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ORIGINAL REPORT

Risk-Adapted Dose-Dense Immunochemotherapy Determined by Interim FDG-PET in Advanced-Stage Diffuse Large B-Cell Lymphoma

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ABSTRACT

Purpose

In studies of diffuse large B-cell lymphoma, positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG-PET) performed after two to four cycles of chemotherapy has demonstrated prognostic significance. However, some patients treated with immunochemotherapy experience a favorable long-term outcome despite a positive interim FDG-PET scan. To clarify the significance of interim FDG-PET scans, we prospectively studied interim FDG-positive disease within a risk-adapted sequential immunochemotherapy program.

Patients and Methods

From March 2002 to November 2006, 98 patients at Memorial Sloan-Kettering Cancer Center received induction therapy with four cycles of accelerated R-CHOP (rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by an interim FDG-PET scan. If the FDG-PET scan was negative, patients received three cycles of ICE (ifosfamide, carboplatin, and etoposide) consolidation therapy. If residual FDG-positive disease was seen, patients underwent biopsy; if the biopsy was negative, they also received three cycles of ICE. Patients with a positive biopsy received ICE followed by autologous stem-cell transplantation.

Results

At a median follow-up of 44 months, overall and progression-free survival were 90% and 79%, respectively. Ninety-seven patients underwent interim FDG-PET scans; 59 had a negative scan, 51 of whom are progression free. Thirty-eight patients with FDG-PET–positive disease underwent repeat biopsy; 33 were negative, and 26 remain progression free after ICE consolidation therapy. Progression-free survival of interim FDG-PET–positive/biopsy-negative patients was identical to that in patients with a negative interim FDG-PET scan ($P = .27$).

Conclusion

Interim or post-treatment FDG-PET evaluation did not predict outcome with this dose-dense, sequential immunochemotherapy program. Outside of a clinical trial, we recommend biopsy confirmation of an abnormal interim FDG-PET scan before changing therapy.

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INTRODUCTION

In the diagnosis of diffuse large B-cell lymphoma (DLBCL), positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG-PET) has proved to be highly sensitive for determining sites of disease.[1,2] In addition, residual FDG positivity at the end of therapy was predictive for survival.[3] Furthermore, initial reports have suggested that an interim FDG-PET scan performed after two to four cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy could identify patients who are likely to relapse.[4,5] Subsequent data, using different chemotherapy regimens such as R-CHOP (rituximab + CHOP) or ACVBP (cyclophosphamide, doxorubicin, vindesine, bleomycin, and prednisone with or without rituximab) partially confirmed the value of interim FDG-PET scans in prognostication; however, a significant portion of patients do well long-term despite FDG-positive disease on the interim scan.[6,7]

This study was a risk-adapted sequential immunochemotherapy program that incorporated both pretreatment clinical prognostic factors (International Prognostic Index [IPI]) and interim evaluation with FDG-PET scans to direct therapy. We

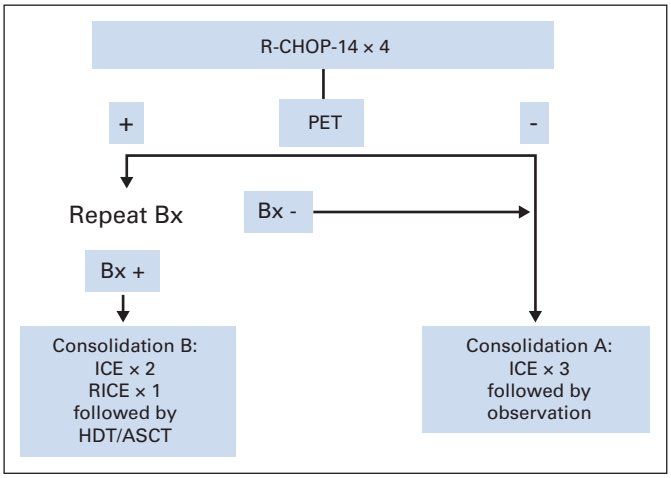

Fig 1. Treatment schema: R-CHOP dosing: rituximab at 375 mg/m^2, cyclophosphamide at 1,000 mg/m^2, doxorubicin at 50 mg/m^2, vincristine at 1.4 mg/m^2 (uncapped), and prednisone at 100 mg/d for 5 days. ICE dosing: ifosfamide at 5,000 mg/m^2 admixed with mesna at 5,000 mg/m^2 as a 24-hour infusion starting on day 2, carboplatin dosed to achieve an area under the serum concentration-time curve to equal 5 mg/mL (capped at 800 mg) on day 2, and etoposide at 100 mg/m^2 on days 1 to 3. PET, positron emission tomography; Bx, biopsy; RICE, rituximab + ICE; HDT, high-dose therapy; ASCT, autologous stem-cell transplantation.

