Positron emission tomography response at the time of autologous stem cell transplantation predicts outcome of patients with relapsed and/or refractory Hodgkin's lymphoma responding to prior salvage therapy

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ABSTRACT

Background

High-dose chemotherapy followed by autologous stem cell transplantation is the standard treatment for relapsed and/or refractory Hodgkin's lymphoma although half of patients relapse after transplantation. Predictive factors, such as relapse within 12 months, Ann-Arbor stage at relapse, and relapse in previously irradiated fields are classically used to identify patients with poor outcome. Recently, 18-fluorodeoxyglucose positron emission tomography has emerged as a new method for providing information to predict outcome. The aim of this study was to confirm the predictive value of positron emission tomography status after salvage therapy and to compare single *versus* tandem autologous stem cell transplantation in patients with relapsed and/or refractory Hodgkin's lymphoma.

Design and Methods

We report a series of 111 consecutive patients with treatment-sensitive relapsed and/or treatment-refractory Hodgkin's lymphoma who achieved complete (positron emission tomography-negative group) or partial remission (positron emission tomography-positive group) at positron emission tomography evaluation after salvage chemotherapy and who underwent single or tandem autologous stem cell transplantation.

Results

Five-year overall and progression-free survival rates were 81% and 64%, respectively. There were significant differences in 5-year progression-free survival (79% *versus* 23%; $P<0.001$) and 5-year overall survival (90% *versus* 55%, $P=0.001$) between the positron emission tomography-negative and -positive groups, respectively. A complete response, as determined by positron emission tomography evaluation, after salvage therapy predicted significantly better 5-year overall survival rates in both intermediate (91% *versus* 50%; $P=0.029$) and unfavorable (89% *versus* 58%; P=0.026) risk subgroup analyses. In the positron emission tomography-positive subgroup, tandem transplantation improved 5-year progression-free survival from 0% (in the single transplantation group) to 43% ($P=0.034$). Multivariate analysis showed that positron emission tomography status (hazard ratio: 5.26 [2.57-10.73]) and tandem transplantation (hazard ratio: 0.39 [0.19-0.78]) but not risk factors at relapse (hazard ratio: 1.77 [0.80-3.92]) significantly influenced progression-free survival, while only tomography status significantly influenced overall survival (hazard ratio: 4.03 [1.38-11.75]).

Conclusions

In patients with relapsed/refractory Hodgkin's lymphoma responding to prior salvage therapy, positron emission tomography response at time of autologous stem cell transplantation favorably influences outcome and enables identification of patients requiring single or tandem transplantation.

Key words: Hodgkin's lymphoma, PET, outcome, relapsed refractory, ASCT.

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The online version of this article has a Supplementary Appendix.

Introduction

Hodgkin's lymphoma (HL) is nowadays considered as a curable disease with more than 85% of patients achieving long-term survival. In advanced HL, first-line treatment with ABVD or BEACOPP is considered the standard of care, producing a 5-year overall survival rate ranging between 80% and 90%.[1-3] However, the outcome of patients with relapsed and/or refractory HL remains poor with a 5-year overall survival rate ranging from 30% to 70%.[4] The adverse prognostic factors which have been reported in the literature include an interval of less than 12 months between the end of first-line therapy and relapse, Ann-Arbor stage III or IV at relapse, and relapse in a previously irradiated field.[5,6] Two randomized studies have shown that intensive chemotherapy followed by autologous stem cell transplantation (ASCT) improves disease control and outcome; however, less than 50% of poor-risk patients are cured.[7,8] The low non-relapse mortality of ASCT encourages us to use high-dose therapy with stem cell support for these poor-risk patients.[9] Several small retrospective studies showed that tandem ASCT is feasible and could also improve the outcome of patients with relapsed and/or refractory HL.[10-12] More recently, a risk-adapted treatment strategy based on adverse prognostic factors at relapse showed that tandem ASCT could improve survival in poor-risk patients.[13] The development of new methods, such as 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), are helpful for physicians, because they can provide a precise evaluation of disease response after treatment. For this reason FDG-PET is now commonly used for tumor evaluation in patients with HL.[14] Some retrospective studies reported its predictive value after salvage therapy and before ASCT.[15,16] We here report a series of patients with relapsed and/or refractory HL who underwent single or tandem ASCT after FDG-PET response assessment.

