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ORIGINAL REPORT

Interim Positron Emission Tomography Response–Adapted Therapy in Advanced-Stage Hodgkin Lymphoma: Final Results of the Phase II Part of the HD0801 Study

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ABSTRACT

Purpose

The clinical impact of positron emission tomography (PET) evaluation performed early during first-line therapy in patients with advanced-stage Hodgkin lymphoma, in terms of providing a rationale to shift patients who respond poorly onto a more intensive regimen (PET response-adapted therapy), remains to be confirmed.

Patients and Methods

The phase II part of the multicenter HD0801 study involved 519 patients with advanced-stage de novo Hodgkin lymphoma who received an initial treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and who underwent an early ifosfamide-containing salvage treatment followed by stem-cell transplantation if they showed a positive PET evaluation after two cycles of chemotherapy (PET2). The primary end point was 2-year progression-free survival calculated for both PET2-negative patients (who completed a full six cycles of ABVD treatment) and PET2-positive patients. Overall survival was a secondary end point.

Results

In all, 103 of the 512 evaluable patients were PET2 positive. Among them, 81 received the scheduled salvage regimen with transplantation, 15 remained on ABVD (physician's decision, mostly because of minimally positive PET2), five received an alternative treatment, and two were excluded because of diagnostic error. On intention-to-treat analysis, the 2-year progression-free survival was 76% for PET2-positive patients (regardless of the salvage treatment they received) and 81% for PET2-negative patients.

Conclusion

Patients with advanced-stage Hodgkin lymphoma for whom treatment was at high risk of failing appear to benefit from early treatment intensification with autologous transplantation, as indicated by the possibility of successful salvage treatment in more than 70% of PET2-positive patients through obtaining the same 2-year progression-free survival as the PET2-negative subgroup.

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INTRODUCTION

Recently, several studies have clearly demonstrated the predictive value of a positron emission tomography (PET) scan performed after two cycles of chemotherapy (ie, interim or PET2) in patients with advanced-stage Hodgkin lymphoma (HL).[1-6] In parallel, large cohort studies have pointed out several well-established pretreatment prognostic factors, although it is still the disease stage that largely determines the initial treatment strategy.[7-9]

Approximately 65% to 70% of patients with advanced-stage HL can be cured with six to eight cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), with or without consolidation radiotherapy.[10,11] Escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) cures around 85% of patients if given as first-line therapy, but concerns regarding its acute toxicity and the possible onset of second myeloid neoplasia are limiting factors for its widespread use.[12,13]

Despite an improvement in the therapeutic management of patients with HL, early identification of those patients in whom the chances of cure by conventional treatment are low and for whom an escalated BEACOPP or an intensified high-dose regimen with a subsequent peripheral stem-cell autograft can be justified is still a crucial problem. As it happens with early-stage disease, pretreatment prognostic tools for advanced-stage disease, notably the International Prognostic Score (IPS), do not accurately predict which patients will likely receive a benefit from more intensive therapy.[8] A negative interim PET scan is a strong predictor of favorable outcomes with standard therapy: long-term progression-free survival (PFS) rates of approximately 95% have been consistently shown in patients with advanced-stage HL treated with ABVD who display an early PET negativity.[1-6] Consequently, patients with a poor prognosis can be identified according to their early response to induction treatment, as documented by an interim PET evaluation. Therefore, a response-adapted therapy may be tailored for patients with poor response.

Several trials that take into account a PET response-adapted therapy for patients with advanced-stage HL are ongoing or have recently been completed. The common aim of these trials is to de-escalate therapy in patients with a favorable early PET response or to escalate therapy in those who do not respond well or to do both.[14-20] The cost-benefit ratio of two different strategies will be tested by using interim PET as a surrogate indicator for chemotherapy sensitivity. The first strategy uses the initiation of first-line therapy with the most intensive regimen (escalated BEACOPP) and then de-escalating treatment in patients with a negative interim PET result. Alternatively, a standard ABVD treatment can be started and then escalated to either BEACOPP or high-dose chemotherapy and autologous bone marrow transplantation (ABMT) only in PET2-positive patients, who can presumably benefit from an intensified treatment.

Herein we present the final results of the phase II part of an Italian multicenter trial (HD0801; Early Salvage With High-Dose Chemotherapy and Stem-Cell Transplantation in Advanced Stage Hodgkin's Lymphoma) conducted in centers adhering to the Italian Lymphoma Foundation guidelines. This phase II trial included patients with advanced-stage HL that was PET positive after two cycles of ABVD who were offered a chemotherapy salvage treatment followed by high-dose chemotherapy with autologous stem-cell support.

PATIENTS AND METHODS

Study Oversight

HD0801 was a multicenter study involving patients with newly diagnosed advanced-stage HL, all receiving first-line ABVD treatment and undergoing a PET2 evaluation. The study will produce an estimate of the efficacy of an early PET response-adapted strategy in advanced HL. In addition, this trial was designed to address two specific questions: whether an early PET-guided salvage treatment consisting of high-dose chemotherapy with a subsequent ABMT could be considered safe and effective compared with data in the literature (phase II; Fig 1, shaded area) and whether PET2-negative patients could benefit from radiotherapy consolidation for areas of bulky disease, provided they maintained PET negativity upon completion of the planned six ABVD courses (phase III; Fig 1, white area). The follow-up of the randomized comparison between patients treated with radiotherapy versus observation is still ongoing; therefore, results will be reported separately in the future.

The applied salvage treatment (phase II) was made up of four courses of ifosfamide, gemcitabine, and vinorelbine (IGEV)[21] chemotherapy, which allowed stem-cell mobilization in peripheral blood with harvesting after the third course,[22] and was followed by carmustine, cytarabine, etoposide, and melphalan (BEAM)–conditioned ABMT treatment if patients had obtained a PET-documented complete response (CR). In case of a positive post-IGEV PET evaluation, patients with an HLA-matched donor were scheduled to receive high-dose melphalan-conditioned ABMT followed by a reduced-intensity allogeneic transplantation; conversely, those lacking an HLA-matched donor received high-dose melphalan ABMT followed by a BEAM-conditioned treatment.