sought to determine whether interim FDG-PET scans could identify patients who might benefit from high-dose therapy/autologous stem-cell rescue (HDT/ASCR) as part of initial treatment and to determine whether HDT/ASCR could be avoided in patients with multiple IPI risk factors but normal interim restaging (defined as a negative interim FDG-PET scan and/or a negative biopsy of FDG-positive disease), using our strategy of dose-dense sequential therapy. We also prospectively evaluated the prognostic significance of individual biomarkers and cell of origin. The chemotherapy regimen for this study was based on sequential trials at Memorial Sloan-Kettering Cancer Center that attempted to improve outcome with CHOP, which was established by the National Intergroup study as the standard of care.[8]

PATIENTS AND METHODS

Eligibility Criteria

Eligible patients were age 18 to 65 years with a histologic diagnosis of CD20$^+$ DLBCL or primary mediastinal DLBCL (PMBL). Patients with DLBCL with concurrent small cleaved cells in bone marrow were also eligible. Patients were required to have one to three of the following adverse risk factors: Karnofsky performance status ≤ 70%; lactate dehydrogenase above normal; or stage III or stage IV disease according to age-adjusted IPI (aaIPI),[9] corresponding to low-intermediate risk (LIR), high-intermediate risk (HIR), or high-risk (HR) disease, respectively. Patients with LIR, non-bulky, localized disease were excluded.

All patients were eligible for transplantation and had FDG-PET–positive evaluable disease, normal left ventricular function, serum creatinine ≤ 1.5 mg/dL (or creatinine clearance > 60 mL/min), absolute neutrophil count of > 1,000/μL, and platelet count of > 50,000/μL. Patients had to be HIV-negative, hepatitis B surface antigen–negative, and hepatitis C antibody–negative. Patients with CNS involvement were excluded. All patient data were presented at the weekly lymphoma staging conference. Those patients with a positive interim FDG-PET scan were presented again before a second biopsy.

Treatment

Induction chemotherapy consisted of four doses of accelerated R-CHOP (R-CHOPac) administered within a 14-day cycle. One additional dose of rituximab preceded cycle 1 on day −2. R-CHOPac was given as follows: rituximab at 375 mg/m^2 intravenous (IV) infusion, cyclophosphamide at 1,000 mg/m^2 IV piggyback, doxorubicin at 50 mg/m^2 IV push (IVP), vincristine at 1.4 mg/m^2 (uncapped) IVP, and prednisone at 100 mg/d orally for 5 days. Either filgrastim or pegfilgrastim was administered after each cycle. If grade 3/4 neurotoxicity developed, vincristine was reduced or discontinued. If necessary, treatment was delayed until absolute neutrophil count was > 1,000/μL and platelet count was > 50,000/μL (Fig 1).

Concomitant medications included oral acyclovir at 200 mg twice daily, sulfamethoxazole/trimethoprim 160 mg/800 mg orally every other day, and fluconazole at 100 mg orally every day. Allopurinol at 300 mg was administered orally during the first 14 days of the first cycle starting on day −2.

Interim Restaging

Computed tomography (CT) and FDG-PET scans were repeated 10 to 14 days after the start of the fourth cycle of R-CHOPac. Patients who had resolution of all FDG-positive sites of disease (without development of new sites) proceeded to consolidation A (three cycles of ICE [ifosfamide, carboplatin, etoposide] chemotherapy).[10] Patients with residual FDG-positive disease that correlated with CT findings underwent repeat biopsy. If the biopsy was

Table 1. Patient Characteristics (N = 98)

Characteristic	No.	%
Clinical		
Age, years		
Median	47	
Range	20-65	
≥ 60	16 of 98	16
Sex		
Male	57	
Female	41	
LDH > ULN	83 of 98	85
KPS ≤ 70%	39 of 98	40
Stage		
IV	64 of 98	65
III/IV	83 of 98	85
ENS ≥ 1	53 of 98	54
BM+	14 of 98	14
R-IPI high	64 of 98	65
aaIPI		
LIR	21 of 98	21
HIR	49 of 98	50
HR	29 of 98	29
Bulk ≥ 10 cm	33 of 98	34
Pathologic		
CD10$^+$	26 of 91	29
BCL-6+	60 of 89	67
MUM1+	36 of 87	41
p53+	38 of 85	45
BCL-2+	52 of 89	58
Ki-67 ≥ 80	32 of 87	37
Cell of origin		
GC	37 of 93	40
NGC	28 of 93	30
PM	28 of 93	30

NOTE. Median follow-up for patients alive is 44 months (range, 25 to 80 months). Total number of patients varies from 98 because not all patients had enough tissue available for all pathologic specimens to be fully analyzed.

Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal; KPS, Karnofsky performance status; ENS, extranodal sites of disease; BM, bone marrow; R-IPI, revised International Prognostic Index; aaIPI, age-adjusted International Prognostic Index; LIR, low-intermediate risk; HIR, high-intermediate risk; HR, high risk; GC, germinal center; NGC, non-germinal center; PM, primary mediastinal.

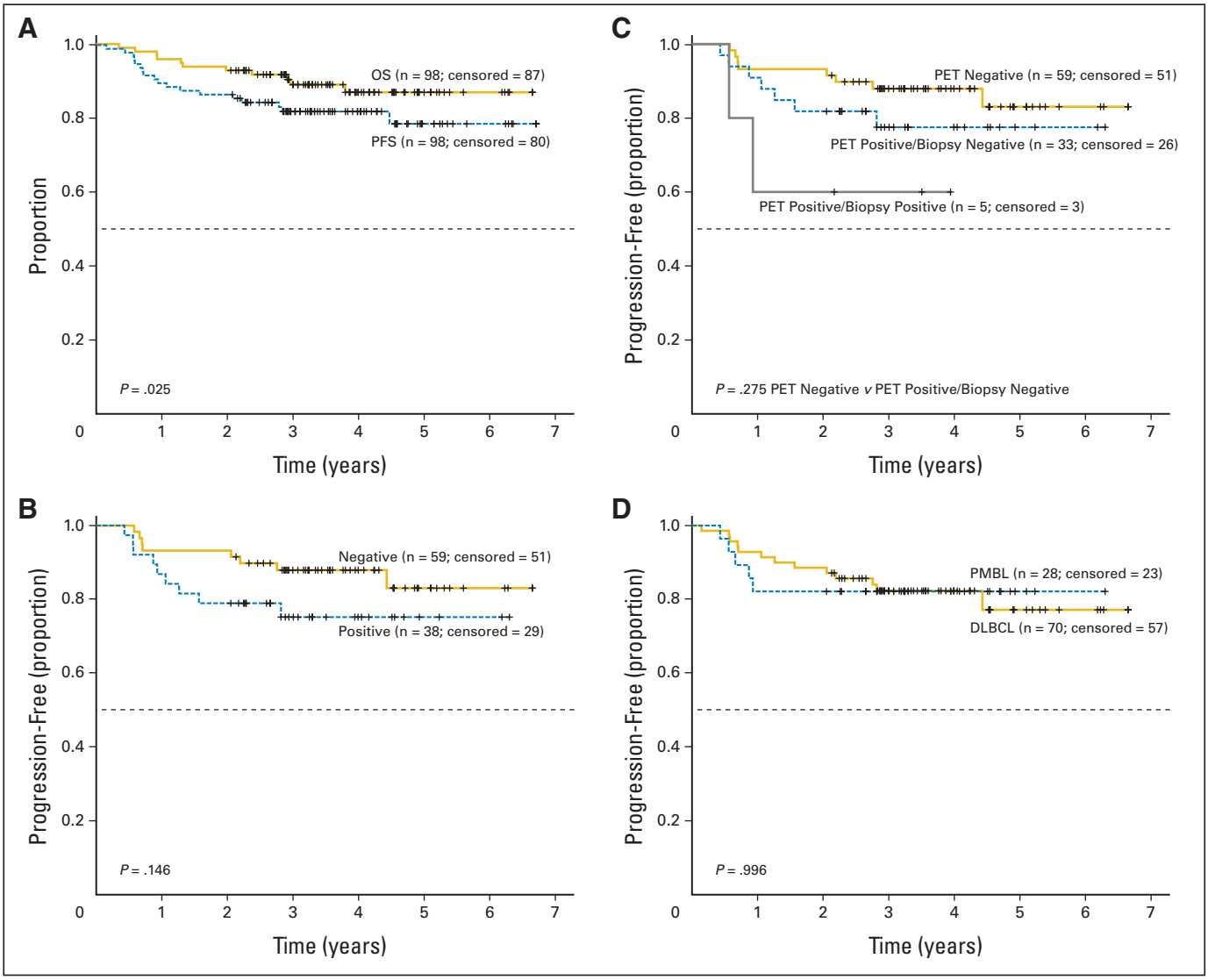

Fig 2. Outcome estimates based on Kaplan-Meier analysis. (A) Progression-free survival (PFS) and overall survival (OS) analyzed by intent to treat. (B) PFS based on interim positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG-PET): positive versus negative. (C) PFS based on interim FDG-PET and biopsy result: interim FDG-PET–negative versus FDG-PET–positive biopsy-negative versus FDG-PET–positive biopsy-positive. (D) PFS based on histology: diffuse large B-cell lymphoma (DLBCL) versus primary mediastinal DLBCL (PMBL).

negative, the patient received consolidation A therapy; if the biopsy was positive, the patient received consolidation B (two cycles of ICE and then one cycle of RICE [rituximab + ICE] followed by HDT and autologous stem-cell transplantation). Those patients whose bone marrow was initially positive and remained positive after induction received consolidation B (Fig 1). Consolidation B therapy was divided into three parts: (1) two cycles of ICE, (2) one cycle of RICE with peripheral blood progenitor stem-cell collection,[11] and (3) HDT/ASCR.[12] (See Appendix, online only, for more detail.)

Radiation Therapy and Intrathecal Prophylaxis

Consolidative radiation therapy was permitted only in testicular lymphoma. Intrathecal prophylaxis with four to six doses of either methotrexate (12 mg) or cytarabine (60 mg) was administered to all patients with IPI HR disease, as well as those with nasopharyngeal, sinus, or testicular disease.

FDG-PET Analysis

All interim scans were reviewed alongside baseline scans to verify residual abnormal uptake at sites of previously identified disease; decision to biopsy a residual abnormality was based on this review. FDG-PET scans were interpreted visually with correlation to a concurrent or simultaneous CT scan of the chest, abdomen, and pelvis (when done as integrated PET/CT). No standard uptake value (SUV) exists to distinguish between malignant and nonmalignant FDG-avid disease. We instead relied on visual comparison with the baseline FDG uptake and uptake in surrounding normal tissue at interim. Prior studies applied similar criteria for visual interpretation.