Inspection of the Hodgkin’s Lymphoma (HL) mortality curve (Fig 1) shows a dramatic improvement in survival over the past 30 years. In the United States, mortality remained above 1.8 per 100,000 per year in the 1950s and early 1960s, but decreased to 0.47 by 1994. Whereas HL accounted for 30% of total lymphoma deaths in 1950, it accounted for only 6% (1,440 US deaths) in 1994.

Figure 1: HD mortality in white males and females in the United States from 1950-1994. (Reprinted from Ries et al.1)

Juan A. del Regato, 1909-1999, was a superb clinician-educator who recognized the radiocurability of Hodgkin’s Lymphoma but questioned treatment without late effects, particularly in children. The remarkable progress in paediatric Hodgkin’s disease today is a tribute to this influential pioneer, who served as a role model to many. Combined modality therapy using low-dose, involved-field radiation and multiagent chemotherapy today results in a 5-year relative survival rate of 94% among American children with Hodgkin’s disease.2 However, several areas hold promise for future advances, new noninvasive staging techniques, including 18F-fluorodeoxyglucose-positron emission tomography; the definition of risk groups on the basis of a prognostic index, facilitating risk-adapted therapy; Finally, novel therapies, such as the anti-CD20 antibody, rituximab, may be useful for children with CD20+, lymphocyte-predominant Hodgkin’s disease. The universal goal of cure without late effects is realistic for almost all children with Hodgkin’s disease today.

Epidemiology Of Hodgkin’s Lymphoma And Epstein-Barr Virus

Hodgkin’s “disease” is a B cell lymphoma.3 The mystery embodied in the term Hodgkin’s disease, which defines neither the affected tissue nor the disease process, is underscored by the name of the cell required for diagnosis: Reed-Sternberg. The malignant character of the disease is now beyond dispute and the cellular lineage is clearly understood to be B cell. The explanation for the difficulty in identifying the tumor may be attributed to two of its defining characteristics: the tumor cells are rare in the mass of the tumor and fail to express many B cell markers—most notably immunoglobulin.

Whereas the incidence of non-Hodgkin’s lymphoma has been rising since World War II, the incidence of Hodgkin’s lymphoma has been flat. Two age-incidence peaks have long been recognized in North America and Western Europe: young adult and older adult. In developing countries and in parts of Asia, the young adult peak is much less prominent or even absent. Several epidemiologic studies suggested an association with small family size and other factors that might result in delayed exposure to common viral infections.
Figure 2: Different pathways lead to lymphoma.

Detection of EBV in Tumor

EBV nucleic acids and proteins have been identified in the tumor cells in a subset of patients. Approximately 30% of Hodgkin’s lymphoma in the United States and North America harbor these nucleic acids and proteins, while much higher percentages of tumor cells show evidence of virus in some developing countries (approaching 100% in parts of Latin America, Africa and Asia). Formal guidelines for interpretation and comparisons of methods for detecting virus in fixed tissues have recently been published (Figure 2). With some well-documented exceptions EBV is present in each of the tumor cells in a particular patient at all sites of disease, at presentation and at relapse.

Epstein-Barr Virus and Hodgkin’s

Serologic studies have suggested modestly higher titers to Epstein-Barr virus (EBV) antigens in patients with Hodgkin’s lymphoma than in controls, but the differences in titers have been modest. EBV is a ubiquitous virus and the vast majority of Hodgkin’s patients (and adults) are EBV seropositive.