Design and Methods

Study design

We retrospectively analyzed consecutive patients with treatment-sensitive relapsed and/or treatment-refractory HL who underwent high-dose therapy followed by ASCT between 2002 and 2010 at two institutions (*Institut Paoli Calmettes*, Marseille, France and the *Istituto Clinico Humanitas*, Milan, Italy). Patients were eligible if they had classical HL histology proven by a new biopsy at relapse, were serologically negative for human immunodeficiency virus, had primary relapsed and/or refractory HL and achieved a complete or partial response before ASCT [as determined by computed tomography (CT) scanning and FDG-PET evaluation]. Patients who did not achieve at least a partial response after salvage therapy and before ASCT were excluded from the study. We evaluated the predictive value of PET status before ASCT and compared a single *versus* tandem ASCT strategy in the setting of relapsed and/or refractory HL patients responding to salvage therapy before ASCT. Patients were informed of the investigational nature of the study and informed consent was required in compliance with institutional guidelines. This protocol was approved by our institutional review board. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Risk stratification

Patients were first staged at diagnosis according to the Ann Arbor classification. Disease risk at relapse was evaluated according to the *Société Française de Greffe de Moelle* (SFGM) adverse prognostic factors: interval from end of first-line therapy to relapse < 12 months; Ann-Arbor stage III or IV at relapse; and relapse in a previously irradiated field. Patients with 0, 1 or ≥ 2 of the previous factors were considered as having a favorable, intermediate or unfavorable risk, respectively. Patients with primary refractory disease were also classified as having an unfavorable risk. Primary refractory disease was defined as disease progression during first-line chemotherapy, or only a transient response (complete or partial response lasting ≤3 months) after induction treatment. Progressive disease required the following: (i) a ≥25% increase from nadir in the sum of the products of the greatest diameter of any previously identified abnormal node for partial responders or non-responders; and (ii) the appearance of any new lesion within ≤3 months after the end of therapy.

Salvage therapy and autologous stem cell transplantation

Salvage therapies consisted of DHAP[17] (dexamethasone, high-dose cytarabine and cisplatin/carboplatin), IVA[13] (ifosfamide, etoposide and doxorubicin) or ICE[18] (ifosfamide, carboplatin and etoposide) in the French institute and IGEV[19] (ifosfamide, gemcitabine, vinorelbine) in the Italian institute. Autologous peripheral blood stem cells were collected by apheresis after mobilization with granulocyte colony-stimulating factor (G-CSF) following salvage chemotherapy. From 2×10^6 to 5×10^6 $CD34^+$ cells/kg were collected for each planned transplantation, processed for cryopreservation and thawed according to institutional standard operative procedures. Patients received either BEAM[4] (carmustine, etoposide, cytarabine and melphalan) or BEAM followed by NCBV[11] (mitoxantrone, cyclophosphamide, carmustine and etoposide) as the conditioning regimen for single or tandem ASCT, respectively. In the Italian program, patients received high-dose melphalan or BEAM as the conditioning regimen for single ASCT and high-dose melphalan followed by BEAM for a tandem ASCT. The choice of single or tandem transplantation was made on the basis of both SFGM risk factors at relapse and PET response after salvage therapy. Initially, patients in the unfavorable risk group according to SFGM factors were selected for tandem ASCT. We, therefore, also considered PET response to prior salvage therapy in order to select patients for single or tandem ASCT.

Response as determined by positron emission tomography assessment

FDG-PET was performed after two or three courses of salvage chemotherapy depending on the type of chemotherapy. All imaging data were acquired with a combined PET/CT inline system (hybrid Biograph LSO system, multislice spiral scanner Siemens). Patients fasted for at least 4 hours, and glycemia was controlled (<7mmol/L) before the intravenous administration of 370 to 450 MBq (5MBq/Kg) ^{18}FDG. They were orally hydrated with 500 mL of water during the FDG uptake period and asked to empty their bladder before being positioned for PET/CT imaging, which started 1 hour after the FDG injection. PET/CT images were taken from the skull base to the proximal thighs. The first CT images (4 mm slice collimation, 130 Kv, 90 mA, bed speed of 8 mm/s, pitch of 2) were obtained without injection of contrast medium. These were followed by PET acquisition using six or seven bed positions for 3 minutes each (4 minutes if the patient weighed more than 100 kg). The FDG-PET images were reconstructed using an iterative algorithm, and attenuation was corrected by using CT images. All corrected PET and non-corrected PET and fused PET/CT images were first independently interpreted by qualitative visual analysis by one experienced nuclear medicine specialist with clinical information about the patients. Before 2007, a lesion with increased uptake of ^{18}FDG as compared with the mediastinal back-

ground uptake was classified as malignant. The standardized uptake value, defined as the activity per milliliter within the region of interest divided by the injected dose (MBq) per gram of body weight, was also evaluated: lesions with a standardized uptake value > 2-2.5 in the mediastinum were deemed malignant. After 2007, the criteria published by Cheson *et al.*[20] were used: patients with a negative PET were considered in complete response and patients with greater than 50% regression of measurable disease and a positive PET were considered in partial response.

