select subgroup depending on the protocol used. It is important to follow these patients for relapse in the first five years and life-long for late effects as most of them will be cured.

Keywords Hodgkins lymphoma · Chemotherapy · Radiotherapy

Introduction

Pediatric Hodgkins lymphoma (HL) is a highly curable malignancy. The emphasis of treatment in pediatric Hodgkins lymphoma has shifted towards risk stratified approach, so that long term side-effects of chemotherapy and radiotherapy can be reduced. The age standardised rates (ASR) of Hodgkins lymphoma in India is 0.4/100000 population, whereas the global ASR varies between 0.3/100000 in less developed countries and 0.6/100000 in developed countries [1]. Hodgkins lymphoma is more common in boys than in girls with the gender gap being wider in developing countries than developed countries [2]. Children with Hodgkins lymphoma in India present at a younger age when compared to Western patients [2]. Long term outcomes reported from various centres in India are comparable to outcomes reported from western centres. The current manuscript

✉ Gauri Kapoor
kapoor.gauri@gmail.com

[1] Department of Medical Oncology and Pediatric Oncology, Cancer Institute (W.I.A), Adyar, Chennai, India

[2] Department of Pediatric Hematology & Oncology, Rajiv Gandhi Cancer Institute & Research Center, Rohini, Sector 5, Delhi 110085, India

[3] Department of Pediatric Oncology, Tata Memorial Hospital, Parel, Mumbai, India

[4] Pediatric Hematology Oncology Unit, Department of Pediatrics, Advanced Pediatric Center, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[5] Department of Radiation Oncology, Tata Memorial Hospital, Parel, Mumbai, India

[6] Department of Pediatric Surgery, All India Institute of Medical Sciences, New Delhi, India

[7] NCD Division, Indian Council of Medical Research (ICMR), New Delhi, India

[8] Dr. B.R.A Institute-Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

[9] Department of Medical Oncology, Dr. B.R.A Institute-Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

is written with the objective of developing a consensus guideline for practitioners at a National level.

Material and Methods

This document on consensus guidelines for management of Hodgkins lymphoma was arrived at after an initial round of meetings with National experts in the field of Pediatric Hematology Oncology. Thereafter an exhaustive review of literature of National and International data was undertaken and the manuscript was drafted. This was then presented in a second round meeting with the experts till a final consensus was obtained after mutiple rounds of discussion. The final consensus document was once again sent to all the authors for proofing and then submitted.

Treatment Philosophy for Pediatric Hodgkins Lymphoma [3]

There is no one standard treatment regimen for pediatric Hodgkins lymphoma. The treatment of an individual patient is based on various parameters like 1. Risk stratification, 2. Response to initial chemotherapy, 3. Age and Gender, 4. Associated co-morbidities like cardiac and pulmonary diseases, and 5. Stage of disease. The goal is to minimise treatment related short term and long term toxicity without compromising cure.

Chemotherapy is indicated in all patients with Hodgkins lymphoma as use of radiotherapy alone does not lead to complete cure in majority of the patients and is associated with significant long-term toxicities. Combination chemotherapy is preferred over single agent drugs. It is important to remember that alkylating agents like procarbazine and cyclophosphamide can cause sterility especially in males and therefore should be omitted or used with caution. Anthracyclines like doxorubicin in higher cumulative doses can cause cardiac dysfunction and when combined with mediastinal radiotherapy can contribute to long-term cardiac toxicities like ischemic heart disease. Etoposide can cause secondary leukemia which is dependent on the cumulative dose used, whereas bleomycin induced pulmonary toxicity is idiosyncratic. Therefore it is essential to limit the cumulative doses of the above drugs in chemotherapy regimens used for treating pediatric Hodgkins lymphoma. Emphasis is shifting from Involved Field radiotherapy (IFRT) to Involved Nodal RT (INRT) in pediatric Hodgkins lymphoma due to long-term concerns of second malignancies, growth retardation, endocrine dysfunction, sterility if gonads are irradiated and cardiovascular disease when mediastinum is irradiated. The radiation field in IFRT will depend on the location of the nodes. Radiotherapy dose used varies from 20 to 36 Gy depending upon the response to chemotherapy. The pre-treatment nodal size needs to be irradiated.

Risk Stratification [4]

Risk stratification is used in all the protocols for treating Hodgkins lymphoma to tailor the treatment. The risk stratification has also evolved over the last few decades. The goal of risk stratification is to minimise treatment in patients with favourable disease thereby reducing long-term toxicity and escalate treatment in patients with high-risk disease so as to not to compromise on survival. There is considerable variation in risk stratification among various trials and treatment groups and therefore, it becomes difficult to compare trials in pediatric Hodgkins lymphoma. The general risk stratification followed by various groups are given below

- **Favourable**: Stage I or II without adverse prognostic factors
- **Intermediate**: Stage I or II with adverse prognostic factors (presence of "B" symptoms, bulky lymphadenopathy, extranodal extension to contiguous structures, involvement of three or more nodal areas)
- **Advanced**: Stage II BE, II BX, IIIAE, IIIAX, IIIB-IV

Review of Literature

Management of pediatric Hodgkins lymphoma has evolved over the last 5–6 decades. Multiple prospective randomised controlled trials in pediatric Hodgkins lymphoma have been conducted in North America and Europe. Majority of the data on Hodgkins lymphoma management from India has been retrospective in nature. The current guidelines therefore will be based mainly on the results of prospective randomised controlled trials (RCT) data from the western countries.

