Hodgkin’s Disease

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Table of Contents

Introduction ........................................... 2
Biology and Pathology ................................. 2
Clinical Presentation ................................. 3
Staging ..................................................... 4
Treatment .................................................. 7
Summary Points ........................................ 10
References .............................................. 10

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Hospital Physician Board Review Manual

I. INTRODUCTION

A. Definition. Hodgkin’s disease is a lymphoproliferative disorder that is defined histologically by characteristic Reed-Sternberg (RS) cells. A hallmark of this neoplasm is a paucity of malignant cells surrounded by abundant “bystander” cells, including eosinophils, lymphocytes, histiocytes, and neutrophils.

B. Incidence. Age-specific incidence rates suggest a bimodal distribution, with one peak occurring between ages 15 to 34 years (increasing in part due to an association with HIV) and a second peak occurring after age 50 years. Approximately 7500 patients are diagnosed with Hodgkin’s disease in the United States each year.1

C. There are several patterns of presentation, but the disease generally involves lymph nodes, is unicentric in origin, progresses in a predictable manner, and is fatal without therapy.

D. Although the majority of patients with Hodgkin’s disease are cured, significant limitations to therapy remain. Treatment-related morbidity, including a rising incidence of secondary malignancies, mandates improved staging and minimization of toxic therapy as important future goals for patients with a favorable prognosis.

E. Patients with advanced-stage disease who relapse early after standard therapy, who achieve only a partial initial remission, or who relapse with clinically high-risk features represent a poor prognostic group. Even with aggressive approaches, the long-term overall survival of these patients is less than 50%.2,3

II. BIOLOGY AND PATHOLOGY

A. The etiology of Hodgkin’s disease is unknown; however, epidemiologic studies, including case-clustering, familial associations, and relationship to infectious mononucleosis, support the role of viral infection in its pathogenesis.4

B. Biology

1. Molecular studies have determined that diagnostic RS cells are clonal populations of transformed germinal-center B-cells with immunoglobulin gene mutations.5

2. Diagnostic RS cells contain Epstein-Barr virus (EBV) DNA in a subset of patients.6 These EBV genomes have been shown to be monoclonal in origin, suggesting that defective immune control of EBV-infected cells may contribute to Hodgkin’s disease.

   a. Patients with Hodgkin’s disease that contains EBV or specifically expresses the EBV antigen LMP1 have a more favorable response to primary therapy and improved disease-free survival rates compared to patients with EBV-negative Hodgkin’s disease.7

   b. Moreover, RS cells have been shown to express viral antigens in vitro, and they can be lysed by EBV-specific cytotoxic T-lymphocytes that have been isolated from patients with Hodgkin’s disease.8

3. CD30, a member of the tumor necrosis factor receptor family, is present in the majority of RS cells.

C. Pathology. In all cases, the malignant RS cells and variants are the minority of cells in the specimen, which consists of a rich inflammatory infiltrate of lymphocytes, eosinophils, neutrophils, histiocytes, and plasma cells. It is critical for specimens to be reviewed by an experienced hematopathologist to confirm the diagnosis.

1. Nodular sclerosis (Figure 1) is the most common subtype of Hodgkin’s disease in the United States. Diagnosis requires a nodular growth pattern, bands of fibrosis, and “lacunar” RS cells, with abundant cytoplasm. The disease usually presents in young adults, and anterior mediastinal involvement is very common.

2. Mixed cellularity subtype is associated with diffuse architectural effacement and classic RS cells with prominent inclusion-like nucleoli.
It is more common in men and is associated with disseminated disease at presentation.

3. **Classical Hodgkin’s lymphoma, lymphocyte-rich**, is similar in clinical presentation to nodular sclerosis and must be differentiated from nodular lymphocyte predominance. The immunophenotype is classical Hodgkin’s, with CD15 and CD30 generally positive.

4. **Nodular lymphocyte predominance** Hodgkin’s disease differs from classical (nodular sclerosis or mixed cellularity) Hodgkin’s disease in its immunophenotypic profile and clinical behavior. Classic RS cells are rare. The neoplastic cells (“popcorn cells”) are CD20- positive and CD15-negative. The disease has an indolent course that is characterized by sensitive relapses, much like indolent B-cell lymphomas.