Infectious Agents and Lymphomagenesis

There are two very different pathways by which infectious agents drive malignant lymphoproliferative diseases: some infectious agents activate extrinsic pathways through lymphocyte antigen receptors, while others activate intrinsic pathways bypassing antigen receptors (Figure 1). Helicobacter drives the proliferation of B cells in an antigen-specific manner and treatment with anti-infective agents sometimes results in tumor regression. Hepatitis C may similarly act through immunoglobulin receptors and may similarly respond to treatment with anti-infective agents. In contrast, human T cell leukemia virus-1 (HTLV1) drives the proliferation of infected T lymphocytes independent of the specificity of the T cell receptor. Similarly, in post transplant lymphoproliferative disease, EBV drives lymphoproliferation independent of the specificity of the immunoglobulin. Several different EBV genes are required to act in concert to bring about this transformation, including five of the six EBV nuclear antigens.
patients with serologically confirmed infectious mononucleosis. There was no increase in the relative risk of EBV-negative Hodgkin’s lymphoma. The median estimated time interval from the diagnosis of mononucleosis to EBV-positive Hodgkin’s lymphoma was approximately 4 years. Thus infectious mononucleosis is clearly linked to EBV-positive Hodgkin’s lymphoma and there is no evidence to suggest that it is linked to EBV-negative Hodgkin’s lymphoma.

**Other Infectious Agents and Hodgkin’s Lymphoma**

The incidence of Hodgkin’s lymphoma is increased in incidence among human immunodeficiency virus (HIV)-infected patients. In contrast to non-Hodgkin’s lymphomas that are “AIDS-defining” malignancies, the increased incidence of Hodgkin’s lymphoma is more subtle. The increased risk of Burkitt’s lymphoma and brain lymphoma in AIDS patients is hundreds- or thousands-fold, whereas the increased incidence of Hodgkin’s lymphoma in AIDS is approximately 3- to 10-fold. A recent population-based study of HIV Hodgkin’s lymphoma in the San Francisco Bay area showed that 90% of Hodgkin’s tumors in HIV patients were EBV-positive, that nodular sclerosis histology was only half as common among HIV-infected patients as in the general population, and that lymphocyte-depleted disease was much more common. HIV patients were also more likely to have advanced-stage disease. Whether the contribution of HIV to Hodgkin’s lymphomagenesis is simply related to generic immunodeficiency or reflects some more specific contribution of particular HIV proteins or HIV-induced immune dysregulation is not clear. However, it is worth bearing in mind that the CD4 T cell count in HIV Hodgkin’s is typically much higher than that in some other EBV-associated malignancies in HIV patients, such as brain lymphoma. Interesting evidence regarding measles has also been presented. Immunohistochemical, reverse transcriptase-polymerase chain reaction and in situ hybridization studies have shown evidence of measles virus in Hodgkin’s tumor tissues in slightly more than half of patients. These include patients with and without EBV in their tumors. Any contribution to pathogenesis remains highly speculative at this point. Despite extensive investigation, no evidence has emerged to support a role for cytomegalovirus, varicella-zoster virus, mumps, pertussis, human herpesvirus 6, 7, or 8, JC virus, adenovirus or HTLV1 or 2.

### Viral Proteins in Hodgkin’s Pathogenesis

The EBV latency membrane protein 1 (LMP1) has been recognized as a likely contributor to tumorigenesis. Expression of the protein is transforming in immortalized murine cell lines and leads to lymphoma when expressed in B cells in a transgenic model. The protein is a member of the tumor necrosis factor receptor (TNFR) superfamily and most closely resembles CD40. However, in contrast to CD40, LMP1 signaling is constitutively active and requires no ligand. Among the multitude of activities of LMP1, it activates NF-κB by promoting the turnover of IκB alpha. Latency membrane protein 2A (LMP2A) also seems likely to play an important role. As noted above the tumor cells of Hodgkin’s lymphoma do not express immunoglobulin genes. B cells that lack functional Ig would be expected to die by apoptotic mechanisms as has clearly been shown in transgenic mouse models. However, LMP2A has been shown to provide a tonic signal that mimics that associated with immunoglobulin expression so as to prevent apoptosis of such cells—at least in a murine model. The role of this viral protein in preventing apoptosis in tumor cells suggests the possibility that related pathways may be targeted by small molecules for therapeutic purposes.

