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The Role of Positron Emission Tomography with 18F-Fluorodeoxyglucose Integrated with Computed Tomography in the Evaluation of Patients with Multiple Myeloma Undergoing Allogeneic Stem Cell Transplantation

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A B S T R A C T

Positron emission tomography (PET) integrated with computed tomography (PET/CT) has been reported to be useful for screening myelomatous lesions at diagnosis in patients with multiple myeloma (MM) and for monitoring response to autologous stem cell transplantation (auto-SCT). The aim of the study was to evaluate the prognostic significance of PET/CT in MM patients who received allogeneic stem cell transplantation (allo-SCT). Patients who underwent upfront auto-SCT followed by allo-SCT, either as consolidation or salvage treatment, were studied with PET/CT before and/or within 6 months after allo-SCT. The number, the maximum standard uptake value (SUV), and the location (medullary or extramedullary) of focal lesions (FLs) were recorded and investigated as predictors of progression-free survival (PFS) and overall survival (OS) by univariate and multivariate analyses. Fifty-four patients had a PET/CT scan before allo-SCT. Of these, 22 patients (41%) had a negative PET/CT scan, 11 patients (20%) showed 1 to 3 FLs, and 21 patients (39%) had either a diffuse bone marrow involvement or more than 3 FLs. SUV was >4.2 in 21 patients (39%) and extramedullary disease (EMD) was present in 6 patients (11%). Multivariate analysis of prognostic factors before allo-SCT showed that persistence of EMD at transplantation was an independent predictor of poor PFS, whereas OS was negatively influenced by unrelated donor and SUV > 4.2. Fifty-nine patients had a PET/CT scan within 6 months after allo-SCT. Multivariate analysis of post-treatment variables showed that persistence of EMD and failure to obtain complete response or very good partial response after allo-SCT were strongly associated with shorter PFS and OS. Of the 46 patients with evaluable PET/CT scans both before and 6 months after allo-SCT, the 23 patients who maintained or reached a PET complete remission showed a significantly prolonged PFS and OS compared with the 23 patients with persistence of any PET positivity (2-year PFS: 51% versus 25%, $P = .03$; 2-year OS: 81% versus 47%, $P = .001$). This study indicates that PET/CT imaging before and after allo-SCT is significantly associated with the outcome, suggesting the utility of this technique for MM staging before allo-SCT and for response monitoring after the transplantation.

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INTRODUCTION

The majority of patients with multiple myeloma (MM) present bone disease at diagnosis or develop it during the course of the disease. Traditionally, bone disease is detected by skeletal X-ray survey and is characterized by sharply defined lytic lesions, vertebral collapses, and pathological fractures, which could persist unchanged for a long time after therapy, despite effective treatment. In recent years, there has been an increasing interest in improving imaging techniques in MM. Features of an optimal imaging technique include high sensitivity for detecting lytic bone lesions and infiltrative focal lesions (FLs) in the bone marrow (BM), reliability in detecting extramedullary disease (EMD), and ability to assess response to treatment [1]. Low-dose computed tomography, magnetic resonance (MR), and positron emission tomography (PET) integrated with computed tomography (PET/CT) using the positron emitting radionucleotide 18F-fluorodeoxyglucose (FDG) have some of the above-mentioned characteristics. In particular, PET/CT can provide anatomic and functional information in MM. In fact, PET/CT is useful for detecting the extent of bone disease in patients with newly diagnosed MM because it is superior to skeletal X-ray survey in terms of its ability to reveal medullary and extramedullary bone lesions, leading in some cases to a change in disease stage and treatment [2-6]. Therefore, the updated criteria for the diagnosis of MM have recently established that PET-CT is 1 of the new tools to precociously identify bone disease [7]. Moreover, PET/CT at diagnosis is a reliable technique for predicting long-term outcome in MM patients. In fact, 2 independent prospective studies showed that PET/CT at diagnosis provides prognostic information on both progression-free survival (PFS) and overall survival (OS) in MM patients treated with induction therapy with novel agents and autologous stem cell transplantation (auto-SCT) [5,6]. The Little Rock study showed a close correlation between the number of FLs found by MR (>7 lesions) and PET/CT (>3 lesions) and other biological prognostic factors and gene expression profiling results [5]. The Bologna group demonstrated that patients with newly diagnosed MM who presented with more than 3 FLs, a high standardized uptake value (SUV), and extramedullary disease (EMD) on diagnostic PET/CT had a poor PFS [6]. PET-CT has been an useful tool not only for staging at diagnosis, but also for monitoring the response after treatment, as demonstrated by some studies mainly conducted on patients undergoing auto-SCT [8,9].