The optimum treatment of Hodgkins lymphoma in children is not clearly defined. There is wide variation among the treatment protocols used in various centres in India and abroad. Although protocols using ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen are standard for treating adults, their use in children is limited due to the cumulative toxicity of the regimen.

Summary of Important Trials

The pediatric oncology group response based risk adapted therapy showed that in patients with favourable risk (stage

IA, IB, IIA, IIIA), 2 cycles ABVE (Doxorubicin, bleomycin, vincristine, etoposide) with IFRT (25.5 Gy) was equivalent to 4 cycles of ABVE with IFRT (25.5 Gy) in patients who achieved complete response (CR) after 2 cycles [5]. In patients with unfavourable advanced disease, patients who achieved rapid response after 3 cycles of dose dense ABVE-PC (Doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) had outcomes comparable to patients who achieved rapid response and received 5 cycles of dose dense ABVE-PC [6]. All patients received 21 Gy IFRT [6]. The Children's Cancer Group (CCG) trial compared COPP/ABV (Cyclophosphamide, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine) hybrid chemotherapy followed by randomisation to IFRT or no IFRT in patients achieving CR. In this trial, Event Free Survival (EFS) was inferior in patients in whom IFRT was omitted [7]. In another CCG trial, response adapted de-escalation treatment was planned in patients with stage IIB, IIIB and stage IV disease. Patients with rapid early response after four cycles of dose intensive BEACOPP (Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine) could be de-escalated to 4 cycles of COPP/ABV without IFRT in girls and 2 cycles of ABVD followed by IFRT in boys [8]. IFRT was avoided in girls to reduce the long-term risk of breast cancer. The Stanford, St Jude and Boston Consortium trials showed that patients with favourable Hodgkins lymphoma who achieved early CR with 4 cycles, VAMP (Vinblastine, doxorubicin, methotrexate, prednisone) chemotherapy had outcomes similar to patients who received 4 cycles VAMP with 25.5 Gy IFRT [9].

The HD-95 trial done in Germany has shown that omission of radiotherapy in intermediate or high risk patients who achieve CR leads to inferior outcome. However, omission of radiotherapy in favourable risk group patients did not result in inferior outcome. All patients received OEPA (Vincristine, etoposide, prednisone, doxorubicin) or OPPA (Vincristine, procarbazine, prednisone, doxorubicin) /COPP (Cyclophosphamide, vincristine, procarbazine, prednisone) chemotherapy in this trial [10]. The interim analysis of Euronet Trial which is an ongoing multi-centre trial in Europe has revealed that COPP and COPDac (Cyclophosphamide, vincristine, prednisone, dacarbazine) are similarly efficacious and therefore, procarbazine (COPP) can be eliminated in boys thereby decreasing risk of sterility. EFS of all patients did not differ whether they received radiotherapy [11]. Tables 1 and 2 summarise the results of prospective trials in low risk (favourable) and Intermediate and Advanced Hodgkins lymphoma from the Western world.

Indian Experience

A meta-analysis of all published data on Hodgkins lymphoma from India reported the outcomes in 958 children [16]. The median age at presentation was 7–9 y in majority of the studies and the median male to female ratio was 4.4:1. Majority (median 64%, range 33–92%) had stage IIB/III Hodgkins lymphoma at presentation. Mixed cellularity was the most common histology (median 50%, range 27–86%). Positive Emission Tomography (PET) combined with computed tomography (CT) was not used in any centre. Treatment consisted of chemotherapy and radiotherapy, but there was considerable variation among centres. Several chemotherapy regimens were used, most commonly ABVD. Table 3 provides the details of studies on Hodgkins lymphoma published from India.

Review of literature from India suggests that multi-agent chemotherapy without radiotherapy may be sufficient to treat majority of Hodgkins lymphoma patients. Radiotherapy can be reserved for patients with bulky disease not responding to chemotherapy alone. A survey of main pediatric cancer centres in India has shown that 75% of them use ABVD protocol for treating pediatric Hodgkins lymphoma. In India, the management of Hodgkins lymphoma will be influenced by the availability of PET/CT imaging and radiotherapy facilities. PET/CT and radiotherapy add significant costs to the treatment of Hodgkins lymphoma and are not available in various parts of the country. Therefore, the practice of PET/CT based response tailored treatment may not be feasible (though desirable), in various centres across India.

Response Assessment

Further refinement of risk classification may be performed through assessment of response after initial cycles of chemotherapy or at the completion of chemotherapy.

