Original Article

Pretransplantation [18-F]Fluorodeoxyglucose Positron Emission Tomography Scan Predicts Outcome in Patients With Recurrent Hodgkin Lymphoma or Aggressive Non-Hodgkin Lymphoma Undergoing Reduced-Intensity Conditioning Followed by Allogeneic Stem Cell Transplantation

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BACKGROUND: The use of positron emission tomography (PET) scanning in Hodgkin lymphoma (HL) and aggressive non-Hodgkin lymphoma (HG-NHL) has recognized prognostic value in patients who are receiving chemotherapy or undergoing autologous stem cell transplantation (SCT). In contrast, the role of PET before reduced-intensity conditioning (RIC) and followed by allogeneic SCT has not been investigated to date. **METHODS:** PET was used to assess 80 patients who had chemosensitive disease (34 patients with HG-NHL and 46 patients with HL) before they underwent allogeneic SCT: 42 patients had negative PET studies, and 38 patients had positive PET studies. Patients underwent allograft from matched related siblings (n = 41) or alternative donors (n = 39). **RESULTS:** At the time of the last follow-up, 48 patients were alive (60%), and 32 had died. The 3-year cumulative incidence of nonrecurrence mortality and disease recurrence was 17% and 40%, respectively. The cumulative incidence of disease recurrence was significantly lower in the PET-negative patients (25% vs 56%; $P = .007$), but there was no significant difference between the patients with or without chronic graft-versus-host disease ($P = .400$). The patients who had negative PET studies before undergoing allogenic SCT also had significantly better outcomes in terms of 3-year overall survival (76% vs 33%; $P = .001$) and 3-year progression-free survival (73% vs 31%; $P = .001$). On multivariate analysis, overall survival was influenced by PET status (hazard ratio [HR], 3.35), performance status (HR, 5.15), and type of donor (HR, 6.26 for haploidentical vs sibling; HR, 1.94 for matched unrelated donor vs sibling). **CONCLUSIONS:** The current results indicated that PET scanning appears to be an accurate tool for assessing prognosis in patients who are eligible for RIC allografting. ***Cancer* 2010;116:5001–11.** *© 2010 American Cancer Society.*

KEYWORDS: positron emission tomography, allogeneic transplantation, Hodgkin lymphoma, aggressive non-Hodgkin lymphoma.

Patients with Hodgkin lymphoma (HL) or aggressive non-Hodgkin lymphoma (NHL) who develop disease recurrence after autologous stem cell transplantation (SCT) or who have refractory disease often are candidates for allogeneic SCT (alloSCT). The use of reduced-intensity conditioning (RIC) regimens followed by alloSCT has been investigated

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mainly in such patients or those with comorbidities; however, although the majority of studies have reported a reduction in nonrecurrence mortality (NRM), the risk of disease recurrence remains considerable.

All of the published studies in patients with HL who underwent RIC alloSCT reported 2-year progression-free survival (PFS) rates of 30% to 40% with better long-term outcomes in patients who had chemosensitive disease or who developed chronic graft-versus-host disease (GVHD).[1-3] RIC regimens also have been investigated in patients with aggressive lymphomas: Most of those studies included various B-cell and T-cell histotypes, and the estimated 3-year PFS rates have been 15% to 20% in patients with chemoresistant disease and 45% to 55% in patients with chemosensitive disease.[4-7]

Chemosensitivity is 1 of the most important prognostic factors affecting final outcomes in patients who receive myeloablative conditioning, and is also important for patients who receive RIC regimens. We recently demonstrated better overall survival (OS) and PFS in patients with lymphoma who underwent an allograft in complete remission compared with the survival of patients who underwent transplantation in partial remission or with refractory disease.[8]

Because RIC regimens involve less chemoradiotherapy and rely more on the so-called graft-versus-tumor effect that takes several months to occur, it is important to know whether residual disease is present at the time of alloSCT. Over the last 10 years, it has been established that 18-fluoro-deoxyglucose (FDG)-positron emission tomography (FDG-PET) is useful in the pretreatment staging, therapeutic monitoring, and post-therapeutic evaluation of patients with lymphoma. It is highly sensitive and specific in HL and in the majority of aggressive lymphoma subtypes, and it is noteworthy that the results are predictive of outcome in patients with recurrent HL or NHL who receive high-dose chemotherapy and undergo autologous SCT.[9-11] The objective of the current retrospective study was to assess the prognostic role of FDG-PET in patients with chemosensitive HL or aggressive NHL before RIC alloSCT.

MATERIALS AND METHODS

Patient Characteristics

Between May 2001 and December 2007, 80 patients were enrolled retrospectively in a study that involved departments of hematology from 4 Italian institutions; although the period of enrolment was 6 years, the majority of patients (63 of 80; 79%) received allografts between 2004 and 2007. The patients were selected from the database of each department of hematology if they meet the following criteria: 1) patients with recurrent HL or aggressive NHL who had a clinical response (complete or partial remission) to salvage therapy; 2) patients who were eligible for RIC alloSCT from related or alternative donors; 3) patients who had FDG-PET studies obtained in addition to contrast-enhanced computed tomography (CT) studies no more than 60 days before starting the RIC regimen. The median time interval between the last salvage therapy and FDG-PET was 30 days (range, 6-60 days).

