Hodgkin's Disease : Risk Stratification and Multidisciplinary Treatment

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Hodgkin's Disease (HD) was one of the first malignant disorders in which curative approach was established almost half a century back (1). The earliest reported cures were in selected cases. Treatment approach before 1960 was largely palliative, the median survival for patients with advanced disease was 2 years or less and fewer than 10% of patients survived for 5 or more years. Advances in the field of oncology saw the disease-oriented approach giving way to treatment-oriented approach in the initial three to four decades. However, lately the patient-oriented approach has become the foremost. This has enabled us to limit the toxicity of therapy without compromising cures. The ability to cure over 50% of patients with even advanced-stage HD with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) regimen was a major factor in the growing possibilities for curative treatment (2,3). Other major factors which contributed to the advances in the management of HD are:

a) Better radiation equipment and techniques,
b) Better understanding of the prognostic factors for relapse and survival, leading to tailoring of the treatment to the stage and bulk of disease, and
c) Improvements of approaches to staging.

The major questions in the current therapy of HD are:

a) Can prognostic factors stratify patients for a risk-adapted therapy?
b) Which primary therapy regimen can be used for each risk category with least morbidity without compromising efficacy?
c) Which subgroup of patients should be considered for combined modality treatment in early as well as advanced-stage HD?
d) What is the role of high-dose chemotherapy with stem-cell rescue?

Treatment and prognosis of HD depends upon the staging of the patients

Classification for Hodgkin's Disease

Stage-I   Involvement of a single lymph node region or lymphoid structure (e.g. spleen, thymus, Waldeyer's ring) or involvement of a single extra lymphatic site (IE).

Stage-II Involvement of two or more lymph node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage-II disease); localized contiguous involvement of only one extranodal organ or site and lymph node region(s) on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a subscript (e.g. II_3).

Stage-III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (IIIs) or by localized contiguous involvement of only one extranodal organ site (IIIE) or both (III SE).
III_1 With or without involvement of splenic, hilar, celiac, or portal nodes
III_2 With involvement of para-aortic, iliac, and mesenteric nodes

Stage IV Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement.

Designations applicable to any disease stage

A: No symptoms
B: Fever (temperature, >38⁰C), drenching night sweats, unexplained loss of >10% of body weight within the preceding 6 months.
X: Bulky disease (a widening of the mediastinum by more than one-third of the presence of a nodal mass with a maximal dimension greater than 10 cm)

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F: Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

CS: Clinical stage

PS: Pathologic stage (as determined by laparotomy)

Primary Therapy for Early–Stage HD

Currently available treatment approaches have made it clear that most patients with early-stage HD can be cured with minimal long-term toxicity and complications. However, the continuing challenge has been to optimize this curative approach. By definition, early-stage HD has two subsets of patients i.e.:

1)   Early-stage with favourable prognosis,

2)   Early-stage with unfavorable prognosis.

Patients with clinical stage I or II without any of the adverse risk factors:

a)   Age >50 years,

b)   Erythrocyte sedimentation rate >50 mm/hour

c)   Erythrocyte sedimentation rate >30 mm/hour in the presence of B symptoms,

d)   Four or more separate sites of nodal involvement

e)   Mediastinal mass ratio >0.35.

Treatment of choice for early-stage patients with favourable prognosis is combined-modality approach incorporating 4 cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) regimen and involved-field radiotherapy 36-40Gy (4,5). Since the major role of chemotherapy is to eradicate the subclinical disease outside the planned irradiation ports, it is desirable to keep its duration to 2 to 4 months which also eliminate any substantial risk of infertility, premature menopause, leukemia, or cardiopulmonary toxicity.

Patients of early-stage HD with unfavourable prognosis are defined as those having stage I or II disease with presence of the adverse risk factors:

a)   Age >50 years,

b)   Erythrocyte sedimentation rate >50 mm/hour

c)   Erythrocyte sedimentation rate >30 mm/hour in the presence of B symptoms,

d)   Four or more separate sites of nodal involvement,

e)   Mediastinal mass ratio >0.35.

f)   Stage IIIA (some studies have included)

Combined modality treatment is essential for these cases. This should optimally include 6 cycles ABVD and involved field radiotherapy 36-40 Gy.

Two unusual and special presentations of HD merit individualized treatment approach. When lymphocyte-predominant disease (6) presents in unilateral high neck or epitrochlear locations, the risk of disease elsewhere is small. Such patients should be staged meticulously and treated with involved-field irradiation if they have non-bulky disease at any of these two sites. Similar recommendations apply to non-bulky stage IA nodular-sclerosing HD of the anterior mediastinum.

Advanced Stage Hodgkin's Disease

Hasenclever et al (7) collected data from 23 cooperative groups or treatment centres involving more than 5000 patients treated for advanced-stage HD. This was the first international effort to characterize patients in the reporting of clinical trials. Of the twenty factors considered, seven were found to have a major impact on tumor control. The 5 year freedom from progression (FFP) for patients with three or more factors, who comprise 42% of the patients in this data from 23 co-operative groups, is 55% compared with 74% for those with zero or two factors.

These prognostic factors afford the best available tool for identification of low-and high-risk patients who may be considered for trials designed to reduce toxicity or increase efficacy. These factors identified by the international collaborative group require further validation.

The stage and the bulk of disease at presentation, apart from histology and other risk factors, remain the basis for decision making in the treatment of early as well as advanced-stage HD. Risk factors identified in the international prognostic factors project on advanced HD.