The purpose of this study is to analyze the prognostic significance of PET/CT performed before and after transplantation in a series of patients with MM who received allogeneic stem cell transplantation (allo-SCT).

METHODS

Patients

Data on 67 MM patients were retrospectively collected in 4 centers under a protocol approved by the institutions participating in this study. This study was structured as follows: (1) a synopsis of the study was sent to the centers; after their agreement to join the study, they received a letter explaining how to collect the data required on a specific patient form; (2) each center designated an investigator in charge of the study; (3) the centers reviewed all MM patients who underwent allo-SCT between 2004 and 2011 and included those patients who were studied with PET/CT before the procedure and/or during the follow-up after allo-SCT (with at least an evaluable scan within 6 months after allo-SCT); and (4) the patient forms coming back from the centers were reviewed by a statistician and a senior hematologist and, if necessary, specific queries were sent back to the centers.

Disease response was evaluated through clinical examination, blood chemistry, and BM biopsy. Besides PET/CT, bone disease was studied with standard imaging techniques (whole skeleton X-ray survey and spine MR, according to the policy of each center). Karyotype was analyzed at diagnosis by the fluorescence in situ hybridization (FISH) technique, if available, to assess the following baseline abnormalities: t(4;14), deletion 17p13, and deletion 13q14. Response was evaluated according to the international Uniform Response Criteria for MM [10].

Imaging Studies

Whole body (including skull, superior limbs, and femurs) PET/CT was carried out using standard procedures, as previously described [11]. All of the PET/CT scan were evaluated by a team of nuclear medicine physicians with extensive experience in MM field. The interpretation criteria for the baseline PET scans and the PET response adopted in this study were used in 2 previous papers of the groups of Bologna and Udine [6,9] and were shared by the physicians of nuclear medicine of the 4 centers. In case of doubt, the case was reviewed by the Bologna team. Criteria to define PET/CT positivity included the following: (1) presence of focal areas of detectable increased tracer uptake within bones (excluding articular processes) with or without any underlying lesion identified by CT; or (2) maximum SUV (SUVmax) $\geq$ 2.5 within bone lytic CT areas exceeding 1 cm in size; or (3) SUVmax $\geq$ 1.5 within osteolytic CT areas ranging between .5 and 1 cm in size.

The number, size, and location of hypermetabolic FLs were recorded. BM uptake on PET/CT was described as negative, diffuse, or focal according to the degree of FDG uptake. BM was considered diffusely involved if the tracer uptake was diffusely increased, with an SUVmax equal to or greater than the uptake in the spleen. In this case, the SUVmax was measured in the hottest area within the BM. The degree of FDG uptake was represented by the SUVmax in the hottest lesion. *EMD*, defined by soft tissue or visceral FDG uptake that can be adjacent to a bone lesion (bone-related EMD) or not linked to the bone (soft-tissue–related EMD) [12], was described by location, size, number, and SUV.

PET/CT scans were performed within 30 days before allo-SCT and/or during the follow-up after allo-SCT (between the third and the sixth months after allo-SCT and then every 12 months, according to the decision of the attending physician).

In patients in whom 1 PET/CT scan before allo-SCT and 1 or more PET/CT scans after allo-SCT were evaluable, *PET/CT complete remission* (PET-CR) was defined as disappearance of every area of increased tracer uptake found at baseline. *PET/CT partial remission* (PET-PR) was defined as a decrease in the number of sites of FDG uptake and/or a decrease of at least 20% in the SUVmax of the lesions. *PET relapse* or *progression* was defined as an increase > 50% of the residual FLs or appearance of new FLs or EMD by PET/CT.

Statistical Analysis

Data were collected in an XLS database and imported into Stata/SE 9.0 for Windows for statistical analysis. The close-out date for analysis was October 2013.

Nonrelapse mortality (NRM) was defined as death due to all causes not related to myeloma. *OS* was defined as the time (months) from allo-SCT to either death or last observation. *PFS* was defined as the time from allo-SCT to relapse, progression, death, or last observation. OS and PFS were described using the Kaplan-Meier approach. The cumulative incidence method was used to estimate relapse and NRM, accounting for the presence of competing risk. NRM and overall mortality were considered as events. The time to event was measured as months from transplantation. Graphs of time to event were based on the Kaplan-Meier method. OS and PFS were analyzed using Cox proportional hazard models, after the proportional hazards assumption had been verified.

