Management of Hodgkin Lymphoma

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Approximately 7350 new cases of Hodgkin lymphoma (HL) are diagnosed annually in the United States. The incidence of HL has a bimodal pattern, with the highest incidence seen in young adults and in elderly patients. The disease is composed of 2 distinct entities: the more commonly diagnosed classical HL and the rare nodular lymphocyte-predominant HL. Classical HL includes the subgroups nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte rich. Selection of the appropriate therapy is based on accurately assessing the stage of disease. Patients with early-stage disease are treated with combined modality strategies using abbreviated courses of combination chemotherapy followed by involved-field radiation therapy, whereas those with advanced-stage disease receive a longer course of chemotherapy without radiation therapy. Currently, more than 80% of all patients with newly diagnosed HL are expected to be long-term survivors. Although many patients respond well to initial therapies and have durable long-term remissions, a subset of patients has resistant disease and experiences relapse even after subsequent high-dose chemotherapy and autologous stem cell transplantation. New therapies are clearly needed for these patients.


ABVD = doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; ASCT = autologous stem cell transplantation; BEACOPP = bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone; COPP = cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone; CT = computed tomography; EORTC = European Organization for the Research and Treatment of Cancer; FDG-PET = positron emission tomography with fluorodeoxyglucose F 18; GHSG = German Hodgkin Study Group; HDCT = high-dose chemotherapy; HIV = human immunodeficiency virus; HL = Hodgkin lymphoma; MOPP = mechloethamine, vincristine (Oncovin), procarbazine, prednisone; MOPP = mechlorethamine, vincristine (Onovin), procarbazine, prednisone

Hodgkin lymphoma (HL) affects approximately 7350 new patients in the United States annually.1 The incidence of this disease varies considerably, and the highest incidence is in young adults and in patients 55 years and older.2 During the past 40 years, advances in radiation therapy and in combination chemotherapy have significantly increased the cure rate of patients with HL. This year, more than 80% of all patients younger than 60 years with newly diagnosed HL are likely to be cured of their disease.

The cause of HL remains unknown, and no clearly defined risk factors exist for the development of this disease. Factors associated with HL include familial factors, viral exposures, and immune suppression.3 In support of familial factors playing a role in HL, same-sex siblings of patients with HL have been found to have a 10-fold higher risk of developing the disease.3,4 Also, parents and children more commonly develop HL than a spouse of a patient. Furthermore, a monozygotic twin of a patient with HL has a significantly increased risk of developing HL compared with a dizygotic twin sibling of a patient with HL.5,6

Although familial factors may imply a genetic cause of HL, other findings suggest that an abnormal immune response to an infectious agent may also play a role in the pathogenesis of this disease. Epstein-Barr virus has been implicated in the etiology of HL by epidemiological and serological studies, as well as by the detection of the Epstein-Barr virus genome in tumor specimens.7 Moreover, a possible association exists with human immunodeficiency virus (HIV) infection, and HIV-infected patients have a significantly increased risk of HL compared with the general population.8 Furthermore, in HIV-positive patients, HL is associated with advanced stage of disease at presentation, unusual sites of disease, and a poorer outcome after initial therapy.5,10

DIAGNOSIS

More than 80% of patients with HL present with lymphadenopathy above the diaphragm that commonly involves the anterior mediastinum. At the time of diagnosis, patients commonly have involvement of the cervical, supraclavicular, and axillary regions, whereas the inguinal areas are involved less frequently. Approximately one third of patients present with systemic symptoms that include fevers, night sweats, and weight loss. Many patients also present with chronic pruritus. Symptoms occur more frequently in elderly patients and are associated with a poor prognosis. In addition, HL may affect extranodal tissues by direct invasion or by hematogenous dissemination, and the most commonly involved extranodal sites are the spleen, lungs, liver, and bone marrow.

