



EVIDENCE-BASED MANAGEMENT OF HODGKIN'S DISEASE: THE ROLE OF AUTOLOGOUS STEM CELL TRANSPLANTATION

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Introduction

Hodgkin's disease is the most common malignancy in individuals in the 10- to 30-year-old age group. This malignancy develops in approximately 20,000 individuals in the United States and Canada each year, accounting for an incidence of approximately 3 per 100,000.^{1,2} The disease is notable in that the malignant cells, the Hodgkin's-Reed Sternberg (H-RS) cells, constitute less than 5% of the tumor mass; the majority of the mass is comprised of T and B cells as well as a variety of other inflammatory cells such as eosinophils, macrophages, histiocytes, plasma cells, neutrophils, stromal cells, and fibroblasts.² The histologic subtype of Hodgkin's disease depends on the reactive cellular environment in which the H-RS cells are found. Classic Hodgkin's disease is categorized as nodular sclerosis, mixed cellularity, lymphocyte depletion, and a provisional subtype called lymphocyte rich (formerly the diffuse lymphocyte predominance subtype).^{1,2} The disease is typically unifocal in origin, arises in lymph nodes, and spreads to contiguous nodal groups.²

The importance of cytokines and cytokine receptors in Hodgkin's disease has been increasingly recognized. H-RS cells express a number of adhesion and costimulatory molecules, as well as members of the tumor necrosis receptor family such as CD30, CD40, and Fas/CD95 receptors. The CD30 ligand may exert biologic activities ranging from stimulation of proliferation to induction of

apoptosis. H-RS cells also excrete a number of cytokines, which may contribute to the activation of immune cells at the sites of tumor and to the development of the constitutional (B) symptoms often seen in Hodgkin's disease.² With modern cytotoxic therapy, the mortality rate from Hodgkin's disease has decreased from 1.8 per 100,000 to 0.47 per 100,000.¹ Cure is clearly the goal of therapy, and recent efforts have focused on achieving cure with the least toxicity and at the lowest cost.

A modification of the Ann Arbor staging system is the most common staging classification used.^{1,2} A simplified grouping for treatment purposes divides patients into those with early-stage and those with advanced-stage disease. Patients with early-stage disease are those with Ann Arbor stage I or II (disease limited to involvement of a single lymph node region or structure or two or more lymph nodal regions on the same side of the diaphragm) who do not have bulky disease or B symptoms. Patients with advanced-stage disease have stage III or IV disease (involvement of lymph node regions above and below the diaphragm or diffuse/disseminated involvement of extranodal organs), bulky disease, or B symptoms.²

Results of Conventional Therapy

Patients with early-stage Hodgkin's disease are highly curable with conventional therapy. Several treatment options, which

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may or may not involve staging laparotomy, are available for those with favorable prognostic features.³ Radiation therapy alone is effective in patients who have a negative laparotomy. In clinically staged patients, irradiation to the mantle (either mantle, para-aortic, and splenic fields) or combined-modality treatment with several cycles of chemotherapy and less extensive radiotherapy may be considered. Patient preference and the short- and long-term side effects of therapy are important issues in determining the treatment of individual patients.³ Studies are in progress to determine the optimal management of different prognostic subsets in early-stage disease.

Approximately two thirds of patients with more advanced Hodgkin's disease can be cured with chemotherapy, with or without additional radiation therapy.^{1,2,4} Data from randomized clinical trials have established the superiority of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) over other regimens such as MOPP (nitrogen mustard mechlorethamine, vincristine, procarbazine, and prednisone) or combinations of MOPP and ABVD in terms of both antitumor efficacy and toxicity.⁴ Newer chemotherapy protocols are also undergoing evaluation.¹

Although Hodgkin's disease represents a relative success story for modern oncology, many critical management decisions remain unclear. These include decisions regarding not only the best management of early-stage disease, but also the use of prognostic factors to

direct therapy in newly diagnosed patients with advanced-stage disease and the optimal management of recurrent disease. This discussion focuses on the role of intensive therapy in autologous stem cell transplantation (ASCT) in Hodgkin's disease.