Interim Response Assessment

Assessment of response to treatment after completing 2–3 cycles of chemotherapy has been found to be useful in de-escalating treatment in patients with good response or escalating treatment in patients with poor response. The interim assessment can be performed using CT scans or PET/CT scan. There is no standard definition of a good response or poor response and various protocols have used their own definitions to define response. Clinical findings and laboratory investigations have also been incorporated along with radiological findings to define response. The Lugano classification is

Table 1 Results of recent trials for pediatric low-risk Hodgkins lymphoma

Group	Study	n	Stage	Chemotherapy	RT (dose, field)	EFS or DFS, OS (year)
Europe						
French Society of Pediatric Oncology	MDH90 [12]	202	IA, IB, IIA, IIB	VBVP × 4 (+ OPPA × 1–2 if PR after cycle 4)	20-40Gy IF	91.1%, 97.5% (5y)
German Society of Pediatric Oncology and Hematology	GPOH-HD-95 [10]	328	IA, IB, IIA	OPPA (female); OEPA (male) × 2.	CR after cycle 2: no RT PR after cycle 2: 20- 30Gy IF	93.2%, 98.8% (10y)
	GPOH-HD-2002 [13]	195	IA, IB, IIA	OPPA (female); OEPA (male) × 2	CR after cycle 2: no RT PR after cycle 2: 20- 30Gy IF	92%, 99.5% (5y)
North America						
Stanford, Dana Farber, St. Jude Consortium [9]		110	IA, IB, IIA, IIB no bulk, no E	VAMP × 4	15–22.5 Gy IF	89.4%, 96.1% (10y)
		88	IA, IIA, <3 nodal sites, no bulk, no E	VAMP × 4	CR after cycle 2: no RT PR after cycle 2: 25.5Gy IF	EFS: 90.8% (2y)
CCG, POG, and COG	CCG 5942 [14]	294	IA, IB, IIA without adverse features+	COPP/ABV × 4	CR after cycle 4: randomized to 21Gy IFRT *vs*. no RT PR: 21Gy IF	10 y EFS IFRT: 100% no RT: 89.1% ($p = 0.001$) 10 y OS: RT: 97.1% no RT: 95.9% ($p = 0.5$)
	P9426 [5]	294	IA, IB, IIA, IIIA	DBVE × 2–4 (based on response after cycle 2)	25.5 Gy IF	86.2%, 97.4% (8y)
	AHOD0431 [15]	287	IA, IIA, no bulk	AV-PC × 3	CR after cycle 3: no RT PR after cycle 3: 21 Gy IF	79.8%, 99.6% (4y)

VBVP Vinblastine, bleomycin, etoposide, prednisone; *PPA* Vincristine, procarbazine, prednisone, doxorubicin; *OEPA* Vincristine, etoposide, prednisone, doxorubicin; *VAMP* Vinblastine, doxorubicin, methotrexate, prednisone; *COPP/ABV* Cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine; *DBVE* Doxorubicin, bleomycin, vincristine, etoposide; *AV-PC* Doxorubicin, vincristine, prednisone, cyclophosphamide; *IF* Involved field; *RT* Radiation therapy; *M* Male; *F* Female; *RER* Rapid early responder; *SER* Slow early responder; *CR* Complete response; *PR* Partial response; *EFS* Event free survival; *OPPA* Vincristine, procarbazine, prednisone, doxorubicin; *DFS* Disease free survival; *OS* Overall survival; *E* Extralymphatic organ or site

the most widely accepted classification for response assessment [25].

Guidelines for Histopathology

Lymph node biopsy is mandatory for confirming the diagnosis [26]. Wherever possible, excisional lymph node biopsy is strongly recommended over core-needle biopsy. However, in inaccessible sites like retroperitoneum and mediastinum, core-needle biopsy will be acceptable. Fine needle aspiration is usually not sufficient for diagnosis of lymphoma in children and is not recommended. For histological diagnosis and subtyping, immunohistochemistry is recommended, where feasible. Immunostaining for CD15, CD30, CD3, CD20, and CD45 is ideal for classical HL (cHL) but a limited profile with CD15 and CD30 may be adequate if histopathology is classical. For nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), CD20 is recommended.

Pathological diagnosis should be made according to the World Health Organization (WHO) classification from a sufficiently large surgical specimen or excisional lymph node biopsy to provide enough material for fresh frozen and formalin-fixed samples. In cHL, the presence of Hodgkin and Reed–Sternberg (HRS) cells is disease-defining while the detection of lymphocyte predominant (LP) cells is required for the diagnosis of NLPHL. The immunophenotype of the malignant cells in cHL and NLPHL differs significantly. In contrast to HRS cells that stain consistently positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45, LP cells are characterised by the expression of CD20 and CD45 but they lack CD15 and CD30.