The initial diagnosis of HL can be made only by a biopsy. Because reactive hyperplastic lymph nodes may be present, multiple biopsies of suspicious lymph nodes may be necessary to confirm the diagnosis. Needle aspiration or needle biopsies are inadequate because the architecture of the lymph node is extremely important for an accurate diagnosis and histological subclassification of HL. To con-
TABLE 1. Ann Arbor Staging System

<table>
<thead>
<tr>
<th>Stage*</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region (I) or a single extranodal organ or site (I_E)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of ≥2 lymph node regions on the same side of the diaphragm (II) or localized involvement of an extranodal organ or site of ≥2 lymph node regions on the same side of the diaphragm (II_E)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of an extranodal organ or site (III_L), involvement of the spleen (III_S), or both (III_L+S)</td>
</tr>
<tr>
<td>IV</td>
<td>Widespread involvement of ≥1 extranodal sites with or without associated lymph node involvement or isolated extranodal organ involvement with distant lymph node involvement</td>
</tr>
</tbody>
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*Each stage may be subdivided into A or B according to the absence or presence of general symptoms. These so-called B symptoms may include any of the following: temperatures >38°C (100.4°F), drenching night sweats, or the unexplained loss of >10% body weight in the previous 6 mo. Bulky disease is defined as any lymph node site ≥10 cm in largest dimension, or by a mediastinal mass whose largest diameter is greater than one third of the widest transverse diameter of the thorax on standard chest radiography. Bulky disease is denoted by a subscript X.

Painless lymphadenopathy is the most common clinical manifestation of classical HL. However, each histological subtype has its own unique clinical features.15 Nodular sclerosis, the most common subtype, tends to affect adolescents and young adults more commonly and usually presents as localized disease that involves cervical supraclavicular and mediastinal regions. Mixed cellularity HL is more prevalent in the pediatric and older age groups and is commonly associated with a more advanced stage of disease and a poorer prognosis. The incidence of lymphocyte depletion HL appears much lower than previously reported, with many of these cases reclassified as non-HL. This subtype occurs mainly in older patients, and these patients present with symptomatic extensive disease without peripheral lymphadenopathy. This subtype is most often associated with acquired immunodeficiency syndrome.

Lymphocyte-rich classical HL represents a recently introduced subtype similar to lymphocyte-predominant HL on morphologic grounds, but the Reed-Sternberg cells appear to have a more classical immunophenotype, and therefore this subgroup is classified with classical HL.

**NODULAR LYMPHOCYTE-PREDOMINANT HL**

Nodular lymphocyte-predominant HL constitutes a unique clinical pathologic entity that is significantly different from classical HL. Pathologically, lymphocyte-predominant HL lesions lack the typical Reed-Sternberg cells and instead are characterized by a neoplastic population of larger cells with folded lobulated nuclei known as lymphocytic and histiocytic cells. Unlike classical HL, these cells are CD20 positive and commonly negative for CD30 and CD15.16 Lymphocyte-predominant HL is more frequently seen in men and usually presents as limited nodal disease that classically affects the neck region and spares the mediastinum. Constitutional symptoms at presentation and extranodal disease are rare in this disease subtype. Also, the natural history of lymphocyte-predominant HL differs from classical HL in that it appears to have a more indolent course with a tendency for late recurrences. The persistent relapses seen in this disease (often >10 years after completion of treatment) make its behavior similar to indolent non-HL.17 Therefore, aggressive treatment initially may not be required.

**CLASSICAL HL**

A common factor for classical HL is that the neoplastic cells constitute a minority of the cells in the affected tissue, often corresponding to only 2% to 3% of the total cells in the tumor. The presence of these malignant multinucleated giant cells, known as Reed-Sternberg cells, within the characteristic reactive cellular background is the histological hallmark of this disease.

**STAGING AND PROGNOSTIC FACTORS**

Accurately assessing the stage of disease in patients with HL is critical for the selection of appropriate therapy (Table 1). The staging system for patients with HL is based on the number of involved sites, whether the involved lymph nodes are on one or both sides of the diaphragm, whether the sites of involvement are bulky, whether there is con-
tiguous extranodal involvement or disseminated extranodal disease, and whether typical systemic symptoms (B symptoms) are present.