Evidence-Based Decisions Regarding ASCT in Hodgkin's Disease

Evidence-based medical decision-making involves first formulating a question. In this case, the key question is whether ASCT is better than conventional therapy in patients with Hodgkin's disease. Various clinical trials are then reviewed and evaluated for the quality of evidence supporting ASCT. Large randomized trials or meta-analyses obviously represent the highest level of evidence, followed by historic cohort comparisons and, lastly, case series such as phase II studies and registry analyses. The results of clinical trials are expressed in terms of progression-free survival (PFS) and overall survival (OS). In Hodgkin's disease, the PFS rate is the preferred outcome to follow because it reflects the potential for cure more appropriately than the OS rate, particularly since Hodgkin's patients may have a chronic relapsing course before succumbing to the disease.

In comparative studies of conventional therapy vs ASCT, the absolute reduction of the risk of an unfavorable outcome when ASCT is performed can be measured. In addition, the number of patients

needed to treat (NNT) with ASCT to produce one more survivor compared with conventional therapy and the NNT with ASCT to produce one additional treatment-related death (NNH = number needed to harm) may also be assessed.

ASCT in Relapsed or Refractory Disease

The use of ASCT for relapse after initial radiotherapy alone for early-stage disease is not appropriate since such patients have satisfactory results after conventional chemotherapy.^{2,4} However, many ASCT studies have been performed for patients who have recurred despite chemotherapy.

The single randomized clinical trial comparing ASCT and non-ASCT therapy that has been published in detail involved 40 patients with relapsed or refractory Hodgkin's disease after chemotherapy.⁵ These patients received intensive therapy with BEAM (high doses of BCNU [carmustine], etoposide, cytosine arabinoside, and melphalan) followed by autologous bone marrow transplantation (ABMT) vs the "mini-BEAM" regimen — a chemotherapy regimen using the same drugs in lower doses. Mini-BEAM produces considerable myelosuppression but does not require stem cell support. The study was closed prematurely due to increasing patient refusal to enter the mini-BEAM arm. At 3 years, the PFS rate was 53% in the ABMT arm compared with 10% in the mini-BEAM arm. Treatment-related deaths within the first 100

days after ASCT, hence referred to as nonrelapse mortality, were more common in the transplant arm (10% vs 0%).⁵ The absolute risk reduction for PFS was 43% for ABMT, and the number needed to treat (NNT) to achieve one additional favorable outcome was only 2. Counterbalanced against this, the number of patients who, if treated with ABMT, would lead to 1 additional individual being harmed (NNH) was 10.

Another important and larger randomized study has been carried out under the aegis of the German Hodgkin's Lymphoma Study Group (GHSG) and the European Group for Blood and Marrow Transplantation (EBMT), and the initial analysis has been reported in abstract form.⁶ In this trial, patients in relapse after chemotherapy were randomized to receive either 4 cycles of an aggressive chemotherapy regimen similar to mini-BEAM called DexamBEAM (dexamethasone, carmustine, etoposide, cytarabine, and melphalan + G-CSF) vs 2 cycles of DexamBEAM followed by BEAM and ASCT. Of 142 patients in first relapse or second or greater relapse responsive to the initial cycles of DexamBEAM, 115 were randomized, and the results were analyzed on an intention to treat basis. Although the OS was similar, the PFS rate of 53% seen in the ASCT group was significantly better than that of 39% in the patients given DexamBEAM.

A historic cohort study by Yuen et al⁷ from Stanford University has also compared the results of conventional therapy and ASCT in

relapsed or refractory patients. This analysis looked at the treatment results for all relapsed or refractory patients and then for specific subgroups separately. In the entire group of 60 ASCT recipients and 108 conventionally treated patients, the PFS was again significantly better with ASCT (53%) vs 27% with conventional therapy. The absolute risk reduction was 26% with an NNT of 4. The NNH was 14, as the early nonrelapse mortality rates were 10% and 2.9%, respectively.