5. **Lymphocyte-depletion** Hodgkin’s disease is extremely rare and in most cases represents an atypical non-Hodgkin’s lymphoma, such as T cell-rich B cell lymphoma.

D. The cumulative incidence of non-Hodgkin’s lymphoma after primary Hodgkin’s disease ranges from to 1% to 6%, and secondary non-Hodgkin’s lymphoma in this setting has a poor prognosis.

### III. CLINICAL PRESENTATION

A. Hodgkin’s disease evolves in a highly predictable manner. The primary sites of disease are the peripheral and mediastinal lymph nodes. Abdominal lymph nodes and spleen frequently are diseased at the time of diagnosis but are infrequently the only sites of disease. Unlike the non-Hodgkin’s lymphomas, Hodgkin’s disease of extranodal origin is rare.

B. About 90% of patients with Hodgkin’s disease present with painless enlargement of a superficial lymph node. In about 75% of cases, the first node appreciated is in the neck. Most patients who present without peripheral lymphadenopathy have a mediastinal tumor discovered on chest radiograph examination that was performed routinely for pulmonary symptoms (usually cough) or, rarely, for intractable itching.

C. Approximately one third of Hodgkin’s disease patients have systemic symptoms at the time of diagnosis. Fever is present in about 25% of patients at diagnosis. Pruritus often correlates with disease and may predate symptomatic lymphadenopathy. Other rare symptoms include Pel-Ebstein fevers, which are classic intermittent fever recurring at variable intervals of days to weeks, and pain occurring a few minutes after ingestion of alcohol in sites of bone and nodal involvement of Hodgkin’s disease.

D. **Prognostic features**

1. The negative influences of male gender, advanced age, unfavorable histology (mixed cellularity), and advanced stage have been demonstrated in many studies. Several investigators have looked at constitutional symptoms more closely.

2. Tumor bulk is a second parameter that has been quantitatively linked to Hodgkin’s disease prognosis. Several centers reported that cure was reduced to about 50% when the tumor mass exceeded one third of the maximum chest diameter.

3. Several groups have developed prognostic scoring systems to identify patients at presentation...
who may benefit from minimization of therapy.\textsuperscript{13} Age at presentation, stage, bulk of disease, gender, lymphocyte count, anemia, lactate dehydrogenase, and bone marrow involvement have all been predictive in univariate analyses.\textsuperscript{14–16} More recently, the data from 5141 patients with advanced-stage Hodgkin’s disease were used to develop a parametric model for predicting freedom from disease progression. Seven factors had similar prognostic effects that were independent on multivariate analysis: serum albumin less than 4 g/dL, age older than 45 years, male sex, stage IV disease, leukocytosis greater than 15,000 /mL\textsuperscript{3}, and lymphopenia less than 600 /mL\textsuperscript{3} or less than 8%. Although only 19% of patients had a score of 4 or higher, these patients had a 47% rate of freedom from disease progression at 5 years.\textsuperscript{2}

IV. STAGING

A. Table 1 summarizes the current approach to evaluating a patient newly diagnosed with Hodgkin’s disease. Patients with relapsed disease should be staged in a fashion similar to patients presenting de novo.\textsuperscript{17}

B. The 4-part Ann Arbor Staging Classification remains in general use.\textsuperscript{18} In 1988, a group of experts met in Cotswold, England, to revise the staging scheme.\textsuperscript{19} The general framework of the Ann Arbor classification was maintained; however, computed tomography (CT) scanning was recommended for the detection of intra-abdominal disease, and the concept of bulky disease comprising a greater than 10-cm or one-third widening of mediastinum was introduced. The Cotswolds revision of the Ann Arbor classification continues to be the standard scheme for staging patients with Hodgkin’s disease and is shown in Table 2.

C. History and physical examination

1. A detailed history should be obtained, including the presence or absence of constitutional “B symptoms” of weight loss, night sweats, and fevers. In order to be considered a B symptom, weight loss should exceed 10% of body weight over the preceding 6-month period. Risks of HIV infection should be assessed, as Hodgkin’s disease appears to be increased in this population and such history may have important implications regarding choice of therapy.\textsuperscript{20}

2. On examination, involved nodes are typically nontender and possess a rubbery consistency on palpation. Splenomegaly may be present in up to 30% of patients at presentation. Hepatomegaly, although rare, can occur. Skin lesions that have been associated with Hodgkin’s disease include excoriations from severe pruritus, urticaria, hyperpigmentation, and direct skin infiltration with lymphoma.