Statistical analysis

The patients' characteristics were compared with the χ^2 and Fisher's exact tests. Progression-free survival was measured from the date of first ASCT until progression, relapse, or death from any cause. Overall survival was measured from the date of first ASCT until death from any cause. Progression-free survival and overall survival were estimated with 95% confidence intervals. Survival curves were generated using the Kaplan-Meier estimation[21] and compared using the log-rank test, with P values <0.05 being defined as statistically significant. We performed univariate and multivariate analyses with Cox regression.[22] Hazards ratios were estimated with 95% confidence intervals. All analyses were computed on the Statistical Package for the Social Sciences (SPSS) software.

Results

Patients' characteristics

One hundred and eleven consecutive patients with relapsed and/or refractory HL were included in this retrospective study. The characteristics of the patients and their disease are summarized in Table 1. At diagnosis, 58 patients (54%) presented with advanced stage HL and 41 patients (37%) with B symptoms. Thirty-five patients (32%) had primary refractory disease while the remaining 76 (68%) patients had relapsed in a median time of 16 months after diagnosis (range, 2-220 months). The unfavorable (≥ 2 risk factors or primary refractory), intermediate (1 risk factor) and favorable (0 risk factor) groups comprised 67 (62%), 36 (33%) and 5 (5%) patients, respectively. Because of the low number of patients in the favorable risk group, these patients were analyzed together with the patients in the intermediate group. Relapse characteristics were not fully available for three patients.

After salvage chemotherapy, PET assessment showed that 85 (77%) patients had had a complete response (PET^- group) and 26 (23%) had had a partial response (PET^+ group). The median age at transplantation was 33 years (range, 17-71). Forty-seven (42%) and 64 (58%) patients underwent single or tandem ASCT respectively. The second ASCT was performed a median time of 64 days (range, 39-276) after the first. The median follow up after the first ASCT was 36 months. No factor at diagnosis or at relapse was associated with a higher PET-assessed complete response rate (*Online Supplementary Table S1*). There was no difference in the baseline characteristics of patients according to whether they underwent single or tandem ASCT (Table 2).

Table 1. Patients' characteristics.

	Effective (n=111)	
	n	%
Sex (males)	65	59%
Median age at ASCT (year)	33	[17-71]
B symptoms at diagnosis	41	37%
Ann Arbor stage at diagnosis		
Localized (I / II)	50	46%
Advanced (III / IV)	58	54%
Unknown	3	
Time from diagnosis to relapse (months)		
Median [range]	16	[2-220]
Relapse modality		
Primary refractory	35	32%
Relapse	76	68%
Risk factors at relapse		
Favorable	5	5%
Intermediate	36	33%
Unfavorable	67	62%
Unknown	3	
PET status after salvage		
PET negative	85	77%
PET postive	26	23%
ASCT strategy		
Single	47	42%
Tandem	64	58%
Median follow up (months)	36	

Outcome and follow-up

Five-year progression-free and overall survival rates were 64% and 81%, respectively, for the whole population. No difference was found in progression-free or overall survival between patients treated in the *Institut Paoli Calmettes* or the *Istituto Clinico Humanitas* (*data not shown*). Disease progressed after ASCT in 32 patients in a median time of 5.9 months (range, 1.1-37.3), with these patients having a 5-year overall survival rate of 42% (median, 19 months) from the relapse after ASCT. Ten out of these 32 patients underwent allogeneic stem cell transplantation as salvage treatment, which gave these patients a 5-year overall survival rate of 75% (*versus* 26% for the 22 remaining patients; P=0.063)

Three patients died of causes other than relapse (2.7%).

Table 2. Baseline characteristics of patients according to ASCT strategy.