Patient Enrollment and Study Conduct

Patients age 18 to 70 years were considered eligible if they had previously untreated and histologically documented HL (with the exception of nodular lymphocyte–predominant subtype) in clinical stage IIB to IV according to Ann Arbor staging and at least one bidimensionally measurable target lesion (even if extranodal only). Patients were excluded from the study if they had a severe disease that impaired normal life, presented an active infection, or had an inadequate liver or renal function, unless this was a result of the lymphoma. Those with a history of previous malignancy (except basal cell skin carcinoma and in situ carcinoma of the cervix) were considered ineligible.

Responses were primarily evaluated by centrally reviewed PET scan after two cycles of ABVD and at the end of the scheduled treatment plan, provided that all patients had undergone a complete staging workup, including PET examination, before the start of treatment. The depth of response was graded according to the revised response criteria for malignant lymphomas.[23]

All local ethic committees at each center approved the study protocol and its amendments, in accordance with the Italian law and in compliance with the Declaration of Helsinki. Patients provided written informed consent before being included in the study.

Central PET Review

In this study, central PET review played a pivotal role in reducing the variability of visual scan interpretation between various readers, because treatment decisions were made on the basis of the result of PET2 scans. PET scans were interpreted according to Juweid's criteria,[24] which used mediastinal uptake as a reference. Central review of all uncertain results took place within 5 days of the PET scan at a central imaging core laboratory at the University of Florence; a panel of 11 nuclear medicine physicians served as reviewers for all procedures. The reviewing process proceeded as follows: first, a local nuclear medicine physician sent the initial and interim PET scans to the core laboratory along with the available clinical information; then, an answer from five reviewers was sent to the study data center and to local physicians. In case of discrepancy between the local PET evaluation and the central review, the result of the latter was considered predominant. All PET2-positive scans were reviewed at the end of the trial and were interpreted by using the Deauville[25] criteria, now regarded as the standard criteria for PET interpretation. These criteria were elaborated and published while the study was ongoing.

End Points

The primary end point of the phase II part of the study was 2-year PFS calculated from the date of the PET2 scan to the date of lymphoma progression, death as a result of any cause, or completion of the 2 years of follow-up. Overall survival (OS), defined as the time from PET2 scan until death as a result of any cause or the date of the last follow-up, was a secondary outcome. In addition, the estimations of OS and PFS calculated from entry into the study (registration) until the end of follow-up were provided for the entire study population. Exploratory analyses of factors predicting response and toxicity will be performed after a longer follow-up becomes available.

Statistical Analysis

The sample size of the phase II part of the trial has been estimated according to the Fleming-A'Hern design. The primary efficacy end point