### Does EBV in Hodgkin’s Lymphoma Provide a Suitable Target for Immunotherapy?

Viral antigens expressed in Hodgkin’s lymphoma are commonly recognized by CD8 T cells (Figure 3). The antigens are generally not mutated in Hodgkin’s lymphoma. Most EBV-associated Hodgkin’s tumors express class I MHC antigens and studies of cell lines suggest that the antigen-processing machinery is intact. Studies using adoptive cellular immunotherapy approaches have been initiated with limited success to date. However, improved targeting of the T cell lines to antigens such as LMP2A actually expressed in Hodgkin’s lymphoma holds promise as may therapeutic vaccine strategies.
The Utility Of Pet In Managing Patients With Hodgkin’s Lymphoma

Fluorodeoxyglucose (FDG)–positron emission tomography (PET) has a number of potential advantages for the hematologist-oncologist in refining and improving the management of Hodgkin’s lymphoma. (see figure 4)

Staging

Hodgkin’s lymphoma is generally treated according to stage and risk profile; therefore, staging provides the basis for different treatment strategies such as RT, chemotherapy or a combination of both. Recently, metabolic imaging with PET has been increasingly used in the management of lymphoma patients. Since PET relies on the detection of metabolic alterations observed in cancer cells, this examination yields data that are independent of associated structural characteristics. Furthermore, the ability to perform whole body imaging within one examination without increasing the radiation burden makes PET an ideal technique to “screen” patients for cancer deposits. The most frequently used tracer is the glucose analogue FDG. The use of FDG for in vivo cancer imaging is based upon the higher rate of glucose metabolism of cancer cells compared with nonmalignant tissue. With the exception of small lymphocytic and MALT lymphomas, most lymphomas, including Hodgkin’s lymphoma, exhibit moderate to high FDG uptake. Several studies have investigated the role of FDG-PET for the initial staging of lymphoma (see also a recent review of Schiepers et a).

Compared with gallium scintigraphy, FDG-PET appears to have advantages that include inherent superior resolution, higher sensitivity (especially in the abdomen and bone), lower radiation burden (10 mSv/PET versus 44 mSv/gallium scintigraphy) and a shorter examination time (2 hours for PET versus 3 days for gallium scintigraphy). FDG-PET was also found to be more sensitive and specific than bone scintigraphy for the detection of cortical bone involvement and complementary to bone marrow biopsy for detection of marrow involvement distant from the biopsy site. Most reports have focused on comparisons of PET with CT. In most cases, PET was found to be more sensitive for detecting of both nodal (e.g., small sized nodes) and extra-nodal (especially spleen and bone) involvement, but PET-negative, CT-positive lesions do occur in a small number of cases. High FDG uptake in brown fat tissue or muscle can hamper the interpretation of the head and neck and mediastinal regions. Moreover, physiological uptake in gut and the renal collecting system can obscure evaluation of lymphoma in adjacent nodal sites. Therefore, optimum use of FDG-PET is likely in combination with CT. Combined use of PET-CT can improve accuracy by increasing the certainty of diagnosis in those difficult regions. Incorporating PET in the initial staging in lymphomas results in upstaging or downstaging in 10%–20% of patients, but the impact on treatment management is less obvious. Naumann et al analyzed the potential impact of PET staging on therapy decision in 88 patients with Hodgkin’s lymphoma. Concordant findings between PET and CT were found in 70/88 patients (80%). In 11 patients (13%), PET detected additional sites, which would have resulted in treatment intensification in 9 of them, all with early stage disease. Focusing on the patients with stage IA-IIB disease only (n = 44), treatment would have been intensified in 20%. Compared to conventional diagnostics, PET downstaged 7 patients (8%) but this was only correct in 1 patient (inflammatory enlarged cervical node). False negative PET findings would have erroneously led to a minimization of therapy in 6 patients (7%). Therefore, FDGPET should not be used instead of but in combination with conventional diagnostics.
Evaluation of Residual Masses After Treatment

Approximately two-thirds of patients with Hodgkin’s lymphoma will have a residual mass seen with standard imaging tests at the end of treatment, but only 20% of these patients will eventually relapse. Several recent reports have shown the effectiveness of FDG-PET in the evaluation of residual disease at the end of treatment, including studies assessing patients with Hodgkin’s lymphoma. A high negative predictive value (NPV) of FDG-PET (81%–100%) has been consistently reported by most studies, clearly showing the ability of PET to identify patients with an excellent prognosis. The question of whether, after first-line chemotherapy, RT can be omitted in patients with a negative PET scan is still unanswered. Prospective randomized trials are needed to compare the PFS, overall survival (OS) and long-term complications observed in patients with a negative PET after chemotherapy who receive no further therapy or standard RT as planned at the initiation of treatment.

