TRANSPLANTATION

Prognostic value of FDG-PET prior to autologous stem cell transplantation for relapsed and refractory diffuse large B-cell lymphoma

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Key Points

- FDG-PET–assessed response to ST according to Deauville criteria predicts outcome post-ASCT for rel/ref DLBCL.

High-dose chemotherapy (HDT) plus autologous stem cell transplantation (ASCT) is the standard of care for chemosensitive relapsed and refractory diffuse large B-cell lymphoma (rel/ref DLBCL). Interim restaging with functional imaging by positron emission tomography using ^{18}F-deoxyglucose (FDG-PET) has not been established after salvage chemotherapy (ST) and before HDT-ASCT by modern criteria. Herein, we evaluated 129 patients with rel/ref DLBCL proceeding to HDT-ASCT, with ST response assessment by FDG-PET according to the contemporary Deauville 5-point scale. At 3 years, patients achieving a Deauville response of 1 to 3 to ST experienced superior progression-free survival (PFS) and overall survival (OS) rates of 77% and 86%, respectively, compared with patients achieving Deauville 4 (49% and 54%, respectively) ($P < .001$). No other pre-HDT-ASCT risk factors significantly impacted PFS or OS. Despite achieving remission to ST, patients with Deauville 4 should be the focus of risk-adapted investigational therapies. (*Blood*. 2015;125(16):2579-2581)

Introduction

High-dose therapy (HDT) plus autologous stem cell transplantation (ASCT) is standard-of-care as consolidation for patients with relapsed and refractory (rel/ref) diffuse large B-cell lymphoma (DLBCL).[1] HDT-ASCT is indicated in other rel/ref aggressive B-cell non-Hodgkin lymphomas (B-NHL), including transformed histology.[2] Two recent large prospective randomized phase III studies with interventions of conditioning modification[3] and maintenance therapy[4] failed to improve long-term disease-free survival rates above 50% to 60%.

Eligibility for HDT-ASCT is based on the presence of chemosensitive disease to salvage therapy (ST) as defined by complete or partial remission assessed by computed tomography (CT) imaging.[5] The controversy surrounding the prognostic significance of interim positron emission tomography (PET) using ^{18}F-deoxyglucose (FDG) restaging during induction therapy for DLBCL has prompted the generation of revised criteria for more accurate determination of chemosensitive response.[6] The prognostic significance of FDG-PET pre-HDT-ASCT for DLBCL has been demonstrated previously[7-10]; however, not with modern criteria. We aimed to determine the prognostic impact of FDG-PET-assessed response to ST before HDT-ASCT for rel/ref DLBCL/transformed B-NHL by modern criteria established at the first international workshop on FDG-PET reporting in lymphoma held in Deauville, France [11] and recently recommended at the 12th International Conference of Malignant Lymphoma.[12]

Study design

Patients

We retrospectively reviewed a database of 129 adult patients with rel/ref DLBCL and transformed B-NHL previously exposed to at least1 prior line of induction chemotherapy and who were chemosensitive to ST and proceeding to HDT-ASCT after a restaging FDG-PET scan at Memorial Sloan-Kettering Cancer Center (MSKCC) from 2002 to December 2012. Rel/ref disease was confirmed by biopsy in 123 of 129 (95%) of patients. Eligibility for HDT-ASCT was based on ST response per above, as well as adequate organ function, performance status, and CD34$^+$ stem cells for re-infusion per institutional standard. A waiver of authorization to carry out this analysis was approved by the MSKCC Institutional Review Board.

Pre-HDT-ASCT FDG-PET scans and risk factors

Chemosensitivity was assessed per standard CT criteria for B-NHL.[5] All PET/CT scans were obtained 60 minutes after radiotracer injection, extending from skull base to upper thigh, on Discovery STE or LS cameras (GE Medical Systems, Milwaukee, WI). A low-dose CT scan (120-140 kV, ~80 mA) was followed by emission images (3 minutes per bed position). Deauville criteria[11] for FDG-PET response was applied for purposes of analysis on the 5-point scale: 1, no uptake; 2, uptake ≤mediastinal blood pool; 3, uptake > mediastinal blood pool but ≤ liver; 4, uptake > liver at any site; and 5, uptake > liver and/or new sites of disease. No patients had Deauville 5 response, because this represented progression of disease to ST, thus determining ineligibility to proceeding to HDT-ASCT consolidation. Two staff nuclear medicine radiologists (H.S. and

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Table 1. Patient characteristics (N = 129)