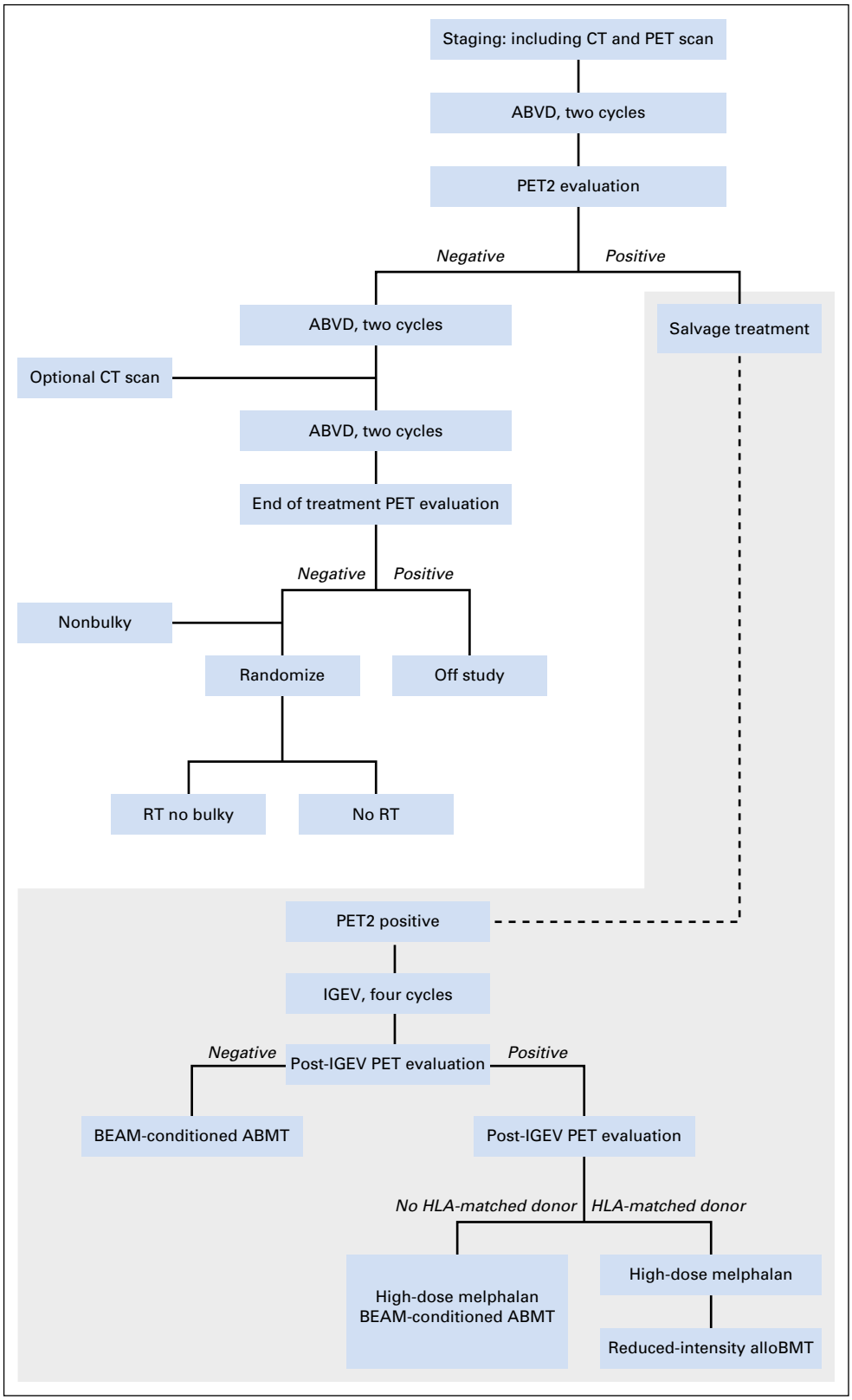

Fig 1. Study outline. The shaded area indicates the phase II part of the study. ABMT, autologous bone marrow transplantation; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; alloBMT, allogeneic bone marrow transplantation; BEAM, carmustine, cytarabine, etoposide, and melphalan; CT, computed tomography; IGEV, ifosfamide, gemcitabine, and vinorelbine; PET, positron emission tomography; PET2, PET scan performed after two cycles of chemotherapy; RT, radiotherapy.

(2-year PFS) was calculated as the cumulative proportion of patients alive and progression free at 2 years. All other time-to-event end points included in the study have been estimated by using the Kaplan-Meier method. For all point estimates, the corresponding confidence intervals were also provided.

Baseline patient characteristics were compared according to PET2 positivity by using the Mann-Whitney U test and χ^2 test (or Fisher's exact test, if appropriate) for continuous variables and categorical variables, respectively. For the safety analyses, frequency of toxicities was reported by

type and grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0). All analyses were performed by using STATA version 11.1 (STATA, College Station, TX).

RESULTS

In all, 520 patients who had enrolled onto the study started ABVD treatment between September 2008 and April 2013 in 50 Italian centers. Of those patients, 512 (99%) underwent a PET2 scan, one patient withdrew consent before therapy, and seven patients interrupted the treatment before the end of the second ABVD cycle. The demographic and baseline disease characteristics for the entire population and according to PET2 evaluation are listed in Table 1.

Median age of the patients was 33 years (range, 18 to 68 years). Most of the patients (73%) had a nodular sclerosis HL subtype, 46% presented with stage IV disease, and 35% had bulky disease. The marrow was involved in 49 patients (10%). An IPS $\geq$ 3 was seen in 206 patients (44%).

Response to Treatment

Among the 512 patients with an interim PET2 scan evaluated by central review, 409 (80%) were PET negative and 103 (20%) were PET positive. Once the PET2-positive scans had been reviewed and interpreted by using the Deauville 5-point scale, 70% had a score $\geq$ 4 (and 20% had a score of 5). The remaining 30% of PET2-positive scans received a score of 3.

As stated by the protocol, all 409 PET2-negative patients proceeded to four more ABVD cycles, whereas the remaining patients were moved to the IGEV salvage arm. However, among the 103 patients with PET2 positivity, 22 did not receive the scheduled treatment: two because of a diagnostic error and the remaining 20 because of the patients' refusal to move to high-dose treatment at that time. Therefore, the latter 20 patients continued the treatment with four more ABVD cycles (15 patients) or shifted to a different salvage regimen (five patients). More specifically, among the 15 patients who continued with ABVD therapy, nine presented with a minimally positive PET2 scan (ie, just above background, which was compatible with a Deauville score of 3 upon central revision of the cases, as stated above in Patients and Methods), and one patient had a false-positive result, as demonstrated by a negative lymph node biopsy. One patient refused the high-dose treatment and the transplantation procedure.

Regarding the other 81 PET2-positive patients, all received four courses of IGEV and were able to provide peripheral blood stem cells, which allowed them to proceed to subsequent high-dose chemotherapy with autologous stem-cell support. At the end of IGEV therapy, 43 patients were PET-negative and underwent BEAM-conditioned ABMT therapy. Among the 38 patients with a positive post-IGEV scan, 24 received tandem ABMT therapy, and 11 of them had a PET-negative result at the end of treatment. Conversely, 14 patients underwent allogeneic transplantation, and

Table 1. Clinical Characteristics of the Patients Who Underwent PET2 Evaluation

Characteristic	PET2 Negative (n = 409), No. (%)	PET2 Positive (n = 103), No. (%)	Total (n = 512), No. (%)	*P*
Median age	33	32	33	.198
Male sex	222 (54)	53 (51)	275 (54)	.608
IPS*				.996
0-2	209 (56)	52 (56)	261 (56)	
$\geq$ 3	165 (44)	41 (44)	206 (44)	
Histology				.520
Nodular sclerosis	292 (71)	80 (78)	372 (73)	
Mixed cellularity	60 (15)	11 (11)	71 (14)	
Lymphocyte depletion	10 (2)	1 (1)	11 (2)	
Lymphocyte rich	18 (4)	2 (2)	20 (4)	
Unspecified	29 (7)	9 (9)	38 (7)	
No systemic symptoms	144 (35)	42 (41)	186 (36)	.294
B symptoms	265 (65)	61 (59)	326 (64)	
LDH increase	129 (32)	37 (36)	166 (32)	.396
Performance status				.966
0	271 (66)	68 (66)	339 (66)	
1	112 (27)	30 (29)	142 (28)	
2	26 (6)	4 (4)	30 (6)	
3	0 (0)	1 (1)	1 (0)	
Ann Arbor stage				.810
II	80 (20)	19 (18)	99 (19)	
III	145 (35)	34 (33)	179 (35)	
IV	184 (45)	50 (49)	234 (46)	
Bulky disease	143 (35)	38 (37)	181 (35)	.714
Extranodal involvement	182 (44)	54 (52)	236 (46)	.149
Marrow involvement†	37 (9)	12 (12)	49 (10)	.454

Abbreviations: IPS, International Prognostic Score; LDH, lactate dehydrogenase; PET2, positron emission tomography scan performed after two cycles of chemotherapy.
*Unavailable data in 45 patients (9%).
†Unavailable data in 12 patients (2%).

four were PET negative after treatment. Twenty-three patients (28%) were still PET-positive at the end of the entire therapeutic course (as can be extrapolated from Fig 2).