Approval was obtained from the institutional review boards of the participating centers, and all patients provided written informed consent. Tables 1 and 2 summarizes the patient characteristics. The median age patient was 36 years (range, 17-65 years). Forty-six patients had HL, and 34 patients had NHL, including 22 with diffuse large B-cell lymphoma (DLBCL) and 12 with T-cell NHL (T-NHL) (11 peripheral T-cell lymphomas and 1 lymphoblastic T cell lymphoma). Sixty-four patients (80%) had failed a previous autologous SCT (42 patients with HL and 22 patients with NHL). The population included 12 patients with primary refractory disease who underwent a tandem autologous SCT and alloSCT. Only a few patients had bulky disease before salvage therapy (10%).

Salvage Therapy and Conditioning Regimens

Different salvage therapies were used and are summarized in the Table 1. Forty-three patients received grafts from related siblings (41 from matched siblings and 2 from 1-antigen mismatched, related siblings), 20 patients received grafts from matched unrelated donors (MUDs), and 17 patients received grafts from haploidentical family donors. Thirty patients (69%) who received allografts from related siblings also received an RIC regimen containing thiotepa (10 mg/kg), cyclophosphamide (60 mg/kg), and fludarabine (60 mg/m^2)[8]; 8 patients received a combination of fludarabine (90 mg/m^2) and cyclophosphamide (900 mg/m^2); and 5 patients received a combination of treosulfan (42 g/m^2) and fludarabine (150 mg/m^2). In case of related siblings, GVHD prophylaxis consisted of cyclosporine A adjusted to maintain blood levels of 200 to 300 ng/mL and a short course of methotrexate (10 mg/m^2 on Day +1 and 8 mg/m^2 on Days +3 and +6).

Twelve patients who received allografts from MUD donors also received a combination of thiotepa (10 mg/kg) and cyclophosphamide (100 mg/kg); 3 patients received a combination of fludarabine (150 mg/m^2) and

Table 1. Patient Characteristics

Characteristic	No. of Patients (%) HL, n = 46	Aggressive NHL, n = 34
Median age at AlloSCT [range], y	30 [17-55]	48 [17-61]
Median time from diagnosis to AlloSCT [range], mo	41 [11-170]	19 [5-87]
No. of previous therapy lines		
≤2	17 (37)	19 (56)
>2	29 (63)	15 (44)
Previous AutoSCT	42 (91)	22 (65)
Time to AutoSCT-AlloSCT, mo[a]		
≤12	20 (47)	14 (64)
>12	22 (53)	8 (36)
Donor type		
HLA-matched sibling	27 (58)	16 (47)
MUD	7 (16)	13 (38)
Haploidentical	12 (26)	5 (15)
Salvage therapies before AlloSCT		
Cisplatin-based: Gem/cisplatin, DHAP	13 (28)	6 (18)
IGEV	6 (13)	—
MOPP	4 (9)	—
Anthracycline-based: CHOP/CNOP	—	4 (12)
High-dose cytarabine	13 (28)	13 (38)
AutoSCT	7 (15)	5 (15)
Others therapies	3 (7)	6 (17)

HL indicates Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; AlloSCT, allogeneic stem cell transplantation; AutoSCT, autologous stem cell transplantation; HLA, human leukocyte antigen; MUD, matched unrelated donor; Gem, gemcitabine; DHAP, dexamethasone, cisplatin, and cytarabine; IGEV, ifosfamide, gemcitabine, vinorelbine, and prednisolone; MOPP, mechloretamine, vincristine, prednisone, and procarbazine; CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisone; CNOP, cyclophosphamide, mitoxantrone, vincristine, and prednisone.

[a] Data were available only for patients who underwent AutoSCT.

melphalan (140 mg/m^2); and 5 patients received a combination of treosulfan and fludarabine. The grafts were depleted of T cells using rabbit antithymocyte globulin (thymoglobulin 3.5 mg/kg daily on Days −4 and −3). Post-transplantation GVHD prophylaxis consisted of cyclosporine A and a short course of methotrexate (10 mg/m^2 on Day +1 and 8 mg/m^2 on Days +3 and +6).

All 17 patients who received allografts from haploidentical donors received conditioning with thiotepa (10 mg/kg), cyclophosphamide (60 mg/kg), and fludarabine (120 mg/m^2) along with total-body irradiation (2 grays); CD34-positive cell selection and alemtuzumab treatment (15 mg/m^2 on Day −2) were used for ex vivo and in vivo T-cell depletion.[12] Those patients did not receive any GVHD prophylaxis. Acute GVHD was defined on the basis of the criteria published by Glucksberg et al, and

Table 2. Patient Characteristics According to [18-F]Fluorodeoxyglucose-Positron Emission Tomography

