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Brief Articles

Pretransplantation Fluorine-18-Deoxyglucose–Positron Emission Tomography Scan Lacks Prognostic Value in Chemosensitive B Cell Non-Hodgkin Lymphoma Patients Undergoing Nonmyeloablative Allogeneic Stem Cell Transplantation

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A B S T R A C T

Whether chemosensitivity, as determined by positron emission tomography using fluorine-18-deoxyglucose (FDG-PET), is a requirement for successful allogeneic hematopoietic stem cell transplantation (allo-SCT) has yet to be established. We analyzed 88 patients with B cell non-Hodgkin lymphoma (B-NHL) for event-free (EFS) and overall survival (OS) according to computed tomography (CT) and FDG-PET criteria before uniform nonmyeloablative (NMA) allo-SCT. Patients who were chemosensitive, according to CT criteria, experienced significantly greater EFS ($P < .001$) and OS ($P < .03$) compared with those who were chemorefractory at the time of allo-SCT. Of 58 patients within this cohort who were chemosensitive by CT criteria, there was no difference in EFS ($P = .85$) or OS ($P = .96$) between FDG-PET–positive (Deauville 4 to 5, n = 24) and FDG-PET–negative (Deauville 1 to 3, n = 34) patients. There was no difference in survival according to age < or ≥ 60 years, prior autologous-stem cell transplantation, allograft characteristics, or histology. FDG-PET adds no prognostic value in chemosensitive B-NHL before NMA-allo-SCT.

INTRODUCTION

Although high-dose chemotherapy followed by autologous stem cell transplantation (HDT-ASCT) is a standard treatment approach for relapsed and refractory diffuse large B cell lymphoma (DLBCL) [1], the most common B cell non-Hodgkin lymphoma (B-NHL), recent data suggest many failures of this treatment modality in the post-rituximab era [2]. Additionally, HDT-ASCT is considered unlikely curative for patients with indolent histology B-NHL, such as follicular and mantle cell (MCL) lymphoma. Allogeneic hematopoietic stem cell transplantation (allo-SCT) is increasingly utilized for relapsed and refractory B-NHL with the intent that a graft-versus-lymphoma effect will provide disease control and, ultimately, cure in patients at risk of succumbing to their otherwise poor prognostic disease.

Functional imaging by fluorine-18-deoxyglucose positron emission tomography (FDG-PET) is a more accurate modality for assessing response to therapy, and viable tumor, in patients with Hodgkin lymphoma (HL) and most subtypes of indolent and aggressive NHL, compared with computed tomography (CT) criteria [3]. Disease response to salvage therapy by FDG-PET before HDT-ASCT has demonstrated prognostic significance in both HL [4,5] and NHL [5,6]. Recently, interim response criteria have been established according to the Deauville meeting [7]. Although multiple studies have reproduced the significant prognostic impact of chemosensitivity before allo-SCT based upon CT response criteria [8], there are no data pertaining to the prognostic value of contemporary FDG-PET interim response criteria [7] in B-NHL patients who are chemosensitive before conventional nonmyeloablative (NMA) allo-SCT.

METHODS

Patients and Treatment

We retrospectively reviewed a database of 88 adult patients with relapsed or primary refractory B-NHL who underwent uniformly conditioned NMA allo-SCT at Memorial Sloan-Kettering Cancer Center (MSKCC) for relapsed and refractory B-NHL from February 2006 to October 2012.

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Approval for this retrospective review was obtained from the Institutional Review and Privacy Board at MSKCC. Fifty-one of these patients were treated on a prospective phase II clinical trial, MSKCC IRB #06-150 (NCT00425802) [9]. Patients with aggressive histology B-NHL by World Health Organization criteria were required to demonstrate chemosensitivity, either complete or partial remission, to salvage therapy as determined by International Working Group Criteria [10] before allo-SCT. Patients with indolent histology B-NHL, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), had to have previously failed at least 1 line of combination chemotherapy, though chemosensitivity was not required. Patients with MCL were eligible in first remission if primary histology was either blastoid histology or p53 expressing on immunohistochemistry. Patients required a fully matched or single HLA allele disparate related or unrelated donor at 10-loci (HLA-A, HLA-B, HLA-C, HLA-DRβ, or HLA-DQ).

Conditioning consisted of cyclophosphamide 50 mg/kg for 1 dose on day -6 followed by fludarabine at 25 mg/m^2 i.v. daily from day -6 to day -2. One dose of total body irradiation at 200 cGy was delivered on day -1. Equine antithymocyte globulin 30 mg/kg was given daily on day -3 and day -2 to recipients of HLA-matched unrelated or HLA-single allele disparate allografts. Peri–allo-SCT rituximab at 375 mg/m^2 was given on day −8 or −7 and weekly for 4 doses, beginning day +21 (± 2 days). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine-A and mycophenolate mofetil (n = 19) and later changed to tacrolimus, sirolimus, and methotrexate day +1, 3, and 6 at 5 mg/m^2 (n = 69).