Associations with clinical characteristics were compared by the chi-square method for categorical data and the *t*-test was used to compare continuous variables. In univariate analysis, variables considered as possible prognostic factors were age at transplantation (years), stage according to Durie and Salmon (I+II versus III), time between diagnosis and allo-SCT (months), donor (HLA-identical sibling versus unrelated), timing of allo-SCT (at diagnosis versus at relapse), response before allo-SCT (CR+very good partial response [VGPR] versus $\leq$PR), number of FLs at PET scan before transplantation (0 versus $\geq$ 1), SUV at PET scan before transplantation (<4.2 versus $\geq$4.2), EMD sites at PET scan before transplantation (0 versus $\geq$1), response 6 months after allo-SCT (CR+VGPR versus $\leq$ PR), number of FLs at PET scan 6 months after allo-SCT (0 versus $\geq$1), SUV at PET scan 6 months after allo-SCT (<4.2 versus $\geq$4.2), and EMD sites at PET scan 6 months after allo-SCT (0 versus $\geq$1). International Staging System score (ISS) and karyotype were not considered as possible variables of the univariate analysis because of the high number of missing data (58% and 52%, respectively). The cutoffs for FLs and SUV were identified after applying the sequential log-rank test and selecting the most powerful values for discriminating the outcome. Multivariate stepwise analysis included all variables significant at $P \leq .10$ in the univariate analysis and was conducted separately for

Table 1
Clinical Characteristics of the Patients and Transplantations

Characteristic	All Patients	Patients with an Evaluable PET/CT before Allo-SCT	Patients with an Evaluable PET/CT after Allo-SCT
No. of patients	67	54	59
Age at allo-SCT, median (range), yr	55 (32-69)	50 (32-65)	50 (32-65)
Stage according Durie & Salmon			
I	8 (12%)	8 (15%)	6 (10%)
II	2 (3%)	2 (4%)	2 (3%)
III A	51 (76%)	39 (72%)	46 (78%)
III B	6 (9%)	5 (9%)	5 (9%)
Stage according ISS			
1	8 (34%)	7 (29%)	6 (26%)
2	6 (26%)	5 (21%)	5 (22%)
3	14 (50%)	12 (50%)	12 (52%)
Not evaluated	39	30	36
Karyotype			
Standard risk	20 (63%)	18 (64%)	16 (59%)
High-risk: del13, del17, t(4;14)	12 (37%)	10 (36%)	11 (41%)
Not evaluated	35	26	32
Tandem auto-SCT + RIC allo-SCT	27 (40%)	17 (31%)	25 (42%)
RIC allo-SCT at relapse	40 (67%)	37 (69%)	34 (58%)
Donor			
HLA-matched sibling	29 (43%)	18 (23%)	26 (44%)
Unrelated	38 (57%)	36 (77%)	33 (56%)
Disease status before allo-SCT			
CR	13 (19%)	13 (24%)	12 (21%)
VGPR	17 (26%)	9 (18%)	14 (24%)
PR	17 (26%)	13 (24%)	14 (24%)
SD or progression	19 (29%)	18 (34%)	18 (31%)
Not evaluated	1	1	1

RIC indicates reduced-intensity conditioning; SD, stable disease.
Data presented are n (%) unless otherwise indicated.

pretransplantation and post-transplantation variables. Retention in the stepwise model required that the variable be significant at $P \leq .05$ in multivariate analysis.

RESULTS

Patients Clinical Features and Clinical Outcome

A total of 67 patients with a median age of 55 years (range, 32 to 69) at the time of allo-SCT were analyzed. The main characteristics of the patients and of the treatment are summarized in Table 1. Thirteen patients (19%) showed high-risk clinical features at onset of MM: 6 patients presented with renal impairment (creatinine > 2 mg/dL), 3 had hypercalcemia, 3 had meningeal or cerebral plasma cell localizations, and 1 had plasma cell leukemia. Because MM was diagnosed before 2004 in 64% of the patients, ISS staging data at diagnosis were evaluable only in 28 patients and 14 of them (50%) had ISS stage II and III. Overall, 32 patients (48%) were screened for cytogenetics abnormalities by FISH analysis performed on BM CD138+ plasma cells, and it indicated that translocation(4;14) and/or deletion 17p13 and/or deletion 13q14, occurred in 12 patients (37%).

