Normalization of pre-ASCT, FDG-PET imaging with second-line, non–cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma

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We previously reported that remission duration < 1 year, extranodal disease, and B symptoms before salvage chemotherapy (SLT) can stratify relapsed or refractory Hodgkin lymphoma (HL) patients into favorable and unfavorable cohorts. In addition, pre-autologous stem cell transplant (ASCT) ^{18}FDG-PET response to SLT predicts outcome. This phase 2 study uses both pre-SLT prognostic factors and post-SLT FDG-PET response in a risk-adapted approach to improve PFS after high-dose radiochemotherapy (HDT) and ASCT. The first SLT uses 2 cycles of ICE in a standard or augmented dose (ICE/aICE), followed by restaging FDG-PET scan. Patients with a negative scan received a transplant. If the FDG-PET scan remained positive, patients received 4 biweekly doses of gemcitabine, vinorelbine, and liposomal doxorubicin. Patients without evidence of disease progression proceeded to HDT/ASCT; those with progressive disease were study failures. At a median follow-up of 51 months, EFS analyzed by intent to treat as well as for transplanted patients is 70% and 79%, respectively. Patients transplanted with negative FDG-PET, pre-HDT/ASCT after 1 or 2 SLT programs, had an EFS of > 80%, versus 28.6% for patients with a positive scan (P < .001). This prospective study provides evidence that the goal of SLT in patients with Hodgkin lymphoma should be a negative FDG-PET scan before HDT/ASCT. The study was registered at www.clinicaltrials.gov as NCT00255723. (*Blood*. 2012;119(7): 1665-1670)

Introduction

The standard treatment for relapsed or refractory Hodgkin lymphoma (HL) is high-dose chemoradiotherapy followed by autologous stem cell transplant (HDT/ASCT). The ability of a preceding salvage chemotherapy (SLT) program to produce a response that will document that the disease is still chemosensitive is mandatory. With the use of modern supportive care, transplant-related mortality is minimal and long-term event-free survival (EFS) is approximately 50%.[1,2]Unfortunately, outcome has improved marginally in the past 15 years.[3] The lymphoma disease management team at Memorial Sloan-Kettering Cancer Center (MSKCC) has conducted and reported 4 sequential phase 2 clinical trials in this setting and has made the following observations: accelerated fractionated radiotherapy (RT) can be incorporated safely into transplant-conditioning regimens; ifosfamide, carboplatin, and etoposide (ICE)–based SLT is effective with greater than 80% of patients demonstrating chemosensitive disease; 3 pre-SLT risk factors predict outcome (remission duration < 1 year, B symptoms, and extranodal sites of disease [ENS]); and augmentation of SLT in patients with multiple risk factors appears to improve EFS.[4] Finally, we have proposed that chemosensitive disease should be defined by pretransplant ^{18}fluorodeoxy glucose–positron emission tomography (FDG-PET) status; those patients with a negative scan have a 5-year EFS of 75% compared with 25% for those patients with improvement of CT but with persistent FDG-PET positivity.[4-8] Similar FDG-PET data were recently confirmed by the transplant group from Washington University.[9] The current comprehensive study incorporates non–cross-resistant SLT and individually tailored RT and HDT/ASCT. It builds on the previous programs using 3 pretreatment prognostic factors to risk-adapt SLT, as well as FDG-PET response (negative or positive) to ICE-based therapy to determine whether additional therapy was warranted before HDT/ASCT in an attempt to improve outcome in patients with relapsed or refractory HL.

Methods

After obtaining informed consent, transplant-eligible patients with relapsed or refractory HL were enrolled in MSKCC Institutional Review Board-approved protocol 04-047 (www.clinicaltrials.gov, NCT00255723).