Among the 15 patients who completed the induction phase with ABVD, 11 (73%) obtained a CR; four patients achieved the CR after consolidation radiotherapy. One patient achieved a partial response (PR) and then received high-dose chemotherapy with stem-cell rescue and obtained a final CR; the remaining three patients relapsed or progressed. No follow-up data are available for the five patients who were shifted to a different treatment plan because they withdrew consent for the study.

Patients were compliant with follow-up procedures, and all scheduled computed tomography (CT) and PET scans were performed at the correct time points, with a tolerance of 7 days. No PET protocol violations occurred.

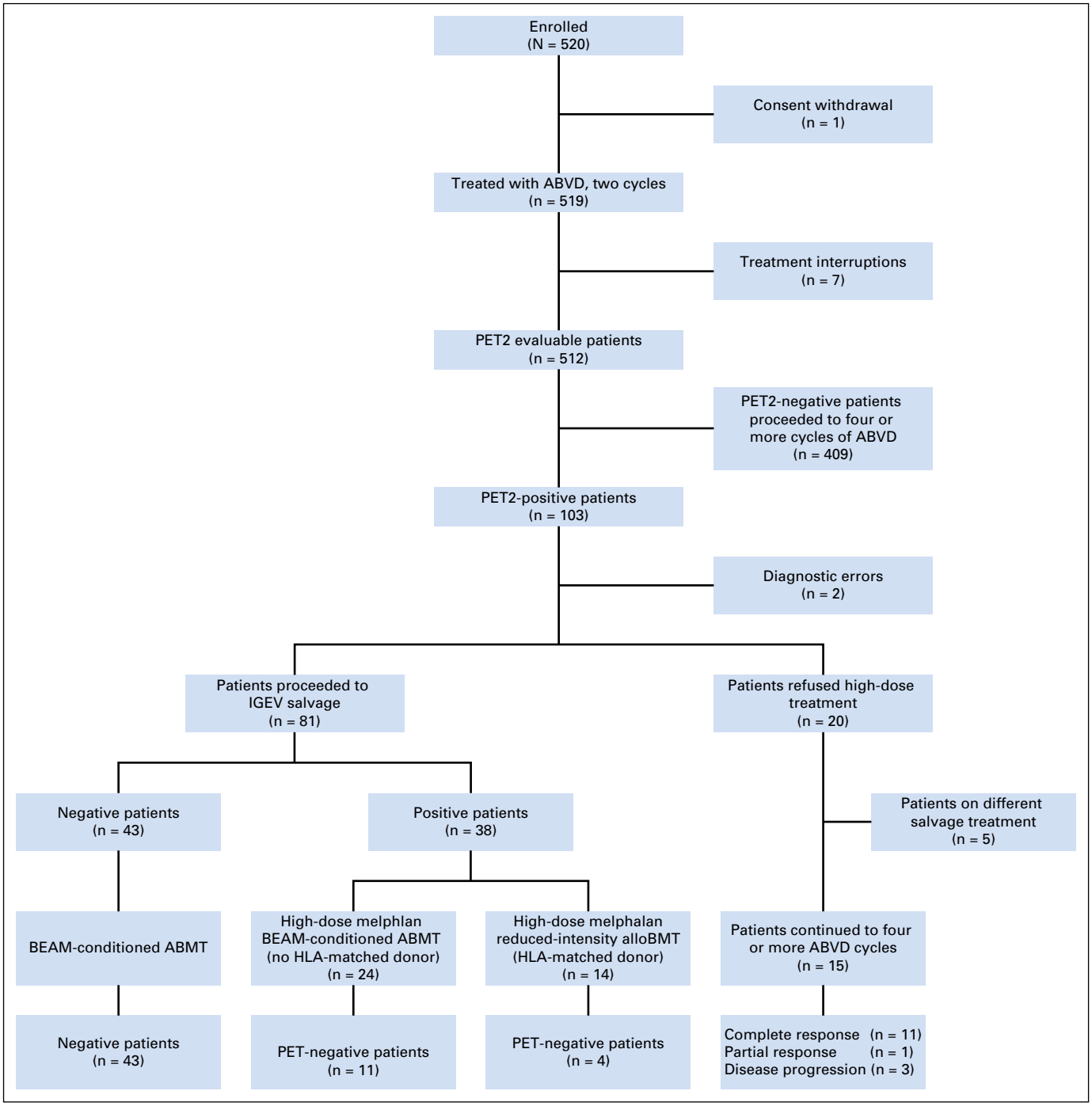

Fig 2. Patient flow diagram. ABMT, autologous bone marrow transplantation; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; alloBMT, allogeneic bone marrow transplantation; BEAM, carmustine, cytarabine, etoposide, and melphalan; IGEV, ifosfamide, gemcitabine, and vinorelbine; PET2, positron emission tomography scan performed after two cycles of chemotherapy.