Median age, y (range)	56.5 (21-73)
Gender	
Male	77 (59.7)
Female	52 (40.3)
Deauville response to ST	
1	64 (49.6)
2	10 (7.8)
3	7 (5.4)
4	48 (37.2)
IFRT pre-HDT-ASCT	
No	75 (58.1)
Yes	54 (41.9)
Remission duration	
<12 mo*	81 (62.8)
≥12 mo	48 (37.2)
Histology	
Activated B-cell phenotype	47 (41.2)
Germinal center phenotype	39 (34.2)
Primary mediastinal large B-cell lymphoma	9 (7.9)
T-cell histiocyte-rich large B-cell lymphoma	4 (3.5)
Transformed	15 (13.2)
Missing	15
ST	
DHAP	17 (13.2)
EPOCH	11 (8.5)
ICE	87 (67.4)
Other	6 (4.7)
ST × 2	8 (6.2)
sAA-IPI	
High	43 (35.0)
Low	80 (65.0)
Missing	6

Values are n (%) unless otherwise indicated.

DHAP, dexamethasone/cytarabine/cisplatin; EPOCH, etoposide, doxorubicin, vincristine, prednisone, cyclophosphamide; ICE: ifosfamide/etoposide/carboplatin; IFRT, involved-field radiotherapy.

*Includes primary refractory disease.

G.A.U.) reviewed and scored all images. Traditional pre-ST risk factors[4] were applied for purposes of analysis, including histologic phenotype at relapse (including cell of origin in DLBCL as determined by Hans criteria[13]), secondary age-adjusted International Prognostic Index (sAA-IPI), and previous remission duration to initial induction chemotherapy.

Statistical analysis

Overall survival (OS) and progression-free survival (PFS) were defined as the time from HDT-ASCT until death from any cause and time from HDT-ASCT to disease progression or death, respectively. Univariate probabilities and 95% confidence intervals (CIs) of OS and PFS were estimated using Kaplan-Meier methodology, and survival distributions were compared across patient and treatment characteristics using a log-rank test, with P values <.05 considered significant.

Results and discussion

The characteristics of the 129 patients appear in Table 1. The majority of patients (66%) were de novo rel/ref DLBCL. All patients were previously exposed to rituximab and were chemosensitive by CT criteria.[5] FDG-PET scans after ST occurred at a median of 34 days (range: 5-173 days) before HDT-ASCT and at a median of 14 days after ST. Of the 6 patients with pre-HDT-ASCT FDG-PET occurring >3 months from HDT-ASCT, all received pre-HDT-ASCT IFRT. The median follow-up among survivors was 43.6 months (range: 4.6-135.6 months). PFS and OS rates for the entire cohort at 3 years were 67% (95% CI: 58-75) and 74% (95% CI: 65-81), respectively (Figure 1A). No significant differences in PFS and OS were observed according to standard pre-ST risk factors including sAA-IPI, relapse <12 months or primary refractory disease vs relapse ≥12 months, and type of ST. In addition, transformed or de novo DLBCL and cell-of-origin factors lacked prognostic significance. The only pre-HDT-ASCT factor associated with PFS and OS was response to ST by FDG-PET Deauville criteria. At 3 years, patients with Deauville 1 to 3 experienced superior PFS (Figure 1A) and OS rates (Figure 1B) of 77% (95% CI: 65- 86) and 86% (95% CI: 75-92), respectively, compared with patients with Deauville 4 who had respective PFS and OS rates of 49% (95% CI: 34-62) and 54% (95% CI: 39-68) ($P < .001$).

This analysis represents the only series of chemosensitive rel/ref DLBCL and transformed B-NHL patients, predominately of de novo DLBCL histologic phenotype, proceeding to HDT-ASCT with responses to ST assessed by FDG-PET according to modern Deauville criteria on the 5-point scale. Our retrospective data demonstrate significant prognostic impact of FDG-PET response to ST (Deauville 1-3) with significant PFS and OS benefit ($P < .001$). Whereas other series' have demonstrated prognostic significance with FDG-PET response before HDT-ASCT,[7-9,14] none has used the contemporary Deauville 5-point scale.[11] This 5-point scale of response criteria was recommended by consensus of the Imaging Working Group at the 12th International Conference of Malignant Lymphoma in Lugano, Switzerland.[12] Additional key differences of previous publications assessing risk by FDG-PET pre-HDT-ASCT, as compared to our study, include patients undergoing HDT-ASCT in first remission,[9] varying lymphoma histologies,[7,14] and smaller numbers of patients.[7-9] In the other larger, and most contemporary, study of 143 patients with rel/ref DLBCL or transformed lymphoma from the Dana-Farber Cancer Institute/Massachusetts General Hospital, a negative FDG-PET scan conferred a rate of OS benefit at 4 years of 75% vs 56% in FDG-PET-positive patients ($P = .025$), results notably similar to those obtained in our study.[10] Response criteria by FDG-PET were not specified in the Dana-Farber Cancer Institute/Massachusetts General Hospital study.