[13,14] A negative interim scan was defined as absence of FDG uptake at any site of FDG-positive disease identified in the baseline study, and lack of new FDG-positive disease. A positive scan was defined as any FDG uptake greater than local background activity, with a corresponding abnormality on CT scan. Exploratory analyses, compared SUV changes from baseline with interim (Δ SUV) between patients with and without residual disease in the biopsy specimen obtained after a positive interim FDG-PET scan (see Results).

Biostatistics

The primary end point was to determine complete response rate. The study was designed to have a 90% power of detecting an increase in complete response rate from 75% to 90% in the LIR group and from 53% to 75% in the

HIR/HR groups. Progression-free survival (PFS) and overall survival (OS) were evaluated as clinical end points. OS was defined as the interval from the start of treatment with R-CHOPac until death or last follow-up for patients who were still alive. PFS was defined as the interval from the start of treatment with R-CHOPac until progression of DLBCL, death from any cause, or last follow-up. The probabilities of being alive and progression free 3 years after therapy initiation were calculated based on Kaplan-Meier estimates.

The secondary objective was to determine whether interim FDG-PET could accurately identify those patients who had a poor prognosis after induction immunochemotherapy and who might benefit from HDT/ASCR consolidation. A landmark analysis was performed at 10 weeks when the interim FDG-PET scan was evaluated, and the PFS of FDG-positive and FDG-negative patients were compared. In addition, we were interested in whether biopsy results could be predicted by SUV values; we used the Wilcoxon signed rank test to compare biopsy-positive/biopsy-negative patients with respect to SUV measurements at the interim PET scan, as well as the changes in SUV from pretreatment to the interim evaluation. Furthermore, we used two established receiver operating characteristic–based methods (Youden's Index and the closest to [0,1] criterion) in an attempt to identify a threshold on the SUV range that best predicted biopsy results.[15-17]

Kaplan-Meier estimates of PFS and OS stratified by various prognostic factor categories were calculated and compared by means of log-rank test statistics. The best cut point for the biomarker Ki-67 in predicting PFS was found by using the method of Mazumdar and Glassman.[18] Associations were considered significant if P was $< .05$. All P values were two-sided. All analyses were conducted using SAS version 9.1 (SAS Institute, Carey, NC).

