The Role of F18-fluorodeoxyglucose Positron Emission Tomography in the Management of Relapsed or Refractory Hodgkin's Lymphoma

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Abstract

Positron emission tomography (PET) is widely used in the diagnosis and response assessment after first-line treatment of Hodgkin's lymphoma (HL). For the approximately 30 % of patients who relapse or have refractory disease, PET can provide valuable prognostic information during second-line therapy, at the time of autologous stem cell transplant (ASCT). Retrospective studies performed over the past decade have consistently found a significant association between a positive PET scan after salvage chemotherapy for HL and progression-free and overall survival after ASCT. In fact, the predictive value of pre-transplant PET appears higher than that of more traditional clinical risk factors. Unfortunately, there is little data to recommend the best treatment course for patients who have a positive pre-ASCT PET, and few studies have addressed the role of PET in other relapsed/refractory HL settings.

Keywords

Hodgkin's lymphoma, positron emission tomography, autologous stem cell transplant, allogeneic stem cell transplant, prognosis

F18-fluorodeoxyglucose positron emission tomography (FDG-PET), commonly combined with computed tomography (CT), is widely used in the initial evaluation and response assessment of patients with Hodgkin's lymphoma (HL). Its sensitivity for nodal and extranodal sites of disease can add to the staging information obtained with CT alone,[1] and PET is valuable in the response assessment at the end of front-line therapy because it can distinguish active disease from fibrosis in residual masses. In fact, the goal of front-line therapy is now a PET-negative complete remission (CR).[2] Interim PET scan, performed during the initial course of therapy, may also have prognostic significance,[3] and treatment adapted to interim PET results is under investigation in ongoing clinical trials.

The role of PET in the response assessment and management of relapsed and refractory HL is less well established than in the front-line setting. Up to 30 % of patients with HL will fail to respond to, or will relapse after, initial therapy, and approximately 50 % of these patients can achieve durable disease-free survival with salvage chemotherapy and autologous stem cell transplant (ASCT). Retrospective studies have consistently demonstrated the prognostic significance of a PET scan performed prior to ASCT, although it is unclear how those PET results should guide the choice of salvage therapy or the transplant approach. This article will focus on the role of PET in the management of patients with relapsed or refractory HL who are candidates for ASCT. It will also address the limited evidence for the use of PET in relapsed HL patients who are not undergoing ASCT.

Positron Emission Tomography in Patients Undergoing Autologous Stem Cell Transplant
Prognostic Significance of Pre-transplant Positron Emission Tomography

Over the past two decades, several groups have identified clinical factors that predict the outcome of salvage therapy in patients with relapsed or refractory HL.[4–9] They identified adverse factors that include time to relapse less than one year, advanced stage or extranodal disease at relapse, and various components of the International Prognostic Score,[10] such as hypoalbuminemia, anemia, older age, and lymphopenia. Because the various proposed prognostic scores are based on factors present at the time of relapse, without incorporating subsequent information about response to salvage therapy, they have the potential to influence the choice of salvage chemotherapy. However, in practice, most patients with relapsed or refractory HL are candidates for ASCT and are treated with standard aggressive combination chemotherapy, regardless of their relapse prognostic score. Instead of clinical factors at relapse, the response to the salvage chemotherapy has emerged as the most important predictor of progression-free survival (PFS) and overall survival (OS) in relapsed HL, and that response is most accurately determined by PET.

Many generally small and retrospective studies published over the past decade consistently concluded that PET scan prior to ASCT was predictive of outcome in patients with lymphoma. A meta-analysis of 16 such studies concluded, despite heterogeneity in the lymphoma

Table 1: Studies of Positron Emission Tomography Performed Before Autologous Stem Cell Transplant in Patients with Relapsed or Refractory Hodgkin's Lymphoma