Pre-NMA Allo-SCT CT and FDG-PET Scans

Chemosensitivity was assessed per standard CT criteria for B-NHL [10], as well as additional criteria for CLL/SLL [11] before allo-SCT for all patients. For patients who underwent FDG-PET before NMA-allo-SCT at the discretion of the treating physician, Deauville criteria [7] were utilized wherein Deauville 4 or 5 (FDG > background liver uptake or new FDG-avid lesions) was considered a positive scan. A radiologist (S.F.) reviewed all images of ambiguous results.

Statistical Analysis

Overall survival (OS) was the time from allo-SCT to death from any cause, and surviving patients were censored at last follow-up. Event-free survival (EFS) was the time from allo-HSCT to progression of disease or death from any cause. The median and 3-year OS and EFS were estimated using Kaplan-Meier methodology. OS and EFS in patients with different characteristics were compared using the log-rank test.

RESULTS AND DISCUSSION

Eighty-eight patients with B-NHL underwent NMA allo-SCT with uniform conditioning as above and 9 patients did not receive peritransplantation rituximab per physician decision. Table 1 outlines full patient characteristics. All patients had been previously exposed to rituximab before allo-SCT.

With a median follow-up of 37 months (range, 4 to 75) for survivors, the Kaplan-Meier estimates of OS and EFS at 3 years after NMA allo-SCT were 73% (95% confidence interval [CI], 63% to 83%) and 69% (95% CI, 58% to 79%), respectively. The cumulative incidences of transplantation-related mortality (TRM) and progression of disease (POD) at 3 years were 21% (95% CI, 11% to 30%) and 11% (95% CI, 4% to 18%), respectively. Analysis of pre-NMA allo-SCT characteristics revealed no difference in EFS or OS among differing B-NHL histologies, previous HDT-ASCT, hematopoietic cell transplantation–comorbidity index of 0 to 1 versus ≥ 2, or graft characteristics. Chemosensitive patients, according to CT criteria, had significantly improved EFS at 3 years compared with patients who were chemorefractory (76% [95% CI, 66% to 88%] versus 36% [95% CI, 18% to 71%]; $P < .001$) (Figure 1A), which translated into OS benefit at 3 years of 77% (95% CI, 67% to 89%) versus 56% (95% CI, 36% to 87%); $P = .03$. Of the 71 chemosensitive, 3 events (4.2%) were relatable to POD.

Table 1
Patient Characteristics

Characteristic	Value
No. of patients	88
Age, median (range), yr	54 (33-70)
Histology	
DLBCL	15 (17%)
FL	34 (39%)
MCL	11 (12.5%)
CLL/SLL	24 (27%)
Other	4 (4.5%)
WHO histologic subtypes	
Indolent	73 (83%)
Aggressive	15 (17%)
HCT-CI, median (range)	1 (0-8)
Prior therapies, median (range)	2 (1-6)
Prior HDT-ASCT	15 (17%)
Disease status at allo-SCT per CT	
CR	37 (42%)
PR	34 (39%)
SD	14 (16%)
PD	3 (3%)
Chemosensitive by CT (n = 58)	
FDG-PET (+)	24 (41%)
DLBCL	4
FL	12
MCL	2
CLL/SLL	6
FDG-PET (-)	34 (59%)
DLBCL	8
FL	15
MCL	4
CLL/SLL	4
Other	3
Graft	
Related	32 (35%)
Unrelated	56 (65%)
MUD	47
MMUD	9
Peri-NMA SCT rituximab	
Yes	79 (90%)
No	9 (10%)

DLBCL indicates diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; WHO, World Health Organization; HCT-CI, hematopoietic cell transplantation comorbidity index; Allo-SCT, allogeneic stem cell transplant; CR, complete remission; PR, partial remission; SD, stable disease; PD, progression of disease; MUD, matched unrelated donor; MMUD, mismatched unrelated donor.
Data presented are n (%) unless otherwise indicated.

There were 58 chemosensitive patients according to CT criteria who additionally underwent restaging FDG-PET scans before NMA allo-SCT. FDG-PET scans were performed at a median of 30 days (range, 10 to 147 days) before NMA-allo-SCT, with 93% of the FDG-PET scans performed within 2 months of NMA-allo-SCT. There was no intervening B-NHL therapy between pre–allo-SCT FDG-PET and allo-SCT. No differences in EFS or OS were demonstrated between 34 patients achieving a negative FDG-PET compared with the 24 with a positive FDG-PET, according to Deauville interim restaging criteria (Figure 1B). The 4 events in the FDG-PET–positive group consisted equally of TRM (n = 2, both GVHD related) and POD (n = 2), whereas of the FDG-PET–negative patients, 5 events were relatable to TRM (all GVHD) and 1 patient experienced POD. Of the 15 patients with DLBCL, 12 patients were chemosensitive