Each patient's eligibility was reviewed at a multidisciplinary lymphoma staging conference. Disease was staged according to the Cotswold Modification of the Ann Arbor system[10] and included an FDG-PET scan. All patients had a repeat biopsy confirming relapsed or refractory HL before enrolling in this study. Primary refractory disease is defined as a repeat biopsy confirming active HL during or at the conclusion of front-line therapy. We stratified patients into 2 risk groups (A and B) based on the previously described risk factor, of remission duration less than 1 year, B symptoms before SLT, and ENS before SLT. Patients with 0 or 1 risk factor were enrolled in Arm A and those with 2 risk factors were enrolled in Arm B. Patients with all 3 risk factors (10% of the relapsed or refractory HL patients) were excluded from this study and treated on another Institutional

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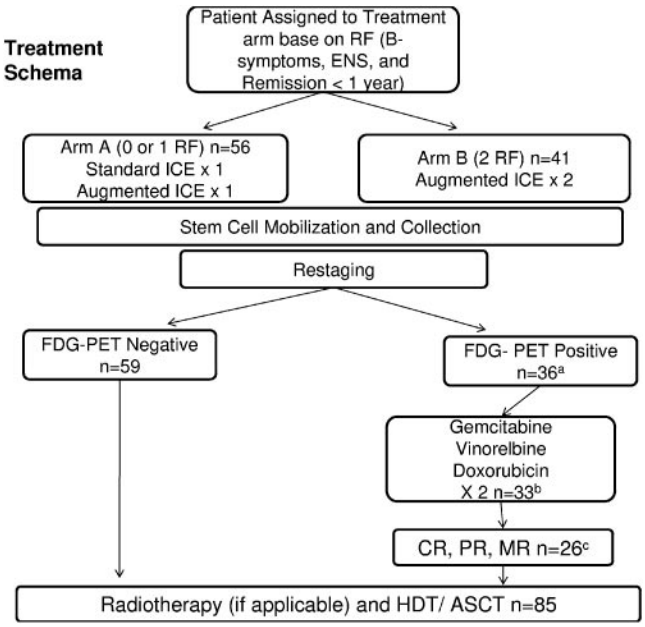

Figure 1. Treatment schema. [a]One patient died of sudden death, and 1 patient did not complete ICE; [b]3 FDG-PET–negative patients did not receive GVD because they progressed on ICE; and [c]2 patients failed to mobilize cells, 3 patients progressed after ICE and GVD, 1 patient had an adverse reaction to liposomal doxil, and 1 patient was treated off study due to physician discretion.

Review Board-approved HL protocol with the intention of proceeding to nonmyeloablative allogeneic stem cell transplant (NMT) as consolidation.

Eligibility criteria included a diagnosis of classic HL confirmed by the Department of Hematopathology at MSKCC. In all cases, primary refractory or relapsed disease was proven by biopsy or fine needle aspiration (cytology) of an involved site. In addition, patients needed to have relapsed or progressed after receiving either a doxorubicin- or nitrogen mustard–containing front-line regimen.

Additional eligibility criteria were as follows: All patients were required to have FDG-PET–positive disease, a cardiac ejection fraction of greater than 45%, measured since last chemotherapy, as well as an adjusted diffusing capacity of greater than 50% on pulmonary function testing, as measured since last chemotherapy was required. In addition, serum creatinine had to be less than or equal to 1.5 mg/dL or, if creatinine more than 1.5 mg/dL, then the measured 12- or 24-hour creatinine clearance must be more than 60 mL/minute; other laboratory values necessary were a neutrophil count more than 1000/μL, platelets more than 50 000/μL, and total bilirubin less than or equal to 2.0 mg/dL in the absence of a history of Gilbert disease. The age range was 18 to 72 years; all patients needed to be hepatitis C virus, hepatitis B virus, and HIV I and II negative. Lastly, patients were not allowed to previously be treated with ifosfamide, carboplatin, cisplatin, gemcitabine, vinorelbine, or liposomal doxorubicin. Patients or their guardians must have been capable of providing informed consent

Treatment

Salvage chemotherapy. Arm A: 1 cycle of ICE followed by 1 cycle of augmented ICE (aICE; this cycle starts 14-21 days after cycle 1 dependent on platelet count recovering to $>$ 50 000; Figure 1).[11] aICE: Ifosfamide (5000 mg/m^2) mixed with Mesna (5000 mg/m^2) IVCI 2 times starting on day 1 carboplatin (area under the curve 5 [maximum dose 800 mg]) IVPB (intravenous piggy back) 1 time on day 3, etoposide (200 mg/m^2) IVPB every 12 hours at 3 doses starting on day 1.