Finally, additional support for ASCT comes from a British case series study that demonstrated the ability of BEAM and ABMT to produce durable PFS even in patients who had failed to respond to mini-BEAM.⁸ Numerous other case series studies have also demonstrated that ASCT has the ability to cure some patients with otherwise incurable Hodgkin's disease.⁹⁻¹⁴

These studies all support the use of ASCT in patients with Hodgkin's disease that has progressed after chemotherapy. However, patients with relapsed or recurrent disease have different natural histories, depending on whether an initial complete remission (CR) was achieved with chemotherapy and also depending on the duration of first CR.¹ Therefore, examination of the use of ASCT in patients at different timepoints in the disease course is useful. The different options for utilizing ASCT include its use in (1) patients whose disease fails to enter remission with induction chemotherapy, (2) those who are in

a first relapse (or second CR) after initial chemotherapy, (3) those in a second or greater relapse, and, as has been suggested recently, (4) newly diagnosed patients with advanced-stage disease who are at high risk of relapse after primary chemotherapy.

Induction Failure

Patients who fail to enter a CR with initial chemotherapy include those who progress after achieving an initial partial remission (PR), those who progress during therapy, and those who have evidence of residual disease on biopsy.¹⁴ Patients in a PR with residual radiographic masses of unknown etiology are best excluded from this category due to the well-known phenomenon that such masses can represent fibrosis rather than active disease.^{1,4} Results of conventional therapy in patients whose disease fails to respond are uniformly poor. Two studies have demonstrated a PFS rate of 0% in such patients with long-term follow-up.^{15,16} In contrast, ASCT in this setting produced PFS rates of approximately 30% (range: 25% to 52%), at median follow-up periods of 3 to 8 years (Table 1). The early nonrelapse mortality rate seen with ASCT in this subgroup has been relatively high by current standards (8% to 17%).^{7,9,14,17-21}

Two nonrandomized historic cohort studies comparing ASCT and conventional therapy have been published recently. The first was an analysis of data from the French Transplant Registry by André et al,²⁰ which included a

high proportion of patients in the ASCT group who had actually progressed during initial chemotherapy rather than those who met other criteria of induction failure. The PFS rate was 25% in the ASCT group but was not available in the conventionally treated group. The OS rate at 6 years was 38% with ASCT and 29% for conventional therapy. Early nonrelapse mortality occurred in 8.1% and 6.4% in patients receiving ASCT and conventional therapy, respectively. In the second study, Yuen et al⁷ looked separately at the subset of induction failure patients within their entire group of patients described previously. The 4-year PFS rate was 52% in the ASCT group compared with only 19% in the conventional therapy group. The benefit with ASCT was therefore considerable.

These reports all support ASCT as the preferred treatment in patients with disease failing induction chemotherapy. Due to the dismal results of conventional therapy, interest in future randomized studies to definitively prove that ASCT is superior is minimal.

The use of allogeneic SCT has been proposed as an alternative to ASCT in induction-failure patients. Allogeneic SCT has the advantage of a "graft-vs-lymphoma" effect presumably mediated by donor lymphocytes. Studies of allogeneic SCT in Hodgkin's disease are limited at this time. However, one matched comparison indicated that the beneficial graft-vs-lymphoma effect was counterbalanced by the higher nonrelapse mortality rates seen with allografting.²² The development of so-called nonmyeloabla-

tive or other novel allogeneic SCT protocols may well broaden the application in poor-prognosis patients who have a suitable donor because the toxicity profile is better.²³ It is possible that allogeneic SCT might prove to be an attractive strategy in younger induction-failure patients or other poor-risk patients such as those with extensive bone marrow involvement.