Early Response Monitoring for Risk Stratification

Since treatments that are more aggressive, but also more toxic, are available, there is a growing interest in the use of risk-directed approaches to utilize prognostic factors that predict for relapse.

The duration of a complete remission (CR) and other long-term outcomes might be more affected by the sensitivity of the tumor to chemotherapy than by the prognostic factors seen at presentation. Promising results with FDG-PET can be obtained when evaluating treatment response. Treatment-induced changes resulting in tumor cell death or growth arrest reduce FDG uptake, making this a sensitive and early marker of response. Romer et al described a rapid decrease of FDG-uptake in patients with NHL as early as 7 days after commencing treatment. However, FDG-uptake at 42 days correlated better with long-term outcomes; early FDG reduction probably reflects initial chemosensitivity of the tumor whereas results of later evaluations are more related to the detection of resistant clones. Since that initial description, several studies have correlated PET (PPV) of PET is more variable (25%–100%). When PET images are interpreted in correlation with clinical history and CT by radiologists/nuclear medicine physicians with specific expertise in PET, the PPV of PET in patients with Hodgkin’s lymphoma is probably equivalent to that observed in NHL (> 80%) and residual positivity is highly suggestive of residual lymphoma for which additional treatment should be considered. In equivocal cases close follow-up or additional diagnostic procedures may be warranted to reduce risks of giving additional treatments that are based on false-positive results.

Current Concepts In Management Of Hodgkin’s Disease

Paediatric Hodgkin’s disease is one of the most curable of childhood malignancies today. Considering that curative therapy has been available for Hodgkin’s disease for more than 30 years, oncologists treating children and adolescents with the disease have an expectation of long-term survival for these patients. For many physicians, patients with Hodgkin’s disease have been the “bright spot” in their practice because they are a group who uniformly respond well to therapy and overcome their disease. Unfortunately, long after their exit from paediatric practices, the true cost of curative therapy becomes readily apparent as aging survivors develop a variety of medical complications unquestionably predisposed by their antineoplastic therapy. Presently used regimens have several therapy related toxicities leading to significant late complications.

After 6 cycles of nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP) there is usually persistent azoospermia in most male patients and there is a 3%-6% risk of secondary leukemias (mostly from nitrogen mustard). Six cycles of ABVD is associated with the risk of chronic cardiomyopathy (cumulative doxorubicin dose of 300 mg/m2) and impaired lung function with Bleomycin (cumulative dose of 120 mg/m2). Breast cancer is the most common solid tumor occurring in female Hodgkin’s survivors with 94% of these tumors occurring in the irradiated field. Current trials in paediatrics are therefore looking to decrease toxicity from chemotherapy and radiotherapy. The desire to prevent or reduce treatment sequelae, especially
second malignancies and cardiopulmonary dysfunction, has continued to motivate therapeutic modifications over the last several decades. While these complications adversely affect quality of life and increase the risk of early mortality, Hodgkin’s disease remains the leading cause of death observed in several cohort studies of long-term paediatric survivors, underscoring the need to proceed cautiously with therapy refinements that do not compromise disease control.38,39

The study by Children’s Cancer Group (CCG) trial designed to evaluate whether outcome of children with Hodgkin’s disease treated with dose-intensive, multiagent chemotherapy is compromised by the omission of radiation.40 is representative of many current risk-adapted paediatric Hodgkin’s trials with the dual objectives of maintaining treatment efficacy while reducing late treatment complications. Long-term follow-up of childhood cancer survivors has permitted identification of specific clinical and treatment factors predisposing to the common sequelae of Hodgkin’s disease. For example, breast cancer is almost exclusively observed in young women treated with thoracic radiation; treatment during puberty and higher cumulative radiation doses seem to enhance this risk.41-43 With the expectation of long-term survival in 85% or more of children and adolescents who present with Hodgkin’s disease, it is essential to consider clinical risk factors predisposing to late complications during treatment planning for newly diagnosed patients.