The standard staging examinations used for most patients with HL include chest radiography; computed tomography (CT) of the chest, abdomen, pelvis, and possibly neck when indicated; complete blood cell count; erythrocyte sedimentation rate; electrolyte evaluation; renal and liver function tests; and serum albumin and serum lactate dehydrogenase measurement. A bone marrow aspirate and biopsy should also be performed except, possibly, in the case of some female patients with clinical stage I to IIA disease that involves the neck who have a low incidence of bone marrow involvement. A staging laparotomy was performed in the past; however, because of the inclusion of chemotherapy for patients even with favorable stage I disease, as well as the substantial improvement in the imaging studies currently available, the importance of this procedure has diminished considerably, and a staging laparotomy is rarely performed.

More recently, positron emission tomography with fluorodeoxyglucose F 18 (FDG-PET) emerged as a powerful technique in the staging of HL. The FDG-PET significantly adds to the staging information obtained using other standard radiographic methods. The sensitivity for detecting sites known to be involved with HL is 75% to 91%, and the use of PET in the staging work-up leads to a change in stage in approximately 15% to 25% of patients. In addition, FDG-PET provides important information with regard to response to treatment and prognosis. Patients with a positive FDG-PET scan at the completion of treatment have been found to have a significantly higher recurrence rate regardless of the findings on CT. A negative PET scan in these studies resulted in a relapse-free survival of 83% to 95% at 2 years. Given these excellent results, FDG-PET has now become a standard staging tool that gives important information both before treatment and at its completion.

Because most patients are expected to be cured with standard treatment, there is a significant risk that patients may be overtreated, leading to potential long-term complications. Therefore, factors that identify patients at low or high risk of recurrence would be most useful in optimizing therapy based on the patient’s expected clinical outcome. Prognostic factors for early-stage HL have been developed by both the German Hodgkin Study Group (GHSG) and the European Organization for the Research and Treatment of Cancer (EORTC). These prognostic models identify disease bulk, either as a single large mediastinal mass or as multiple sites of disease, as the major predictor of a poor prognosis in this subgroup of patients. According to the GHSG, prognosis is unfavorable if the following criteria are met: large mediastinal mass, high erythrocyte sedimentation rate, 4 or more sites, and age of 50 years or older. The EORTC criteria for an unfavorable prognosis are large mediastinal mass, high erythrocyte sedimentation rate, 3 or more sites, extranodal sites, and massive splenic disease.

In patients with advanced HL, however, disease bulk and other traditional prognostic variables have been found to be less predictive of outcome. Therefore, a different prognostic scoring system was developed for these patients by the International Prognostic Factors Project on Advanced Hodgkin’s Disease. This study combined the outcome of 4695 patients treated with combination chemotherapy and identified 7 variables that predicted patient outcome in a multivariate analysis: age of 45 years or older, stage IV disease, male sex, white blood cell count of 15,000 cells/µL or more, lymphocyte count less than 600 cells/µL or less than 8%, albumin level less than 4.0 g/dL, and hemoglobin level less than 10.5 g/dL. Patients with 5 or more factors were found to have a 5-year freedom from progression of 42%, whereas patients with no negative prognostic factors had an 84% likelihood of being free from progression at 5 years (Table 2).

## TREATMENT

Although many prognostic factors have been identified that predict clinical outcome, the predominant factors that determine the choice of therapy for patients with HL are the anatomical stage of disease and the presence of constitutional symptoms. A third prognostic factor that also potentially influences the choice of therapy is the presence of bulky disease, defined as a single site of disease, of 10 cm or greater in diameter.

### INITIAL THERAPY

In the United States, most centers have different treatment strategies for HL patients with early-stage disease with favorable prognostic features, those with early-stage disease but with poor prognostic features, or those with advanced disease. As a general rule, patients with early-stage disease...
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disease are treated with combined modality strategies that use abbreviated courses of combination chemotherapy followed by involved-field radiation therapy, whereas those with advanced-stage disease receive a longer course of chemotherapy without radiation therapy.