RESULTS

From March 26, 2002, through November 3, 2006, a total of 98 newly diagnosed, DLBCL patients who were eligible for transplantation were prospectively enrolled onto Memorial Sloan-Kettering Cancer Center Protocol 01-142, which was approved by the institutional review board. The median age was 47 years; 16 patients (16%) were between age 60 and 65 years. Written informed consent was obtained from all patients. Patient demographics and pretreatment clinical and pathologic characteristics are described in Table 1.

One patient progressed on therapy, and 97 patients received all of the planned therapy. The dose of vincristine was uncapped; however, 18 patients had dose reductions, and all patients received R-CHOP-14 on schedule. No dose reduction with ICE chemotherapy was permitted, but platelet count had to be at least 50,000/μL for cycle 2 and cycle 3 to begin. The planned time interval for the three cycles of ICE was 31 to 37 days; the median time interval in this study was 37 days (range, 29 to 53 days), and delays were nearly always secondary to thrombocytopenia.

Treatment Outcome

At a median follow-up of 44 months, the Kaplan-Meier estimates of patients alive and progression free were 90% (95% CI, 83% to 98%) and 79% (95% CI, 69% to 89%), respectively (Fig 2A). Sixteen of 23 patients had an event related to DLBCL, and nine of these patients died. Four of the 16 patients had primary refractory disease (one during induction, three during consolidation); all died of progressive DLBCL. Twelve patients relapsed, four with parenchymal disease in the brain despite intrathecal prophylaxis. Seven of these 12 patients are currently in second remission, six after HDT/ASCR. The remaining events included three cases of low-grade non-Hodgkin's lymphoma after antecedent DLBCL, two cases of non–small-cell lung cancer (both patients had a history of heavy tobacco use, and one of these patients died), one case of acute myelogenous leukemia, and one case of myelodysplasia (this patient died).

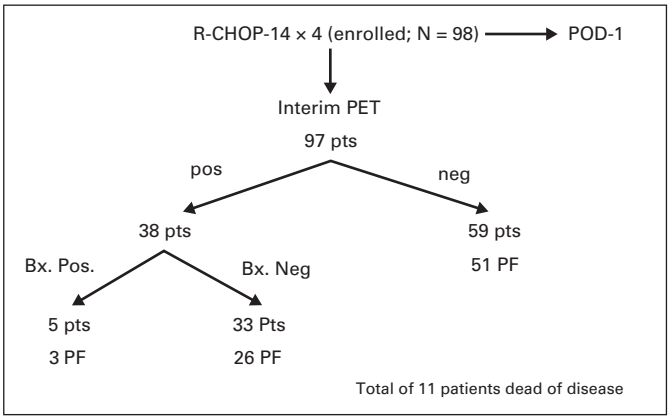

Fig 3. Outcome based on interim evaluation. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; PET, positron emission tomography; POD, progression of disease; Bx, biopsy; pts, patients; Pos, positive; Neg, negative; PF, progression-free.

Interim FDG-PET

At 10 weeks after start of therapy, the results of the interim FDG-PET scan did not correlate with PFS ($P = .146$; Fig 2B). When the PFS of interim FDG-PET–positive biopsy-negative patients was compared with that of patients with a negative interim FDG-PET scan, the outcomes were identical ($P = .27$; Fig 2C). Pretherapeutic FDG-PET scans were positive in all patients with a median maximum SUV (SUV_{max}) value of 17 (range, 6 to 73). Ninety-seven patients had interim restaging FDG-PET scans (Fig 3). Fifty-nine patients had a negative interim FDG-PET scan and received consolidation A; 51 are progression free. The remaining 38 patients had FDG-PET–positive disease at a site that was also abnormal on CT scan. These patients underwent repeat biopsy (Table 2). Five of the 38 patients had a positive biopsy and received consolidative transplantation (consolidation B); three of those five patients are alive and progression free. The 33 patients with a negative biopsy received ICE without ASCR (consolidation A); 26 of those patients remain alive without evidence of DLBCL.

Interim Restaging Biopsy

Thirty-three biopsies showing no residual tumor were analyzed to determine why the FDG-PET scan was false-positive. All specimens showed inflammation. There was no correlation between the degree of inflammation and SUV.

Exploratory Analysis of Interim FDG-PET–Positive Scans

In searching for a cutoff value in patients with a positive interim FDG-PET scan, we found no significant difference in SUV measurements (Table 3). We investigated highest SUV_{max} values at the biopsy site as well as change in SUV_{max} between pretreatment values and interim evaluation values but failed to identify a meaningful threshold. Additionally, there was an overlap between biopsy-negative and biopsy-positive patients with respect to interim SUV and ratio SUV at the biopsy site.