ASCT in First Relapse After Chemotherapy/Second CR

The situation is less straightforward in Hodgkin's disease patients who achieve an initial CR with chemotherapy but then relapse, since some can be cured with further conventional therapy without ASCT.^{1,2,15,16} The best outcome is seen in patients with an initial CR duration of longer than 1 year.^{15,16}

Table 1. — Results of Therapy in Hodgkin's Disease Induction Failure

	Author, Year	Level of Evidence*	Number of Patients	PFS	OS	Early NRM	Follow-up
Conventional Therapy	Longo et al, 1992 ¹⁵	C	51	0%	0%	-	22 yrs
	Bonfante et al, 1997 ¹⁶	C	39	0%	8%	-	8 yrs
	Yuen et al, 1997 ⁷	B	26	19%	38%	-	4 yrs
ASCT	Chopra et al, 1993 ⁹	C	46	33%	-	-	5 yrs
	Prince et al, 1996 ¹⁷	C	30	34%	51%	10%	3 yrs
	Yuen et al, 1997 ⁷	C	13	52%	44%	-	4 yrs
	Reece et al, 1995 ¹⁴	C	30	38%	-	17%	8 yrs
	Moreau et al, 1998 ¹⁸	C	28	26%	34%	-	5 yrs
	Lazarus et al, 1999 ¹⁹	C	122	38%	50%	12%	3 yrs
	André et al, 1999 ²⁰	B	186	25%	35%	8%	5 yrs
Sweetenham et al, 1999 ²¹	C	175	32%	36%	14%	5 yrs	

PFS = progression-free survival rate
 OS = overall survival rate
 NRM = nonrelapse mortality
 * Level of evidence: A = randomized clinical trial or meta-analysis
 B = historic cohort comparison
 C = case series (phase II study or registry analysis)

Other favorable prognostic factors include younger age, initial stage I or II disease, and lack of B symptoms or extranodal disease.^{1,2,15,16}

If ASCT is performed, a few patients can proceed directly to the procedure. In general, these include patients with limited disease and absence of B symptoms who can undergo ASCT expeditiously. However, most patients require several cycles of salvage chemotherapy first. Numerous studies have shown that patients who manifest chemosensitivity to salvage therapy have a better outcome after ASCT than those who are chemorefractory.^{9,11-13,24-27}

Patients who enter a second CR after conventional salvage therapy have been reported to have a better outcome than those with a PR in most^{12,25,26} but not all²⁸ trans-

plant series. It is difficult to determine if this finding reflects the intrinsically better prognosis of those with highly chemosensitive disease or if it supports the need to use repetitive cycles of salvage chemotherapy to try to achieve a full response. There is also the potential concern that extensive salvage chemotherapy before ASCT could be detrimental in terms of increased damage to the hematopoietic stem cells²⁹ or injury to other organs,^{30,31} as discussed below. On the other hand, although first relapse patients who are chemorefractory have an inferior prognosis, 10% to 20% can achieve durable CR after ASCT, and such patients are usually offered the procedure.^{9,12,13}

It is also useful to further subdivide first-relapse patients into those who have had an initial CR

duration of 1 year or less and those with a CR duration of longer than 1 year for a comparison of the results of ASCT and conventional therapy.^{15,16}

Initial CR Duration of 1 Year or Less

Patients who relapse early after first-line chemotherapy have a high likelihood of treatment failure with further conventional therapy alone (Table 2).^{7,15,16} Studies with long follow-up in such patients show that the PFS rate is only approximately 20% at periods of 8 to 22 years after conventional therapy.^{15,16} In contrast, the PFS rate is approximately 40% after ASCT.^{7,9,13,28,32-34} Specific information on the early nonrelapse mortality rate with ASCT is scant for this subgroup alone, but in recent years such toxicity has decreased

Table 2. — Results of Therapy in Hodgkin's Disease First Relapse after CR Duration ≤ 1 year

	Author, Year	Level of * Evidence	Number of Patients	PFS	OS	Early NRM	Follow-up
Conventional Therapy	Longo et al, 1992 ¹⁵	C	53	19%	11%	-	22 yrs
	Bonfante et al, 1997 ¹⁶	C	89	22%	28%	-	8 yrs
	Yuen et al, 1997 ⁷	B	25	19%	38%	-	4 yrs
ASCT	Chopra et al, 1993 ⁹	C	36	41%	-	-	5 yrs
	Bierman et al, 1996 ³²	C	42	32%	44%	-	5 yrs
	Nademanee et al, 1995 ³³	C	39	51%	-	-	2 yrs
	Wheeler et al, 1997 ¹³	C	36	44%	-	-	3 yrs
	Brice et al, 1997 ²⁸	C	74	-	54%	-	4 yrs
	Yuen et al, 1997 ⁷	B	25	56%	58%	-	4 yrs
	Reece et al, 1995, ³⁴ 1998	C	41	59%	58%	5%	8 yrs