**Early-Stage Favorable Disease.** Treatment strategies of early-stage HL (stages I-IIA) have changed considerably in the past few decades. Previously, extended-field radiation was considered the standard therapy. However, because of the recognition of high relapse rates with significant long-term complications, extended-field radiation therapy to involve adjacent lymph node areas is now commonly not performed. Instead, for favorable early-stage disease, short-term chemotherapy for control of occult lesions combined with involved-field radiation therapy restricted only to involved lymph node areas is being administered. Most groups will give 2 to 4 cycles of combination chemotherapy followed by involved-field radiation therapy to a dose of approximately 20 to 35 Gy. Recently, PET scanning was proposed to assist in determining the choice of therapy. Patients with negative PET scans after 2 cycles of treatment are being considered for an abbreviated course of chemotherapy alone, whereas those with a positive PET scan are treated in a more standard fashion with the combination of chemotherapy and radiation therapy. However, it should be stressed that this approach has not yet been tested in a comparative clinical trial.

An exception to the management approach outlined herein are patients with nodular lymphocyte-predominant HL. Patients with favorable stage IA disease with no serious risk factors can commonly be managed with lymph node excision followed by a “watch and wait” approach or with involved-field radiation therapy to a dose of approximately 20 to 30 Gy.

**Early-Stage Unfavorable Disease.** It is generally accepted that patients with stage I and II disease with risk factors should be treated with chemotherapy in combination with radiation therapy. The optimal number of chemotherapy cycles, the optimal chemotherapeutic regimen, and the dose and field sizes of radiation are the subject of ongoing studies and debate. This group of patients usually consists of those with bulky mediastinal masses or those with extranodal disease. In these patients, the use of 4 cycles of combination chemotherapy with involved-field radiation therapy is generally accepted as the treatment of choice. The goal of future studies will be to reduce the dose of radiation therapy and optimize the amount of chemotherapy needed to maintain efficacy but to decrease potential toxic effects in these patients.

**Advanced Disease.** In patients with advanced disease, the challenge is to improve cure rates while minimizing the likelihood of long-term adverse effects. The MOPP (mechloretamine, vincreistine [Oncovin], procarbazine, and prednisone) regimen was initially developed for patients whose disease progressed after radiation therapy, and the long-term results with the MOPP regimen showed a freedom-from-progression rate of 54% and an overall survival of 48% at 20 years. Although the MOPP regimen significantly changed the outcome of patients who previously would have died of progressive disease, approximately one third of patients subsequently experienced disease relapse. Multiple other regimens have been developed in an attempt to improve the efficacy of this regimen.

The ABVD (doxorubicin [Adriamycin], bleomycin, vincristine, and dacarbazine) chemotherapeutic regimen also showed significant clinical activity, which led to a trial comparing alternating cycles of MOPP chemotherapy with ABVD to MOPP chemotherapy alone. The alternating regimen was found to be superior in regard to complete remission rate, freedom from progression, and overall survival. Several major randomized studies during the past 20 years have attempted to identify the regimen with the greatest activity and the most favorable side effect profile. The Cancer and Leukemia Group B studied MOPP, ABVD, and MOPP alternating with ABVD, and the complete response rate was worse for patients receiving MOPP chemotherapy alone compared with those receiving ABVD or the alternating regimen. The freedom from progression was also worse in the MOPP-treated patients. The MOPP/ABVD hybrid regimen was tested against MOPP alternating with ABVD, and the regimens were found to be equivalent. A large Canadian intergroup study compared the MOPP/ABVD hybrid program to MOPP alternating with the ABVD regimen and found equal efficacy but greater toxicity for the hybrid regimen. A similar study comparing the MOPP/ABVD hybrid regimen to ABVD showed superiority with less toxicity for the ABVD arm. The results of these trials have led to ABVD chemotherapy being regarded as the treatment of choice for patients with advanced HL based on its efficacy, relative ease of administration, and acceptable side effect profile.