Reference	Number of Patients	Pre-transplant Chemotherapy (n)	SD/PD at Time of Transplant (%)	Conditioning Regimen	Pre-transplant PET Result, n (%)	PFS (%)	OS (%)
Retrospective Studies							
Jabbour et al., 2007[13]	212 (144 gallium, 68 PET)	ASHAP or ESHAP	7	BEAM, CBV, or BuCy	PET/gallium pos: 68 (32) PET/gallium neg: 144 (68)	23 v. 69 at 3 yr p<0.0001	58 v. 87 at 3 yr p<0.0001
Moskowitz et al., 2010[14]	152 (110 gallium, 42 PET)	ICE	28	Radiation-based or CBV	PET/gallium pos: 42 (28) PET/gallium neg: 110 (72)	31 v. 75 at 5 yr p<0.0001	NS
Devillier et al., 2012[16]	111	DHAP or ifosfamide-based	0	BEAM (58 % had tandem ASCT)	PET pos: 26 (23) PET neg: 85 (77)	23 v. 79 at 5 yr p<0.001	55 v. 90 at 5 yr p=0.001
Mocikova et al., 2011[17]	76	DHAP, ESHAP (41) ICE (15) Other (20)	12	BEAM	PET pos: 20 (26) PET neg: 56 (74)	36 v. 74 at 2 yr p=0.01	61 v. 90 at 2 yr p=0.009
Smeltzer et al., 2011[18]	46	ESHAP (19) ICE (15) Other (11)	7	BEAM	PET pos: 23 (50) PET neg: 23 (50)	41 v. 82 at 3 yr p=0.02	64 v. 91 at 3 yr p=0.08
Sucak et al., 2011[15]	43	GV (30) ICE (7) Other (6)	28	BEAM	PET pos: 26 (60) PET neg: 17 (40)	38 v. 71 at 3 yr p=0.008	75 v. 94 at 3 yr p>0.05
Cocorocchio et al., 2012[21]	40	Various	3	Various	PET pos: 14 (35) PET neg: 26 (65)	43 v. 79 at 5 yr p<0.01	43 v. 92 at 5 yr p<0.01
Castagna et al., 2009[19]	24	IGEV	NS	NS	PET pos: 6 (25) PET neg: 18 (75)	0 v. 78 at 2 yr p<0.001	17 v. 87 at 2 yr p=0.003
Prospective Studies							
Arai et al., 2010[22]	77	DHAP (40) ICE (35) Other (17)	9	GV-CBV	PET pos: 29 (38) PET neg: 48 (62)	45 v. 79 at 2 yr p=0.003	77 v. 91 at 2 yr p=0.07

ASHAP = adriamycin, methylprednisolone, cytarabine, and cisplatin; BEAM = carmustine, etoposide, cytarabine, and melphalan; BCNU = bis-chloroethylnitrosourea; BuCy = busulfan and cytoxan; CBV = cyclophosphamide, BCNU, and etoposide; DHAP = dexamethasone, cytarabine, and cisplatin; ESHAP = etoposide, methylprednisolone, cytarabine, and cisplatin; GV = gemcitabine and vinorelbine; ICE = ifosfamide, carboplatin, and etoposide; IGEV = ifosfamide, gemcitabine, vinorelbine, and prednisone; NS = not stated; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; OS = overall survival; SD = stable disease; v. = versus; yr = year.

populations and methods, that a positive pre-transplant PET was significantly associated with worse PFS and OS.[11] In a more recent study, Palmer et al. reported that in a consecutive series of patients who underwent ASCT for relapsed HL (n=30) or non-Hodgkin's lymphoma (NHL, n=60), negative pre-transplant PET was observed in 61 % and was associated with prolonged PFS (p=0.013) but not OS.[12]

Studies that focused on pre-ASCT PET in patients with relapsed or refractory HL are summarized in *Table 1*. Of note, some of the studies included patients who had stable or progressive disease at the time of transplant, although pre-transplant PET does not add important information when CT scan shows obvious failure to respond to the salvage chemotherapy. The largest studies[13,14] included patients who underwent imaging with either gallium scans or PET, on the reasonable assumption that both modalities provide functional assessment of residual disease. The patients in these and other, mostly single institution studies were treated with common salvage chemotherapy and transplant conditioning regimens, making the results generalizable to contemporary patients. Allowing for variation in sample size and duration of follow-up, the results across these trials are remarkably consistent: positive and negative pre-ASCT PET are associated with PFS of 20–40 % and 70–80 %, respectively.