Arm B: 2 cycles of aICE (administered on a 17- to 21-day schedule, platelet count must be $>$ 50 000 for cycle 2 to start). ICE cycles were supported with either filgrastim for 8 days or pegfilgrastim at investigator discretion; however, for peripheral blood progenitor cell mobilization, filgrastim was used. Stem cell mobilization and collection procedures have been previously reported.[6]

Restaging evaluation

Pretreatment FDG-PET scans were reviewed by 1 of 3 nuclear medicine physicians at MSKCC. Patients had a repeat CT and FDG-PET scan after completion of ICE-based therapy. FDG-PET scan was evaluated visually. Positive scans were defined by site of disease as follows: supradiaphragmatic HL, FDG uptake greater than mediastinal blood pool; and infradiaphragmatic HL, FDG uptake greater than abdominal aortic blood pool. All patients with repeat scans that were abnormal were presented by the reference nuclear medicine physician at a multidisciplinary lymphoma staging conference, and the decision to administer gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) was made at that time. Patients with a positive FDG-PET received GVD; those with a negative scan underwent HDT/ASCT.

Extended salvage chemotherapy: GVD

Those patients who progressed on ICE/aICE or whose response remained ^{18}FDG- PET-positive received non–cross-resistant chemotherapy with the GVD regimen (gemcitabine 1000 mg/m^2, vinorelbine 20 mg/m^2, and liposomal doxorubicin 15 mg/m^2) administered every 2 weeks for 4 doses (2 cycles) with pegfilgrastim support. At the conclusion of GVD, patients, again, underwent lymphoma restaging with CT CAP (chest, abdomen, and pelvis) and FDG-PET. Patients who had progressive disease were protocol failures; the rest proceeded to HDT/ASCT.

HDT/ASCT

Patients received 1 of 2 transplant conditioning regimens based on previous RT and the presence of noncontiguous sites of ENS.

IFRT. Patients with residual radiographic disease or initially bulky sites were eligible for accelerated involved field radiation (IFRT) to a dose of 18 to 36 Gy administered as 1.8-Gy twice-a-day fractions. IFRT was given to patients who had received prior radiotherapy but had disease outside of the prior treatment ports. If patients relapsed in the prior RT field, they were ineligible to receive IFRT.

TLI conditioning regimen. Eligibility includes (1) no prior radiation therapy and (2) nodal disease only.

1. Accelerated IFRT to 18-Gy twice-a-day fractions for 5 days (total dose, 18 Gy) when relapsed/refractory disease was limited to 1 or 2 radiation portals.
2. Total lymphoid irradiation (TLI) or STLI (subtotal lymphoid irradiation) administered in 1.8-Gy twice-a-day fractions (total dose, 18 Gy) for 5 days.
3. Cyclophosphamide 900 mg/m^2 every 12 hours for 8 doses (total dose, 7200 mg/m^2).
4. Etoposide 500 mg/m^2 administered as a 24-hour infusion, for 4 doses (total dose, 2000 mg/m^2).

Non-TLI conditioning regimen. (CBV [cyctophosphamide, carmustine, and etoposide]; for patients with prior radiation or contraindication of TLI) was administered as follows:

1. IFRT: administered in 1.8-Gy twice-a-day fractions for 5 to 10 days (total dose, 18-36 Gy) if clinically indicated.
2. Cyclophosphamide 900 mg/m^2 every 12 hours for 8 doses (total dose, 7200 mg/m^2).
3. Etoposide 500 mg/m^2 administered as a 24-hour infusion, for 4 doses (total dose, 2000 mg/m^2).
4. Carmustine 360 mg/m^2 administered on day -2.

Peripheral blood progenitor cells were infused 24 to 36 hours after completion of chemotherapy. The supportive measures for the transplant phase have been previously reported.[6]

Restaging and follow-up

Repeat imaging with CT occurred between days 90 and 100 and then every 6 months through 2 years after ASCT and then at the discretion of the attending physician. FDG-PET scanning was repeated if positive before ASCT and then at the discretion of the attending physician.