	Single ASCT (n=47)		Tandem ASCT (n=64)		P
Sex					
Male	24	51%	41	64%	0.119
Female	23	49%	23	36%	
Age at ASCT (years)					0.223
Median [range]	34	[17-71]	33	[20-65]	
Time from diagnosis to relapse (months)					0.099
Median [range]	30	[2-191]	14	[4-220]	
Relapse modality					
Refractory	19	40%	16	25%	0.064
Relapse	28	60%	48	75%	
Risk factors at relapse					
Favorable/intermediate	18	38%	23	36%	0.432
Unfavorable	27	57%	40	63%	
PET status after salvage					
PET negative	35	74%	50	78%	0.410
PET positive	12	26%	14	22%	

One death was related to a myelodysplastic syndrome 5 years after ASCT, another to a pulmonary infection 3 months after ASCT, and the third to a pancreatic carcinoma 4 years after ASCT. All these three patients (2 or whom had had a single transplant and 1 of whom had had a tandem transplant) were still in complete remission.

Prognostic value of positron emission tomography status before transplantation

There were significant differences in 5-year progression-free survival (79% *versus* 23%, *P*<0.001) and 5-year overall survival (90% *versus* 55%, *P*=0.001) rates between the PET⁻ and PET⁺ groups, respectively (Table 3; Figure 1A and 1B). Although the unfavorable risk group also had a significantly lower 5-year progression-free survival rate than the favorable/intermediate risk group (59% *versus* 77%, *P*=0.046), there was no statistically significant difference in overall survival between these groups, with the 5-year overall survival rates being 80% and 85%, respectively (*P*=0.417) (Table 3).

The prognostic value of post-induction PET was demonstrated convincingly in both prognostic groups. In the favorable/intermediate risk group, the 5-year progression-free survival rates were 88% and 17% (*P*<0.001) in PET⁻ and PET⁺ patients, respectively, while the corresponding 5-year overall survival rates were 91% and 50% (*P*=0.029).

Table 3. Outcome according to PET status before ASCT and disease risk at relapse.

	5-year PFS	P	5-year OS	P
All patients (n=111)	64%		81%	
PET status				
PET negative (n=85)	79%	<0.001	90%	0.001
PET positive (n=26)	23%		55%	
Disease risk at relapse				
F/Int-risk group (n=41)	77%	0.046	85%	0.417
UF-risk group (n=67)	59%		80%	

F/Int: favorable/intermediate; UF: unfavorable; PFS: progression-free survival; OS: overall survival.

Table 4. (A) Outcome of either favorable/intermediate (F/Int) or unfavorable (UF) risk group patients according to PET status before transplantation. (B) Outcome of PET⁻ and PET⁺ groups according to single or tandem transplant.

(A)

	5-year PFS	P	5-year OS	P
F/Int-risk group (n=41)				
PET⁻ (n=35)	88%	<0.001	91%	0.029
PET⁺(n=6)	17%		50%	
UF-risk group (n=67)				
PET⁻ (n=49)	74%	<0.001	89%	0.026
PET⁺ (n=18)	24%		58%	

(B)

	5-year PFS	P	5-year OS	P
PET⁻ group (n=85)	79%		90%	
Single ASCT (n=35)	75%	0.05	84%	0.046
Tandem ASCT (n=50)	87%		93%	
PET⁺ group (n=26)	23%		55%	
Single ASCT (n=12)	0%	0.034	47%	0.838
Tandem ASCT (n=14)	43%		56%	

PFS: progression-free survival; OS: overall survival.

In the unfavorable risk group, the 5-year progression-free survival rates were 74% and 24% (*P*<0.001) in PET⁻ and PET⁺ patients, respectively, while the corresponding 5-year overall survival rates were 89% and 58%, respectively (*P*=0.026) (Table 4A).

Single transplant versus tandem transplant

For the whole population, tandem ASCT significantly improved the 5-year progression-free survival from 48% with single ASCT to 74% (*P*=0.002) but not 5-year overall survival (75% *versus* 84%, *P*=0.144). The effects of ASCT strategy according to subgroup of PET status are summarized in Table 4. In the PET⁻ group, there were significant differences in 5-year progression-free survival rates (75% *versus* 87%, *P*=0.05) and 5-year overall survival rates (84% *versus* 93%, *P*=0.046) between patients treated with single and tandem ASCT, respectively (Table 4B; Figure 2A and 2B). In the PET⁺ group, tandem ASCT significantly improved 5-year progression-free survival rates from 0% with single ASCT to 43% (*P*=0.034) but not overall survival rates (47% to 58%, *P*=0.838) (Table 4B; Figure 3A and 3B).

Multivariate analysis showed that PET status (HR: 5.26 [2.57-10.73]) and tandem ASCT (HR: 0.39 [0.19-0.78]) but not disease risk at relapse (HR: 1.77 [0.80-3.92]) significantly influenced progression-free survival, while only PET status significantly influenced overall survival (HR: 4.03 [1.38-11.75]) (*Online Supplementary Table S2*).