D. Laboratory evaluation

1. A complete blood count, differential, and

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Table 1. Recommended Evaluation for Patients with Newly Diagnosed Hodgkin’s Disease

| Adequate biopsy sample reviewed by experienced hemato-pathologist |
| History and physical examination |
| Specific attention to “B symptoms” (fevers, weight loss, night sweats), nodal sites, liver size, spleen size, skin, and sites of bone discomfort |
| Laboratory studies |
| CBC, differential, platelet count, erythrocyte sedimentation rate |
| Alkaline phosphatase, transaminase evaluation, bilirubin, and albumin |
| Renal function testing |
| Radiographic studies |
| Plain chest radiograph |
| CT of chest, abdomen and pelvis |
| FDG-PET |
| Bone marrow evaluation |
| Only for advanced stages, B symptoms, relapsed disease, or abnormal CBC |
| Optional procedures for specific indications |
| Laparotomy with splenectomy and liver biopsy |
| Pulmonary function testing |
| Echocardiography or radionucleotide ventriculography |
| Lymphangiography |
| MRI |
| Bone radiographs or nuclear bone scan |
| Pregnancy testing (premenopausal female) |
| Semen analysis and cryopreservation (males desiring fertility preservation) |

platelet count should be performed on every patient at diagnosis. Leukocytosis is seen in 25% of patients at diagnosis (usually with a neutrophil predominance) and, along with lymphopenia, is considered a poor prognostic factor.\(^2\) Eosinophilia is common and is thought to be a cytokine-mediated phenomenon.\(^2\) An additional 5% of Hodgkin’s disease patients present with leukopenia, another finding that can be based on marrow infiltration. Anemia and thrombocytopenia are less frequently seen in newly diagnosed Hodgkin’s disease patients. Anemia is usually normochromic and normocytic, with a “chronic-disease” picture. Thrombocytosis is commonly observed as an acute phase reactant.

2. The erythrocyte sedimentation rate (ESR) is a useful but highly nonspecific index of Hodgkin’s disease activity.\(^2\) ESR has been shown to correlate with the extent of disease.\(^2\)

3. Although they do not contribute directly to staging, liver function tests, particularly alkaline phosphatase, may influence therapy and should be performed in all patients.\(^2\) Low serum albumin is a negative prognostic factor for advanced-stage disease\(^2\) and rarely may be secondary to nephrotic syndrome.\(^2\)

4. Other studies. Serum calcium levels may be elevated in advanced disease or when bone involvement is present secondary to elevated calcitriol levels.\(^2\) Baseline thyroid studies may be helpful in all patients with planned mantle irradiation therapy because a significant number of these patients will develop thyroid abnormalities after therapy.\(^2\)

E. Reproductive issues. Premenopausal female patients should have a pregnancy test and should be counseled on the use of birth control. Male patients requiring chemotherapy should undergo semen analysis and discussions regarding sperm cryopreservation. A significant number of these patients have limited viable sperm, likely due to disease factors.\(^2\)

F. Bone marrow biopsy. Bone marrow dissemination is reported in up to 5% to 15% of patients with newly diagnosed Hodgkin’s disease. There is significant controversy and variation in clinical practice over the role of routine unilateral or bilateral bone marrow biopsy in the staging of de novo Hodgkin’s disease, since it rarely affects choice of therapy.\(^2\) Thirty-two percent of stage IV patients had bone marrow involvement in one large series.

### Table 2. Cotswolds Revision of the Ann Arbor Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Involvement of a single lymph node region or lymph node structure</td>
</tr>
<tr>
<td>Stage II</td>
<td>Involvement of 2 or more lymph node regions on the same side of the diaphragm</td>
</tr>
<tr>
<td>Stage III</td>
<td>Involvement of lymph node regions or structures on both sides of the diaphragm</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Involvement of extranodal sites beyond “E” sites</td>
</tr>
</tbody>
</table>

Annotations:

- A: No B symptoms
- B: Fever, weight loss > 10% over 6 months, or night sweats
- E: Involvement of a single extranodal site contiguous or proximal to known nodal site
- X: Bulky disease as defined by > 1/3 widening of medias-tinum at T5–T6, or > 10 cm maximum dimension of nodal mass

Generally, unilateral marrow biopsy is advocated for patients with B symptoms, bulky disease, or advanced-stage disease, unless the peripheral blood count is abnormal and not easily explained. All patients receiving radiation therapy alone should undergo bone marrow biopsy.