Table 2 Results of recent trials for pediatric intermediate and high-risk HL

Group	Study	n	Stage	Chemotherapy	RT (dose, field)	EFS or DFS, OS (year)
Europe						
German Society of Pediatric Oncology and Hematology	GPOH-HD- 95 [10]	341	Intermediate: IEA/B; IIEA; IIB; IIIA High: IIEB; IIIEA/B; IIIB; IV	2 OPPA/OEPA + 4 COPP	CR after cycle 2: No RT PR after cycle 2: 20-35Gy IF	84.5%, 93.2% (10y)
	GPOH-HD- 2002 [13]	Intermediate: 139 High: 239	Intermediate: IEA/B; IIEA; IIB; IIIA High: IIEB; IIIEA/B; IIIB; IV	OPPA (female); OEPA (male) × 2 Intermediate: COPDac × 2 High: COPDac × 4	19.8–35 Gy IF	Intermediate: 88.3%, 99.5% High: 86.9%, 94.9% (5y)
North America						
CCG, POG, and COG	CCG 5942 [14]	Intermediate: 394 High: 141	Intermediate; IA, IB, IIA with adverse features^{+}; IIB, III High: IV	Intermediate: COPP/ABV × 6 High: COPP/ABV, CHOP, Etoposide / Cytarabine × 2	CR after cycle 6: randomized to 21Gy IFRT *vs*. no RT PR: 21Gy IF	Intermediate: RT: 87%, 95% No RT: 83%, 100%; High: RT: 90%, 100% No RT: 81%, 94% (EFS $p < 0.05$)
	P9425 [6]	Intermediate: 53 High: 163	Intermediate: IB, IIALMA, IIIA High: IIB, IIIB, IV	DBVE-PC × 3–5 (based on response after cycle 3)	25.5 Gy IF	Intermediate: 84%, OS NR High: 85%, OS NR (5y)
	C59704 [8]	99	IIB/IIIB + bulk, IV	BEACOPP × 4 M RER: ABVD × 2 F RER: COPP/ABV × 4 SER: BEACOPP × 4	M RER: 21 Gy IF F RER: No RT SER: 21 Gy IF	94%, 97% (5 y)
	AHOD0031 [15]	1712	IA, IIA + bulk, IB, IIB, IIIA, IVA	ABVE-PC × 4 SER: Randomized DECA × 2	Randomized RER after cycle 2 and CR after cycle 4: No RT All others: 21 Gy IF	85.6%, 98.2% (3 y)

OEPA Vincristine, etoposide, prednisone, doxorubicin; *VAMP* Vinblastine, doxorubicin, methotrexate, prednisone; *COPP/ABV* Cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine; *COPDac* Cyclophosphamide, vincristine, prednisone, dacarbazine; *CHOP* Cyclophosphamide, doxorubicin, vincristine, prednisone; *DBVE-PC* Doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; *BEACOPP* Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine; *ABVE-PC* Doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; *DECA* Dexamethasone, etoposide, cisplatin, cytarabine; *IF* Involved field; *RT* Radiation therapy; *M* Male; *F* Female; *RER* Rapid early responder; *SER* Slow early responder; *CR* Complete response; *PR* Partial response; *LMA* Large mediastinal adenopathy; *EFS* Event free survival; *DFS* Disease free survival; *OS* Overall survival; *OPPA* Vincristine, procarbazine, prednisone, doxorubicin; *NR* No response; *ABVD* Doxorubicin, bleomycin, vinblastine, dacarbazine

Table 3 Studies on pediatric Hodgkins lymphoma from India

Author	N	Stage	Treatment	Comments	5-y PFS %	5-y OS%
Laskar et al. [17]	251	Stage I-IV (approx. 50% less than 15 y age)	6 ABVD + IFRT *vs.* 6 ABVD alone	Prospective RCT. EFS and OS better in ABVD + RT arm compared to ABVD alone	CT: 76 CT + RT: 88	CT: 89 CT + RT: 100
Trehan et al. [18]	206	Stage I-IV	Multiple regimens, RT (1%)	Retrospective study. B symptoms associated with poor outcome	92	77
Arya et al. [19]	148	Stage I-IV	ABVD, COPP alternating, no RT	Retrospective study. Anemia and splenomegaly associated with poor prognosis	87	91
Chandra et al. [20]	35	Stage I-IV	COPP, COPP + ABVD, ABVD, RT (10%)	Retrospective study	80	NA
Sagar et al. [21]	134	Stage I-IV	COPP/ABV, RT (5%)	Retrospective study. Bulky disease, anemia (HB < 8.5 g%) and increased LDH associated with poor prognosis	NA	Stage 1: 90 Stage 4: 84
Kapoor et al. [22]	147	Stage I-IV	COPP (108), COPP/ABVD (33), ABVD (6)	Retrospective study	7-y EFS: 64	7-y OS: 73
Jain et al. [23]	167	Stage I-IV	ABVD	Retrospective study. Stages III and IV, >4 lymph node regions involved, and serum lactate dehydrogenase >500 IU/l associated with poor prognosis	5-y FFTF: 79	95.9
Radhakrishnan et al. [24]	172	Stage I-IV	ABVD (120), ABV/COPP (52)	Advanced stage, response on interim radiologic assessment, and presence of B symptoms significantly predicted inferior PFS and OS	83.1	92.9