Biostatistics

The goal of this phase 2 trial was to determine whether the incorporation of non–cross-resistant chemotherapy followed by a tailored radiation-based transplant conditioning regimen could improve EFS in patients with 0 to 2 risk factors who failed or had a suboptimal response (FDG-PET–positive) to ICE-based chemotherapy before HDT/ASCT. The primary endpoint of this trial was EFS of patients who were FDG-PET–positive after ICE-based therapy, measured from the initiation of GVD until documented progression or death from any cause, including treatment-related mortality.

Sample size calculation was based on the subgroup of patients who would be FDG-PET–positive after ICE-based treatment (and thus informative for the primary endpoint); based on past experience, patients with 0 to 2 risk factors who were FDG-PET–positive after ICE-based chemotherapy achieve a 25% EFS at 3 years. With the addition of GVD as non–cross-resistant chemotherapy for FDG-PET–positive patients after ICE-based chemotherapy as additional debulking before transplant, a 45% EFS at 3 years was defined a priori as a promising result. Accepting a type I error rate of 0.05 and type II error rate of 0.2, 33 FDG-PET–positive patients (after ICE) needed to be accrued onto this study to detect such a difference. To accrue 33 FDG-PET–positive patients after ICE-based chemotherapy, we anticipated a total sample size of between 96 and 100 patients for this trial based on prior experience with risk-adapted ICE-based therapy.

The Kaplan-Meier method was used to describe the EFS in patients who were FDG-PET–positive after ICE. This method was also used to analyze the whole cohort. EFS and overall survival (OS) were analyzed both in an intent to treat of all patients as well as for the transplanted patients alone. Both univariate and multivariate analyses were performed. For the multivariate analysis, only significant factors were retained in the final model, and hazard ratios were estimated from Cox regression models. The rates of grade 3 or 4 (serious toxicity) that required hospitalization were tabulated; grade 1 or 2 toxicities were not captured.

Results

Patient demographics

Ninety-seven patients were enrolled in this intent-to-treat clinical trial; all patients were evaluable for outcome. The median age was 35 years (range, 19-72 years), and 56 (58%) were female. Forty-one patients (42%) had primary refractory disease; and of the 56 patients (58%) who had relapsed HL, 35 (63%) had relapsed within 1 year of primary treatment. At study entry, ENS, B symptoms, or a bulky nodal mass (> 5 cm) was present in 38%, 11%, and 33%, respectively. Primary chemotherapy was ABVD in 79 patients (81%) and 26 patients (27%) received IFRT as a component of their original treatment; of the latter group, 18 (67%) relapsed within the RT field. Fourteen patients had zero risk factors, 41 had 1 risk factor, and 42 had 2 risk factors of the 3 factors (remission duration < 1 year, B symptoms, and ENS; Table 1).

Table 1. Patient characteristics

	Arm A (0-1 RF)	Arm B (2 RF)	Total
Pretreatment			
Patients	56	41	97
Age, y	36.2 (18.7-64.3)	33.1 (21.3-71.5)	35.3 (18.7-71.5)
Female/male	35/21	21/20	56/41
> 5 cm	15	17	32
Previous RT	15	11	26
Relapse in RT field	10	8	18
Refractory	16	25	41
Relapse > 1 year	19	2	21
Relapse < 1 year	21	14	35
ENS	5	32	37
B symptoms	0	11	11
Pre-ASCT			
FDG-PET negative	47	29	76
IFRT/TLI	35	22	56
CBV/IFRT	7	2	9
CBV	8	12	20

Survival analyses

The median follow-up for surviving patients is 51 months (range, 16-86 months). The Kaplan-Meier estimate of OS and EFS by intent to treat, at the median follow-up time, is 80% and 70%, respectively; for the transplanted patients, it was 88% and 79%, respectively (Figure 2); there were no differences in outcome based on transplant conditioning regimen ($P = .141$) Twelve patients were not transplanted per protocol and are study failures. The reasons were as follows: 4 patients progressed after both courses of SLT, 2 patients needed emergent RT after progression on ICE and were then ineligible for GVD, and 1 patient each had the following: sudden death, renal failure, ifosfamide-induced confusion, anaphylaxis during liposomal doxorubicin infusion, and septic shock. All grade 3 or 4 toxicity that required hospitalization is reported in Table 2. One patient underwent an NMT instead of an ASCT because of physician preference. One patient developed myelodysplasia 22 months after his CBV autotransplant.