G. Laparotomy and splenectomy. A complete staging laparotomy includes splenectomy, liver biopsy, bone marrow biopsy, and sampling of the following nodal groups: splenic, celiac, hepatic, portal, and paraaortic. Survival rates in the European Organization for Research and Treatment of Cancer H6F trial (randomization to clinical staging plus subtotal nodal irradiation or to staging laparotomy plus treatment adaptation) were equivalent in both arms.\(^3\) Presently, the vast majority of large centers have abandoned the use of staging laparotomy. The growing use of combined modality therapy for patients with early-stage disease and effective salvage chemotherapy regimens for patients who fail radiation as initial treatment have limited the value of accurate abdominal staging; however, patient preferences for therapy need to be considered.\(^3\)

H. Radiographic evaluation (Figures 2 and 3)

1. Evaluation of the chest. Conventional chest
radiography is typically the initial radiologic examination obtained in patients with suspected Hodgkin’s disease. CT is more sensitive in the assessment of chest disease than is conventional chest radiography and is considered standard.33

2. Evaluation of the abdomen. Historically, bipedal lymphangiography was the procedure of choice for staging abdominal Hodgkin’s disease. Although lymphangiography is extremely sensitive, specific, and overall accurate in assessing the retroperitoneal and pelvic lymph nodes, CT has supplanted it as the imaging modality of choice for evaluating the abdomen and pelvis due to the expense and considerable expertise required for performance and interpretation of lymphangiography.

Figure 2. Pretreatment studies. (A) Chest computed tomography (CT) scan at the level of the aortic arch demonstrates bulky mediastinal and axillary disease in a young man (arrows = axillary nodes). (B) CT scan at the level of the carina shows massive anterior mediastinal nodes. Normal vascular structures (v) are displaced posteriorly. (C) Positron emission tomography scan showing abnormal fluorodeoxyglucose uptake at multiple sites including bilateral axillary nodes (black arrows). Normal cardiac uptake (gray arrow) and bladder uptake (black arrowhead) are also present. (D) Gallium scan showing similar areas of abnormal uptake in superior mediastinum, both axillae, and bilateral cardiophrenic angles. Normal liver uptake (L) is present.

Figure 3. Studies after therapy. (A) Computed tomography (CT) scan at a level above the aortic arch in the same patient as Figure 2. Prior superior mediastinal adenopathy has completely resolved. (B) CT at the level of the carina. A residual mass remains in the anterior mediastinum (large white arrows). There is also new gynecomastia (white arrow) on the left. (C) Positron emission tomography scan shows no abnormal uptake of fluorodeoxyglucose. Normal cardiac (black arrow), renal (black arrowheads), and bladder uptake is seen. Uptake in the lower left abdomen is within colon (white arrow). (D) Gallium scan shows complete resolution of prior abnormal mediastinal and axillary uptake. Uptake in lacrimal glands (arrows) is commonly seen after treatment, as well as uptake in the nose.
3. Evaluation of bone. Bone radiographs are obtained in patients who are symptomatic, and typically reveal predominantly osteoblastic or mixed lesions; lytic lesions are much less common. In the spine, an “ivory vertebrae” may be seen, and is often associated with an adjacent soft tissue mass.34

I. Nuclear imaging

1. Gallium-67 scintigraphy has been the most widely used scintigraphic modality for the staging evaluation of Hodgkin’s disease. However, the overall sensitivity of gallium scanning is fairly low despite high overall specificity. This modality is largely being replaced by positron emission tomography (PET) scanning in many institutions.