IFRT Involved Field Radiotherapy; *RT* Radiotherapy; *OS* Overall survival; *PFS* Progression free survival; *EFS* Event free survival; *HB* Hemoglobin; *CT* Chemotherapy; *N* Number of patients enrolled; *RCT* Randomised controlled trial; *FTFF* Freedom from treatment failure; *ABVD* Doxorubicin, bleomycin, vinblastine, dacarbazine; *RCT* Randomised controlled trials; *COPP* Cyclophosphamide, vincristine, procarbazine, prednisone; *AVD* Adriamycian, vinblastine, dacarbazine; *NA* Not available; *LDH* Lactate dehydrogenase

2008 WHO Classification of Lymphoid Neoplasms

- Nodular Lymphocyte Predominant
- Classical Hodgkins Lymphoma
  - Nodular Sclerosing Classical Hodgkins Lymphoma
  - Lymphocyte-Rich Classical Hodgkins Lymphoma
  - Mixed Cellularity Classical Hodgkins Lymphoma
  - Lymphocyte- Depleted Classical Hodgkins Lymphoma

Staging

It is essential that every patient undergoes staging investigations prior to starting disease directed therapy. Stage is determined by anatomic evidence of disease using CT scanning in conjunction with functional imaging (wherever possible) and bone marrow biopsy. The staging classification used for Hodgkin lymphoma was adopted at the Ann Arbor Conference held in 1971 and revised in 1989 [27].

Ann Arbor Staging Classification of Hodgkin Lymphoma

Stage I

Involvement of a single lymphatic site (*i.e.*, nodal region, Waldeyer"s ring, thymus, or spleen) (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE).

Stage II

Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE).

Stage III

Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S).

Stage IV

Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but

in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (other than by direct extension from another site), or cerebrospinal fluid.

Annotations of Stage

HL will be sub-classified into A and B categories. Patients with any of the following specific symptoms will be classified as B:

- Unexplained loss of more than 10% of body weight in the 6 mo before diagnosis.
- Unexplained fever with temperatures above 38 °C for more than 3 d.
- Drenching night sweats.

Definition of Bulky Disease

Bulky mediastinal disease is defined as a mediastinal mass with horizontal tumor diameter > 1/3rd the thoracic diameter (measured transversely at the level of the dome of the diaphragm on a 6 ft upright posterior-anterior chest x-ray). In the presence of hilar nodal disease, the maximal mediastinal tumor measurement may be taken at the level of the hilum. This should be measured as the maximum mediastinal width (at a level containing tumor and any normal mediastinal structures at the level) over the maximum thoracic ratio.

Bulky disease outside the mediastinum is defined as a single node or continuous aggregate of nodal tissue that measures >6 cm in the longest diameter in any nodal area.

Diagnostic Work-Up

1. Clinical evaluation: The workup should include a thorough history and physical examination including B symptoms (unexplained fever, more than 10% weight loss and/or drenching night sweats).
2. Physical examination should be careful and complete:
    a. Common lymph node areas to be palpated.
    b. Number of sites / lymph node regions is to be noted.
    c. Measurement of largest mass (bulky disease).
    d. The size of liver / spleen in cm below costal margin.
    e. Baseline pubertal status.
3. Essential laboratory investigations:
    a. Complete blood counts (CBC) & differential leukocyte counts (DLC) and erythrocyte sedimentation rate (ESR).
    b. Lactate dehydrogenase (LDH), liver function tests (LFT) and serum creatinine.
    c. Contrast enhanced CT neck, chest and whole abdomen are mandatory (unless PET scan is done).
    d. Adequate bilateral bone marrow (BM) biopsy should be performed on patients who have stage III or IV disease or B symptoms. BM biopsy can be omitted in patients who undergo PET/CT for staging.
    e. Pleural cytology, if there is pleural effusion.

Other Investigations

1. Hepatitis B, Hepatitis C and Human Immunodeficiency (HIV) screening
2. Baseline Echocardiography and Pulmonary function test.
3. PET/CT scan should be done wherever feasible.
4. Bone scan: indicated in case of bone pain, elevated alkaline phosphatase; it is not needed if PET/CT scan has been done.
5. Reproductive counseling (in younger patients) and semen preservation for older male patients and serum pregnancy test (in female patients).

Treatment Recommendations

Treatment recommendations for pediatric Hodgkins lymphoma patients is given below. It is important to remember that if one treatment regimen or protocol is selected then the said protocol or regimen should be followed and not mixed and matched with other regimens. The chemotherapy and radiotherapy doses and schedule given in the protocol should be followed. Definition of good response or poor response after 2–3 cycles of chemotherapy will vary according to the treatment protocol used. Patients who have achieved CR on PET/CT or CT after 2–3 cycles of chemotherapy are considered good (rapid) responders and patients who have stable disease are considered poor (slow) responders. Patients with partial response (PR) on PET/CT or CT can be either good or poor responders based on the protocol/study being followed. Patients with progressive disease after 2 cycles of chemotherapy should be considered for escalation to more intense chemotherapy protocols. The protocols recommended below are not in any particular order of preference. Table 4 provides the schedule and doses for commonly used chemotherapy protocols in pediatric Hodgkins lymphoma.