All patients received upfront auto-SCT at a median time of 9 months (range, 3 to 54) after MM diagnosis. Auto-SCT was followed by allo-SCT within 3 months in 27 cases (auto-allo approach), whereas in the other 40 cases allo-SCT was performed after failure of previous auto-SCT. Induction therapy was based on vincristine, adriamicin, and dexamethasone in 10 patients or included immunomodulating agents and/or bortezomib in the other 14 patients treated with the auto/allo approach. Among the 40 patients who underwent allo-SCT at relapse, 26 patients (65%) had received 1 line of salvage therapy and the other 14 patients (35%) were treated with ≥2 lines of antimyeloma therapy, including immunomodulating agents and/or bortezomib in 96% of cases. Median time between diagnosis and allo-SCT was 36 months (range, 8 to 128).

Preparative regimens before allo-SCT were reduced-intensity conditioning or nonmyeloablative regimens. These regimens consisted of fludarabine plus melphalan 140 mg/m^2 in 36 patients (54%), fludarabine plus 2 Gy total body irradiation in 23 patients (34%), and miscellaneous combinations in the remaining 8 patients.

Twenty-nine patients (43%) underwent transplantation from HLA-identical sibling donors and 38 (57%) from unrelated donors.

At a median follow-up of 6 months (range, 1 to 122) after allo-SCT for the whole population and of 41 months (range, 5 to 122) for the surviving patients, 34 patients (51%) experienced relapse and 35 patients (52%) had died. Two-year cumulative incidence of NRM was 23% and 2-year estimates of PFS and OS after allo-SCT were 44% and 67%, respectively. Patients treated with the auto-allo approach showed 2-year estimates of PFS and OS after transplantation of 56% and 80%, respectively, compared with 36% ($P = .027$) and 58% ($P = .051$) for the patients who received allo-SCT after failure of previous auto-SCT.

Table 2
Characteristics of PET/CT Scan

Time of Evaluation	Before Allo-SCT	After Allo-SCT
No. of patients	54	59
No focal lesions	22 (41%)	29 (47%)
1-3 FL (%)	11 (20%)	8 (15%)
> 3 FL or diffuse (%)	21 (39%)	22 (38%)
SUV (%)		
Low (≤4.2)	30 (61%)	43 (85%)
High (>4.2)	21 (39%)	15 (15%)
Not evaluated	3	1
Extramedullary disease	6 (11%)	8

PET/CT Imaging before Allo-SCT and Its Prognostic Significance

Fifty-four patients had an evaluable PET/CT scan before allo-SCT (Table 2). Of these, 22 patients (41%) had a negative PET/CT scan, 11 (20%) showed 1 to 3 FLs, and 21 (39%) had either diffuse BM involvement or more than 3 FLs. In 21 patients (39%), baseline FDG uptake was severe (defined as SUV > 4.2). EMD was present in 6 patients (11%) in the following sites: paranasal sinuses (n = 1), pleura (n = 1), central nervous system (n = 1), soft tissue of the pelvis (n = 2), and liver (n = 1).

Among the 53 evaluable patients, according the Uniform Response Criteria, depth of response correlated with PET results before allo-SCT. In fact, 8 of 13 (61%) patients in CR were PET negative compared with 13 of 40 (32%) patients in VGPR or less ($P = .04$). However, 3 patients in CR showed 1 to 3 FLs at PET scan and the other 2 patients in CR presented more than 3 FLs.

On univariate analysis, transplantation in relapse, achievement of less than CR or VGPR, persistence of at least 1 FL, SUV > 4.2, and EMD before allo-SCT adversely affected PFS and OS after allo-SCT. Moreover, allo-SCT from an unrelated donor was significantly associated with shorter PFS and