In multivariate analyses, pre-transplant PET has been significantly associated with both PFS and OS,[12–15] and this association is stronger than the predictive value of the traditional clinical risk factors. For example, Devillier et al. classified relapsed HL patients as favorable/intermediate or unfavorable risk based on the presence of one or less or at least two of the following risk factors: relapse less than 12 months after first-line therapy, stage III-IV at relapse, and relapse in a previously radiated field. PET status at transplant was significantly associated with PFS and OS in both risk groups, and PET status at transplant was the only significant risk factor in multivariate analysis.[16] In Mocikova et al.'s series of 76 HL patients, pre-transplant PET was the only factor significant for PFS and OS in univariate analysis, but PET was not significant in multivariate analysis, due to correlation between the variables examined.[17] Smeltzer et al. compared the predictive value of pre-transplant PET and several clinical prognostic models and found that PET, but not the prognostic models, was significantly associated with PFS, although the relatively small patient number may have limited the ability to detect significance with the prognostic models.[18] Taken together, these studies demonstrate that pre-transplant PET is predictive of outcome in all prognostic groups, and PET is more strongly associated with outcome than the traditional risk factors such as duration of first remission and disease characteristics at relapse.

Although the retrospective studies detailed in *Table 1* have consistent conclusions about the value of PET before ASCT, there are several important issues that affect the prospective use of pre-transplant PET in clinical practice.

First, the criteria for interpreting a PET scan performed after two to four cycles of salvage therapy for relapsed lymphoma are not standardized. Investigators have used the International Harmonization Project criteria[15,17–19] (which define a positive site as one with FDG uptake greater than mediastinal blood pool[20]), Gallamini's criteria[21,22] (which define 'minimal residual' uptake as negative[3]), or simple review of written radiology reports.[12,13] The 5-point London scale or the change in maximum standardized uptake value (SUV) from baseline to post-salvage PET are two other criteria that could be applied in this setting, since they have been studied in the interpretation of interim PET performed during the initial course of chemotherapy.[23] Further complicating the use of these PET criteria is the observation that application of the response scales varies among nuclear medicine physicians, even experienced ones working in the context of a clinical trial.[24]

A second issue affecting the performance of pre-transplant PET is the timing of the scan relative to the cycles of salvage chemotherapy. Response criteria for PET at the end of front-line therapy recommend six to eight weeks between chemotherapy and PET,[2] but that interval is not practical for patients approaching stem cell transplant. Three weeks after chemotherapy is probably a reasonable interval, consistent with the timing of interim PET during frontline therapy. PET can be performed after two to four cycles of salvage therapy, and it is not clear which of these time-points is optimal. PET after two cycles is preferable to allow time to change the transplant decision if the PET is positive, but PET after three or four cycles of salvage chemotherapy may provide a more accurate response assessment.

Schot et al. addressed the timing of post-salvage PET in 39 patients with relapsed or refractory HL (n=11) or aggressive NHL (n=28).[25] PET was performed after two cycles of salvage chemotherapy (PET2) and again after three cycles (PET3) only in patients who had abnormal PET2. Forty-four percent of patients had negative PET2, and six of 22 patients (27 %) had negative PET3. Both PET2 and PET3 predicted 2-year PFS (27 versus 71 % for PET2 positive or negative; 18 versus 60 % for PET3 positive or negative). The positive predictive value for relapse was 89 % for PET2 and 100 % for PET3. In a retrospective study that included only HL patients, Castagna et al. performed PET after two and four cycles of salvage chemotherapy.[19] Two-year PFS and OS were significantly associated with PET performed at both time-points. Ultimately, rigorous timing and interpretation of pre-transplant PET may not be crucial if the scan is simply providing prognostic information. On the other hand, if the PET is going to drive the treatment plan, the criteria for interpretation and the timing of pre-transplant PET will need to be further investigated and standardized.

Changing Therapy Based on Positron Emission Tomography Result

Given the evidence that a positive PET scan prior to ASCT predicts a 60–75 % risk of progressive disease in the two to five years after transplant, the question naturally follows: should patients with a positive pre-transplant PET receive additional therapy? Options for these patients could include a change in the salvage chemotherapy regimen, tandem ASCT, radiation or maintenance therapy post-ASCT, or allogeneic SCT. Ongoing clinical trials are investigating post-ASCT maintenance therapy with novel agents such as brentuximab vedotin or

lenalidomide, but results of that approach in high-risk patients are at this point unknown. Allogeneic SCT for high-risk relapsed or refractory HL is also investigational. Post-transplant radiation has not been systematically investigated, but it is a reasonable option for patients who have stage I or II disease and PET-positive residual disease in a field that has not been previously radiated.