Table 4 Chemotherapy protocols for pediatric Hodgkins lymphoma

Name	Drugs	Dose	Route	Days	Schedule
COPP [13]	Cyclophosphamide	600 mg/m^2	IV	1, 8	Repeat every 28 d
	Vincristine	1.4 mg/m^2	IV	1, 8	
	Procarbazine	100 mg/m^2	PO	1–15	
	Prednisone	40 mg/m^2	PO	1–15	
COPDAC [13]	Dacarbazine substituted for procarbazine in COPP	250 mg/m^2	IV	1–3	Repeat every 28 d
OPPA [13]	Vincristine	1.5 mg/m^2	IV	1, 8, 15	Repeat every 28 d
	Prednisone	100 mg/m^2	PO	1–15	
	Procarbazine	60 mg/m^2	PO	1–15	
	Adriamycin	40 mg/m^2	IV	1, 15	
OEPA [13]	Vincristine	1.5 mg/m^2	IV	1, 8, 15	Repeat every 28 d
	Etoposide	125 mg/m^2	IV	3–6	
	Prednisone	60 mg/m^2	PO	1–15	
	Adriamycin	40 mg/m^2	IV	1, 15	
ABVD [28]	Adriamycin	25 mg/m^2	IV	1, 15	Repeat every 28 d
	Bleomycin	10 U/m^2	IV	1, 15	
	Vinblastine	6 mg/m^2	IV	1, 15	
	Dacarbazine	375 mg/m^2	IV	1, 15	
COPP/ABV [7]	Cyclophosphamide	600 mg/m^2	IV	0	Repeat every 28 d
	Vincristine	1.4 mg/m^2	IV	0	
	Procarbazine	100 mg/m^2	PO	0–6	
	Prednisone	40 mg/m^2	PO	0–13	
	Adriamycin	35 mg/m^2	IV	7	
	Bleomycin	10 U/m^2	IV	7	
	Vinblastine	6 mg/m^2	IV	7	
VAMP [29]	Vinblastine	6 mg/m^2	IV	1, 15	Repeat every 28 d
	Adriamycin	25 mg/m^2	IV	1, 15	
	Methotrexate	20 mg/m^2	IV	1, 15	
	Prednisone	40 mg/m^2	PO	1–14	
DBVE [5]	Doxorubicin	25 mg/m^2	IV	1, 15	Repeat every 28 d
	Bleomycin	10 U/m^2	IV	1, 15	
	Vincristine	1.5 mg/m^2	IV	1, 15	
	Etoposide	100 mg/m^2	IV	1–5	
ABVE-PC [6]	Doxorubicin	30 mg/m^2	IV	0, 1	Repeat every 21 d
	Bleomycin	10 U/m^2	IV	0, 7	
	Vincristine	1.4 mg/m^2	IV	0, 7	
	Etoposide	75 mg/m^2	IV	0–4	
	Prednisone	40 mg/m^2	PO	0–9	
	Cyclophosphamide	800 mg/m^2	IV	0	
BEACOPP [8]	Bleomycin	10 U/m^2	IV	7	Repeat every 21 d
	Etoposide	200 mg/m^2	IV	0–2	
	Doxorubicin	35 mg/m^2	IV	0	
	Cyclophosphamide	1200 mg/m^2	IV	1, 8	
	Vincristine	2 mg/m^2	IV	7	
	Prednisone	40 mg/m^2	PO	0–13	
	Procarbazine	100 mg/m^2	PO	0–6	
CVP [30]	Cyclophosphamide	500 mg/m^2	IV	1	Repeat every 21 d
	Vincristine	6 mg/m^2	IV	1, 8	
	Prednisolone	40 mg/m^2	PO	1–8	

Favourable Risk

1. Stage IA and IIA without risk factors: 4 cycles of chemotherapy regimens like ABVD, ABVE, or VAMP or 2 cycles of OEPA
2. Patients with poor response in interim assessment and those with residual disease after 4 cycles of chemotherapy should be given involved field RT at a dose of 15–30 Gy. Omission of IFRT can be considered in patients achieving CR on PET/CT or CT after 2 cycles of chemotherapy

Intermediate Risk

Good initial response to 2 cycles of chemotherapy

1. 4 cycles of ABVD with IFRT (20–26 Gy)
2. 4 cycles ABVD +2 cycles COPP
3. 4 cycles of ABVE-PC (Doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) +/− IFRT (Involved field radiotherapy) (20–26 Gy)
4. 2 cycles O(E/P)PA [Vincristine(etoposide/procarbazine) prednisone, adriamycin] + 2 COP(P/Dac) [Cyclophosphamide, vincristine, prednisone, (procarbazine/ dacarbazine)] + 20–35 Gy IFRT