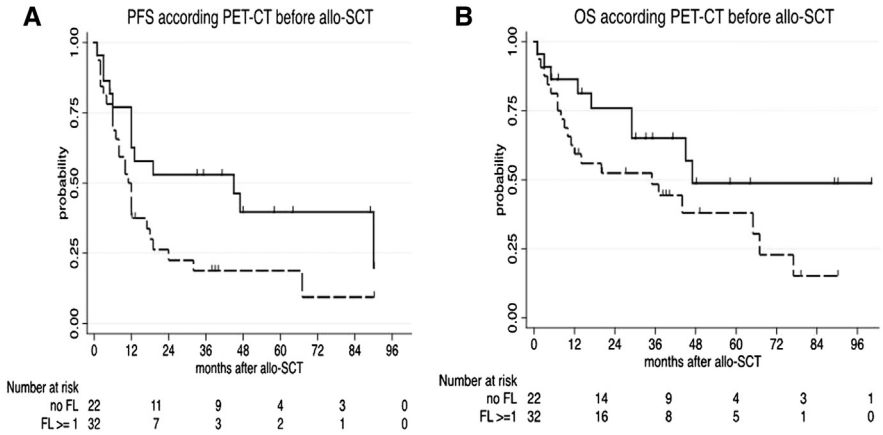

Figure 1. Comparison of PFS (A) and OS (B) from the time of allogeneic transplantation between patients with no focal lesions (FLs) and patients with ≥1 FLs at pretransplantation PET/CT ($P = .033$ and $P = .075$, respectively). Continuous line ____: no FL; dotted line – – –: ≥1 FLs.

OS compared with transplantation from an HLA-identical sibling donor. In more detail, patients with ≥1 FL had 2-year estimates of PFS and OS of 21% and 49%, respectively, compared with 56% ($P = .033$) and 72% ($P = .075$) for those without FLs at PET/CT scan before allo-SCT (Figure 1A,B). Similarly, 2-year estimates of PFS and OS from the time of allo-SCT for patients with baseline SUV values >4.2 were significantly shorter that those observed for patients with SUV < 4.2 (PFS: 16% versus 51%, $P = .031$; OS: 42% versus 72%, $P = .013$) (Figure 2A,B). Moreover, patients with EMD had 2-year PFS and OS estimates of 12% and 33%, respectively, compared with 50% ($P = .010$) and 62% ($P = .016$) for those without EMD.

In a Cox regression analysis of prognostic factors before allo-SCT, persistence of EMD at transplantation was an independent predictor of poor PFS after allo-SCT. OS was negatively influenced by unrelated donor and SUV > 4.2 (Table 3).

PET/CT Imaging after Allo-SCT and Its Prognostic Relevance

Fifty-nine patients had a PET/CT scan within 6 months after allo-SCT. Of these, 29 patients (47%) had a negative PET/CT, whereas 8 (15%) showed between 1 and 3 FLs and 22 (38%) had more than 3 FLs.

On univariate analysis, achievement of less than CR and VGPR and persistence of EMD after allo-SCT adversely affected PFS and OS, whereas presence of at least 1 FL was significantly associated with shorter OS after allo-SCT. Two-year estimates of PFS and OS of patients with positive EMD were significantly lower than those of patients without EMD (PFS: 12% versus 52%, $P = .000$; OS: 25% versus 82%, $P = .001$). Multivariate analysis of post-treatment variables showed that persistence of EMD and failure to obtain CR or VGPR after allo-SCT were strongly associated with shorter PFS and OS from the time of allo-SCT (Table 4).

Response Assessment after Allo-SCT by PET/CT Scans

Forty-six patients had a PET/CT scan before allo-SCT and at 6 months after the procedure. Before allo-SCT, 14 of the 46 patients (30%) had a negative PET/CT, whereas the other 32 (70%) had at least 1 positive FL. The 23 patients who maintained or reached a PET/CR at the sixth month after allo-SCT showed a significantly prolonged PFS and OS compared with the other 23 cases with persistence of any PET positivity (2-year PFS: 51% versus 25%, $P = .03$; 2-year OS: 81% versus 47%, $P = .001$) (Figure 3A,B).

A total of 69 PET/CT scans were performed during the follow-up after allo-SCT in 17 patients, with a median of 4 yearly examinations. Five patients maintained or reached