It is instructive to review the evolution of paediatric Hodgkin’s therapy to appreciate the current treatment biases of many paediatric oncologists. In early treatment regimens, the patient’s age or physical maturity was not considered during treatment planning. Standard-dose (35 to 44 Gy) radiation therapy to extended treatment volumes was the norm, for both children and adults, producing respectable disease-free survival rates for children with localized disease. However, long-term follow-up revealed treatment toxicity unique to children in the form of musculoskeletal growth inhibition.44 A desire to avoid these deformities led to the development of treatment protocols specifically designed for children, which used low-dose, involved-field radiation and fewer cycles of non-cross-resistant combination chemotherapy.45 Standard-dose radiation therapy was subsequently reserved for older, skeletally mature patients with localized disease until concerns about radiation-induced cardiovascular disease and second malignancies eventually led to the abandonment of radiation as a primary treatment modality by most paediatric oncologists.41-43,46

Despite results from numerous paediatric trials supporting the efficacy of a combined-modality treatment approach, the desire to avoid radiation-related toxicity, particularly second malignancies, has motivated continued investigation of chemotherapy-alone treatment regimens.47 Chemotherapy alone has long been established as an effective alternative to combined-modality therapy, but it confers risks associated with higher cumulative doses of anthracyclines, alkylating agents, and bleomycin.48 This is particularly significant as early trials prescribed considerably more months (usually in the range of 8 to 12 months) of chemotherapy than is typically used today. Early chemotherapy trials used MOPP or similar regimens derived from MOPP. Chemotherapy-related acute toxicity was acceptable, but limited data on long-term treatment effects support the expected high incidence of gonadal toxicity.49 Contemporary chemotherapy-only trials have used non–cross-resistant chemotherapy typically derived from MOPP and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Early outcomes seem comparable with those achieved with combined-modality therapy, but long-term effects on cardiac, pulmonary, and gonadal function have not been reported.49 Interpretation of these treatment results is further complicated by the fact that most of the studies comprised small numbers of clinically staged patients, assigned to treatments in a nonrandom fashion. In fact, some protocols specifically excluded patients with unfavorable features such as bulky or extensive lymphadenopathy, clinical features reported to benefit from a combined-modality treatment approach.

The Nachman et al40 study joins the ranks of the relatively few prospective randomized trials evaluating treatment outcomes for paediatric Hodgkin’s disease using chemotherapy alone compared with combined-modality therapy.
previous trials for advanced-stage paediatric Hodgkin’s disease organized by North American cooperative groups failed to show a statistically significant advantage in event-free survival or overall survival with the addition of radiation therapy to non-cross-resistant chemotherapy. The CCG compared 12 cycles of alternating MOPP/ABVD to six cycles of ABVD plus low-dose (21 Gy) radiation, and the Paediatric Oncology Group evaluated the benefit of adding low-dose radiation to eight cycles of alternating MOPP/ABVD. The trend in event-free and overall survival, although not statistically significant, suggested an advantage for the combined-modality approach over chemotherapy alone for the CCG trial. For the Paediatric Oncology Group trial, the intent-to-treat analysis did not indicate an event-free or overall survival advantage for the group randomized to receive radiation after completion of eight cycles of alternating MOPP/ABVD, but the as-treated analysis showed superior outcomes for patients treated with combined-modality therapy. The findings of both of these studies suffer from the fact that contemporary investigators have little desire to treat paediatric patients with 8 or 12 cycles of alternating MOPP/ABVD, with or without radiation therapy.