Prognostic Factors:

1)   Age $\geq$45 years

2)   Male sex

3)   Stage IV

4)   Albumin <4.0 gm/dL

5)   Hemoglobin <10.5 gm/dL

6)   WBC count $\geq$15,000/μL

7)   Lymphocyte count <600/μL or <8% of WBC count

International Prognostic Factors Study (7) Results		
No. of Factors	Proportion of Population (%)	5-Years FFP (%)
0	07	84
1	22	77
2	29	67
3	23	60
4	12	51
5+	07	42

Primary Therapy for Advanced-Stage Hodgkin's Disease

Balancing the risk of progression or relapse, which is usually early, with toxicity, which is often delayed, is the major challenge faced in the treatment of advanced-stage HD. The major late morbidities of MOPP, sterility and leukemogenesis, however, remained with derivative regimens like ChIVPP (chlorambucil, vinblastine, procarbazine, and prednisone) and MVPP (mechlorethamine, vinblastine, procarbazine, and prednisone).

Early studies (8,9) with ABVD regimen demonstrated both the ability of this combination to successfully treat MOPP failures and its efficacy in primary therapy as well. The mature results of clinical trials (10-15) comparing ABVD, alone or in combination with radiotherapy, with MOPP demonstrate the superiority of ABVD. The incidence of sterility and leukemia are far less with ABVD, whereas pulmonary fibrosis, occurring in about 1% to 6% patients, is essentially restricted to ABVD. From these trials it appears that ABVD should be considered an acceptable standard treatment regimen for advanced-stage HD.

Radiation therapy has been often combined with chemotherapy even in advanced-stage HD. The rationale for such a combination is based on the fact that relapse occurs in previously involved sites of nodal disease even in stage IV disease. Based on this rationale, and the reliability of radiation therapy to provide local control, several studies have incorporated combined-modality therapy. However, randomized, cooperative group trials have failed to show substantial benefit for low dose, consolidative irradiation in all patients of advanced-stage HD. Only patients with bulky, particularly mediastinal disease, are likely to benefit with radiation following chemotherapy. Multiple clinical trials have shown further response in partial responders treated with radiotherapy. Moreover, the failure rate may be brought down to 20% with combined-modality therapy compared with 50% with chemotherapy alone in patients with bulky mediastinal disease. Given the chances of high cure rate in bulky stage II patients (~80+%) with combined-modality therapy, and propensity for residual disease, combined-modality therapy is considered the standard of care with bulky mediastinal disease.

Bleomycin, etoposide, doxorubicin, cyclophosph-amide, vincristine, procarbazine, prednisone (BEACOPP) regimen is the only one broadly tested in a large phase III trial that appears to be superior to ABVD-containing treatment, although it must be remembered that the majority of patients in the German Hodgkin's Study Group (GHSG) study (7,16) received combined modality therapy. Because BEACOPP sterilizes men and women and has a worrisome secondary leukemia risk, it may be best reserved for higher risk patients, such as those with international prognostic score 5+.

Role of High-Dose Therapy and Stem-Cell Transplantation (HSCT) in the Management of Hodgkin's Disease

High-dose chemotherapy with autologous stem-cell transplant can be performed at various time points during the course of HD. These time points are:

a) As part of initial therapy for a patient who achieves a complete remission and has adverse prognostic factors or a patient who achieves a partial response.

b) Failure of induction chemotherapy.

c) First relapse after chemotherapy-induced first complete remission.

d) Second or subsequent remission/relapse (17,18).

Across studies (19-23) involving autologous HSCT, there has been wide variation in factors such as extent of prior therapy, chemosensitivity status, conditioning regimen, source of stem cells, and use of conventional chemotherapy and radiation therapy before and after transplantation. Moreover, there is a considerable heterogeneity in terms of timing of autologous haematopoietic stem-cell transplant. In such studies, the long-term progression-free survival rates have ranged from 35-50%. With improvements in supportive care, the early transplant-related mortality has- come down from 25% reported in early studies to 5-10% in recent reports.

Adverse prognostic factors identified in these studies are:

1) Failure of more than two or three prior regimens,

2) Bulky-disease,

3) Performance status,

4) Chemo resistance,

5) Extranodal disease,

6) Presence of B symptoms,

7) Lack of complete response at autologous HSCT,

8) Female sex,

9) Elevated lactate dehydrogenase level,

10) Relapse in a previously irradiated field.

The available data indicate that pre-or-post-transplantation involved-field radiotherapy can decrease recurrence in sites of previous disease and that post-transplantation radiotherapy can convert incomplete responses to CR in some patients. In addition, a beneficial effect on freedom from relapse and overall survival has been described. Autologous transplantation is the treatment of choice in:

a) Patients in whom conventional induction chemotherapy fails.
b) First relapse for those patients with initial complete response duration of less than 1 year as well as for patients with any length of first complete remission who have other poor prognostic features such as B symptoms or extranodal disease.
c) Second relapse or later in the course of the disease.

Currently most centres use autologous mobilized peripheral blood progenitor cells because of the ability to perform transplantation even in patients with marrow disease, more rapid engraftment, the potential economic advantage, and the comparable anti-tumour results when compared with the use of bone marrow.

Future Directions

In future, treatment failures will have to be defined on the basis of biological characteristics. Genomic studies of single Reed-Sternberg cells and application of a variety of new antibodies in diagnosis and therapy may lead to better therapeutics. This may also lead to new prognostic parameters enabling us to select patients likely to fail conventional treatment and, in turn, may require stem-cell transplantation as part of initial treatment. Also, in order to further reduce the toxicity of treatment newer concepts like two or three drug combinations and single nodal radiation for highly selected low risk patients are going to be tested in future.

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