2. PET. Radiotracers used in PET imaging have been primarily metabolic substrates, such as fluorodeoxyglucose (FDG), that tend to accumulate in malignant cells. These radionuclides are taken up and metabolized by malignant cells. Positrons are emitted in this process, creating a functional image. FDG-PET appears to accurately assess Hodgkin’s disease activity, and several studies have shown at least equal sensitivity and increased specificity of PET when compared to CT or magnetic resonance imaging.35–37 Moreover, PET, in contrast to gallium scintigraphy (which is of limited value below the diaphragm), may be useful in detecting splenic involvement as well as bone marrow involvement.38,39 Confirmation of residual FDG-avid lesions following biopsy should be strongly considered, until further prospective trials are complete.

J. Cardiac and pulmonary evaluation. Patients with any history of cardiac disease or symptoms or who are above ages 40 to 50 years should undergo evaluation of cardiac function if therapy is to include chest irradiation or an anthracycline. Patients with abnormal function at baseline require aggressive monitoring to limit the incidence of doxorubicin-associated cardiomyopathy.40 Complete pulmonary function testing, including carbon monoxide dissolved in the lungs (DLCO) adjusted for volume and hemoglobin, is recommended if the patient is to receive mantle irradiation or bleomycin as part of a chemotherapy regimen. Although significant controversy exists on the relationship between DCLO and development of bleomycin-induced pulmonary toxicity, patients with significant abnormalities at baseline warrant an aggressive monitoring strategy.41

V. TREATMENT

A. Radiation therapy fields

1. Mantle field is the most commonly used treatment field in patients with supradiaphragmatic Hodgkin’s disease. It includes the submental, cervical, supra- and infra-clavicular, axillary, hilar, and mediastinal lymph nodes.

2. Mantle and paraaortic (MPA) with or without splenic field. Also known as subtotal nodal or lymphoid irradiation, it treats the paraaortic lymph nodes in addition to the mantle field. The spleen is included in the treatment field in patients who do not undergo surgical staging and splenectomy.

3. Total nodal irradiation (TNI) or total lymphoid irradiation encompasses most of the lymphoid tissue, with the addition of a pelvic field to the mantle and paraaortic field. However, nodal groups that are rarely involved in Hodgkin’s disease, such as the brachial, epitrochlear, popliteal, sacral, and mesenteric nodes, are not specifically included in the total nodal irradiation field.

4. Inverted-Y field is used in patients presenting with infradiaphragmatic Hodgkin’s disease, and includes treatment to the paraaortic and pelvic lymph nodes.

5. “Involved field” radiation typically is given as part of combined modality therapy. By definition, an involved field includes at least the entire contiguous lymph node group but also may contain the next echelon of nodes.

B. Dose, field size, and complications of radiation therapy

1. The German Hodgkin’s Lymphoma Study Group conducted a randomized trial on clinical stage (CS) IA to IIB patients, comparing 30 Gy with 40 Gy extended-field radiation therapy.42 Patients with large mediastinal adenopathy, extranodal disease or 3 or more nodal involvements were excluded. At median follow-up of 86 months, there were no significant differences in relapse-free survival and overall survival between the 2 arms, suggesting that the 30 Gy dose is adequate for clinically noninvolved areas.43

2. In a meta-analysis combining data from 8 randomized trials on early-stage patients, a significantly lower relapse rate was found in the more versus less extensive radiation therapy.
with risks of recurrence of 31.3% and 43.4%, respectively. The difference in relapse rate did not translate into survival differences. However, in carefully selected early-stage patients who have been pathologically staged to rule out infradiaphragmatic disease, elimination of the paraaortic field may be possible. In a more recent trial, radiotherapy volume size reduction from extended field to involved field after COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) + ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy for 2 cycles produced similar results and less toxicity in patients with early-stage unfavorable Hodgkin's disease.

3. Some of the common, non-life-threatening complications of radiation therapy for Hodgkin's disease include hypothyroidism, localized herpes zoster, and transient xerostomia. More serious and potentially fatal long-term complications of radiation therapy include pulmonary toxicities, overwhelming sepsis, cardiac complications, and second malignancies.