Variable	No. of Patients (%) FDG-PET Negative, n = 42	FDG-PET Positive, n = 38
Median age at AlloSCT [range], y	37 [17-59]	36 [17-65]
Karnofsky performance status		
≥80%	36 (86)	26 (68)
<80%	6 (14)	12 (32)
Histology		
HL	23 (55)	23 (61)
Aggressive NHL[a]	19 (45)	15 (40)
Time from diagnosis to AlloSCT, mo		
≤24	21	16
>24	21	22
Previous therapy lines		
≤2	22	13
>2	20	25
Previous AutoSCT	33 (79)	31 (82)
Extranodal disease		
Yes	12 (29)	11 (29)
No	29 (69)	27 (71)
NA	1 (2)	—
Bulky disease		
Yes	3 (7)	5 (13)
No	38 (91)	33 (67)
NA	1 (2)	—
CT results		
CR	21 (50)	8 (21)
PR	17 (40)	27 (71)
NA	4 (10)	3 (8)
Time to AutoSCT-AlloSCT, mo		
≤12	17 (52)	17 (55)
>12	16 (48)	14 (45)
Donor sex		
Male patient/female donor	8 (19)	10 (26)
Other combinations	34 (81)	28 (74)
Donor type		
HLA-matched sibling	24 (57)	19 (50)
MUD	10 (24)	10 (26)
Haploidentical	8 (19)	9 (24)

FDG-PET indicates [18-F]fluorodeoxyglucose positron emission tomography; AlloSCT, allogeneic stem cell transplantation; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; AutoSCT, autologous stem cell transplantation; NA, not available; CT, total body computed tomography; CR, complete remission; PR, partial remission; HLA, human leukocyte antigen; MUD, matched unrelated donor.

[a] In total, there were 13 patients with diffuse large B-cell lymphoma (DLBCL) and 6 patients with T-cell NHL (T-NHL) in the FDG-PET–negative group and 9 patients with DLBCL and 6 patients with T-NHL in the FDG-PET–positive group ($P = 0.72$). Aggressive NHL categorized according to the International Prognostic Index was well balanced in the FDG-PET–negative and FDG-PET–positive groups ($P = .75$).

chronic GVHD was classified as limited or extensive on the basis of the criteria of Sullivan et al.[13,14]

Staging Procedure and FDG-PET Imaging

Disease status before and after alloSCT was assessed by means of a physical examination, blood chemistry, contrast-enhanced CT, bone marrow biopsy (when clinically indicated), and FDG-PET imaging (FDG-PET/CT from 2004 onward). PET/CT is more sensitive and specific than contrast-enhanced CT for the evaluation of lymph node and extranodal lymphomatous involvement.

Clinical response was evaluated on the basis of the criteria published by Cheson et al.[15] These older criteria were used because the patients received allografts before December 2007, and new criteria were defined in 2007.

Whole-body FDG-PET imaging was performed using a General Electric Discovery LS 2-dimensional mode (GE Medical Systems, Waukesha, Wis) in 59 patients (74%), a Siemens Biograph Duo LSO 3-dimensional mode in 11 patients, and a Siemens Eccat Accel 3-dimensional mode in 10 patients (Siemens Healthcare, Erlangen, Germany). After the patients had refrained from eating or drinking for at least 6 hours, all 2-dimensional (2D) or 3D FDG-PET scans were performed with the injection of approximately 370 megabecquerels of 18-fluorodeoxyglucose (18-FDG). After a 60-minutes uptake period, a CT scout was acquired to define the body axial extension to be imaged (from the pelvis to the base of the skull); then, a helical CT scan was acquired during shallow breathing. At the end of the CT scan, the bed position was translated into the FDG-PET field of view for the acquisition of FDG-PET data of whole-body tracer distribution, and the FDG-PET images were reconstructed using an interative algorithm.

The images were reviewed by 3 experienced nuclear medicine physicians who were blinded to the patients' clinical, radiologic, and follow-up data. The PET scans from each patient recorded before and after alloSCT were obtained in the same department of nuclear medicine.

The FDG-PET scans were interpreted using the criteria of Juweid et al.[16] Briefly, a positive scan was defined as visually analyzed focal or diffuse FDG uptake above the background (mediastinal blood pool activity is recommended as the reference background activity) in a location incompatible with normal anatomy/physiology.[16]

Study Endpoints and Statistical Analysis

The objective of this study was to evaluate the role of FDG-PET in predicting the risk of disease recurrence and NRM, PFS, and OS. The OS and PFS curves were estimated using the Kaplan-Meier method and were compared using log-rank tests, and Cox regression models were used for multivariate analyses. Crude cumulative incidence curves of disease recurrence and NRM were estimated in a competing risk framework[17]: When analyzing NRM, disease recurrence was regarded as a competing event, and vice versa. Univariate comparisons of the cumulative incidence curves were made by means of the Gray test,[18] and Fine and Gray models were applied for multivariate analyses.[19] Age was modeled as a continuous variable using 3-knot, restricted cubic splines.[20]

The effect of chronic GVHD on the cumulative incidence of disease recurrence was investigated by using the "semilandmark" analysis described by Baron et al[21] with a landmark time of 5 months (the modal time of chronic GVHD onset in our case series). Chronic GVHD also was included as a time-dependent variable in a multivariate Cox analysis of its prognostic effect on OS, and the model also included FDG-PET status and the type of donor as covariates. A multivariate binary logistic model was used to test the dishomogeneity between the FDG-PET-negative and FDG-PET-positive groups in relation to common characteristics, the effects of which were tested in 2-sided Wald tests.