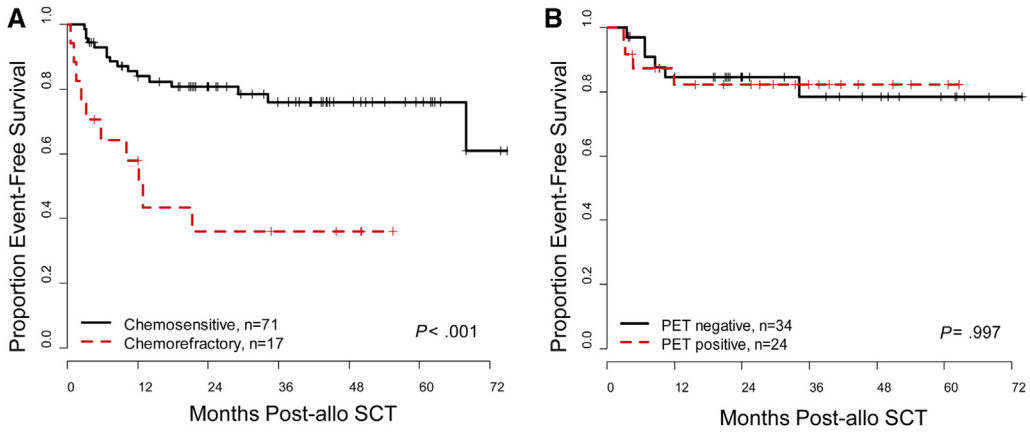

Figure 1. Event-free survival (A) according to chemosensitivity and (B) according to fluorine-18-deoxyglucose positron emission tomography in chemosensitive patients.

and underwent FDG-PET scans before allo-SCT. Four of these 12 patients were FDG-PET positive before allo-SCT, with 1 patient subsequently experiencing POD after allo-SCT.

This is the first report demonstrating lack of prognostic value of FDG-PET, according to contemporary consensus response criteria [7], in chemosensitive B-NHL patients undergoing conventional allo-SCT conditioned with a uniform NMA program. In studies to date, chemosensitivity, as determined by traditional CT imaging, has reproducibly affected OS in reduced-intensity (RIC)/NMA allo-SCT for B-NHL [8]. This has been demonstrated with indolent histology B-NHL [12,13], including prospectively in a contemporary CLL/SLL study [14], as well as with aggressive histology disease [15]. We have reproduced this finding with significant improvement in EFS and OS in chemosensitive patients. However, herein, we demonstrate no prognostic impact of normalizing FDG-PET scan below liver uptake (Deauville score < 4) in those patients demonstrating chemosensitivity by CT criteria [10,11] before conventional NMA-conditioned allo-SCT. The group from University College London has previously published similar findings in chemosensitive patients proceeding to RIC allo-SCT [16]. Their cohort differed from ours' with respect to use of in vivo T cell depletion with alemtuzumab and utilization of older International Harmonization Project criteria for FDG-PET restaging response [17]. Additionally, their study included patients treated with risk-adapted donor lymphocyte infusions after allo-SCT. A study conducted by a group of Italian centers determined FDG-PET to be prognostic in 80 chemosensitive patients with aggressive histology NHL and HL proceeding to RIC allo-SCT from related and unrelated donors [18]. This finding may be attributable to the increased dependence of chemosensitivity in aggressive histology lymphoma before RIC allo-SCT, wherein graft-versus-lymphoma effects may prove relatively belated in more rapidly kinetic disease. Lastly, a small 14-patient study of lymphoma patients, wherein 11 were FDG-PET–positive before allo-SCT, treated with predominately myeloablative conditioning was previously reported without conclusive impact of FDG-PET on prognosis [19].

Limitations of our study include the retrospective nature and unplanned analysis in the patients undergoing this uniform NMA allo-SCT treatment program toward the endpoints analyzed. Additionally, the relatively small numbers of patients within the subhistologies of B-NHL potentially limits the power of detecting differences in the primary endpoints within these groups. Lastly, potential selection bias is introduced given the physicians' choice to obtain or not obtain FDG-PET before NMA allo-SCT.

In conclusion, our study has found that FDG-PET scan offers no prognostic benefit for B-NHL patients before NMA allo-SCT who have attained chemosensitivity by traditional CT-based criteria. The majority of failure events (7 of 10) in the chemosensitive patients who underwent FDG-PET scan were TRM relatable to GVHD, underscoring the importance of introducing more effective prophylaxis and treatment strategies for this life-threatening complication. The limitation of our study is the inclusion of heterogenous B-NHL histologies, with the majority being indolent histology disease. Although most of the predictive power of pre–HDT-ASCT FDG-PET is seen in patients with aggressive histology lymphomas [4,5], FDG-PET has proven significantly prognostic for both 2-year progression-free and OS on interim restaging during induction chemotherapy utilizing the same criteria as our analysis [20]. Additionally, positive FDG-PET for MCL, a disease considered of more indolent histology relative to DLBCL or HL, has recently demonstrated prognostic significance for OS pre-HDT-ASCT [21]. Findings from our study warrant prospective confirmation. If prospectively validated, the lack of prognostic significance of positive FDG-PET in chemosensitive patients before NMA allo-SCT would greatly reduce resources, expense, and radiation exposure associated with FDG-PET scans.

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designed the study and wrote the manuscript. C.S.S., L.L., M.S., S.E.F., J.Z., and S.M.D. analyzed the data and wrote the manuscript.

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