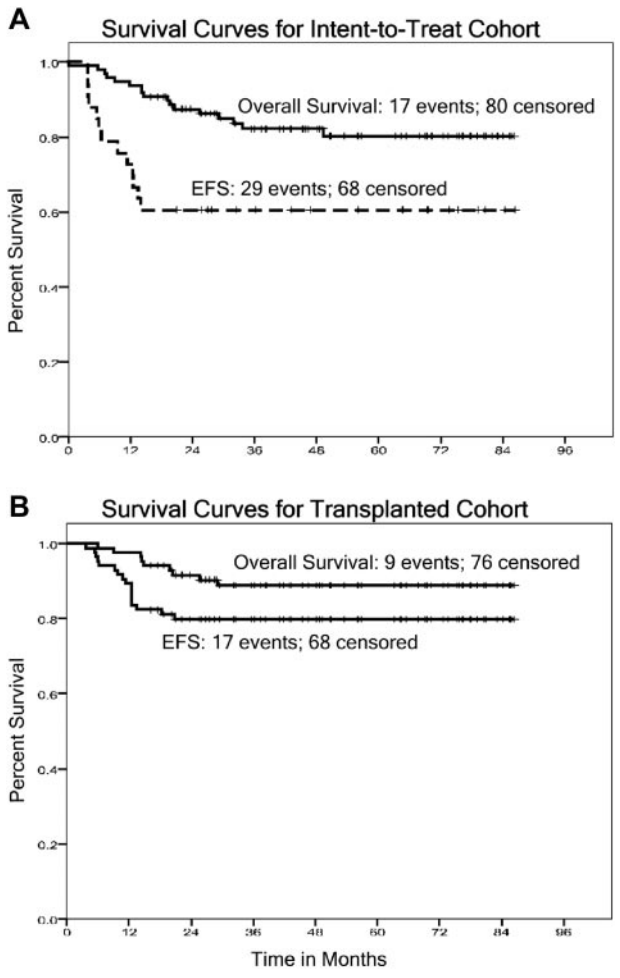

Figure 2. Survival curves. (A) Intent-to-treat cohort. (B) Transplanted cohort.

Table 2. Adverse events

Grade 3 or 4 toxicity*	ICE (56 courses)	aICE (138 courses)	GVD (132 courses)	TLI (56 patients)	CBV (29 patients)
Febrile neutropenia	3	22	0	0	0
Catheter-related infection/thrombosis	1	8	0	0	0
Acute renal failure	1	0	1	0	0
Clostridium difficile	1	0	0	0	2
Viral meningitis	1	0	0	0	0
Pneumonia	1	1	0	0	0
Pulmonary embolism	0	1	0	0	0
Cellulitis	0	1	0	0	0
Anaphylaxis	0	0	1	0	0
Radiation esophagitis	0	0	0	1	0
Depression	0	0	0	1	1
Radiation pneumonitis	0	0	0	1	0
Disseminated zoster	0	0	0	1	0
Autologous graft vs host	0	0	0	1	0
Pericardial tamponade	0	0	0	1	0
Multisystem organ failure	0	0	0	1	0
Myelodysplasia	0	0	0	0	1

*Once a patient failed either ICE or GVD, the patient was taken off study and subsequent treatment was not dictated in the protocol patients.