Moskowitz et al. explored risk-adapted salvage chemotherapy in a prospective study of 97 patients.[26] Patients underwent PET after two cycles of ifosfamide, carboplatin and etoposide (ICE), and scans that had residual FDG uptake greater than blood pool were considered positive. Patients with positive PET, including those with progressive disease on ICE, were treated with two cycles of gemcitabine, vinorelbine and liposomal doxorubicin (GVD), and PET was then repeated. Patients with negative PET after ICE or stable disease or better after GVD underwent ASCT. Eighty-six percent of patients received involved field radiation with or without total lymphoid irradiation at the time of transplant. Thirty-eight patients (39 %) had a positive PET after ICE, and 33 of them went on to treatment with GVD. Fifty-two percent of patients treated with GVD achieved a negative PET and, remarkably, these patients had an identical event-free survival (EFS) to the patients who underwent ASCT after a negative PET post-ICE (EFS approximately 80 % at a median 51 months follow-up). These results suggest that a negative pre-transplant PET retains its good prognostic value whether it is achieved after one or two salvage regimens.

Devillier et al. proposed that tandem ASCT improves the outcome of patients who have a positive PET after salvage chemotherapy.[16] They drew on the results of the GELA/Société Française de Greffe de Moelle (SFGM) H96 trial, which demonstrated a benefit from tandem ASCT in patients who had high-risk relapsed or refractory HL based on clinical risk factors.[27] In the Devillier study, patients with primary refractory disease, unfavorable clinical risk factors, or positive pre-transplant PET were considered for tandem transplant. In the 26 PET-positive patients, tandem ASCT was associated with a significant improvement in PFS (0–43 %, p=0.034) but not OS (47–58 %, p=0.84). However, PFS was still relatively low, and the small sample size and retrospective design preclude the conclusion that tandem ASCT improves the prognosis of all patients with a positive PET pre-transplant.

Prognostic Significance of Positron Emission Tomography after Autologous Stem Cell Transplant

Extrapolating from the significant predictive value of PET performed at the end of front-line HL therapy, one might assume that a PET performed after ASCT would have a strong association with outcome, since that time-point represents the end of second-line therapy. In fact, the available data do support the prognostic significance of post-transplant PET. Sucak et al. reported that none the 13 patients in their series who had a positive post-ASCT PET were free of progression, versus PFS in 73 % of patients with a negative post-transplant PET.[15] Of note, PFS and OS for the 23 % of patients who converted to a negative PET after ASCT were not statistically different than the PFS and OS of patients who had a negative PET both before and after ASCT. In multivariate analysis, both pre- and post-transplant PET were independently associated with PFS. In another retrospective study, Cocorocchio et al. reported that 60 of 78 HL patients (77 %) had a negative PET after ASCT, and five-year PFS was

significantly higher for the patients with a negative post-transplant PET (86 versus 22 %, p<0.01).[21] Both pre- and post-transplant PET were significant for PFS and OS in univariate analysis. In contrast, Palmer et al. did not find a correlation between post-ASCT PET and either PFS or OS.[12] However, their study included a mixed population of both HL and NHL patients, and some patients underwent post-transplant chemotherapy or radiation. Although the studies addressing the significance of post-ASCT PET are few and small, it seems fair to conclude that the presence of residual detectable disease at the conclusion of salvage chemotherapy and ASCT portends a high risk of relapse.