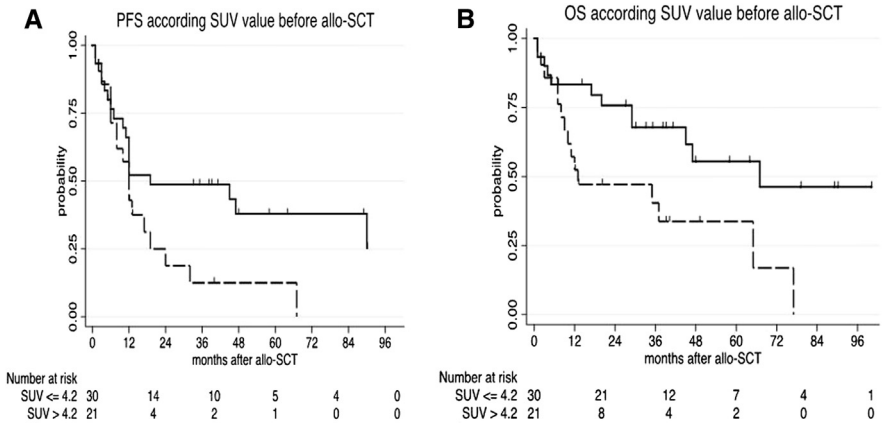

Figure 2. Comparison of PFS (A) and OS (B) from the time of allogeneic transplantation between patients with standard uptake value (SUV) ≤ 4.2 and patients with SUV > 4.2 at pretransplantation PET/CT ($P = .031$ and $P = .013$, respectively). Continuous line ____: SUV ≤ 4.2; dotted line – – –: >4.2.

Table 3
Multivariate Analysis of Pretransplantation Factors Affecting PFS and OS

Factor	PFS			OS		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Donor						
Sibling matched	/	/	/	1		
Unrelated	/	/	/	2.71	1.00-7.32	.049
SUV at T0 PET				1		
<4.2	/	/	/	3.00	1.29-6.99	.010
≥4.2	/	/	/			
Extramedullary sites at T0 PET						
0	1			/	/	/
≥ 1	3.89	1.57-9.64	.003	/	/	/

HR indicates hazard ratio; CI, confidence interval; T0 PET, PET before allogeneic transplantation.

PET-CR after allo-SCT: 3 died because of NRM and 2 are in continuous CR according to the Uniform Response Criteria and imaging after 75 and 105 months. Two patients showed worsened PET/CT scans after allo-SCT and died of progression at 10 and 30 months after transplantation. The other 10 patients showed 1 or more improved PET/CT scans after allo-SCT. Of these, 4 patients showed a transient PET-PR followed by clinical relapse and death due to progression, 1 patient died of NRM, and the other 5 patients are long-term survivors and present evidence of PET response to immunomanipulation (cyclosporine withdrawn or administration of donor lymphocyte infusions) and antimyeloma therapy.

DISCUSSION

Several studies have investigated the role of FDG-PET or PET/CT in monitoring the response to treatment in patients with MM, suggesting that persistence of metabolically active lesions after conventional treatment or auto-SCT is an unfavorable prognostic factor [13-19]. The most remarkable results have come from the prospective studies of the Little Rock and Bologna groups in newly diagnosed MM patients treated with bortezomib-based induction therapy and auto-SCT. In these studies, incomplete FDG suppression after auto-SCT was strongly associated with a worse PFS and OS, both for the 239 patients treated with "total therapy 3" program [20] and for the 192 patients treated with novel agent–based induction and auto-SCT [9,21]. Moreover, the Little Rock group recently reported the prognostic value of early PET/CT performed at day 7 of the induction treatment: patients presenting more than 3 FLs had a 3-year OS and PFS of 63% and 56%, respectively, compared with 78% and 82% for patients with 1-3 FLs [8].

Our study is the first investigation focused on the prognostic relevance of PET/CT results in patients undergoing allo-SCT and the first PET scan was performed before allo-SCT. There is strong evidence that the quality of clinical and biochemical response before transplantation correlates with the subsequent outcome after myeloablative transplantation as well as after reduced-intensity conditioning regimens [22-24]. Moreover, the degree of HLA matching significantly influences NRM [25]. We confirmed that failure to achieve CR and VGPR before allo-SCT was significantly associated with an unfavorable outcome, but we also showed that, similar to what has already been described in patients treated with conventional and high-dose therapy and auto-transplantation, PET/CT added prognostic information, since the entity of PET/CT involvement as reflected by persistence of at least 1 FL, high intensity of tumor metabolism (SUV value > 4.2), and presence of EMD before allo-SCT were predictors of shorter PFS and OS. In multivariate analysis, only PET/CT data (persistence of EMD and higher SUV value before allo-SCT) and transplantation from unrelated donors were found to be independent prognostic factors for a worse outcome, suggesting that PET is a useful tool to define the extent of disease before allo-SCT in order to choose the proper intensity of the conditioning regimen and GVHD prophylaxis.