PFS = progression-free survival rate
 OS = overall survival rate
 NRM = nonrelapse mortality
 * Level of evidence: A = randomized trial or meta-analysis
 B = historic cohort comparison
 C = case series (phase II study or registry analysis)

in general to the range of 5% or less after ASCT, except in induction failure patients.^{13,14,17,19,21}

The historic cohort study of Yuen et al⁷ demonstrated a PFS rate of 56% in the subgroup of patients with a CR duration of 1 year or less who were transplanted compared with 19% in those given only conventional therapy. Therefore, a substantial advantage was seen for ASCT, with an absolute risk reduction of 37%. The GHSG/EBMT randomized study⁶ also noted a significant advantage for ASCT in chemosensitive patients with a short initial CR duration, although details are not yet available. Taken together, the data indicate that ASCT also represents the treatment of choice for patients with an initial CR duration of 1 year or less.

Initial CR Duration of Longer Than 1 Year

Long-term PFS rates of 20% to 40% have been reported in Hodgkin's disease in patients who relapse after a longer (more than 1 year) initial CR duration and then receive further conventional therapy alone,^{7,15,16,35} and the early nonrelapse mortality rate is 2% or less (Table 3).³⁵ The PFS rate is approximately 50% to 60% after ASCT, which is also associated with a low early nonrelapse mortality rate.^{7,9,13,28,32-34} The historic cohort study by Yuen et al⁷ did not show a benefit for OS for ASCT at 4 years, although the PFS rate was 52% with ASCT compared with 40% with conventional therapy. This 12% absolute risk reduction was not statistically sig-

nificant. Of interest, the actuarial PFS curves appear to diverge after 4 years, suggesting that a benefit for ASCT may be realized with longer follow-up. As well, the GHSG/EBMT randomized study reported a significantly better outcome with ASCT in patients with an initial CR duration of longer than 1 year.⁶

The data, then, favor the use of ASCT in patients with a longer initial CR duration. Although there may be occasional patients with a localized, asymptomatic relapse who could be considered for conventional therapy, our own policy has been to proceed with ASCT in virtually all patients. After ASCT, involved-field radiotherapy is utilized, if possible, to try to maximize the cure rate.^{9,10,24,27}

Table 3. — Results of Therapy in Hodgkin's Disease First Relapse after CR Duration >1 year

	Author, Year	Level of Evidence*	Number of Patients	PFS	OS	Early NRM	Follow-up
Conventional Therapy	Longo et al, 1992 ¹⁵	C	54	19%	24%	0%	22 yrs
	Canellos et al, 1995 ³⁵	C	45	38%	-	2%	3 yrs
	Bonfante et al, 1997 ¹⁶	C	44	44%	54%	-	8 yrs
	Yuen et al, 1997 ⁷	B	42	40%	62%	-	4 yrs
ASCT	Chopra et al, 1993 ⁹	C	36	57%	-	-	5 yrs
	Bierman et al, 1996 ³²	C	43	47%	-	-	5 yrs
	Nademanee et al, 1995 ³³	C	37	63%	-	-	2 yrs
	Wheeler et al, 1997 ¹³	C	32	48%	-	-	3 yrs
	Brice et al, 1997 ²⁸	C	146	-	73%	-	4 yrs
	Yuen et al, 1997 ⁷	B	22	52%	55%	-	4 yrs
	Reece et al, 1995, ³⁴ 1998	C	22	77%	80%	0%	8 yrs

PFS = progression-free survival rate
 OS = overall survival rate
 NRM = nonrelapse mortality
 * Level of evidence: A = randomized trial or meta-analysis
 B = historic cohort comparison
 C = case series (phase II study or registry analysis)