Poor initial response to 2 cycles of chemotherapy

1. 5 cycles of ABVE-PC +/− IFRT (20–26 Gy)
2. 2 cycles O(E/P)PA + 4 COP(P/Dac) + 20–35 Gy IFRT
3. 6–8 cycles of BEACOPP

Advanced Stage

Good initial response to 2 cycles of chemotherapy

1. 2 cycles O(E/P)PA + 4 COP(P/Dac) + 20–35 Gy IFRT
2. 5 cycles ABVE-PC + 20–26 Gy IFRT
3. 6 cycles ABVD + 20–26 Gy IFRT
4. 8 cycles BEACOPP + 20–26 Gy IFRT

Treatment of Relapse/ Refractory Disease

Approximately 10–20% of patients with advanced stage Hodgkins lymphoma relapse after front-line treatment. Most relapses in patients with Hodgkins lymphoma occur within the first three years. Response to salvage therapy is directly related to duration of initial response. Progression during induction therapy or within 12 mo of completion of treatment has a dismal prognosis with 5-y disease-free survival rates of 0% and 20% respectively. Relapses occurring 12 mo or greater have better outcomes with salvage chemotherapy followed by autologous stem cell transplant. Because of the small number of patients that fail primary therapy, no uniform second-line treatment strategy exists for this patient population. Patients with late relapse and good response to initial two cycles of chemotherapy can be salvaged in 40–50% of cases with high dose chemotherapy and autologous stem cell transplant (SCT) [31, 32]. Various relapse regimens have been used, the most popular among them being ifosfamide, carboplatin, etoposide (ICE) [33]. The commonly used conditioning regimen for autologous SCT is BEAM (BCNU, etoposide, cytosine arabinoside, and melphalan) [33]. Allogenic SCT represents an option in a small subset of highest risk patients in whom there are probably no other realistic options for cure at present. However, treatment related toxicity and relapse rates are very high.

Follow-Up of Treated Patients and Late Effects

Patients need clinical evaluation by the physician once in every 3 mo for the first 2 y after completing treatment and then once in every 6 mo till 5 y after completing treatment and following which they can be reviewed annually. No imaging studies or blood investigations to detect relapse are routinely recommended during follow-up if the patient is asymptomatic and clinical examination is normal [34].

Pediatric Hodgkins lymphoma patients are at risk of second malignancies, cardiovascular and pulmonary diseases and infertility secondary to the effects of chemotherapy and/or radiotherapy received by them. Female patients who have received mediastinal radiation should be screened for breast cancer as per guidelines when they become adults. Patients who receive radiation to the neck should be closely followed up for thyroid dysfunction. Patients should be encouraged to lead healthy life style with avoidance of alcohol and tobacco, control of blood pressure and diabetes and regular exercise to reduce pulmonary and cardiovascular morbidities [34].

Acknowledgements This article is prepared as an outcome of Indian Council of Medical Research (ICMR) Sub-Committee on Pediatric Lymphomas (PL) and Solid Tumors (ST) coordinated by the Division of Non-Communicable Diseases, ICMR.

Contributions VR, GK, BA, DB, TV, MP, GC, SL, SA: Wrote the scientific content of the article and proofing; TK and GKR: Conceptualizing and proofing; SB, Chairperson on Subcommittee on PL & ST, ICMR. GK will act as guarantor for the paper.

Compliance with Ethical Standards

Conflict of Interest None.

Source of Funding ICMR organized the meeting and funded the travel.