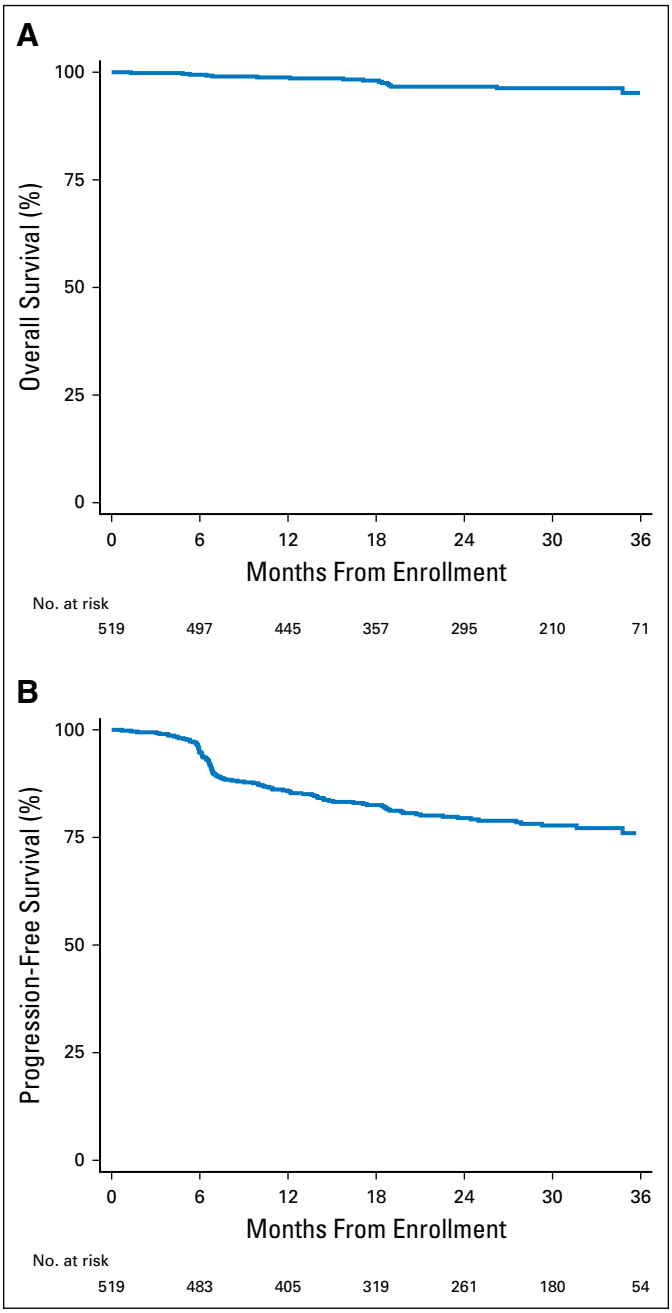

Fig 3. (A) Overall survival and (B) progression-free survival for the entire study population, as determined from the time of enrollment.

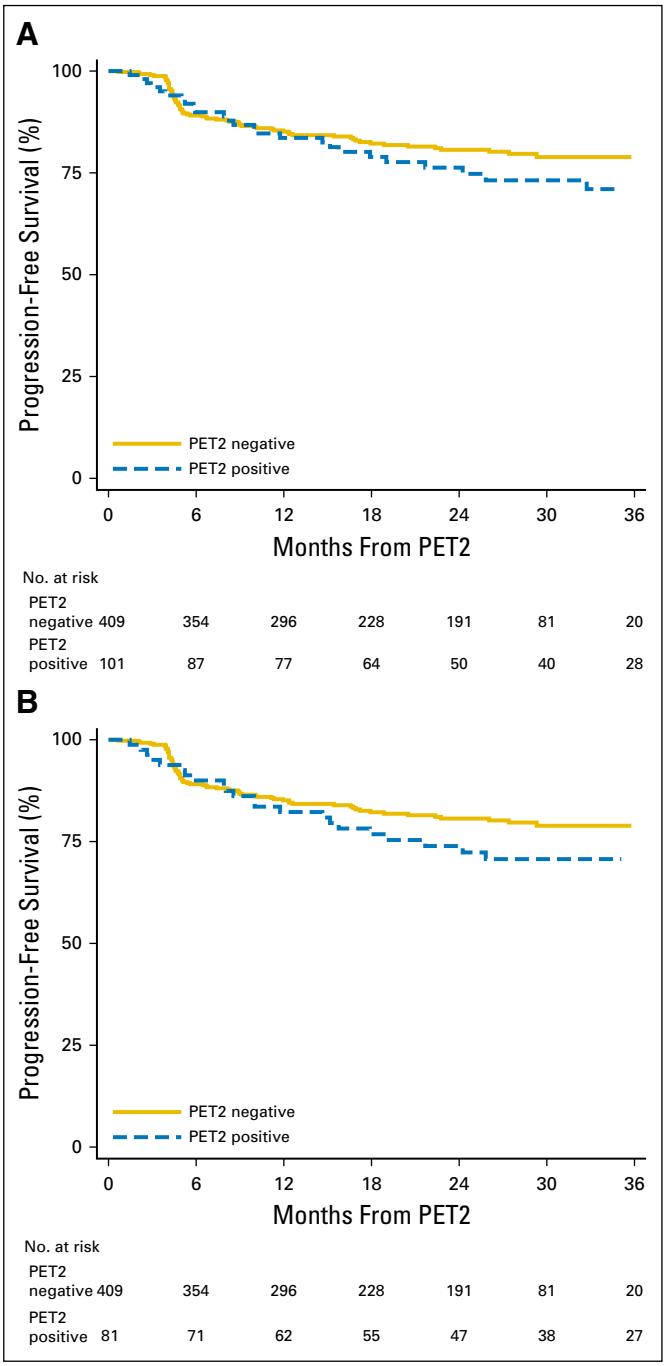

Fig 4. (A) Progression-free survival on an intention-to-treat basis for PET 2-positive (dashed line; n = 101) and PET2-negative (solid line; n = 409) patients who received either IGEV chemotherapy and transplantation or an alternative salvage treatment (including four more ABVD cycles). (B) Progression-free survival for PET2-negative patients (n=409, solid line), all of whom were scheduled to receive six cycles of ABVD, compared with PET2-positive patients who actually received IGEV chemotherapy and transplantation (n=81, dashed line). ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; IGEV, ifosfamide, gemcitabine, and vinorelbine; PET2, positron emission tomography scan performed after two cycles of chemotherapy.