In the recent CCG trial reported by Nachman et al., a contemporary chemotherapy regimen is prescribed, cyclophosphamide, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine (COPP/ABV), which substitutes cyclophosphamide for the more leukemogenic nitrogen mustard and compacts the traditional alternating non-cross-resistant chemotherapy combinations into a dose-intensive hybrid. This treatment approach offers the advantage of a reduced duration of therapy and lower cumulative doses of individual agents. For stages I through III, a risk-adapted treatment assignment was based on the presence of adverse clinical features such as hilar adenopathy, involvement of more than four nodal regions, bulky mediastinal (> 33% of chest diameter) or peripheral (more than 10 cm) lymphadenopathy, and “B” symptoms. Patients with favorable disease presentations received four COPP/ABV cycles, whereas patients with adverse disease features received six COPP/ABV cycles. Stage IV patients with extranodal disease received a more intensive therapy including sequential cycles of high-dose cytarabine and etoposide, COPP/ABV, and cyclophosphamide, vincristine, doxorubicin, and methylprednisolone. Treatment was also response-based, as patients who achieved a complete response to initial chemotherapy were eligible either for randomization to receive low-dose involved-field radiation or no further treatment. The randomization was stopped earlier than anticipated because of results indicating a significantly higher number of relapses on the no-radiotherapy arm. The 3-year event-free survival estimates by both an intent-to-treat and as-treated analysis were significantly lower for patients treated with chemotherapy alone, with differences being most marked in stage IV patients. Because of successful salvage therapy for relapsed patients, estimates for overall survival are not different between the randomized groups in early follow-up. However, studies of long-term survivors from other series clearly indicate that treatment for relapse increases the risk of second malignancies and early mortality. The authors conclude that chemotherapy alone is not as effective as combined-modality therapy, although they allude to preliminary data analyses suggesting that there may be a subset of patients in whom the likelihood of microscopic residual disease is small and who may benefit from treatment with chemotherapy. This information is critical to more accurately guide risk assessment and treatment assignment in the risk-adapted era.

Reaching consensus about the characteristics of the paediatric patient with Hodgkin’s disease for whom therapy intensification is appropriate because of a high risk of treatment failure, or for whom outcome will not be compromised by further therapy reductions, has often been difficult to accomplish. For many trials, adverse prognostic features have included advanced (stage IIIB or IV) or unfavorable (bulky, symptomatic) disease presentations. To date, prognostic factor analyses in paediatric trials have revealed various findings related to laboratory parameters and tumor histology that have not yet been used to direct therapy. Likewise, only a few studies have correlated treatment outcome with biologic tumor activity, eg, interleukin-2 receptor elevation, but these features have not been studied prospectively to delineate their relationship with disease response.
and long-term outcome.52 More recent trials have demonstrated the prognostic significance of rapid early response, a paradigm that will be tested by upcoming Children’s Oncology Group Hodgkin’s trials.53 Clearly, future progress in therapy for paediatric Hodgkin’s disease will require an improved understanding of the clinical and biologic features that contribute to pathogenesis and treatment response. Until this information is available, paediatric investigators will persist with their careful manipulations of therapy in an effort to improve disease control and reduce long-term complications for children and adolescents with Hodgkin’s disease.

Late Effects
Children with Hodgkin’s disease require long-term follow up. Cardiac function should be followed using echocardiography or MUGA scans since cardiac dysfunction can appear several years after anthracycline therapy54. Pulmonary function including diffusion capacity should be monitored following bleomycin use55. Thyroid profile should be followed closely since an asymptomatic patient with an elevated TSH is an indication to start thyroid replacement therapy56. Skeletal growth measurements with growth charts should be maintained and sexual maturation should be monitored. Screening for second malignancy57 is necessary and in female patients, breast examinations and consideration for an early mammogram are required, if the breast tissue was in the irradiated field58. Historically, treatment has involved the use of procarbazine and alkylating agents such as chlorambucil, mustine and cyclophosphamide. However, whilst this treatment leads to good survival rates, the majority of male patients have subsequently developed permanent azoospermia59. Mackie et al60 studied children who had received treatment with ‘ChlVPP’, a chemotherapy regimen containing chlorambucil and procarbazine. The mean age at diagnosis of the male patients investigated was 12.2 years, and of these 89% subsequently had evidence of severe damage to the seminiferous epithelium up to ten years following therapy. This study demonstrates both the gonadotoxicity of these agents, and also the susceptibility of the prepubertal testis. Whitehead et al61 similarly followed up children treated with ‘MOPP’ chemotherapy, a regimen containing mustine and procarbazine, and also demonstrated subsequent long-term testicular damage in the majority of male patients. In view of these studies, treatment for Hodgkin’s lymphoma has been modified in an attempt to reduce the gonadotoxicity, whilst maintaining long-term survival62. Semen cryopreservation should always be considered for young men undergoing treatment for Hodgkin’s lymphoma with potentially gonadotoxic treatment, fertility preservation in the female for those at risk of a truncated window of opportunity for fertility is more complex63.

