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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 $\geq$ 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