Other regimens currently being used include the Stanford V regimen, which incorporated the active agents from MOPP and ABVD into a brief dose-intense regimen and combined this 12-week regimen with radiation therapy. The results initially obtained in 142 patients showed a 5-year freedom from progression of 89% and an overall survival of 96%. Similar results were obtained in a multi-institutional Eastern Cooperative Oncology Group study. This regimen is currently being tested against ABVD in a randomized intergroup trial in the United States. However, 2 recent studies from Europe have suggested that ABVD may be superior to the Stanford V regimen.
The GHSG developed new regimens for patients with advanced HL, including standard and dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin [Adria-myacin], cyclophosphamide, vincristine [Oncovin], procarbazine, and prednisone).57 A large randomized trial comparing COPP (cyclophosphamide, vincristine [Oncovin], procarbazine, and prednisone) alternating with ABVD to dose-escalated and standard BEACOPP showed better tumor control and overall survival for patients receiving dose-escalated BEACOPP.58 These results are encouraging, but 9 cases of acute myeloid leukemia or myelodysplastic syndrome developed in the dose-escalated BEACOPP-treated patients, 4 cases developed in the standard BEACOPP-treated patients, and 1 case developed in the COPP-ABVD–treated patients.

The role of high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) has been evaluated as part of initial therapy for patients with advanced HL with poor prognostic features. Patients with advanced unfavorable HL achieving a complete or partial remission after 4 courses of doxorubicin-containing regimens were found to have a favorable outcome with conventional chemotherapy. No benefit from an early intensification with HDCT and ASCT was shown.39

In summary, ABVD chemotherapy remains the most widely used treatment in the United States for patients with advanced-stage HL. Alternative therapies include Stanford V and dose-intense regimens such as BEACOPP.

**Salvage Therapy**

Despite the high cure rate with initial therapy, in approximately 5% to 10% of patients with HL, the disease is refractory to initial treatment, and 10% to 30% of patients will experience disease relapse after achieving an initial complete remission.40 The standard of care for many patients who experience relapse after a response to initial chemotherapy is HDCT followed by ASCT.

**Primary Refractory Disease.** Patients with primary refractory disease, defined as progression or nonresponse during induction treatment or within 90 days of completing treatment, generally have a dismal clinical course. Second-line chemotherapy for these patients produces low response rates, with long-term disease-free survival in only 5% to 10% of patients.42 Therefore, in these patients, HDCT with ASCT is currently considered the treatment of choice. Several retrospective analyses have suggested that patients treated with ASCT have a superior long-term outcome compared with patients treated with chemotherapy.44-45 An analysis of treatment outcome in patients with primary progressive disease showed that the 5-year freedom from failure and overall survival for all patients were 17% and 26%, respectively, compared with 31% and 43% for those treated with HDCT and ASCT.45 Other studies have further confirmed that patients receiving HDCT followed by ASCT have a better outcome than patients treated with chemotherapy.46-48 However, most patients still experience disease relapse after HDCT and ASCT.

**Relapsed Disease.** Between 10% and 30% of patients will experience disease relapse after an initial chemotherapeutic regimen. In the past, it was standard practice for patients with HL with late relapses after an initial complete response (>1 year) to be treated with the same chemotherapeutic regimen they had received as first-line treatment. More than 80% of patients with a late relapse achieve a second complete response, with a median survival of approximately 4 years.42 In contrast, for patients with a relapse within 12 months, different salvage chemotherapeutic regimens were tested, incorporating drugs not used in the initial combination.49-51 However, no randomized trials have been performed comparing the effectiveness of different conventional salvage chemotherapeutic regimens, and no standard salvage regimen has been identified. Despite the responses to these therapeutic approaches, however, patients relapse and subsequently die of disease progression or complications of treatment. Most eligible patients with relapsed disease are now treated with ASCT.

Initial phase 2 studies suggested that HDCT followed by ASCT may produce a better long-term disease-free survival than expected with conventional chemotherapy in 30% to 65% of patients.52,53 Two subsequent randomized studies confirmed an improved outcome in patients with relapsed HL treated with HDCT followed by ASCT compared with conventional salvage chemotherapeutic regimens.54,55 In both studies, the event-free survival after 3 years for patients treated with HDCT was more than 50%.

Not all patients are eligible for or may benefit from ASCT. Elderly patients treated with ASCT have increased treatment-related mortality and commonly have an inferior event-free survival compared with younger patients.56 Some patients have relentlessly progressive disease and have been treated with tandem ASCT57 or allogeneic transplantation.58 Preliminary results have suggested that these therapies are feasible, but toxicity and relapses have been common.

