Published in final edited form as:
Bone Marrow Transplant. 2011 June ; 46(6): 847–851. doi:10.1038/bmt.2010.203.

Early post transplant (F-18) 2-fluoro-2-deoxyglucose positron emission tomography does not predict outcome for patients undergoing auto-SCT in non-Hodgkin and Hodgkin lymphoma

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Abstract

Positron emission tomography (PET) in conjunction with computed tomography is a frequently used modality for staging patients with lymphoma. Utility of PET-computed tomography before or early following auto-SCT has not been as rigorously evaluated. We retrospectively analyzed patients who received auto-SCT for treatment of relapsed or refractory non-Hodgkins lymphoma or Hodgkins disease between the years of 1996 and 2007. Patients who had either a PET scan following salvage chemotherapy within 14 weeks of transplantation (pre-PET), and/or a PET scan 6–14 weeks following transplantation (post-PET) were included. A total of 90 patients were identified for analysis. The median follow-up time is 3.3 years, with a range of 0.13–12.0 years. The median PFS was 4.6 years, and median OS was 5.1 years. At the time of this analysis, 34 patients (37%) experienced disease relapse, and 25 (27%) of the patients died from disease progression. In multivariate Cox proportional hazards analysis, post-PET did not predict for outcome, pre-PET positivity predicted for decrease in PFS. In conclusion, post-PET scan did not predict for PFS or OS in multivariate analysis. Positive pre-PET scan did predict for PFS as seen in previous studies, and may help identify patients who would benefit from innovative post transplant therapies.

Keywords

autologous; HSCT; lymphoma; FDG-PET

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Conflict of interest: The authors declare no conflict of interest.

Introduction

(F-18) 2-Fluoro-2-deoxyglucose positron emission tomography (PET) in conjunction with computed tomography is used to stage and monitor disease in Hodgkins disease (HD) and non-Hodgkins lymphoma (NHL).[1–6] PET provides accurate staging and response to treatment because of its ability to differentiate between necrotic/scar tissue and active lymphoma.[1] The use of PET after 1–2 cycles of chemotherapy and post-treatment has been demonstrated to be predictive of outcome in patients with NHL or HD.[5–11] Furthermore, several studies have shown that pre-transplant PET is predictive for PFS,[12–17] and a subset of those also demonstrate it is predictive for OS,[12,16] though the data is limited in this regard. The role of early post transplant-PET is less well studied. Our hypothesis is that PET would have a role early post transplant, given its sensitivity to detect minimal amounts of active disease and potentially identify those patients who would benefit from post transplant therapy. We have therefore reviewed our 12-year experience to investigate the impact of pre-transplant and early post transplant PET in predicting response, duration of response and survival in those patients with NHL or HD undergoing high-dose therapy with stem cell support. The aim of this study was to evaluate whether pre-transplant PET or early post transplant PET were predictive of PFS or OS.

Patients and methods

Patients

After receiving approval from the Duke University Institutional Review Board, records from consecutive patients who underwent either auto-SCT for relapsed or refractory HD or aggressive NHL (including all NHL except grade I–II follicular lymphoma) between the years of 1996 and 2007 at Duke University Medical Center were reviewed. Patients who had either a PET scan following salvage chemotherapy within 14 weeks of transplantation (pre-PET), and/or a PET scan 6–14 weeks following transplantation (post-PET) were included in the analysis. The PET scans were done at either Duke University Medical Center or an outside facility with interpretations performed by radiologists trained in PET interpretation in lymphoma patients.

For the PET scans, the patients were without caloric intake for 4h and had a blood sugar of <200mg/dl at the time of the FDG administration (140μCi/kg; minimum 10mCi, maximum 20mCi). Images (2–4min per bed position) were acquired from the skull base to the mid thigh starting 60 min after FDG administration. From 1996 to 2003, a GE advance PET scanner (General Electric Healthcare, Waukesha, WI, USA) was used with germanium-68 attenuation correction. From 2003 to 2006, a GE Discovery ST PET/CT (General Electric Healthcare) was used and attenuation correction was based on computerized tomography (CT) images. From 2006 to 2007, imaging was performed on a GE Discovery STE PET/CT (General Electric Healthcare), also with attenuation correction based on CT images. Corrections for scattered events, random events and dead time were all performed. Images (128 × 128 matrix) were reconstructed either with filtered back-projection (1996–1999) or ordered-subsets expectation-maximization (1999–2007). SUV's were calculated from radioactivity concentration, injected dose and patient weight. The PET images with the CT scans available were interpreted by radiologists and nuclear medicine physicians experienced in interpreting scans in patients with lymphoma. Areas of suspected abnormality on the PET scan were correlated with the CT to determine the significance of the abnormality.