Survival Analysis

Overall, 97 patients experienced disease progression (21 in the PET2-positive group, 73 in the PET2-negative group, three in the group of patients without PET2), and 18 patients died (eight in the PET2-positive group: lymphoma [n = 4], heart failure [n = 1], viral encephalitis [n = 1], graft-versus-host disease [n = 2]; nine in the PET2-negative group: lymphoma [n = 3], pneumonia [n = 1], septic shock [n = 1], lung infection [n = 2], secondary neoplasm [n = 1], graft-versus-host disease [n = 1]; and one in the group of patients without a PET2 scan who died as a result of lymphoma).

After a median follow-up of 27 months from enrollment, the Kaplan-Meier estimates for the entire population (calculated from entry onto the trial) are 97% (95% CI, 94% to 98%) for 2-year OS (Fig 3A) and 80% (95% CI, 76% to 83%) for 2-year PFS (Fig 3B). On an intention-to-treat analysis, after a median follow-up of 25 months from PET2 scanning, the 2-year PFS for the PET2-negative patients planned to receive six courses of ABVD was 81% (95% CI, 76% to

Table 2. Toxicities

Toxicity	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%
Hematologic	16	20	1	1	6	7	7	9	51	63
Granulocytes	19	23	—	—	4	5	9	11	49	60
Hemoglobin	19	23	15	19	33	41	6	7	8	10
Platelets	18	22	4	5	7	9	12	15	40	49
WBC	19	23	—	—	6	7	8	10	48	59
Nonhematologic	20	25	5	6	15	19	37	46	4	5
Cardiac	81	100	—	—	—	—	—	—	—	—
Supraventricular arrhythmia	81	100	—	—	—	—	—	—	—	—
Ventricular arrhythmia	81	100	—	—	—	—	—	—	—	—
Ischemia/infarct	81	100	—	—	—	—	—	—	—	—
Hypertension	81	100	—	—	—	—	—	—	—	—
Hypotension	81	100	—	—	—	—	—	—	—	—
Pericarditis	81	100	—	—	—	—	—	—	—	—
Pulmonary hypertension	81	100	—	—	—	—	—	—	—	—
Valvular defects	81	100	—	—	—	—	—	—	—	—
Febrile neutropenia	55	68	—	—	—	—	25	31	1	1
Gastrointestinal	36	44	10	12	20	25	14	17	1	1
Constipation	76	94	4	5	1	1	—	—	—	—
Diarrhea	65	80	4	5	9	11	3	4	—	—
Mucosal	36	44	10	12	21	26	13	16	1	1
Hemorrhagic toxicity	79	98	1	1	—	—	1	1	—	—
Hepatic and/or pancreatic	74	91	1	1	4	5	1	1	1	1
Hepatic dysfunction	74	91	1	1	4	5	1	1	1	1
Pancreatitis	81	100	—	—	—	—	—	—	—	—
Infective	59	73	2	2	7	9	11	14	2	2
Bacterial	62	77	1	1	6	7	10	12	2	2
Fungal	78	96	1	1	1	1	1	1	—	—
Viral	75	93	2	2	3	4	1	1	—	—
Metabolic	80	99	1	1	—	—	—	—	—	—
Hyperbilirubinemia	81	100	—	—	—	—	—	—	—	—
Hyperglycemia	80	99	1	1	—	—	—	—	—	—
Hyperuricemia	81	100	—	—	—	—	—	—	—	—
Hypoglycemia	81	100	—	—	—	—	—	—	—	—
Neurologic	81	100	—	—	—	—	—	—	—	—
Cranial nerve neuropathy	81	100	—	—	—	—	—	—	—	—
Cerebrovascular ischemia	81	100	—	—	—	—	—	—	—	—
Motor neuropathy	81	100	—	—	—	—	—	—	—	—
Pulmonary	78	96	1	1	—	—	2	2	—	—
Dyspnea	78	96	1	1	—	—	2	2	—	—
Pulmonary fibrosis	80	99			—	—	1	1	—	—
Renal failure	78	96	—	—	3	4	—	—	—	—
Vascular	79	98	—	—	1	1	1	1	—	—
Phlebitis	80	99	—	—	1	1	—	—	—	—
Thrombosis/embolism	80	99	—	—	—	—	1	1	—	—
Other toxicities	64	79	5	6	9	11	1	1	2	2

84%), whereas the 2-year PFS for the PET2-positive patients (n = 101, independently from the IGEV, ABVD, or other salvage treatment they received) was 76% (95% CI, 66% to 84%; Fig 4A). When calculated for only the 81 PET2-positive patients who received IGEV salvage treatment, the 2-year PFS was 74% (95% CI, 62% to 82%; Fig 4B).

In an intention-to-treat analysis (independently from the salvage treatment patients received), we compared PET-negative patients with PET-positive patients excluding those with Deauville score 3: the 2-year PFS of the PET-positive group was 75% (95% CI, 57% to 86%; Fig 5).

Toxicity

Among the 81 patients who received the scheduled salvage procedure, grade 3 and 4 adverse events were primarily hematologic and directly correlated with the treatment itself. Grade 3 and 4 neutropenia was documented in 11% and 60% of patients, respectively, and grade 3 and 4 thrombocytopenia was seen in 15% and 49% of patients, respectively. The incidence of severe anemia was lower, with grade 3 in 7% of the patients and grade 4 in 10%; 41% of the patients had grade 2 anemia. No treatment toxicity–related hospitalization or treatment-related deaths occurred.

The most significant grade 3 and 4 extrahematologic adverse events (documented in at least 10% of the patients) were febrile neutropenia (grade 3; 31%), mucositis (grade 3; 16%), and bacterial infections (grade 3; 12%); all patients recovered rapidly. All the other grade 3 and 4 adverse events were rare: one grade 4 hepatic dysfunction and eight grade 3 events (diarrhea [n = 3], dyspnea [n = 2], hemorrhagic toxicity [n = 1], pulmonary fibrosis [n = 1], and

thrombosis [n = 1]). The remaining toxic effects were mild (grade 1 and 2) and transient. A complete list of toxic events is provided in Table 2.