Limitations of our study should be noted. First, this is not a prospective study and, thus, it is subject to the inherent limitations of retrospective data. Patient selection within this single-center study may account for the improved PFS and OS over historic controls of 2 recent prospective multicenter studies of HDT-ASCT for de novo rel/ref DLBCL.[3,4] Also, our study contained 15 patients (12% of the cohort) with transformed histology DLBCL and 8 patients (6%) who received 2 lines of ST, which was different from the recent prospective HDT-ASCT studies for de novo DLBCL. Lastly, 54 of the 129 patients with limited-stage disease received pre-HDT-ASCT IFRT after post-ST restaging as part of the HDT-ASCT[15,16] at the discretion of the treating physician. It is important to note that the PFS and OS rates between pre-HDT-ASCT IFRT and no pre-HDT-ASCT IFRT were similar ($P = .20$ and $P = .73$, respectively), even when restricted to the 48 patients who achieved Deauville 4 response to ST (PFS: $P = .32$; OS: $P = .40$).

In conclusion, our study represents the first report of the prognostic impact of pre-HDT-ASCT FDG-PET response to ST according to Deauville criteria in chemosensitive rel/ref DLBCL. Clearly, given the inferiority of patients achieving a Deauville 4 response to ST, this group of patients should be the subject of risk-adapted investigation. Such investigational interventions could include, but are not limited to, immunotherapeutic approaches to overcome relative chemotherapy insensitivity such as consolidation with chimeric antigen receptor–modified autologous T-cell therapy directed against CD19 post-HDT-ASCT (NCT01840566), immune-checkpoint blockade post-HDT-ASCT,[17] or allogeneic hematopoietic cell transplantation. With regard to the latter treatment modality, we have recently demonstrated that the allogeneic graft-versus-lymphoma effect may overcome relative

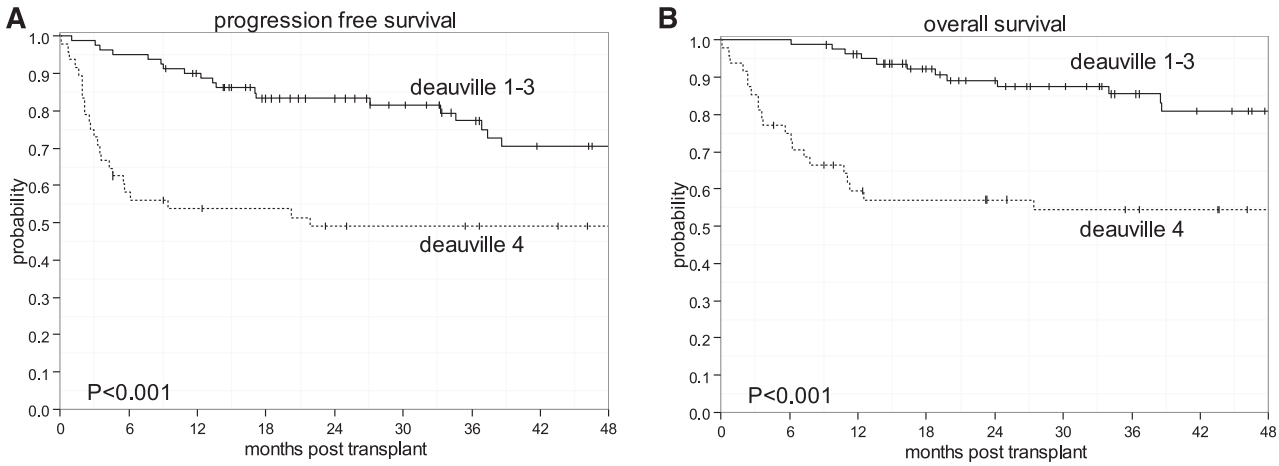

Figure 1. Kaplan-Meier survival estimates based on Deauville responses to ST. (A) PFS. (B) OS.

chemotherapy insensitivity, achieving similar long-term outcomes with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning in chemosensitive patients to ST according to CT criteria across all Deauville responses by FDG-PET.[18]

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Authorship

Contribution: C.S.S. and C.H.M. designed the study; C.S.S., M.J.M., A.D.Z., and C.H.M. interpreted the data; C.S.S., J.M, J.C.M, S.M.D, P.H, G.A.U., and H.S. analyzed the data; all authors wrote the manuscript.

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