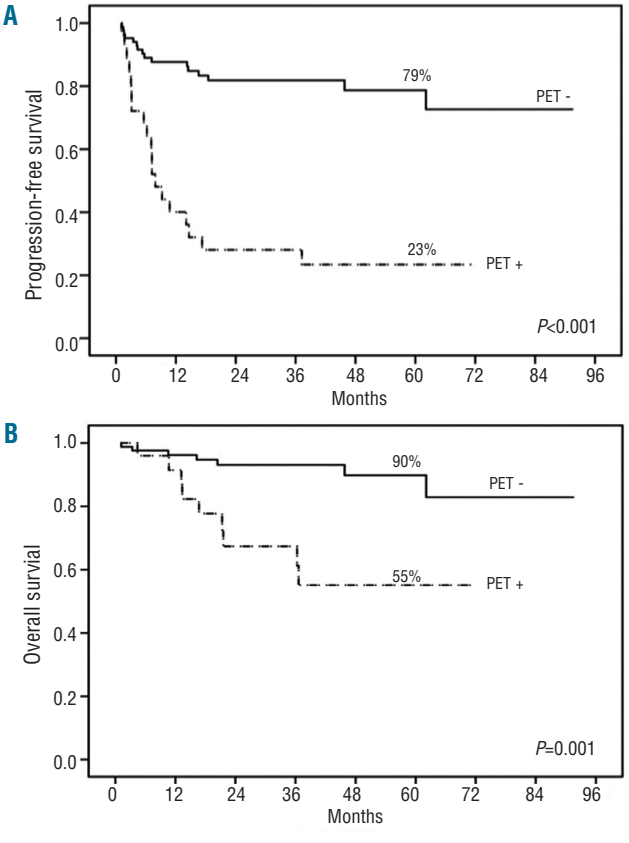

Figure 1. Progression-free survival (A) and overall survival (B) according to PET assessment after salvage chemotherapy.

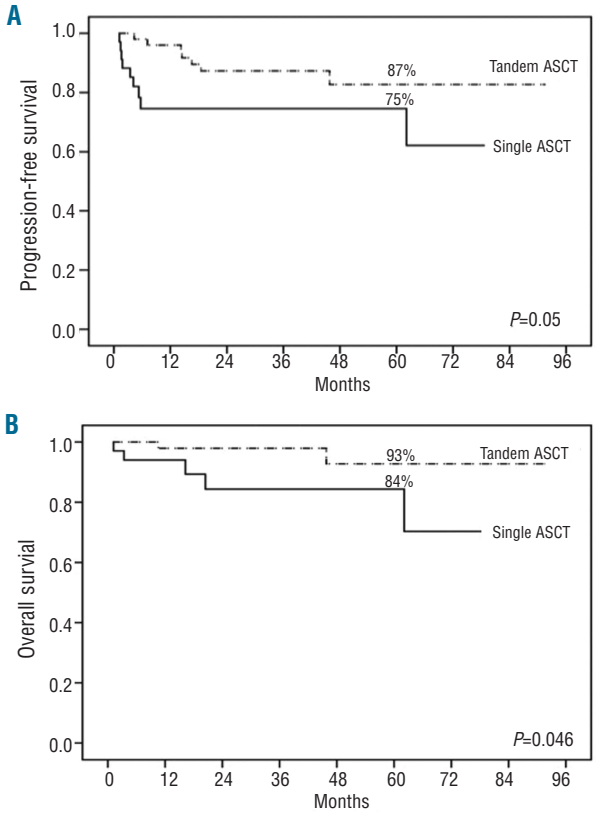

Figure 2. Progression-free survival (A) and overall survival (B) in the PET⁻ group according to single or tandem ASCT.