DISCUSSION

Survival rates for patients with HL, even in advanced stages, have substantially increased over the last few decades. However, a proper balance between risks and benefits of different treatment strategies has not yet been achieved, and the key question of whether to use an intensified chemotherapy for first-line treatment or to reserve it for high-risk or relapsing patients is still without an answer. The standard first-line approach is based on the ABVD regimen.[10,11] A second-line treatment with high-dose chemotherapy followed by ABMT is generally reserved for the 25% of patients who relapse after initial treatment. An alternative approach consists of trying to cure as many patients as possible with a more aggressive regimen (ie, escalated BEACOPP), to be used from the beginning. Systematic review and network meta-analysis have shown better PFS and OS rates, although this more intense approach exposes patients to considerable acute and late chemotherapy-related toxicity.[12,13,26] A randomized comparison of ABVD and BEACOPP in patients with advanced-stage HL has recently been reported,[10] and its results have led some authors to conclude that initial therapy may not necessarily be highly aggressive in all patients because those who relapse may receive subsequent intensive salvage therapy. Others have pointed out that OS was a secondary end point in this study and that the study was small compared with other similar trials.[27] At this time, physicians are not able to predetermine which patients can be cured by ABVD and which patients will benefit from escalated BEACOPP.

PET is now considered an essential component in HL management (because it is widely used for disease staging, restaging, and response evaluation), and the results of an interim PET assessment (generally after the first two cycles of chemotherapy) may be regarded as a strong predictor of the final outcome.[2-4] This has been proven in several studies in which a PET scan performed after one to three cycles of chemotherapy (ABVD was used in all studies) reliably predicted the treatment outcome in more than 85% to 90% of patients with HL.[1-6] Nevertheless, the clinical impact of the interim response assessment during therapy (in other words, if a positive interim PET could justify a shift to a more intensive treatment regimen) remains to be confirmed by the results of ongoing prospective trials. So far, only three studies have reported on the impact of PET response-adapted therapy in advanced-stage HL; however, some studies have methodologic flaws (eg, a small number of patients; use of interim ^{67}Ga scintigraphy in some patients) with the last trial being simply a retrospective analysis.[14,28,29]

What we report here are the results of the first prospective multicenter interim PET-adapted trial in a cohort of 512 patients with advanced-stage HL. The percentage of patients showing a positive PET2 (20%) was similar to that reported in previous studies.[4,5] In the cohort of PET2-negative patients, the 2-year PFS was 81% (overlapping with historical controls), whereas in PET2-positive patients, the 2-year PFS increased from 12% of the historical control to 74% (76% on an intention-to-treat analysis) of this study.[5,10,11,30] One issue in our study is the group of 15 PET2-positive patients who received four more ABVD cycles as a result of the physician's or patient's refusal to switch to the salvage treatment program (among the 15 patients, nine had a minimally positive PET2, which corresponded to Deauville score 3 upon central revision, and one had a negative biopsy of a PET-positive lymph node); 73% achieved a CR, thus indicating the existence of a proportion of patients who can obtain a CR even though they show PET positivity at early evaluation. As reported in all published data sets, this percentage ranges between 10% and 30%; in this study, it is 11%.[1,2,4-6] However, the fact that PET results were assessed qualitatively (the protocol was designed in 2007 before the Deauville criteria were formulated[25]) and that patients with a borderline PET could have been misclassified could represent a potential limitation of this study. This is why we conducted a post hoc revision of all the PET2-positive patients using the Deauville criteria to determine whether the favorable survival outcome obtained by patients who received a transplantation depended on a higher proportion of patients with Deauville score 3 (ie, minimally positive PET 2 scan) being allocated to this arm, which in fact did not. Nearly 70% of the patients in the transplantation arm had a Deauville score $\geq$ 4. An additional PFS analysis comparing PET2-negative and PET2-positive patients (excluding patients with a Deauville score of 3) reported comparable results, which did not change study outcomes.

To the best of our knowledge, these data support, for the first time, the role of early treatment intensification in a small proportion of patients considered at high risk for treatment failure and identified by PET2 positivity. This strategy is opposed to the conventional approach of submitting patients to salvage treatment only after they demonstrate resistance to first-line induction or as soon as the disease relapses. This is confirmed by the possibility of having more than 70% of the PET2-positive patients receive salvage therapy by obtaining the same 2-year PFS as the PET2-negative subgroup.

Reversible grade 3 and 4 cytopenias occurred, as previously reported.[21,22] Neither treatment toxicity–related hospitalization nor treatment-related deaths have been documented so far, thus achieving a favorable toxicity profile for such an intensive therapeutic strategy.

The most relevant theoretical advantages of this approach may be represented by better long-term results because of reduced resistance to induction treatment and a consequently decreased incidence of early and late adverse effects. Conversely, the major disadvantage could be overtreatment of a minority of PET2-positive patients who could benefit from continuation of the

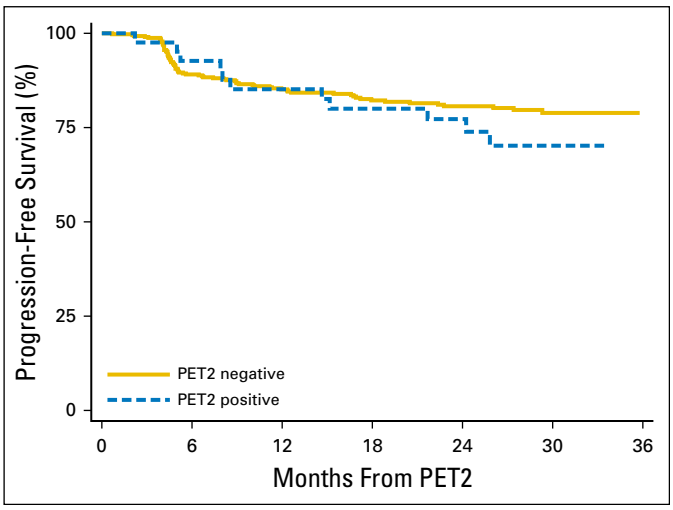

Fig 5. Progression-free survival on an intention-to-treat basis. Solid line, PET2-negative patients; dashed line, PET2-positive patients (Deauville score 4 and 5).