**Therapeutic Options for Relapse After HDCT and ASCT.** Patients with progression of disease after ASCT uniformly have a poor outcome. In a recent study of patients with HL in whom ASCT failed, the median time to progression after the next therapy was only 3.8 months, and the median survival after ASCT failure was 26 months.59 For patients in whom HDCT with ASCT fails, few good treatment options exist. Among the recently developed cytotoxic drugs, only vinorelbine60 and gemcitabine61 have shown promising activity in heavily pretreated patients.
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with HL, including some patients who experienced disease relapse after HDCT. However, the duration of many of the responses was short, and the treatment was commonly associated with serious hematologic toxic effects. For patients with HL treated with reduced-intensity allogeneic transplantation, the treatment-related mortality at 1 year was approximately 20%, and the 2-year overall survival was 50%. The treatment-related mortality and overall survival were significantly worse for older patients. Studies of rituximab, a chimeric monoclonal antibody that binds to CD20 on lymphocytes, in patients with relapsed or refractory lymphocyte-predominant HL and other multiple relapsed CD20-positive cases of HL have shown high response rates, but unfortunately these have been of short duration.

Recent studies have evaluated the optimal dose and potential efficacy of anti-CD30 monoclonal antibodies in relapsed and refractory HL. CD30 is expressed on the Reed-Sternberg cell, and antibodies that target this molecule have shown activity in vitro. Phase 1 and 2 clinical trials of 2 anti-CD30 antibodies, MDX-06065 and SGN-30, have been completed. Both studies found that the antibodies had few adverse effects, but only a limited number of clinical responses were seen.

SPECIAL CIRCUMSTANCES

HL in Elderly Patients
Hodgkin lymphoma displays a bimodal age distribution, and older age is an adverse prognostic factor for survival. In contrast to younger patients, the prognosis of elderly patients with advanced HL has not improved substantially. The poorer outcome of elderly patients is associated with increased treatment-related toxic effects and an increased incidence of early disease relapse often associated with suboptimal therapy. The outcome of elderly patients with recurrent HL is extremely poor, and elderly patients have been shown to have a better survival if they receive a doxorubicin-containing regimen as initial treatment. Therefore, age should not be a contraindication for aggressive treatment, and elderly patients in good physical condition should be managed with stage-adapted treatment analogous to conventional treatment for younger patients. The addition of hematopoietic growth factors to treatment regimens should be considered in elderly patients. In patients not eligible for conventional treatment, novel therapeutic approaches are necessary to define the best palliative care that maintains quality of life.

HL in Pregnant Patients
Hodgkin lymphoma in pregnant patients is rare, and HL in this setting usually presents with typical clinical manifestations. Most studies suggest that HL has no effect on pregnancy and that the pregnancy does not worsen the course of the disease. However, treatment of the mother for HL during this time may put the fetus at risk of complications, particularly during the first trimester. If clinically appropriate, delaying the start of therapy until the end of the first trimester, the delivery of the neonate, or disease progression should be considered provided therapy is started as soon as the delivery is completed or, if there is evidence of disease progression, the overall disease outcome does not appear to be negatively affected. If treatment is necessary before delivery, standard combination chemotherapy or radiation therapy (with appropriate shielding) can be administered. Current data suggest that involved-field irradiation to the neck or axilla can be safely given and chemotherapy at full doses can be safely administered, even during the first trimester if necessary, in a patient who wants to complete her pregnancy but requires immediate therapy for HL.

CONCLUSION

Important progress has been made in the treatment of patients with HL, and these advances have significantly increased the cure rate in these patients. Currently, more than 80% of all patients with newly diagnosed HL are expected to be long-term survivors. Although many patients respond well to initial therapies and have durable long-term remissions, a subset of patients has resistant disease and relapse even after aggressive high-dose therapy. Therapeutic options are limited for patients who have experienced disease relapse after HDCT and ASCT or who are ineligible for HDCT and ASCT, and new therapies are clearly needed for these patients.

REFERENCES


The Symposium on Oncology Practice: Hematological Malignancies will continue in the April issue.