RESULTS

CT and FDG-PET Results

Before alloSCT, 42 patients had negative FDG-PET results, and 38 patients had positive FDG-PET results. The series included 12 patients with primary refractory disease who received a tandem autologous and alloSCT (including 8 patients with negative FDG-PET results, and 4 patients with positive FDG-PET results). The 2 groups were well balanced in terms of pretransplantation characteristics among the variables listed in Table 2.

CT results were statistically significant ($P = .008$) only in the multivariate logistic model. Moreover, the number of patients with DLBCL and T-NHL and the International Prognostic Index (IPI) for each were well balanced between the 2 groups (FDG-PET-negative, 13 DLBCLs and 6 T-NHLs; FDG-PET-positive, 9 DLBCLs and 6 T-NHLs; $P = .72$), with IPI scores ≥ 2 for 13 FDG-PET-negative patients and for 11 FDG-PET-positive patients ($P = .75$).

Thirty-three patients and 31 patients underwent previous autologous SCT in the FDG-PET-negative and FDG-PET-positive groups, respectively. The number of

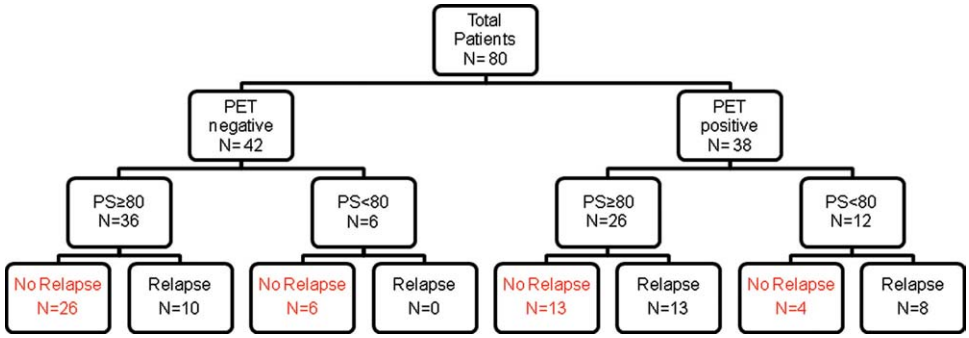

Figure 1. Patient outcomes according to functional imaging are illustrated. PET indicates positron emission tomography; PS: performance status.

patients who developed recurrent disease within 1 year of autograft was not statistically significant.

Before the allograft, 21 of 42 FDG-PET-negative patients (50%) were in complete remission (CR), and 17 of 42 patients (41%) were in partial remission (PR) as assessed by contrast-enhanced CT. The corresponding proportions among the 38 FDG-PET-positive patients were 8 patients in CR (21%) and 27 patients in PR (71%).

The CT results (CR vs PR) did not significantly affect PFS ($P = .232$) or OS ($P = .356$). Because the CT results (CR vs PR) were not significant in univariate analysis, this variable was not included in the multivariate analysis.

Four PET-negative patients and 3 PET-positive patients were identified as chemosensitive during salvage therapy and, thus, did not have repeat CT studies at the time of FDG-PET evaluation. Twenty-seven of 38 PET-positive patients (71%) had multiple FDG uptake sites, and 11 PET-positive patients had only 1 FDG uptake site. Seven of those 11 patients developed disease recurrence after alloSCT; in only 1 of the remaining 4 patients, it is possible that the focal FDG uptake was a false-positive.

Of the 42 PET-negative patients, 32 patients (76%) did not develop disease recurrence: Twenty-seven patients remained alive and in CR after a median of 37 months of follow-up (range, 6-89 months), and 5 patients (3 with HL and 2 with NHL) died of other causes while in remission. The remaining 10 patients (24%) developed disease recurrence a median of 6 months after alloSCT (4 patients died of disease, and 6 patients remained alive). Twenty-one of the 38 PET-positive patients (55%) developed disease recurrence: Fifteen of those patients died of progressive disease, and 6 patients remained alive (all but 1 with chronic GVHD). Of the 17 patients (44%) who did not develop disease recurrence, 8 died of NRM a median of 3 months after alloSCT, and 9 remained alive (only 1 patient had a low performance status, 4 patients experienced limited chronic GVHD, and all patients had a low maximum standardized uptake value) (Fig. 1).

Lymphoma Recurrence

The disease recurred or progressed in 31 of 80 patients and was the cause of death for 19 patients. At a median follow-up of 37 months (interquartile range, 21-51 months), the 1-year and 3-year crude cumulative incidence (CCI) of disease recurrence was37% (95% confidence interval [CI], 28%-50%) and 40% (95%CI, 31%-54%), respectively, indicating that disease recurred during the first year after alloSCT.

Preallograft FDG-PET status significantly influenced the 3-year CCI of disease recurrence, which was 25% in the PET-negative group and 56% in the PET-positive group ($P = .007$) (Fig. 2). There was a trend toward a reduced risk of disease recurrence in the patients who received allografts from alternative donors, with 3-year CCIs of 19% (95%CI, 6%-57%) for those who had haploidentical donors, 31% (95%CI, 15%-61%) for those with MUDs, and 53% (95%CI, 40%-72%) for those with matched related siblings ($P = .050$).