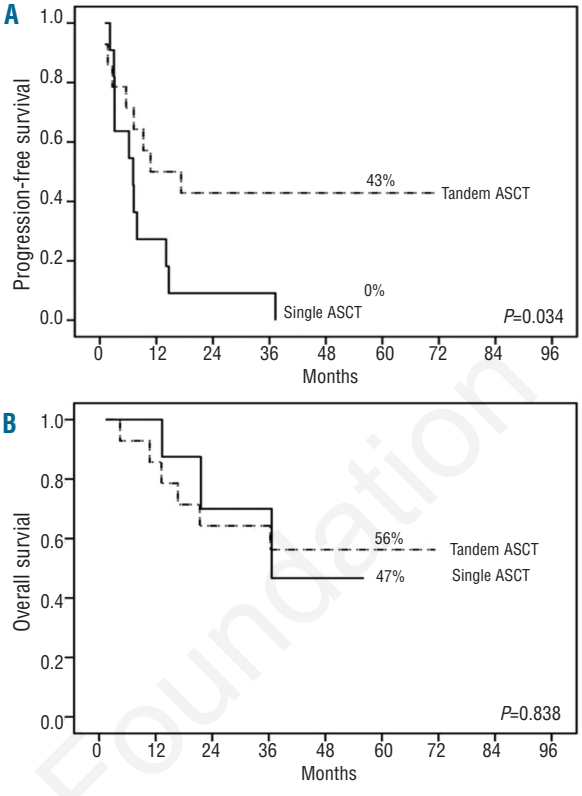

Figure 3. Progression-free survival (A) and overall survival (B) in the PET⁺ group according to single or tandem ASCT.

Discussion

Our results confirm the significant and powerful predictive value of PET status after salvage therapy and prior to ASCT in patients with relapsed and/or refractory HL, with 5-year overall survival rates of 90% and 55% and 5-year progression-free survival rates of 79% and 23% for the PET⁻ and PET⁺ groups, respectively. This predictive value remained significant in both favorable/intermediate and unfavorable subgroup analysis, suggesting that PET status strongly influences outcome regardless of disease risk at relapse. Contrarily, adverse prognostic factors usually used to differentiate the unfavorable-risk group from the favorable-risk group (stage III/IV at relapse, relapse in an irradiated field, and <1 year from the end of treatment to relapse) did not influence outcome in either PET⁻ or PET⁺ subgroup analysis. Moreover, the multivariate analysis showed that only PET status influenced outcome with a significant improvement of both overall survival and progression-free survival rates. Our findings are in accordance with those in previously reported series.[15,16] In a recent study conducted by Mocikova *et al.*,[16] in which 76 patients with relapsed HL were investigated, PET negativity before ASCT was associated with significantly better 2-year rates of progression-free survival (72.7±6.3% *versus* 36.1±11.6%, *P*=0.01) and overall survival (90.3±4.1% *versus* 61.4±11.6%, *P*=0.009). Other factors were not significant. These results are very similar to those of our present study and confirm the high predictive value of PET response in this population. Jabbour *et al.* evaluated functional imaging (PET and gallium scans) assessment before ASCT in relapsed and/or refractory HL patients.[23] PET status was available for 68 patients: 43 were PET⁻ and 25 PET⁺. In line with our findings, relapse occurred in 10 (23%) and 18 (72%) of PET⁻ and PET⁺ patients, respectively. Positive functional imaging conferred a poor prognosis, independently of other traditional adverse prognostic factors. Similar results were confirmed in other recent studies.[24,25] Taken together, PET status before ASCT seems to overshadow classical risk factors at relapse and remains the major predictive factor of outcome.

Next, we analyzed the influence of single or tandem ASCT on outcome. The feasibility and the efficacy of tandem ASCT for patients with relapsed and/or refractory HL have been previously reported in several small sized studies, but to our knowledge, no study comparing single and tandem ASCT has been published.[10-12] The prospective H96 trial conducted by the GELA/SFGM group stratified patients at relapse according to the classical adverse prognostic factors and proposed either a single ASCT or a tandem ASCT with regard to the disease risk at relapse. The reported 5-year overall survival rates were 85% and 57% for the intermediate-risk and poor-risk groups, respectively, and the corresponding 5-year progression-free survival rates were 73% and 46%, respectively. Single and tandem ASCT were not directly compared, but the HD96 trial showed that tandem ASCT improved outcome of poor-risk patients, underlining that risk factors at relapse could identify patients eligible for tandem ASCT. However in this series, disease status before ASCT was not evaluated