Response to salvage treatment

Fifty-eight (60%) patients achieved a negative FDG-PET scan after either ICE/aICE: 9 of 14 (64%) with zero risk factors, 28 of 42 (67%) with 1 risk factor, or 2 cycles of aICE- 22 of 41 (54%) with 2 risk factors ($P = .45$ for number of risk factor). Of the 38 patients with a positive interim FDG-PET, 5 did not receive GVD for reasons noted in the previous paragraph. Seventeen (52%) of the remaining 33 patients achieved a negative FDG-PET scan after GVD: 2 of 5 (40%) with zero risk factors, 8 of 12 (67%) with 1 risk factor, and 7 of 16 (44%) with 2 risk factors ($P = .69$). The EFS curves for patients who achieved a negative FDG-PET after ICE/aICE or GVD were superimposable; these patients had a superior EFS compared with those with a positive FDG-PET scan (Figure 3). In addition, the EFS for patients receiving GVD at the median follow-up time of 51 months was 60% (Figure 4) compared with 25% (patients with 0-2 risk factors) in our previous clinical trial for patients who remained FDG-PET–positive after ICE and were transplanted.

Prognostic factor analyses

Univariate analysis of the intent-to-treat patient population determined that 4 factors were associated with an unfavorable outcome: 2 risk factors, tumor bulk more than 5 cm, FDG-PET–positive disease after GVD, and ENS (Tables 3 and 4). Interestingly, there was no difference in EFS ($P = .079$) or OS ($P = .28$) for relapsed versus primary refractory disease. However, in multivariate analysis, only FDG-PET–positive disease and ENS involvement remained statistically significant. Three cohorts emerged with distinct outcomes based on the combination of factors: FDG-PET–negative without ENS of disease, FDG-PET–negative with ENS of disease, and FDG-PET–positive, regardless of ENS of disease (Figure 5).

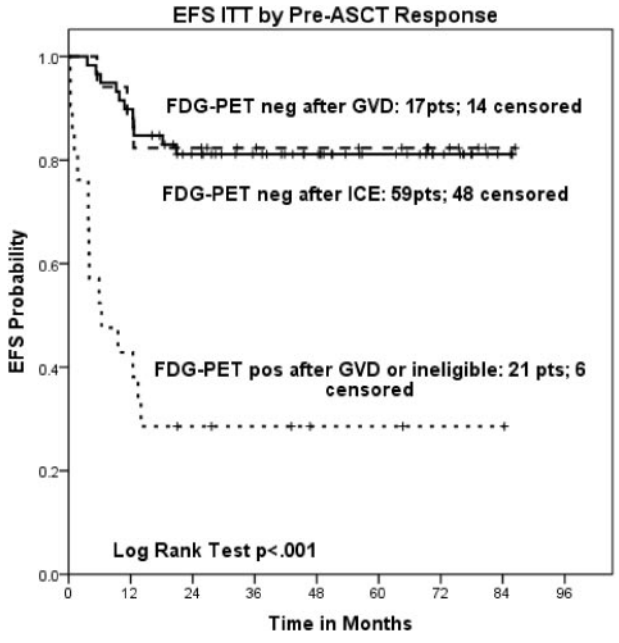

Figure 3. EFS intent to treat by pre-ASCT response.

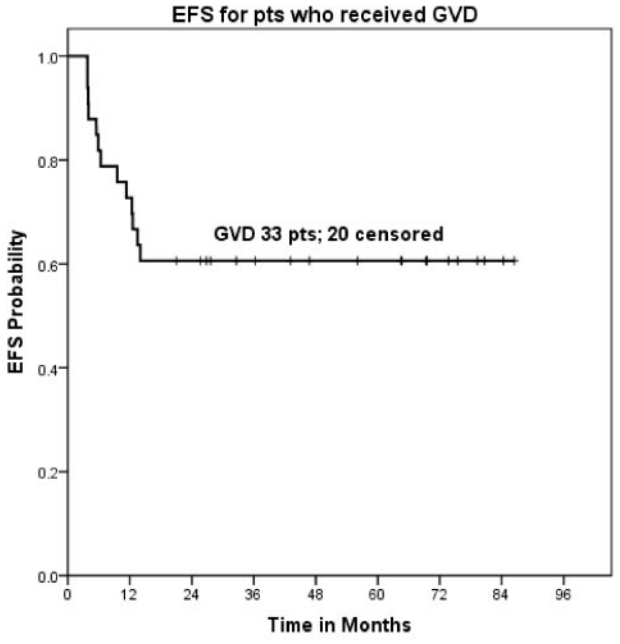

Figure 4. EFS for patients who received GVD.