References

1. Indian Council of Medical Research. Consolidated report of Hospital Based Cancer Registries. Available at: http://www.ncrpindia.org/ALL_NCRP_REPORTS/HBCR_REPORT_2007_2011/ALL_CONTENT/Main.htm. Accessed on 11 July 2015.
2. Dinand V, Arya LS. Epidemiology of childhood Hodgkin's disease: is it different in developing countries? Indian Pediatr. 2006;43:141–7.
3. Metzger M, Krosin MJ, Hudson MM, et al. Hodgkin lymphoma. In: Pizzo PA, Poplack DG, editors. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Wulters Klower/Lippincott, Williams & Wilkins; 2011. p. 639–62.
4. Kelly KM. Management of children with high-risk Hodgkin lymphoma. Br J Haematol. 2012;157:3–13.
5. Tebbi CK, Mendenhall NP, London WB, et al. Response-dependent and reduced treatment in lower risk Hodgkin lymphoma in children and adolescents, results of P9426: a report from the Children's oncology group. Pediatr Blood Cancer. 2012;59:1259–65.
6. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. Blood. 2009;114:2051–9.
7. Nachman JB, Sposto R, Herzog P, et al. Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. J Clin Oncol. 2002;20:3765–71.
8. Kelly KM, Sposto R, Hutchinson R, et al. BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: a report from the Children's oncology group. Blood. 2011;117:2596–603.
9. Metzger ML, Weinstein HJ, Hudson MM, et al. Association between radiotherapy *vs* no radiotherapy based on early response to VAMP chemotherapy and survival among children with favorable-risk Hodgkin lymphoma. JAMA. 2012;307:2609–16.
10. Dörffel W, Lüders H, Rühl U, et al. Preliminary results of the multicenter trial GPOH-HD 95 for the treatment of Hodgkin's disease in children and adolescents: analysis and outlook. Klin Padiatr. 2003;215:139–45.
11. Euronet Hodgkin Lymphoma Protocol. Available at: https://www.skion.nl/workspace/uploads/EuroNet-PHL-Interim-Treatment-Guidelines-2012-12-3v0-2.pdf. Accessed on 2 July 2015.
12. Landman-Parker J, Pacquement H, Leblanc T, et al. Localized childhood Hodgkin's disease: response-adapted chemotherapy with etoposide, bleomycin, vinblastine, and prednisone before low-dose radiation therapy-results of the French Society of Pediatric Oncology Study MDH90. J Clin Oncol. 2000;18:1500–7.
13. Mauz-Körholz C, Hasenclever D, Dörffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. J Clin Oncol. 2010;28:3680–6.
14. Wolden SL, Chen L, Kelly KM, et al. Long-term results of CCG 5942: a randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma–a report from the Children's oncology group. J Clin Oncol. 2012;30:3174–80.
15. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: a report from the Children's oncology group study AHOD0031. J Clin Oncol. 2014;32:3651–8.
16. Aabideen K, Kulkarni KP, Arora RS. Current outcomes of Hodgkin's disease (HD) among children in India: a systematic analysis. 44th Congress of the International Society of Paediatric Oncology (SIOP). London, United Kingdom, 5th–8th October, 2012 SIOP abstracts. Pediatr Blood Cancer. 2012;59:965–1152.
17. Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? J Clin Oncol. 2004;22:62–8.
18. Trehan A, Singla S, Marwaha RK, Bansal D, Srinivasan R. Hodgkin lymphoma in children: experience in a tertiary care Centre in India. J Pediatr Hematol Oncol. 2013;35:174–9.
19. Arya LS, Thavaraj V, Dawar R, et al. Hodgkin's disease in Indian children: outcome with chemotherapy alone. Pediatr Blood Cancer. 2006;46:26–34.
20. Chandra J, Naithani R, Singh V, Saxena YK, Sharma M, Pemde H. Developing anticancer chemotherapy services in a developing country: Hodgkin lymphoma experience. Pediatr Blood Cancer. 2008;51:485–8.
21. Sagar TG, Chandra A, Raman SG. Childhood Hodgkin disease treated with COPP/ABV hybrid chemotherapy: a progress report. Med Pediatr Oncol. 2003;40:66–9.
22. Kapoor G, Advani SH, Dinshaw KA, et al. Treatment results of Hodgkin's disease in Indian children. Pediatr Hematol Oncol. 1995;12:559–69.
23. Jain S, Kapoor G, Bajpai R. ABVD-based therapy for Hodgkin lymphoma in children and adolescents: lessons learnt in a tertiary care oncology centre in a developing country. Pediatr Blood Cancer. 2016;63:1024–30.
24. Radhakrishnan V, Dhanushkodi M, Ganesan S, et al. Pediatric Hodgkin lymphoma treated at cancer institute, Chennai, India: long-term outcome. J Global Oncol. doi:10.1200/JGO.2016.005314. Published online on jgo.ascopubs.org on 9 Nov 2016.
25. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059–68.
26. Pileri SA, Ascani S, Leoncini L, et al. Hodgkin's lymphoma: the pathologist's viewpoint. J Clin Pathol. 2002;55:162–76.
27. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989;7:1630–6.
28. Bonadonna G, Santoro A. ABVD chemotherapy in the treatment of Hodgkin's disease. Cancer Treat Rev. 1982;9:21–35.
29. Donaldson SS, Link MP, Weinstein HJ, et al. Final results of a prospective clinical trial with VAMP and low-dose involved-field radiation for children with low-risk Hodgkin's disease. J Clin Oncol. 2007;25:332–7.
30. Shankar A, Hall GW, Gorde-Grosjean S, et al. Treatment outcome after low intensity chemotherapy [CVP] in children and adolescents with early stage nodular lymphocyte predominant Hodgkin's

lymphoma - an Anglo-French collaborative report. Eur J Cancer. 2012;48:1700–6.
31. Schellong G, Dorffel W, Claviez A, et al. Salvage therapy of progressive and recurrent Hodgkin's disease: results from a multicenter study of the pediatric DAL/GPOH-HD study group. J Clin Oncol. 2005;23:6181–9.
32. Metzger ML, Hudson MM, Krasin MJ, et al. Initial response to salvage therapy determines prognosis in relapsed pediatric Hodgkin lymphoma patients. Cancer. 2010;116:4376–84.
33. Daw S, Wynn R, Wallace H. Management of relapsed and refractory classical Hodgkin lymphoma in children and adolescents. Br J Haematol. 2010;152:249–60.
34. Ng AK. Current survivorship recommendations for patients with Hodgkin lymphoma: focus on late effects. Blood. 2014;124:3373–9.