by PET but by standard CT.[13] Our study compared single and tandem ASCT in homogeneous populations for PET status. The results suggest that tandem ASCT could be superior to single ASCT in the whole population, with 5-year progression-free survival rates of 48% and 74% for single and tandem ASCT, respectively (P=0.002). Furthermore, in the PET$^-$ group, tandem ASCT significantly improved both 5-year progression-free survival (87% *versus* 75%, P=0.050) and overall survival (93% *versus* 84%, P=0.046) compared to single ASCT. These results show that even though PET$^-$ patients had a favorable outcome, a significant additional benefit could be gained from using tandem ASCT. However, considering the moderate improvement in progression-free survival and overall survival after tandem ASCT in this population, further evaluation is needed to establish the best strategy for the treatment of PET$^-$ patients. In the PET$^+$ group, tandem ASCT greatly improved the 5-year progression-free survival rate from 0%, in those undergoing single ASCT, to 43% (P=0.034) but not the 5-year overall survival rate (47% to 56%, P=0.838). Thus, in the PET$^+$ group, unlike in the PET$^-$ group, the benefit in progression-free survival after tandem ASCT does not translate into better overall survival. This could be first explained by the retrospective nature of our series. Moreover, some other factors could explain, in part, the lack of significant difference in overall survival in this poor-risk population. First, there were few patients in the PET$^+$ group (14 tandem *versus* 12 single transplants), leading to an evident lack of power. Second, we supposed that different salvage therapies after ASCT could mask the benefit on overall survival.

Finally, multivariate analysis showed that PET status and tandem ASCT but not conventional risk factors significantly influenced outcome. In all, our data suggest that PET status before ASCT could select patients with a poor outcome for tandem ASCT. A PET-response-adapted strategy needs to be validated in prospective trials, and could help us to manage patients with relapsed and/or refractory HL.

However, this retrospective analysis focuses on chemosensitive patients after salvage treatments. Despite our encouraging results, the management of relapsed and/or refractory HL remains a challenge, and patients not responsiveness to salvage chemotherapy still have a very poor outcome. It has not been clearly established how to treat these patients. Recent reports in the literature demonstrate that allogeneic transplantation, when feasible, can really improve survival.[26-28] Despite the lower non-relapse mortality associated with the procedure, resulting from the development of reduced intensity conditioning regimens, allogeneic transplantation remains controversial.[29] In particular, such a procedure is often reserved for patients in at least partial response after salvage treatment and chemorefractory patients never benefit from allogeneic transplantation. The new conjugated monoclonal antibody, brentuximab vendotin (SNG-35), recently showed very promising results in inducing complete and durable remissions. In a phase 1 trial evaluating tolerance and efficacy of SNG-35, 15 of 42 relapsed/refractory HL patients, mainly after ASCT failure, achieved objective responses, including nine who had complete responses.[30] In the future, these new modalities will certainly help us to manage relapsed and refractory diseases.

We conclude that PET status after salvage therapy could be considered as a significant predictive factor prior to ASCT in patients with relapsed/refractory HL. It enables identification of high-risk patients independently of classical risk factors usually used at relapse. Tandem ASCT could be an interesting strategy for high-risk patients although the benefit observed in our study needs to be confirmed in further prospective randomized trial.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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References

1. Canellos GP, Niedzwiecki D. Long-term follow-up of Hodgkin's disease trial. N Engl J Med. 2002;346(18):1417-8.
2. Federico M, Luminari S, Iannitto E, Polimeno G, Marcheselli L, Montanini A, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. J Clin Oncol. 2009;27(5):805-11.
3. Engert A, Diehl V, Franklin J, Lohri A, Dorken B, Ludwig WD, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009;27(27):4548-54.
4. Ferme C, Mounier N, Divine M, Brice P, Stamatoullas A, Reman O, et al. Intensive salvage therapy with high-dose chemotherapy for patients with advanced Hodgkin's disease in relapse or failure after initial chemotherapy: results of the Groupe d'Etudes des Lymphomes de l'Adulte H89 Trial. J Clin Oncol. 2002;20(2):467-75.
5. Brice P, Bouabdallah R, Moreau P, Divine M, Andre M, Aoudjane M, et al. Prognostic factors for survival after high-dose therapy and autologous stem cell transplantation for patients with relapsing Hodgkin's disease: analysis of 280 patients from the French registry. Societe Francaise de Greffe de Moelle. Bone Marrow Transplant. 1997;20 (1):21-6.
6. Josting A, Franklin J, May M, Koch P, Beykirch MK, Heinz J, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. J Clin Oncol. 2002;20(1):221-30.
7. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet. 2002;359(9323):2065-71.
8. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. 1993;341(8852): 1051-4.
9. Sureda A, Arranz R, Iriondo A, Carreras E, Lahuerta JJ, Garcia-Conde J, et al. Autologous stem-cell transplantation for Hodgkin's disease: results and prognostic factors in 494 patients from the Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea Spanish Cooperative Group. J Clin Oncol. 2001;19(5):1395-404.
10. Castagna L, Magagnoli M, Balzarotti M, Sarina B, Siracusano L, Nozza A, et al. Tandem high-dose chemotherapy and autologous stem cell transplantation in refractory/relapsed Hodgkin's lymphoma: a monocenter prospective study. Am J Hematol. 2007;82(2):122-7.
11. Brice P, Divine M, Simon D, Coiffier B,