Table 3. EFS: intent-to-treat cohort (single variable analysis)

Factor	*P* (log-rank)
Risk factors (0 and 1 vs 2)	.01
Bulky > 5 cm	.047
FDG-PET (positive vs negative)	< .0001
Extranodal sites	.037
Relapse/refractory	.079
B symptoms	.699

Discussion

Despite a high curability rate, approximately 25% of patients with HL have relapsed or refractory disease.[12] Multiple publications have confirmed that prognostic factors before SLT can predict for EFS and OS, but there is little information in the literature addressing risk-adapted approaches for such patients. Previously, we demonstrated that the quality of response to ICE-based SLT predicted for outcome after HDT/ASCT. In that study, patients proceeded to HDT/ASCT as long as they had achieved even a minor response based on either CT or functional imaging (FI, either FDG-PET or gallium scan). In a Cox regression model, the only factor that predicted an unfavorable outcome in the transplanted patients was a pre-HDT/ASCT–positive FI; the hazard ratio for EFS was 4.61. [6]ICE-based (ICE or augmented ICE) treatment was assigned based on previously identified risk factors (remission duration of < 12 months, B symptoms, and ENS of disease). Patients with favorable disease (0 or 1 risk factor) were more likely to respond to SLT by achieving a negative FI than patients with unfavorable disease (2 or 3 risk factors). However, if pre-HDT/ASCT FI was positive, the EFS was poor regardless of the initial risk group. Conversely, the same favorable outcome was seen in both favorable (0 or 1 risk factor) and unfavorable patients (2 or 3 risk factors) who achieve a negative pre-HDT/ASCT FI. These results were surprising and led to the design of the current clinical trial.

We hypothesized that a patient with persistent [18]FDG-PET–positive disease after 2 cycles of ICE-based SLT would achieve little benefit with the addition of more of the same chemotherapy. At the time of protocol initiation, the CALGB had recently reported their promising phase 1 or 2 results with GVD.[13] It had been our experience that a biweekly schedule of this therapy was better tolerated, and we used that schema as consolidation in ICE incomplete responders (those patients with a persistently positive FDG-PET scan). It must be stressed that nearly all of the patients in this study had chemosensitive disease on CT imaging after ICE/aICE and in most centers would have been eligible for HDT/ASCT. Indeed, outside of this clinical trial, our group would also have recommended for these patients to proceed directly to HDT/ASCT. Indeed, it was possible that the 2 months needed for patients to receive GVD might make some patients transplant-ineligible secondary to progression of disease or chemotherapy-induced side effects. We allowed patients to receive HDT/ASCT as long as they did not have evidence of disease progression on GVD (ie, even if their HL remained [18]FDG-PET–positive). Interestingly, 2 patients were transplanted and are event-free despite progression

Table 4. EFS: intent-to-treat cohort (multivariate analysis)

Factor	HR	*P* (Cox)
FDG-PET (positive vs negative)	7.61	< .0001
Extranodal sites	2.61	.011

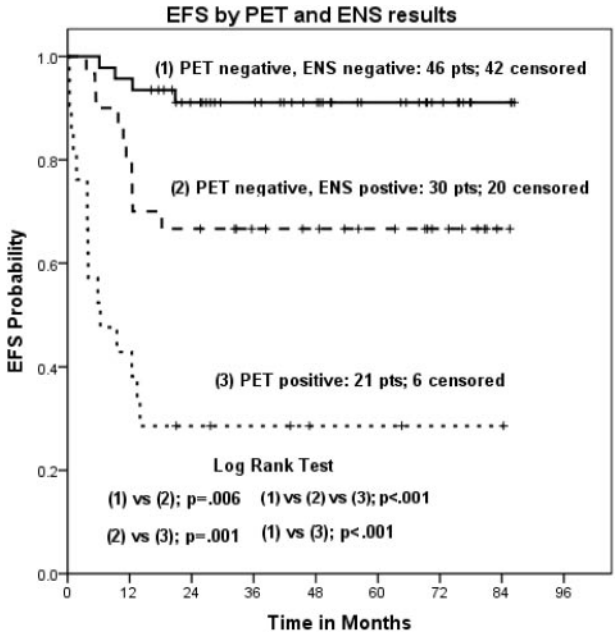

Figure 5. EFS by PET and ENS results.

on our sequential salvage chemotherapy strategy because of a complete response to involved-field radiotherapy; however, by study definition, these patients failed our intent-to-treat program.