ASCT Later in the Disease Course: Second or Greater Relapse

In patients who underwent ASCT at the time of second or greater relapse after chemotherapy, PFS rates of 25% to 52% have been reported.^{9,13,30,33} In contrast, essentially no patients in such advanced relapse are cured with conventional therapy.¹⁵ Although ASCT is warranted in such patients, its use earlier in the disease is recommended, if possible. One retrospective analysis found that the OS rate was significantly worse in patients undergoing ASCT in second relapse compared with those transplanted in first relapse (51% vs 71%).²⁸ Again, there is a concern for greater nonrelapse mortality when the use of ASCT is delayed.^{29,31}

ASCT as Part of Initial Therapy

The use of ASCT as part of initial therapy in patients with high-risk features at diagnosis has recently been proposed. The key to this approach is the identification of reliable prognostic factors early in the disease course that define a group of patients at high risk of relapse. Using clinical and laboratory features present at diagnosis, several prognostic systems have been described.^{36,37} In general, these can identify groups of patients with a good outcome and a smaller group

with an unfavorable prognosis with chemotherapy, with PFS rates of approximately 45% to 50%. The International Prognostic Factors Project for Advanced Hodgkin's Disease has now been completed using a database of more than 5,000 patients and has identified 7 adverse prognostic factors at diagnosis.³⁸ These include an initial hemoglobin of <10.5 g/dL, albumin <4 g/dL, stage IV disease, male sex, white blood cell count of $\geq 15,000$, absolute lymphocyte count of <600 per mm³, and age ≥ 45 years. The presence of each of these factors decreases the 5-year PFS rate by 7% to 8%. This system can discriminate patients with 5-year tumor control rate ranging from 84% in those with no factors to 42% in patients with 5 or more factors.³⁸

It is unclear at this time whether an anticipated PFS rate of 40% to 50% with conventional therapy warrants ASCT, particularly since ASCT can cure a significant proportion of patients if the

disease does recur. Nevertheless, several centers have described the use of ASCT high-risk patients in initial CR or PR (Table 4).^{18,39-42} The criteria for high-risk varied among these studies; none used the new international score.³⁸ The early nonrelapse mortality rates have been low, and long-term PFS rates have been on the order of 70% to 100%.^{18,39-42} However, late complications, such as secondary malignancies, have been described in a small number of these patients.^{41,43}

More information regarding ASCT as part of initial therapy will become available in the future. The EBMT group has completed accrual to a randomized study for high-risk patients,⁴⁴ defined by a modification of the criteria reported by Straus et al.³⁶ In this study, patients received initial therapy with regimens containing ABVD. After 4 cycles, responding patients were randomized to continue chemotherapy or to undergo

Table 4. — Results of ASCT High-Risk Patients in Initial CR/PR

Author, Year	Level of Evidence*	Number of Patients	Status at ASCT	PFS	Early NRM	Follow-up
Bradley et al, 1995 ³⁹	C	23	CR	70%	4%	4 yrs
Carella et al, 1996 ⁴⁰	C	22	CR	77%	4%	6 yrs
Sureda et al, 1997 ⁴¹	C	27	CR	78%	0%	2 yrs
Moreau et al, 1998 ¹⁸	C	130	CR (45) PR (85)	74%	3%	5 yrs
Nademanee et al, 1999 ⁴²	C	20	CR (14) PR (6)	100%	0%	3.5 yrs

PFS = progression-free survival rate
 OS = overall survival rate
 NRM = nonrelapse mortality
 * Level of evidence: A = randomized trial or meta-analysis
 B = historic cohort comparison
 C = case series (phase II study or registry analysis)

ASCT.⁴⁴ The Southwest Oncology Group (SWOG) has also initiated a randomized intergroup study in patients with 3 to 7 adverse risk factors according to the new international criteria. Chemosensitive patients will be randomized to receive further conventional therapy or ASCT.