Prognostic indices

The secondary age-adjusted International Prognostic Indicator (sAA-IPI) is a risk score used to evaluate patients who have relapsed NHL.[18,19] One point is given for each of the following high risk features: elevated LDH, Ann Arbor stage III–IV and ECOG performance status ≥2. For each incremental increase in points, there is increased risk. The presence of no risk factor is considered low risk; one factor is considered intermediate risk, and two to three factors high risk.

The relapsed Hodgkins disease score is a risk score used for patients who have relapsed HD.[20] Patients receive one point for each of the following: CR duration of < 1 year, B symptoms at relapse, Ann Arbor stage III–IV. The risk of relapse increases with each additional characteristic.

Statistics

Survival time estimates were obtained using the Kaplan– Meier method. OS was measured from time of transplant until death and for those patients still alive, it was censored at the last follow-up date. PFS was measured from time of transplant until first progression or death, whichever occurred first, and was censored at the date of last follow-up for those alive without progression. Proportional hazards models were used to determine whether PET measures were predictive of PFS and OS. Hazard ratios are from univariate Cox proportional hazards models. As there were few significant variables in the univariate analysis, the multivariate model was generated using the following covariates, which were felt to be variables best associated with outcome in the literature: Duration of CR, whether a CR was obtained, B symptoms at relapse, age, remission status at transplant, stage at relapse and extranodal disease; LDH was not included as it was not available for 13 of the 48 patients with DLBCL. The backwards stepwise model selection technique was used to determine which covariates remain in the model, using a significance level of 0.50. This very conservative criteria for removal of variables from the model is recommended by Harrell to help prevent over-fitting.[21] An α-level of 0.05/4=0.0125 was used to test the significance of each of the four PET effects, including pre-PET effect on PFS and OS, as well as post-PET effect on PFS and OS.

Results

Patients

A total of 90 patients were identified for analysis based on having FDG-PET done in the appropriate time frame, (Table 1). Mean age of the patients was 46.7 (18–78). In all, 60 (67%) patients had NHL and 30 (33%) had HD (Table 1). Chemo-sensitive disease was documented in 87 (96%) patients based on PET results. In all, 32 (36%) experienced a CR, and 55 (61%) a PR. Three (3%) patients had stable or progressive disease at time of transplant. The median follow-up time is 3.3 years, with a range 0.13–12.0 years. The median PFS and OS were 4.6 and 5.1 years, respectively. At the time of this analysis, 34 (37%) experienced disease relapse, 25 (27%) of the patients have died from disease progression. The sAA-IPI risk stratification for the patients with DLBCL included 3 low-risk patients, 12 intermediate risk patients and 20 high-risk patients. The data were not available for 13 patients. The rHD score was available for 30 patients, 4 patients had a score of 0, 4 with a score of 1, 12 patients with a score of 2 and 10 patients with a score of 3.

A total of 137 PET scans were performed: 67 pre-PET scans and 70 post-PET scans. However, only 65 pre-PET and 68 post-PET were used in the multivariate analysis due to missing variables for the multivariate analysis. We relied primarily on readings at our center, though there were only outside readings for 16 of the pre-PET and 4 of the post PET scans.

The determination of positive vs negative PET scans was determined by the reading radiologist based on interpretation practices at the time of the PET scan. In all, 26 (39%) pre-PET scans were positive, 20 (29%) of the post-PET scans were positive.

In multivariate analysis (see Table 2), the post-PET scan was not predictive of either PFS or OS. Pre-PET scan negativity did correlate with prolonged PFS 2.91 (1.25– 6.77) P=0.013. Neither pre- nor post-PET results were associated with OS (Table 2).