Table 4
Multivariate Analysis for Post-transplantation Factors Affecting PFS and OS

Factor	PFS			OS		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Response to transplantation						
CR + VGPR	1		/	1		
≥PR	2.96	1.37-6.37	.006	3.65	1.34-9.93	.011
Extramedullary sites at T1 PET						
0	1			1		
≥1	7.29	2.79-19.04	.000	7.84	2.44-25.17	.001

T1 PET indicates PET 6 months after allogeneic transplantation.

It is well known that PET/CT is the best imaging technique for detecting EMD because of its wider, whole-body field of view, and that the presence of EMD at diagnosis or EMD development during the disease course negatively affect MM prognosis, which is worse in patients with bone-unrelated EMD compared with those with bone-related EMD [12]. Because of the limited number of patients with EMD, we considered patients with bone-related and those with bone-unrelated EMD together, confirming the results reported in the study of Zamagni et al. [5], which included only the cases with bone-unrelated EMD. In our study, persistence of EMD before allo-SCT and 6 months after transplantation was a strong and independent predictor of unfavorable outcome, indicating that EMD is an aggressive MM entity that can be resistant to new drugs and escape immunological control after allo-SCT. The negative prognostic impact of EMD persistence at PET/CT could suggest that a specific treatment should be given to patients with residual EMD, eg, adding local radiotherapy in involved fields identified by PET scans.

Moreover, during the follow-up after allo-SCT, we observed that patients who maintained or achieved PET negativity (PET/CR) 6 months after allo-SCT had a significant PFS and OS advantage. This information could suggest the addition of consolidation treatment with new drugs, withdrawal of GVHD prophylaxis, or administration of donor lymphocyte infusions in patients with persistence of FDG uptake at PET/CT performed 6 months after allo-SCT. Furthermore, we described the management of a subgroup of 17 patients followed with serial yearly PET scans, in whom modulation of immune-suppression and eventual salvage treatment were driven on the basis of clinical response integrated with PET imaging.

We acknowledge that our study has some limitations. First, its retrospective nature could have induced heterogeneity in the study population (eg, timing of the allo-SCT) and missing information in the data collection (eg, FISH karyotype and ISS staging at diagnosis), which was minimized by sharing treatment policy and study protocol among the participating institutions. Second, PET/CT scan before and after allo-SCT were available only for some of the patients and a serial assessment of the response during the follow-up after allo-SCT was available in a minority of patients. Finally, there is still a need to standardize the criteria for PET/CT imaging definitions and interpretation in MM.

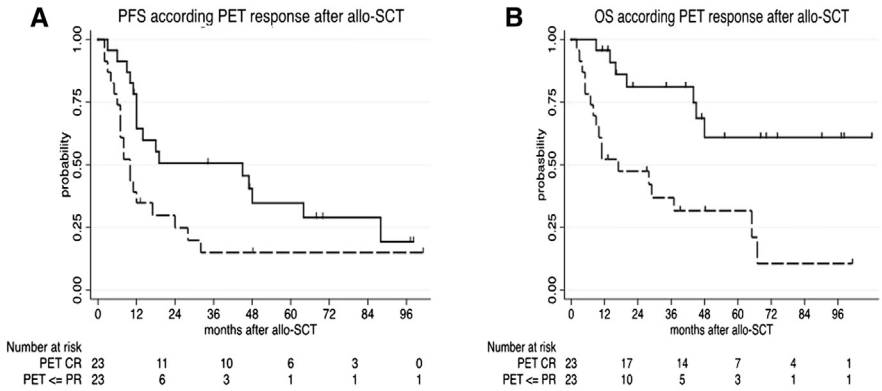

Figure 3. Comparison of PFS (A) and OS (B) from the time of allogeneic transplantation between patients who maintained or reached PET CR 6 months after allo-SCT in comparison with patients with PET PR, stable disease, or PET progression ($P = .03$ and $P = .001$, respectively). Continuous line ____: PET CR; dotted line – – –: PET PR, stable disease, or PET progression.

In conclusion, our study indicates that PET/CT imaging before and 6 months after allo-SCT is a predictor for long-term outcome in allografted patients, suggesting that PET/CT is a reliable technique for MM staging before allo-SCT and response monitoring during follow-up. PET/CT results could contribute to individualization of conditioning regimens and immune-manipulation after transplantation.

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