original treatment plan. Longer follow-up will allow more valid and robust conclusions for long-term efficacy and toxicity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Interim Positron Emission Tomography Response–Adapted Therapy in Advanced-Stage Hodgkin Lymphoma: Final Results of the Phase II Part of the HD0801 Study

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Appendix

Patients and Methods

Patients' enrollment and study conduct. All patients had their medical history collected at the time of enrollment. Staging procedures consisted of a full physical examination; a complete blood cell count with leukocyte differential and platelet count; a computed tomography (CT) scan of neck, chest, abdomen, and pelvis (with and without contrast); an ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan; and a bone marrow aspiration and biopsy. A mediastinal mass was considered bulky if its maximum width on a posteroanterior chest x-ray was equal to or greater than one third of the internal transverse diameter of the thorax at the level of T5/T6; any tumor masses larger than 5 cm at any extramediastinal site were also considered bulky. Patients were tested for serum creatinine, liver function tests (including hepatitis B virus antigens, and hepatitis C virus antibodies), uric acid, lactate dehydrogenase, and HIV, and patients had their cardiac function evaluated by echocardiography.

Responses were primarily evaluated by centrally reviewed PET scan after two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); further CT and PET evaluation was performed at the end of the sixth cycle of ABVD or, alternatively, after the fourth ifosfamide, gemcitabine, and vinorelbine (IGEV) course and at the end of any transplantation procedure. The depth of response was graded according to the revised response criteria for malignant lymphomas.[23] A complete response was defined as the complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy, with residual masses of any size being permitted if the scan was PET negative. Partial response was defined in case of at least a 50% decrease in the sum of the products of the diameters (SPD) of up to six dominant masses without any increase in the size of other nodes, liver, or spleen. Moreover, it was required that splenic and hepatic nodules regressed by at least 50% in their SPD, with the PET scan still positive in at least one prior involved site. The disease was considered stable if the patient failed to attain the criteria needed for a complete response or partial response, without fulfilling those for progressive disease. Progressive disease was defined as the appearance of any new lesion of more than 1.5 cm in any axis, even if other lesions were decreasing in size, or as an increase of at least 50% in the SPD of any previously involved node (or splenic or hepatic nodes). Any increased PET uptake in a previously unaffected site required confirmation with other modalities. Follow-up consisted of clinical and laboratory evaluation every 4 months after the end of the treatment program; CT and PET scans were performed yearly for the first 5 years of follow-up.

PET protocol. FDG PET scans were performed with modern full-ring dedicated PET/CT scanners. For each patient, baseline and follow-up scans were performed at the same nuclear medicine center and with the same instrument. The quality of the studies was guaranteed by quality control processes at each center by means of daily quality control measures and/or daily setup and/or tuning and periodical tests of PET performances according to manufacturers' recommendations and internal procedures. Inspection of uniformity and quantitative accuracy of the reconstructed image were considered to identify technical failures that were not detected by using the routine daily quality control procedures. In addition, sinogram data were visually inspected to check for detector failures. Performance Measurements of Positron Emission Tomographs (National Electrical Manufacturers Association NU2-2001) were scheduled at each PET site according to local procedures. Maintenance of all the other devices involved (eg, dose calibrators, well counters, clocks) was performed according to manufacturers' recommendations.

A dose of approximately 185 to 550 MBq was administered intravenously as a bolus according to routine clinical acquisition protocol for the specified PET scanner. A whole-body acquisition with attenuation correction and with emission scan was performed 60 to 90 minutes after injection, starting from the groin up to the ears. The recommended interval between FDG administration and the start of acquisition is 60 minutes in the latest version of European Association of Nuclear Medicine Procedures Guidelines (Boellaard, et al: Eur J Nucl Med Mol Imaging 37:181-200, 2010). However, this recommended interval may change in clinical trials, depending on disease and study aims: times to scan of 60 to 90 minutes, as stated in the study protocol, have in fact been considered a reasonable interval, given the daily work-up of each center and given that uptake curves seem to become

flatter at 60 to 90 minutes after injection (Shankar, et al: J Nucl Med 47:1059-1066, 2006; Lowe, et al: J Nucl Med 36:883-887, 1995; Hutchings, et al: Blood 107:52-59, 2006; Castellucci, et al: Eur J Nucl Med Mol Imaging 32:749-756, 2005). The time for bed position depended on the PET machine used and was left open. Scans corrected for decay, body weight, and administered activity were reconstructed by using iterative algorithms.

PET results have been scored according to a two-point visual scoring system (0: negative, normal, minimal residual uptake just below background, benign; 1: positive, malignant). Mediastinal uptake was used as a reference. In addition, all PET2-positive scans were reviewed by a board of three independent reviewers who were specifically recruited for this purpose to attribute the Deauville score.[25]

Statistical analysis. Progression-free survival (PFS) comparison between positive and negative positron emission tomography evaluation after two cycles of chemotherapy (PET2) patients was performed by using a Cox proportional hazard model adjusting for age, sex, histology, increased lactate dehydrogenase, stage, systemic symptoms, and bulky disease.

Results

Survival analysis. Regarding patients with stage III to IV disease, the 2-year PFS was 79% (95% CI, 74% to 82%) for the entire population and 76% (95% CI, 65% to 85%) for the PET2-positive patients. In patients with stage II disease, the 2-year PFS was 83% (95% CI, 73% to 90%) for the entire population and 76% (95% CI, 48% to 90%) for the PET2-positive patients.