In a Fine and Gray multivariate model that included preallograft FDG-PET status, performance status, patient age, the type of lymphoma, the type of donor, the number of previous therapies, failed autologous SCT, and the time interval between diagnosis and alloSCT, only FDG-PET status ($P = .008$) and the type of donor ($P = .018$) significantly influenced the CCI of disease recurrence.

Separate analyses of the outcomes for patients with NHL and patients with HL indicated that patients with NHL who had positive pretransplantation FDG-PET

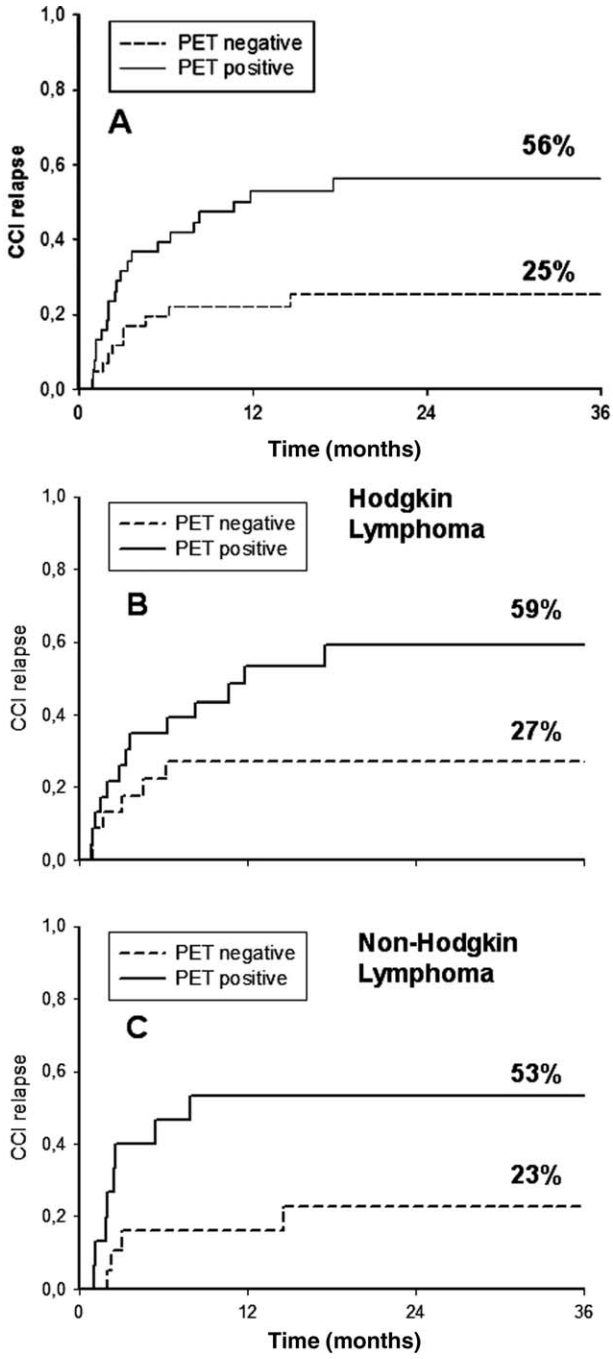

Figure 2. The cumulative incidence of disease recurrence is illustrated according to [18-F]fluorodeoxyglucose positron emission tomography (PET) status before allogeneic stem cell transplantation. (A) The crude cumulative incidence (CCI) of disease recurrence is illustrated for all patients. (B) The CCI of disease recurrence is illustrated for patients with Hodgkin lymphoma. (C) The CCI of disease recurrence is illustrated for patients with non-Hodgkin lymphoma.

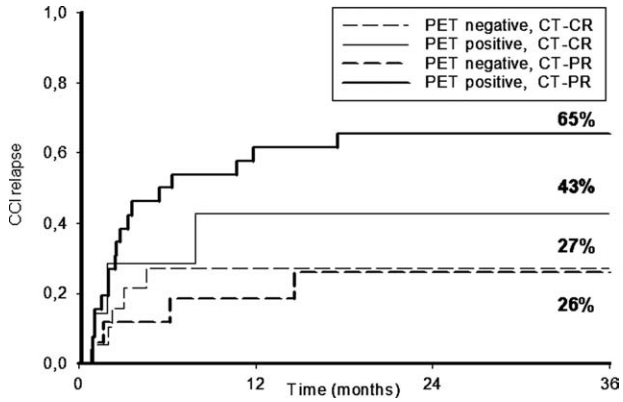

Figure 3. The crude cumulative incidence (CCI) of disease recurrence is illustrated according to [18-F]fluorodeoxyglucose positron emission tomography (PET) status and the results from contrast-enhanced total body computed tomography (CT). CT-CR indicates complete remission as assessed by means of contrast-enhanced total body CT; CT-PR, partial remission as assessed by means of contrast-enhanced total body CT.

scans were at increased risk of disease recurrence (3-year CCI of disease recurrence, 53%; 95%CI, 32%-89%) compared with those who had negative scans (3-year CCI of disease recurrence, 23%; 95%CI, 9%-56%; $P = .049$). The corresponding rates for patients with HL who had positive FDG-PET scans were 59% (95%CI, 41%-86%) and 27% (95%CI, 13%-55%; $P = .066$) (Fig. 2). In addition, the 3-year CCI of disease recurrence did not differ significantly between patients with DLBCL and patients with T-NHL (37% vs 35%, respectively; $P = .99$). When the CT and FDG-PET results were combined, the 3-year CCI of disease recurrence was 27% for CT/PET-negative patients in CR, 43% for CT/PET-positive patients in CR, 26% for CT/PET-negative patients in PR, and 65% for CT/PET-positive patients in PR ($P = .033$, Fig. 3).