Table 5. — Recommendations for ASCT in Hodgkin's Disease by Disease Status

Timing	Recommendations for ASCT
As part of primary therapy (initial CR/PR)	Insufficient data to warrant use outside a clinical trial
Failure of induction chemotherapy	Indicated
First relapse after radiotherapy alone	Not indicated
First relapse/second CR after chemotherapy	
- First CR duration ≤1 year	Indicated
- First CR duration >1 year	Indicated
Second or greater relapse	Indicated

Late Complications

As patients with Hodgkin's disease have been followed for longer periods of time post-ASCT, the impact of late fatal complications, or late nonrelapse mortality, has been increasingly recognized. Late nonrelapse mortality results primarily from chronic lung damage, infection, and secondary malignancies, particularly secondary myelodysplastic syndrome or acute myelogenous leukemia (MDS/AML).³¹ These complications are similar to those that are observed in long-term survivors after conventional therapy.^{43,45}

Late pulmonary fibrosis after ASCT occurs in up to 6% of patients and appears to be related to the use of high-dose BCNU or total body irradiation in the conditioning regimen. Late fatal infections have been described in approximately 1% to 2% of ASCT-transplanted patients; bacterial, viral, and fungal infections have all been observed.³¹ The cumulative incidence of MDS/AML in patients undergoing ASCT for Hodgkin's disease has ranged from 5% to 24%.³¹ However, the use of actuarial methods to calculate the incidence may magnify

the risk, as many patients may be censored at intervals shorter than those at which this complication usually occurs.

Secondary MDS/AML

The precise contributions of stem cell damage from prior cytotoxic therapy vs the intensive transplant procedure itself to the development of MDS/AML are uncertain, although the former process is thought to play the dominant role. First, using data from French registries, a historic cohort comparison by André et al⁴³ found that the incidence of secondary MDS/AML was similar in patients receiving conventional therapy or ASCT. Second, chromosomal abnormalities typical of therapy-related MDS/AML have been detected using sensitive cytogenetic techniques in morphologically normal marrow and peripheral blood stem samples obtained and stored before the transplant. These abnormalities were the same as those detected later when clinical MDS was diagnosed clinically post-ASCT.²⁹ The findings suggest that stem cell procurement early in the disease course might minimize this complication.

Secondary Solid Tumors

A variety of solid tumors, as well as non-Hodgkin's lymphoma, have also been described after both ASCT and conventional therapy for Hodgkin's disease. In the French historic cohort study mentioned above, the risk of secondary solid tumors after ASCT was 3.7% and was significantly higher than that seen in a matched group of patients treated with conventional therapy.⁴³ Etiologic factors are under investigation.

The effect of such late complications may modify future recommendations regarding the optimal role of ASCT in Hodgkin's disease. However, since these complications may take many years to manifest themselves, patients will need to be closely followed for protracted periods of time. Also, due to the relatively low incidence of these complications, large numbers of patients will need to be monitored to determine significant differences.

Conclusions

Two randomized studies^{5,6} and two historic cohort studies^{7,20} are

available to support the use of ASCT in patients with Hodgkin's disease that has relapsed or recurred after initial chemotherapy. These studies consistently show an advantage for ASCT in patients with Hodgkin's disease which has progressed after chemotherapy. The phase II and registry studies available for review also demonstrate the efficacy of ASCT in this malignancy.

Table 5 summarizes recommendations for the use of ASCT. In the setting of induction failure and first relapse after a CR duration of 1 year or less, ASCT is the treatment of choice. ASCT consistently produces cure rates of 50% to 75% in patients with more than 1 year initial CR duration, and preliminary data from the GHSG/EBMT randomized trial support ASCT in this setting.⁶ ASCT is therefore appropriate in patients in first relapse after an initial CR duration of more than 1 year. If conventional therapy is chosen instead, elective collection of stem cells to use in the event of a second relapse should be considered before further cytotoxic therapy is given.

Recommendations regarding the use of ASCT in high-risk patients in an initial PR or CR in Hodgkin's disease will depend on the results of the EBMT and SWOG intergroup randomized trials. Currently, however, there is insufficient data to recommend the routine use of ASCT before progression has occurred.

Although the implementation of randomized trials in Hodgkin's

disease has been difficult until recently, the newer studies will provide more precise information regarding the role of ASCT. Long-term follow-up of these patients will be required to fully assess the risk of late complications of treatment so that such toxicity can be minimized.

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