Treatment Of Refractory Or Relapsed Hodgkin’s Lymphoma
Treatment outcome for patients with Hodgkin’s lymphoma has steadily improved over the last half-century. Whereas a patient treated in the 1960s had an 80% chance of subsequent progression of disease, one treated in the 1990s has less than a 20% chance of developing the same problem. The need to have a strategy for the treatment of Hodgkin’s lymphoma not cured by primary treatment remains important. Very few patients with limited stage Hodgkin’s lymphoma demonstrate refractory or relapsed disease. Thus, a need to find effective secondary treatment for Hodgkin’s lymphoma is confined almost entirely to patients presenting with advanced stage lymphoma.

High dose chemotherapy and irradiation plus autologous hematopoietic stem cell transplantation (HDC/HSCT) has, over the past two decades, become established as the most effective treatment for patients whose Hodgkin’s lymphoma has proven incurable with standard chemotherapy and radiation. Phase II trials, collected series from bone marrow transplantation registries64 and two Phase III randomized trials65,66 have demonstrated that the effectiveness of HDC/HSCT is sufficiently clear that HDC/HSCT has become widely accepted as the best treatment approach for most patients who are not cured by primary treatment programs based on multi-agent chemotherapy. The high levels of toxicity and cost associated with HDC/HSCT demand that it be reserved for patients where it clearly increases the chance of cure compared to alternative treatments. This describes two groups of patients: first, those...
whose disease progresses during primary chemotherapy or fails to enter a complete remission as proven by biopsy demonstrating persistent disease; second, patients who relapse after completing a full course of multi-agent chemotherapy with or without radiation. The first group, usually referred to as having refractory or chemotherapy resistant disease, has very little chance of cure with any program of standard dose chemotherapy with or without irradiation. This group, lacking reliably curative alternatives, is best treated with HDC/HSCT because it offers a definite chance of cure. The use of HDC/HSCT for patients in first relapse after primary chemotherapy is somewhat more controversial, especially if the relapse occurs long after completion of the primary treatment or in an isolated nodal area easily amenable to irradiation. However, when relapse occurs after primary chemotherapy consisting of a regimen as effective as ABVD, the chance of inducing long-term disease-free survival with standard dose chemotherapy is small, probably less than 20 percent.

Two special subgroups may not share this poor prognosis: those who relapse solely in originally involved but unirradiated lymph node groups; and those who relapse more than 1 year after completion of the primary chemotherapy. In the first of these 2 subgroups, wide field irradiation with or without additional chemotherapy may cure 40% to 50% of very carefully selected patients. However, very few patients fit the ideal pattern of having nonbulky disease confined to lymph nodes at diagnosis and relapse, absence of B-symptoms at diagnosis and relapse and, preferably, a long interval from primary treatment to time of relapse. Although those relapsing more than a year after completion of primary chemotherapy may do well with a switch to potentially noncross-resistant chemotherapy with or without irradiation, this approach will only cure 20% to 40% of these specially selected patients.