Positron Emission Tomography in Patients Undergoing Allogeneic Stem Cell Transplant

While the retrospective data presented above consistently demonstrate the prognostic value of PET scan performed before ASCT, the value of PET prior to allogeneic SCT for HL is less clear. Allogeneic SCT is generally reserved for HL patients who relapse after ASCT or who have very refractory disease, and outcomes are determined as much by treatment-related morbidity and mortality as by long-term disease control. Due to the significant toxicity of myeloablative conditioning regimens, especially in patients who have had a prior ASCT, most HL patients who undergo allogeneic SCT receive a reduced intensity conditioning regimen. It may be that chemosensitivity as defined by CR on PET may not be as important for predicting response to reduced intensity allogeneic transplant, since the efficacy of the transplant relies on a graft versus lymphoma effect more than response to the transplant conditioning regimen. On the other hand, patients with frankly chemorefractory disease are unlikely to benefit from allogeneic SCT, and these patients usually do not proceed with the transplant.

One relatively large prospective study addressed the prognostic role of pre-allogeneic SCT PET in a mixed population of lymphoma patients undergoing allogeneic SCT following a reduced-intensity conditioning regimen.[28,29] PET was performed pre-transplant and at regular intervals until 36 months post-transplant. In the total study population of 80 patients, pre-transplant PET was positive in 42 and negative in 38. Among the 22 HL patients in the study, pre-transplant PET was positive in 14 (64 %) and negative in 8 (36 %). At a median follow-up of 45 months, for the whole study population, PFS and OS were not different in the PET-positive and PET-negative groups, and positive predictive value and negative predictive value of pre-transplant PET for relapse were 36 % and 39 %, respectively. Of note, this study included a majority of patients with follicular lymphoma, for whom the graft versus lymphoma effect is particularly effective at eliminating residual disease.

An Italian group performed a retrospective analysis of 80 patients (46 with HL and 34 with aggressive NHL) who had a PET performed prior to reduced-intensity allogeneic SCT.[30] Eighty percent of the patients had failed a prior ASCT, and all had achieved a CR or partial remission at the time of allogeneic SCT. Among the HL patients, 23 had a positive pre-transplant PET and 23 had a negative pre-transplant PET. There was a trend toward a higher risk of disease recurrence in HL patients with a positive PET: 59 % versus 27 % (p=0.066). For the combined study population, PET was also significant for OS in multivariate analysis.

The conflicting prognostic value of PET performed before allogeneic SCT in the above studies may be due to variations in the conditioning regimens and transplant strategies, including the inclusion of tandem autologous/allogeneic transplants and haplo-identical transplants in the Italian study. The most important difference is probably the mix of aggressive versus indolent NHL patients included with the HL population.

Positron Emission Tomography in Patients who are not Candidates for Transplant

No studies have specifically addressed the predictive value of PET in patients who are not candidates for stem cell transplant. For these patients, PET is unlikely to add useful information to the response assessment obtained by CT alone. If a patient is not undergoing potentially curative, intensive therapy with autologous or allogeneic transplant, then the primary goal of salvage therapy is to prolong survival. A negative PET at the completion of a salvage regimen may predict a longer remission, as it does in other treatment settings, but it is unlikely that the therapeutic plan will be altered based on the PET results, if the patient has otherwise met CT criteria for response. There is no evidence that treating to a PET-negative CR in a lymphoma patient who is not a transplant candidate will improve their outcome.

Conclusions

For the majority of patients with relapsed or refractory HL who are candidates for ASCT, PET should be performed approximately three weeks after two to four cycles of salvage chemotherapy. Patients who have a negative PET scan at that time-point should proceed with ASCT, for they have a PFS greater than 70 %, even with refractory disease or poor-risk factors at relapse. On the other hand, patients with a positive PET scan after salvage chemotherapy have a poorer prognosis and could be considered for alternative therapy, including post-transplant radiation or investigational approaches such as maintenance therapy. A change in salvage chemotherapy, with a goal of achieving a PET-negative CR prior to transplant, is a reasonable approach, since one prospective study demonstrated that a negative PET after a second salvage regimen is as favorable as a negative PET after one salvage regimen.[26] However, the benefit of additional salvage therapy needs to be explored further in prospective studies, to establish the appropriate patient selection and minimize treatment-related toxicities prior to ASCT. Ongoing studies incorporating the antibody-drug conjugate brentuximab vedotin into risk-adapted salvage therapy may provide another option to optimize response prior to ASCT. Achieving a negative PET prior to allogeneic stem cell transplant may be less predictive of PFS and OS, and selected patients who have chemosensitive, but FDG-avid, disease may be considered for that approach. ■

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