The results reported herein demonstrate that attainment of FDG-PET–negative status is a major factor in the determination of outcome. The finding that the outcome for patients receiving GVD and having a FDG-PET–negative result is indistinguishable from patients with ICE-based therapy induced FDG-PET–negative response argues that quality of response is an important determinant of outcome. The multivariate analysis provides guidance for physicians in deciding whether patients will benefit from immediate HDT/ASCT after salvage therapy or whether other treatment options offer a greater chance of survival. Patients with persistent FDG-PET positivity after SLT have a poor outcome with HDT/ASCT, and either an attempt of obtaining response with IFRT (if feasible) or investigative approaches are necessary.

NMT has dramatically decreased the nonrelapse mortality after allogeneic stem cell transplantation for HL, although relapse remains the greatest challenge. A recent report by Peggs et al using donor lymphocyte infusion after a T cell–depleted NMT had an impressive 4-year EFS of 59%; however, remission at the time of NMT remains the most important prognostic factor for this modality of therapy.[14] There are now a number of new agents, including brentuximab vedotin,[15] bendamustine, panobinostat, everolimus, or lenalidomide, that can be used as a potential bridge to a NMT.[16] Administering these agents alone or in combination to achieve an FDG-PET–negative response can be followed by referral to an allogeneic stem cell transplant center.

A patient with nodal disease that remains FDG-PET–positive after SLT in a site that has not been previously irradiated is a unique subset of HL. We have used IFRT in daily fractions as a "salvage therapy" for these patients. Notably, 2 patients in this study who failed SLT achieved an FDG-PET–negative state with IFRT, were auto-transplanted, and probably cured (although they are counted as treatment failures for this analysis). The administration of IFRT has been an independent predictor for EFS in all of our previous reports as well as for the transplanted-only patients in this study ($P = .045$); however, the true role of IFRT in this setting remains

controversial because we select patients for this therapeutic modality based on disease distribution and treatment history. Multiple previous reports have determined that patients who have not received IFRT as part of their initial or SLT for HL are more likely to relapse at previous sites of bulky nodal involvement, which we define as a single nodal mass of at least 5 cm. The true role of IFRT as part of transplant conditioning regimens for HL can only be answered by a randomized study, which is unlikely to be done because of patient numbers. Yet, our results support the incorporation of IFRT in HL salvage programs.

Lastly, patients who are FDG-PET–negative after SLT can be divided into 2 groups based on disease distribution: nodal versus ENS. Greater than 90% of patients with nodal only relapsed or refractory HL are cured with our approach. It is of value to investigate whether reducing the intensity of SLT for these patients before HDT/ASCT will maintain these excellent results while at the same time improve quality of life compared with standard SLT. The second group (those with nodal and ENS) have a 67% EFS in this study. The focus of our research program for these patients is to investigate novel post-HDT/ASCT maintenance strategies.

In conclusion, we have developed a novel SLT strategy for transplant-eligible relapsed or refractory a HL patients that is curative in nearly 70% of patients, excluding the 10% of HL patients with all 3 risk factors. In 2011, we cannot use principles developed 25 years ago to determine transplantation eligibility. Response criteria have changed, and new agents are available. We can now identify a group of patients with an EFS of less than 25% by either pre-SLT risk factors or post-SLT response; investigation of novel approaches that includes brentuximab vedotin combined with SLT or early NMT is warranted in this group.

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Authorship

Contribution: C.H.M., A.D.Z., and J.Y. designed and performed research, analyzed data, enrolled patients in the study, and wrote the paper; M.J.M. and A.J.M. analyzed data, enrolled patients in the study, and wrote the paper; S.D.N. designed and performed research and wrote the paper; J.G., P.H., S.H., A.N., L.P., M.-A.P., C.P., and D.S. enrolled patients in the study and wrote the paper; and J.C.M. and H.S. analyzed data and wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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