Univariate Cox proportional hazards model (see Tables 3a and b), demonstrated that pre-PET was predictive of a longer OS, both pre-PET and post-PET were predictive of prolonged PFS. Of all the other variables analyzed, only B symptoms were associated with a decreased PFS and OS.

Discussion

The pre-PET scan has been shown to predict both PFS and OS in the setting of SCT,[12,13,17,19,22] but the value of the early post-PET scan, though well studied in standard chemotherapy, has not been well studied in the setting of auto-SCT. In our study, we found that early post transplant PET did not predict for PFS or OS. Our study did confirm the ability of pre-PET scan to predict for PFS, though not OS.

It is unclear why the FDG-PET findings do not appear to be as useful in the post-auto-SCT setting as compared with the post-chemotherapy setting. One potential confounder is post transplant therapy. In all, 18 patients underwent planned chemotherapy or radiation therapy following autologous transplant. Of those 18, 6 had positive pre-PET and 5 had positive post-PET, therefore, it seems unlikely that there was a significant influence on the outcome.

Another reason why post-PET may not predict PFS or OS is due to the fact that false positive results are frequently obtained when looking at FDG-PET alone. A recent paper by Moskowitz *et al.* evaluating interim and post-treatment PET demonstrated that patients with a positive FDG-PET with a negative biopsy had the same outcome as those patients with a negative PET, confirming the importance of a tissue diagnosis.[23] In this study, there was a high-false positive rate in FDG-PET alone, as biopsy of the positive lesions proved to be negative for active disease. It is possible that the masses with increased FDG uptake following auto-SCT were false positive results, that would have been negative had they undergone a biopsy. In fact, there were two patients in this study who had positive-PET scans following auto-SCT and were followed expectantly but with little or no change to the lesion in question.

Our study also suggests that the PET findings may be more helpful than sAA-IPI or relapsed Hodgkins disease score, as in the univariate analysis, as negative PET was found to be predictive of PFS and OS, and sAA-IPI and relapsed Hodgkins disease score were not. This may have been confounded by the low numbers of patients with HD and the high numbers of patients missing LDH as part of the sAA-IPI score. This observation is similar to that observed by Spaepen *et al.*[6] and Alousi *et al.*[15]

Limitations of our study include the small number of patients, and retrospective nature of the study. During the time frame evaluated, standards in assessing disease stage and response were changing. Initially, those patients who underwent PET were limited by many factors, including physician preference, availability and insurance coverage of these tests. One other possible confounder is that PET was done in patients with high-risk disease. However, as relapse rates and mortality rates are similar to those in the published literature, it seems that is unlikely.

In our retrospective study, we found that in multivariate analysis, pre-PET but not post-PET results were associated with PFS, and neither was predictive of OS. The pre-PET findings in our study is consistent with previous re-ports.[12,13,15,19] These findings suggest that in patients who have a positive pre-transplant PET, additional post transplant therapies should be considered to improve PFS. This hypothesis needs to be studied in a prospective fashion.

Acknowledgments

We thank Bercedis Peterson, PhD for her assistance in statistical methods.

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Table 1

Patient characteristics

Patient characteristics	
Age	46.7 (18–78)
Gender, n (%)	
Female	32
Male	58
Response to salvage therapy, n (%)	
CR	32 (36)
PR	55 (61)
SD/PD	3 (3)
Type of lymphoma, n (%)	
NHL	60 (67)
Int/high-grade B-cell lymphoma	50
Mantle cell	4
T cell/anaplastic	6
Hodgkins lymphoma	30 (33)
Additional radiotherapy, n (%)	18
Pre-txp PET positive	26/67 (39%)
Post-txp PET positive	20/70 (29%)
Stage at relapse, n (%)	
I	1
II	13
III	18
IV	24
Refractory disease	30
Transplanted in first CR	3
Missing	1
Conditioning regimen	
CVB	72
BEAM	10
Other	4
Missing	4
Both pre-PET and post-PET	47
Positive-negative	7
Positive-positive	8
Negative-negative	26
Negative-positive	6
Post transplant events, n (%)	
Experienced disease relapse	34 (37%)
Death from disease	25 (27%)
Post transplant therapy	20 (22%)

Patient characteristics	
Radiation	17
Rituximab	3
Recommended, but not done	10
None	60

Abbreviations: NHL=non-Hodgkins lymphoma; PET=positron emission tomography.