OS, PFS, and NRM

The median follow-up for the population as a whole was 37 months (interquartile range, 21-51 months). At the last follow-up, 48 patients remained alive (60%), and 32 patients had died. The 3-year OS and PFS estimates were 55% (range, 43%-66%) and 54% (range, 41%-65%), respectively.: In the HL and NHL groups, the OS estimates were 56% (38%-70%) and 52% (33%-67%), respectively; and the PFS estimates were 51% (34%-65%) and 58% (38%-73%), respectively. In addition, the subtype of aggressive lymphoma did not significantly affect PFS or OS (3-year PFS, 60% vs 57%; $P = .76$; 3-year OS, 56% vs 47%; $P = .34$) for DLBCL and T-NHL, respectively.

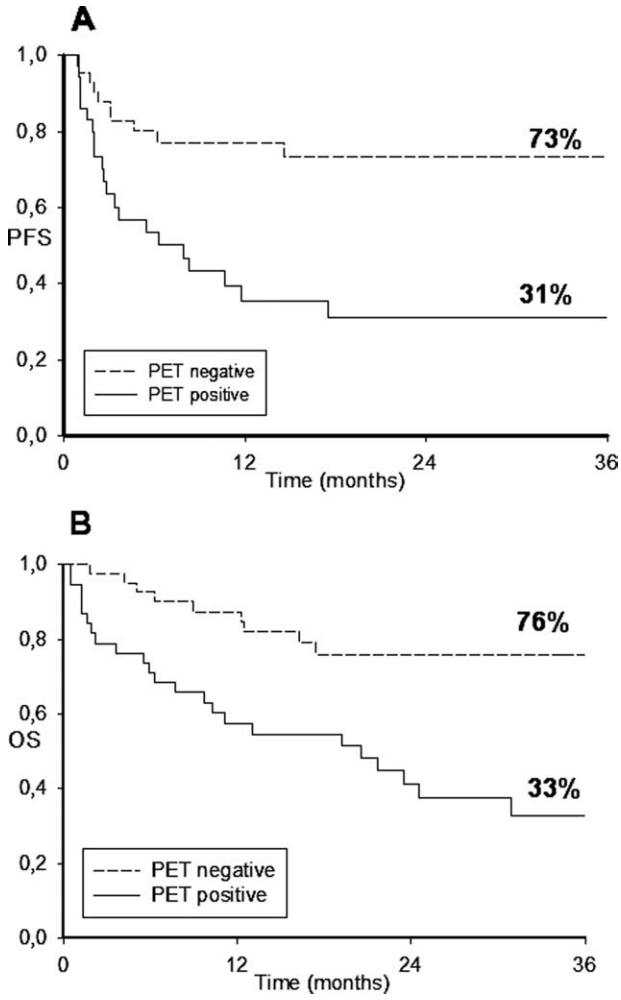

Figure 4. These Kaplan-Meier curves illustrate (A) progression-free survival (PFS) and (B) overall survival (OS) according to [18-F]fluorodeoxyglucose positron emission tomography PET) status.

The PET-negative patients had significantly better outcomes, including a 3-year OS rate of 76% versus 33% for PET-positive patients ($P < .001$) and a 3-year PFS rate of 73% versus 31% for PET-positive patients ($P < .001$) (Fig. 4). The corresponding rates were 82% (58%-93%) versus 28% (8%-52%; $P = .006$) and 72% (47%-86%) versus 30% (11%-52%; $P = .027$) in the HL group, and 69% (40%-86%) versus 33% (12%-56%; $P = .022$) and 76% (48%-91%) versus 34% (11%-60%; $P = .009$) in the NHL group.

In the multivariate Cox model for OS, a positive FDG-PET scan before alloSCT and a poor performance status were independent adverse prognostic factors with a hazard ratio (HR) of 3.35 (95%CI, 1.49-7.52; $P = .003$) and 5.15 (95%CI, 2.19-12.11; $P = .0002$), respectively (Table 3). In addition, significantly shorter survival was associated with the use of an MUD (HR, 1.94; 95%CI, 0.78-4.83) or a haploidentical donor (HR, 6.26; 95%CI, 2.03-19.27; $P = .0048$). The other prognostic factors did not significantly affect outcomes. In the subgroup of patients who had failed a previous autograft, the time since autograft (<12 months or >12 months) did not affect OS in the multivariate analysis.