In contrast, however, this same subgroup is the one with the very best outcome with HDC/HSCT. In theory, the use of allogeneic stem cells, with their potential to add an immunologic attack on the malignant cells and provide a stem cell source free of contaminating tumor cells, should be even more effective that autologous stem cell transplantation following HDC for Hodgkin’s lymphoma. However, this improved potency is more than offset by increased toxicity leaving no net gain for the patient. Any gain in disease control is overshadowed by increased toxicity, often lethal, from graft versus host disease and interstitial pneumonitis. Presently, with the availability of peripheral blood stem cells that appear to be free of clonogenic tumor cells and their proven efficacy and lower toxicity, autologous stem cells are the source of choice for hematologic engraftment when HDC/HSCT is used for Hodgkin’s lymphoma.

Although most of the initial experience employing HDC/HSCT for Hodgkin’s lymphoma was acquired using autologous bone marrow cells, most groups now use autologous peripheral blood stem cells. In addition, most groups currently employ at least some standard dose chemotherapy prior to the high-dose chemotherapy for two reasons. First, it brings the Hodgkin’s lymphoma under control while the logistics of stem cell collection and the hospitalization for HDC/HSCT are arranged. Second, it provides priming for the peripheral blood stem cell collection enhancing the effectiveness of hematopoietic stem cells. However, it is important to remember that the purpose of this pre HDC/HSCT chemotherapy is not to test for chemosensitivity. Hodgkin’s lymphoma, almost uniquely among human neoplasms, can be cured with the use of HDC/HSCT even when the disease does not respond to standard dose chemotherapy.

Although a variety of HDC regimens have been described, no one regimen has been shown to be clearly superior. Currently, popular regimens include CBV (cyclophosphamide, carmustine [BCNU] and etoposide [ETOP]), BEAM (carmustine [BCNU], etoposide, cytarabine and melphalan) or high-dose melphalan with or without total body irradiation. Because none of these regimens has been shown to be superior, it is more important for investigators at an individual center to master the management of the acute and chronic toxicities of their chosen regimen than to switch from one to another seeking some modest but unproved advantage.

**Newer Therapies For Hodgkin’s Disease**

Most series suggest 6% of patients still dying of
progressive lymphoma despite optimal use of primary chemotherapy and secondary HDC/HSCT there is a clear need to find effective new therapeutic agents. Gemcitabine is the most promising traditional type chemotherapeutic agent currently under investigation for Hodgkin’s lymphoma. In small series of heavily treated patients, an overall response rate of approximately 50% has been found with 10%–20% complete responses. Even more encouraging, 2 groups have found an overall response rate higher than 75% when gemcitabine was combined with cisplatin and a corticosteroid. This promising new agent will need further testing and integration into combinations with standard or other novel agents to exert its ultimate impact in the management of Hodgkin’s lymphoma.

One of the most promising new types of treatment for lymphoma, in general, is targeted immunotherapy. The anti-CD20 monoclonal antibody rituximab has proven useful for several different types of B cell lymphomas. The nearly universal expression of CD20 on the neoplastic cells of LPHL suggests rituximab may be useful. Preliminary data from several small series show response rates exceeding 50%, however, the durability of these responses seems limited. Treatment with rituximab is attractive for this disease because of the lack of cumulative or late toxicity with this agent but will need to be integrated with conventional treatments to have a substantial impact. Efficacy of one type of targeted immunotherapy hints that others may also be useful. Monoclonal antibodies aimed at other B cell or lymphocytic antigens, and immunotoxin molecules including bispecific antibodies and, eventually, tumor specific immunization strategies all hold promise. New immunotherapeutic approaches such as those hold substantial promise for Hodgkin’s lymphoma. However, because this disease is already so often cured, finding subjects for the testing of new agents is increasingly difficult. The challenge for clinicians involved in the treatment of Hodgkin’s lymphoma is to maintain the high cure rates but decrease the long-term morbidity, particularly second tumours, cardiac dysfunction and infertility. Combined modality treatment has been the gold standard for three decades and it remains to be seen whether functional imaging in the form of FDG-PET can determine which patients need combined modality treatment and which will be cured by chemotherapy alone.

References