C. Chemotherapy

1. The history of combination chemotherapy for advanced-stage Hodgkin's disease began with the nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP) regimen. A randomized study published in 1992 demonstrated the complete response rate to MOPP was 67%. In this study, the ABVD regimen was superior, with a complete response rate of 82%. Patients who received alternating MOPP-ABVD had a complete response rate of 83%, suggesting benefit to anthracycline-containing regimens (P = 0.006). The rates of failure-free survival at 5 years were 50% for MOPP, 61% for ABVD, and 65% for MOPP-ABV. A second, larger study (n = 856) comparing ABVD to MOPP-ABV revealed similar rates of complete remission (76% versus 80%; P = 0.16), failure-free survival at 5 years (63% versus 66%; P = 0.42), and overall survival at 5 years (82% versus 81%; P = 0.82) for the 2 regimens. However, MOPP/ABV was associated with a greater incidence of acute toxicity, MDS, and leukemia. Since publication of these series, ABVD has emerged as the standard chemotherapy regimen in the United States.

2. The optimal duration of therapy is uncertain, but for advanced-stage disease it generally includes at least 6 cycles (6 months) of therapy. When chemotherapy is combined with radiation therapy, shorter durations may be used safely.

3. Toxicity of chemotherapy includes myelosuppression, nausea, vomiting, mucositis, and neurologic sequelae of vinca alkaloids. The major long-term toxicities of MOPP are sterilization and secondary leukemia. The major long-term toxicity of ABVD is pulmonary toxicity, which, although rare, can be fatal. Doxorubicin-associated cardiac toxicity is very rare in this regimen.

4. Novel regimens under investigation include bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) and doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, and prednisone (Stanford V). In one large study, 1201 eligible patients 15 to 65 years of age who had newly diagnosed Hodgkin's disease in unfavorable stage IIB or advanced stage were randomly assigned to receive 8 cycles of COPP-ABVD, BEACOPP, or increased-dose BEACOPP, each followed by local radiotherapy when indicated. In this study, increased-dose BEACOPP resulted in better tumor control and overall survival than did COPP-ABVD. Long term toxicities remain an unresolved issue with these newer regimens, and until additional randomized studies have been completed, ABVD remains the standard of care.

D. Assessment of response to therapy

1. Bulky masses on conventional CT may resolve slowly and incompletely. A diminished mass that remains after chemotherapy should be investigated by nuclear imaging. A positive gallium or FDG-PET scan after treatment suggests a significant risk of subsequent relapse.

2. Careful follow-up or rebiopsy of patients with faint or equivocal uptake on nuclear imaging is warranted, and inflammation, infection, radiation reaction, or bleomycin-induced injury should be considered as possible etiologies of residual gallium or FDG-uptake.

E. Treatment of early-stage classical Hodgkin's disease

1. Radiation therapy alone has a well-established role in the treatment of early-stage Hodgkin's disease. MPA radiation therapy therapy was until recently considered the standard treatment in patients with favorable prognosis.
stages I to II disease, with long-term disease control rate of 80% to 85%.

2. There are 3 main scenarios in which addition of chemotherapy to radiation therapy is considered in the treatment of patients with early-stage disease.
   a. Patients with CS I–II disease in which addition of chemotherapy to a more limited radiation therapy field is used to eradicate occult infradiaphragmatic disease.
   b. Patients with unfavorable prognostic factors in which treatment with radiation therapy alone is not adequate for the high disease burden and systemic therapy is required to control distant microscopic disease.
   c. Patients in whom the goal of combining chemotherapy with radiation therapy is to reduce the radiation field size and dose, which is especially important in the pediatric population. **With increasing rates of secondary malignancies associated with large XRT fields, this combined modality approach is rapidly becoming standard.**

3. The high relapse rate, along with the decrease in the volume of heart and lung irradiated in patients pretreated with chemotherapy, have led to the general recommendation of combined modality therapy for patients presenting with large mediastinal adenopathy.

4. Patient preference and toxicities of therapy are important factors in the ultimate choice of radiation versus a combined modality approach.52

5. Preliminary results of single institution studies suggest a possible role for full course chemotherapy, without XRT, in patients with early stage Hodgkin’s disease.53,54

F. Treatment of advanced-stage disease

1. The role of adjuvant radiation therapy in advanced-stage Hodgkin’s disease is a subject of continued debate.55 The rationale for addition of radiation therapy to combination chemotherapy in advanced-stage Hodgkin’s disease is based on the patterns of failure after chemotherapy, in which the majority of relapses are at the site of initial disease.56

2. Arguments against the use of radiation therapy as part of treatment for patients with advanced-stage Hodgkin’s disease include the concern for the added toxicity in the use of combined modality therapy and the lack of Phase III data that supports its role in improving survival.57,58 One recently published randomized study suggested a benefit to the addition of consolidation radiation in both event-free and overall survival in patients achieving a complete remission after 6 cycles of ABVD chemotherapy; however, this study included early stage patients.59 The Stanford V program includes radiation for all patients with masses larger than 5 cm. The role of radiation for advanced stage disease using other programs remains controversial.