Leblond V, Simon M, et al. Feasibility of tandem autologous stem-cell transplantation (ASCT) in induction failure or very unfavorable (UF) relapse from Hodgkin's disease (HD). SFGM/GELA Study Group. Ann Oncol. 1999;10(12):1485-8.
12. Fitoussi O, Simon D, Brice P, Makke J, Scrobohaci ML, Bibi TT, et al. Tandem transplant of peripheral blood stem cells for patients with poor-prognosis Hodgkins's disease or non-Hodgkin's lymphoma. Bone Marrow Transplant. 1999;24(7):747-55.
13. Morschhauser F, Brice P, Ferme C, Divine M, Salles G, Bouabdallah R, et al. Risk-adapted salvage treatment with single or tandem autologous stem-cell transplantation for first relapse/refractory Hodgkin's lymphoma: results of the prospective multicenter H96 trial by the GELA/SFGM study group. J Clin Oncol. 2008;26(36):5980-7.
14. Gallamini A, Hutchings M, Rigacci L, Specht L, Merli F, Hansen M, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol. 2007;25(24):3746-52.
15. Castagna L, Bramanti S, Balzarotti M, Sarina B, Todisco E, Anastasia A, et al. Predictive value of early 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) during salvage chemotherapy in relapsing/refractory Hodgkin lymphoma (HL) treated with high-dose chemotherapy. Br J Haematol. 2009;145(3):369-72.
16. Mocikova H, Pytlik R, Markova J, Steinerova K, Kral Z, Belada D, et al. Pre-transplant positron emission tomography in patients with relapsed Hodgkin lymphoma. Leuk Lymphoma. 2011;52(9):1668-74.
17. Josting A, Rudolph C, Mapara M, Glossmann JP, Sieniawski M, Sieber M, et al. Cologne high-dose sequential chemotherapy in relapsed and refractory Hodgkin lymphoma: results of a large multicenter study of the German Hodgkin Lymphoma Study Group (GHSG). Ann Oncol. 2005;16(1):116-23.
18. Moskowitz CH, Nimer SD, Zelenetz AD, Trippett T, Hedrick EE, Filippa DA, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood. 2001;97(3):616-23.
19. Santoro A, Magagnoli M, Spina M, Pinotti G, Siracusano L, Michieli M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica. 2007;92(1):35-41.
20. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-81.
22. Cox DR. Regression models and life tables. J R Statist Soc. Series B (Methodological). 1972;34:187-220.
23. Jabbour E, Hosing C, Ayers G, Nunez R, Anderlini P, Pro B, et al. Pretransplant positive positron emission tomography/gallium scans predict poor outcome in patients with recurrent/refractory Hodgkin lymphoma. Cancer. 2007;109(12):2481-9.
24. Moskowitz AJ, Yahalom J, Kewalramani T, Maragulia JC, Vanak JM, Zelenetz AD, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Blood. 2010;116(23):4934-7.
25. Smeltzer JP, Cashen AF, Zhang Q, Homb A, Dehdashti F, Abboud CN, et al. Prognostic significance of FDG-PET in relapsed or refractory classical Hodgkin lymphoma treated with standard salvage chemotherapy and autologous stem cell transplantation. Biol Blood Marrow Transplant. 2011;17(11):1646-52.
26. Castagna L, Sarina B, Todisco E, Magagnoli M, Balzarotti M, Bramanti S, et al. Allogeneic stem cell transplantation compared with chemotherapy for poor-risk Hodgkin lymphoma. Biol Blood Marrow Transplant. 2009;15(4):432-8.
27. Sarina B, Castagna L, Farina L, Patriarca F, Benedetti F, Carella AM, et al. Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. Blood. 2010;115(18):3671-7.
28. Carella AM, Cavaliere M, Lerma E, Ferrara R, Tedeschi L, Romanelli A, et al. Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic peripheral-blood hematopoietic stem-cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. J Clin Oncol. 2000;18(23):3918-24.
29. Milpied N, Fielding AK, Pearce RM, Ernst P, Goldstone AH. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hodgkin's disease. European Group for Blood and Bone Marrow Transplantation. J Clin Oncol. 1996;14(4):1291-6.
30. Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010;363(19):1812-21.