A positive FDG-PET scan before alloSCT and a poor performance status also were associated with inferior PFS in a multivariate Cox model (positive FDG-PET: HR, 3.03; (95%CI, 1.59-5.76; $P = .0007$; poor performance status: HR, 2.38; 95%CI, 1.16-4.89; $P = .0187$). However, the type of donor had no impact on PFS.

In an analysis that was restricted to 68 patients by excluding those who underwent tandem autologous-alloSCT, the same variables were associated with a worse PFS (positive FDG-PET: HR, 2.56; 95%CI, 1.26-5.21; $P = .0096$; poor performance status: HR, 3.15; 95%CI, 1.36-7.29; $P = .0074$) and OS (positive FDG-PET: HR, 2.61; 95%CI, 1.10-6.21; $P = .0296$; poor performance status: HR, 5.87; 95%CI, 2.27-15.17; $P = .0003$) whereas the type of donor affected only OS ($P = .013$).

In total, 13 patients died of NRM between 1 month and 12.5 months after alloSCT, including 7 patients who received grafts from haploidentical donors, 5 patients who received grafts from MUD donors, and only 1 patient who received a graft from a matched related sibling. The causes of NRM were GVHD (n = 2), thrombotic microangiopathy (n = 1), and infections (n = 10).

The 1-year and 3-year CCIs of NRM were 15% (95%CI, 9%-26%) and 17% (95%CI, 10%-28%). In univariate analysis, transplantation from a haploidentical donor or an MUD was associated with a higher rate of NRM than transplantation from a matched related sibling, with 3-year CCIs of 36% (95%CI, 18%-71%) and 31% (95%CI, 16%-63%) versus 2.5% (95%CI, 0.3%-18%), respectively ($P = .001$). In the Fine and Gray multivariate model, the factors that significantly influenced NRM were type of donor ($P < .001$), previous autologous SCT ($P = .047$), and time from diagnosis to alloSCT ($P = .018$). Performance status did not significantly affect NRM ($P = .080$).

GVHD and Chimerism

Of the 78 evaluable patients (2 died early after alloSCT), 22 patients (28%) developed acute GVHD, including 12 who received allografts from matched siblings and 10 who received allografts from alternative donors. Chronic

Table 3. Multivariate Analyses of Overall and Progression-Free Survival by Cox Regression Model

	OS			PFS		
Variable	HR	95% CI	P^a	HR	95% CI	P^a
FDG-PET status						
Negative	1	—		1	—	
Positive	3.35	1.49-7.52	.0035	3.03	1.59-5.76	.0007
Performance status						
ECOG 0-1	1	—		1	—	
ECOG ≥2	5.15	219-12.11	.0002	2.38	1.16-4.89	.0187
Age at AlloSCT, y						
28	1	—		1	—	
47	1.86	0.81-4.24	.265	0.97	0.49-1.89	.73
Histology						
HL	1	—		1	—	
Aggressive NHL	1.68	0.58-4.92	.341	1.77	0.73-4.33	.209
Time from diagnosis to AlloSCT, mo						
≤24	1	—		1	—	
>24	2.20	0.71-6.80	.172	1.90	0.75-4.82	.178
No. of previous therapy lines						
>2	1	—		1	—	
≤2	1	0.37-2.71	.994	1.14	0.50-2.55	.759
Previous AutoSCT						
No	1	—		1	—	
Yes	1.09	0.36-3.27	.883	1.29	0.48-3.46	.609
Type of donor						
HLA-matched sibling	1	—		1	—	
MUD	1.94	0.78-4.83		1.01	0.47-2.15	
Haploidentical	6.26	2.03-19.27	.0048	1.29	0.50-3.29	.867

OS indicates overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; FDG-PET, [18-F] fluorodeoxyglucose-positron emission tomography; ECOG, Eastern Cooperative Oncology Group; AlloSCT, allogeneic stem cell transplantation; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; AutoSCT, autologous stem cell transplantation; HLA, human leukocyte antigen; MUD, matched unrelated donor.
[a] Wald test.

GVHD was observed in 29 of 72 evaluable patients (40%), including 16 patients with limited GVHD and 13 patients with extensive GVHD (18 who received allografts from matched siblings and 11 who received allografts from alternative donors).A semilandmark analysis indicated that the 3-year CCI for disease recurrence was 12% (95%CI, 3%-47%) for patients with chronic GVHD and 21% (95%CI, 9%-48%) for patients without chronic GVHD ($P = .400$). In the Cox model analysis of OS, chronic GVHD was not statistically significant: The HR of the absence versus the presence of chronic GVHD as a time-dependent variable was 0.83 (95%CI, 0.30-1.35; $P = .710$).

Chimerism analyses were available in 60 patients (75%), including 56 patients with fully donor chimerism (93%) and 4 patients with mixed donor-recipient chimerism (7%) within the first 6 months after alloSCT. Two of 4 patients with mixed chimerism developed disease recurrence after alloSCT. In 9 patients who died early after alloSCT, chimerism analysis was not performed; whereas, in 11 other patients, the results were not available.

DISCUSSION

To our knowledge, this is the first study demonstrating that disease assessment by FDG-PET imaging before alloSCT can predict long-term survival in patients who develop disease recurrence and in patients with chemosensitive HL or aggressive NHL. The patients in this study who had negative PET results were at lower risk of disease recurrence and had better PFS and OS than the PET-positive patients. It is noteworthy that the predictive value of PET was independent of GVHD and of the graft-versus-lymphoma effect.