3. Prolonged disease-free survival has been observed in 50% to 60% of patients with advanced-stage disease treated with full course combination chemotherapy, such as ABVD.

4. Studies evaluating the role of aggressive consolidation therapy with high-dose chemotherapy and autologous stem-cell support in patients with high-risk disease are ongoing. Preliminary results show no benefit to this treatment, and it is currently not recommended outside of a treatment protocol.

G. Treatment of relapsed or refractory disease

1. Patients with limited nodal relapses after chemotherapy are potential candidates for radiation therapy alone salvage.60 A 5-year disease-free survival rate of about 30% and overall survival rates of 55% to 70% have been reported. Factors that are associated with superior outcome include complete response to initial chemotherapy; a disease-free interval of greater than 12 months; absence of B symptoms, bulky disease, or extranodal disease at the time of relapse.

2. Another salvage option for patients with limited nodal relapse after initial chemotherapy is to combine local radiotherapy with alternative non-cross-resistant chemotherapy regimens.61 The rationale for such an approach is that the radiation therapy may irradiate nodal disease, while the chemotherapy may control occult microscopic systemic involvement.

3. A wide variety of second-line chemotherapy regimens have been used, but none is considered superior. If a patient has not received ABVD, this should be given. Patients initially treated with ABVD are generally given modifications of the MOPP regimen, such as ChIVPP (chlorambucil, vinblastine, procarbazine and Oncology Volume 7, Part 4 9.
prednisone) or a regimen containing etoposide and alkylating agents, such as ICE (ifosfamide, carboplatin, etoposide).

4. For most patients, particularly those with high-risk relapse (advanced stage at relapse, relapse within 1 year of initial therapy, relapse after combined modality therapy), high-dose therapy with autologous stem-cell support may result in prolonged disease-free survival in approximately 40% of patients and is the standard of care.

H. Palliative therapy

1. In patients who relapse after high-dose therapy or multiple courses of extensive treatment, in addition to further systemic therapy palliative local irradiation may have a role in prolonging disease control and in providing symptomatic relief.

2. Single-agent chemotherapy with vinca alkaloids or gemcitabine may provide prolonged responses and symptomatic relief. Monoclonal antibodies directed against CD30 are currently under investigation, with promising preliminary results.

3. When possible, patients should be offered participation in a clinical trial.

I. Treatment of lymphocyte predominant Hodgkin’s disease

1. Early-stage disease may be treated with localized radiation therapy, and prolonged disease-free survival has been reported.

2. Alkylating agent-based chemotherapy is preferable to ABVD for patients with advanced-stage disease.

3. Selected asymptomatic patients may be followed without treatment, as this histology may be quite indolent.

4. Responses in refractory disease have been observed with the CD20 monoclonal antibody rituximab.

IV. SUMMARY POINTS

- Hodgkin’s disease is a B-cell malignancy of uncertain etiology that is curable in most patients with standard treatments.
- The vast majority of patients in the United States have classical subtypes of either nodular sclerosis or mixed cellularity.
- Hodgkin’s disease evolves in a highly predictable manner. The primary sites of disease are the peripheral and mediastinal lymph nodes. Abdominal lymph nodes and spleen are frequently diseased at the time of diagnosis but rarely are the only sites of disease.
- For patients with early-stage disease, the prognosis is excellent; treatment options include radiation or, more commonly, abbreviated combination chemotherapy followed by localized radiation therapy.
- For patients with advanced-stage disease, combination chemotherapy with the ABVD regimen remains the standard of care.
- High-dose therapy and autologous stem-cell support is indicated for treatment of high-risk, relapsed disease.
- Long-term toxicity of treatment, particularly secondary malignancies, mandate minimization of toxic therapies whenever possible.

ACKNOWLEDGMENT

We are indebted to Dr. Kitt Shaffer for assistance in preparing the radiographic images.

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