Table 2

Results from proportional hazards multivariate models

Variable	n	*DFS*		*OS*	
		HR (95% CI)	**P-*value***	***HR (95% CI)***	**P-*value***
Pre-PET	65	*2.91 (1.25–6.77)*	*0.013*	2.60 (1.04–6.50)	0.041
Post-PET	68	2.16 (1.02–4.60)	0.045	1.48 (0.62–3.51)	0.38

Abbreviations: CI=confidence intervals; HR=hazard ratios; PET= positron emission tomography.

Each HR/*P*-value pair is representative of the PET results from one multivariate model; results are shown for four separate multivariate models.

Significant *P*-values are in italics.

Table 3a

Univariate Cox proportional-hazards modeling for prediction of OS

Variable	Hazard ratio	Lower 95% CI for HR	Upper 95% CI for HR	Log-rank P-value	
Pre-PET	*2.57*	*1.08*	*6.12*	*0.034*	*Neg vs Pos*
Post-PET	2.01	0.90	4.49	0.087	Neg vs Pos
Any PET	*2.62*	*1.30*	*5.28*	*0.007*	*Neg vs Any Pos*
Stage diagnosis	1.03	0.52	2.05	0.933	Stage I–III vs IV
Stage relapse	1.29	0.65	2.58	0.468	Stage I–III vs IV
B symptoms	*2.17*	*1.06*	*4.44*	*0.034*	*No vs yes*
Age	1.00	0.98	1.03	0.787	1 year increase
Extra nodal disease	1.28	0.62	2.64	0.512	no vs yes
Hodgkin's disease	0.81	0.36	1.82	0.613	Hodgkin's vs NHL
LDH	1.61	0.64	4.05	0.316	normal vs above normal
CR	0.51	0.23	1.14	0.103	CR vs other responses
Duration of CR	0.43	0.18	1.00	0.050	≤1year vs > 1year
sAA-IPI	1.31	0.75	2.29	0.350	1 unit increase
Hdrisk	2.09	0.83	5.30	0.119	1 unit increase

Abbreviations: CI=confidence intervals; HR=hazard ratios; Neg=negative; PET= positron emission; Pos=positive; sAA-IPI=secondary age-adjusted International Prognostic Indicator.

Significant *P*-values ($P<0.05$) are in italics.

Table 3b: Univariate cox proportional-hazards modeling for prediction of progression-free Survival

Variable	*Hazard ratio*	*Lower 95% CI for HR*	*Upper 95% CI for HR*	*Log-rank P-value*	*Comparison*
Pre-PET	*2.23*	*1.01*	*4.92*	*0.047*	*Neg vs Pos*
Post-PET	*2.43*	*1.20*	*4.95*	*0.014*	*Neg vs Pos*
Any PET	*2.56*	*1.36*	*4.82*	*0.004*	*Neg vs Any Pos*
Stage diagnosis	1.50	0.80	2.80	0.204	Stage I–III vs IV
Stage relapse	1.60	0.85	2.99	0.144	Stage I–III vs IV
B symptoms	*2.22*	*1.16*	*4.26*	*0.017*	*No vs yes*
Age	1.01	0.99	1.04	0.391	1 year increase
Extra nodal disease	1.33	0.69	2.55	0.390	No vs yes
LDH	1.41	0.59	3.37	0.437	Normal vs above normal
CR at time of transplant	0.70	0.35	1.37	0.297	CR vs other responses

Table 3b: Univariate cox proportional-hazards modeling for prediction of progression-free Survival

Variable	*Hazard ratio*	*Lower 95% CI for HR*	*Upper 95% CI for HR*	*Log-rank P-value*	*Comparison*
Duration of first CR	0.79	0.40	1.57	0.508	≤1year vs >1year
sAAIPI	1.20	0.72	2.00	0.489	1 unit increase
Hdrisk	2.18	0.99	4.78	0.052	1 unit increase

Abbreviations: CI=confidence intervals; HR=hazard ratios; Neg=negative; PET=positron emission tomography; Pos=positive; sAA-IPI=secondary age-adjusted International Prognostic Indicator.

Significant *P*-values ($P<0.05$) are in italics.

Bone Marrow Transplant. Author manuscript; available in PMC 2013 April 08.