Response assessment in patients with lymphomas includes both conventional and metabolic imaging, because the size of a residual mass correlates poorly with

prognosis, which is why revised response criteria for lymphoma using FDG-PET recently were published. Many studies have confirmed that midtreatment FDG-PET images can predict clinical outcome in patients with HL or aggressive NHL,[22,23] and an association between a negative pretransplantation PET scan and a better outcome has was reported previously in the setting of high-dose therapy and autologous SCT with 2-year event-free survival rates ranging from 60% to 80%.[9,10]

Patients with recurrent or progressive HL or aggressive NHL after autologous transplantation have no potentially curative treatment options other than alloSCT, and identifying the risk factors that influence the outcome of allografting would help to target optimal conditioning and immunologically based post-transplantatoin therapies for individual patients. Currently, the most widely used prognostic factors are chemosensitive disease, comorbidity score, and donor type. Chemosensitive disease before alloSCT has been identified as a strong prognostic factor in patients who receive myeloablative conditioning, but it may be even more relevant in patients who receive RIC regimens.

Today, FDG-PET is used frequently to monitor treatment response, but we believe the current investigation represents the first time FDG-PET has been used to evaluate a large group of patients before alloSCT, although 1 previous small study did consider the significance of pretransplantation FDG-PET in 14 patients who underwent conventional myeloablative alloSCT (including only 1 patient with HL and no patients with DLBCL).[24] Several groups have described the results from alloSCT after RIC in patients with recurrent and refractory HL; and, although the published studies are heterogeneous in terms of RIC protocols and the duration of follow-up, they indicate that disease status at the time of alloSCT influenced outcome in all series and that outcomes were favorable when patients developed recurrences >12 months after autologous SCT.[25] Peggs et al used an RIC regimen of fludarabine/melphalan and alemtuzumab and recorded a 4-year PFS rate of 67% and an OS rate of 100% in patients who were in CR or uncertain CR (CRu) at the time of transplantation.[3] Furthermore, Anderlini et al recently reported a 2-year PFS rate of 57% in patients who achieved CR/CRu before alloSCT using a similar RIC regimen without alemtuzumab.[2] However, none of those reports described a correlation between FDG-PET findings and outcome.

Disease status also is critical to the outcome of patients with aggressive NHL, and Dhedin et al reported a 5-year OS rate of 76% in patients who achieved CR before myeloablative alloSCT.[26] Although there are relatively few published studies of the outcome of RIC in patients with aggressive NHL, it has been reported that transplantation during CR can lead to a PFS rate of 50% to 60%. Moreover, in our previous study, we did not observe a significant difference in outcome between patients with aggressive lymphoma of B-cell or T-cell origin, respectively, at 3 years of follow-up.[8] This observation was confirmed in the current study.

The results from this study indicate that a negative pretransplantation PET scan significantly predicts the risk of disease recurrence, PFS, and OS in both patients with HL and patients with NHL. These findings also were in the analysis that was restricted to 68 patients (excluding those who underwent tandem autologous-alloSCT).

It is noteworthy that, in our multivariate analysis, performance status also was associated significantly with PFS and OS. Previous reports demonstrated that hematopoietic cell transplantation-specific comorbidity index (HCT-CI) and performance status were correlated independently with outcome.[27,28] Recently, Robinson et al investigated a population of 285 patients with affected HL who underwent RIC alloSCT and observed that both performance status and disease status at transplantation important clinical parameters for outcome.[29]

The kinetics of disease recurrence were quite different in PET-positive patients: In patients with HL, disease progression usually was observed within the first 2 years after alloSCT; whereas most patients with aggressive NHL developed disease recurrence within the first 12 months, and then the curve reached a plateau. Although patients with positive pretransplantation PET scans had a dismal outcome, approximately 30% of them survived for a long period.

The main limitations of our study are related to the potential drawbacks and selection biases associated with retrospective analyses. We only considered patients who underwent PET before alloSCT; thus, the population was selected. Furthermore, because we included patients who received allografts from different donor types, multivariate analyses indicated that the type of donor influenced OS and the risk of disease recurrence.

However, with regard to the other factors that may influence outcome, the population was relatively homogeneous in terms of conditioning regimens, and we did not include patients who received nonmyeloablative conditioning regimens, such as 2 grays of total body irradiation and fludarabine, which reportedly are associated with a

higher risk of disease recurrence.[30] In addition, most of our patients (n = 59; 74%) received conditioning regimens that contained thiotepa, cyclophosphamide, and fludarabine or thiotepa and cyclophosphamide. Furthermore, the majority (79%) received allografts between 2004 and 2007, and it is unlikely that there was any substantial change in supportive care strategies over such a short time.

In conclusion, and despite its limitations, the results from our retrospective study indicate that FDG-PET imaging is useful in predicting PFS and OS after RIC alloSCT. This represents a critical issue in the era of new drugs, because patients who have positive scans should receive further treatment to possibly increase the response rate before alloSCT.

CONFLICT OF INTEREST DISCLOSURES

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