Table 2. Outcome of Patients With Interim Restaging of FDG-Positive Disease Using FDG-PET Scan (n = 38)

aaIPI	Cell of Origin	Initial SUV at Biopsy Site	Interim SUV at Biopsy Site	Procedure	Site	Interim Biopsy Result	Status
LIR	GC	16.9	4	CT-guided core biopsy	Bone	Negative	CR2
LIR	PMLBCL	15	3.6	Chamberlin	Hilar mass	Negative	CR2
HIR	GC	11.7	2.8	Laparoscopy	Mesenteric node	Negative	DOD
HR	Non-GC	17	14	CT-guided core biopsy	Retroperitoneal node	Positive	DOD
HR	Non-GC	29.4	5.4	Fine-needle aspirate	Spleen	Positive	DOD
LIR	PMBL	12	2	CT-guided core biopsy	Mediastinal mass	Negative	DOD
LIR	PMBL	12.8	3.2	Thoracotomy	Lung mass	Negative	DOD
HIR	Non-GC	3.9	1.5	CT-guided core biopsy	Soft tissue	Negative	Indolent NHL
HIR	Non-GC	27	3.5	Laparoscopy	Mesenteric node	Negative	Lung cancer
HIR	GC	8	N/R	Colonoscopy	Multiple large bowel lesions	Negative	Dead
HIR	GC	N/R	3.4	CT-guided core biopsy	Bone	Negative	PF
HIR	GC	3.8	3.5	CT-guided core biopsy	Inguinal node	Negative	PF
HIR	GC	15	11.5	Laparatomy	Jejunal mass	Negative	PF
HR	GC	10.3	11	CT-guided core biopsy	Bone	Negative	PF
HR	GC	8.8	11.1	Laparoscopy	Mesenteric node	Negative	PF
LIR	GC	32	N/R	Colonoscopy	Cecal mass	Negative	PF
HIR	Non-GC	11.9	2.9	CT-guided core biopsy	Inguinal node	Negative	PF
HIR	Non-GC	11.9	2.4	CT-guided core biopsy	Mediastinal mass	Negative	PF
HR	Non-GC	18.8	7.1	CT-guided core biopsy	Pelvic mass	Negative	PF
HR	Non-GC	21.6	3.5	Medianstinoscopy	Mediastinal mass	Negative	PF
LIR	Non-GC	43	2.1	Excisional biopsy	Inguinal node	Negative	PF
HIR	Non-GC	13.3	7	CT-guided core biopsy	Mesenteric node	Positive	PF
HIR	PMBL	22.5	2	Chamberlin	Hilar mass	Negative	PF
HIR	PMBL	32	9.2	CT-guided core biopsy	Pleural mass	Negative	PF
HIR	PMBL	19	2.2	CT-guided core biopsy	Mediastinal mass	Negative	PF
HIR	PMBL	14.7	2.5	CT-guided core biopsy	Mediastinal mass	Negative	PF
HIR	PMBL	24.7	3	CT-guided core biopsy	Mediastinal mass	Negative	PF
HIR	PMBL	20.9	3.7	CT-guided core biopsy	Mediastinal mass	Negative	PF
HIR	PMBL	17.5	3.8	Medianstinoscopy	Mediastinal mass	Negative	PF
HR	PMBL	22	2.9	CT-guided core biopsy	Mediastinal mass	Negative	PF
HR	PMBL	29	4.1	Thoracotomy	Lung mass	Negative	PF
LIR	PMBL	15.9	3.2	Medianstinoscopy	Mediastinal mass	Negative	PF
LIR	PMBL	10.6	4.3	Medianstinoscopy	Mediastinal mass	Negative	PF
LIR	PMBL	9.1	3	Thoracotomy	Lung mass	Negative	PF
LIR	PMBL	14	3.2	Thoracotomy	Lung mass	Negative	PF
LIR	PMBL	16.3	5.8	Thoracotomy	Lung mass	Negative	PF
HR	Unknown	13	3.6	CT-guided core biopsy	Retroperitoneal node	Positive	PF
HR	Unknown	10.6	2	Excisional biopsy	Axillary node	Positive	PF

Abbreviations: FDG-PET, positron emission tomography with [^{18}F]fluorodeoxyglucose; aaIPI, age-adjusted International Prognostic Index; SUV, standard uptake value; LIR, low-intermediate risk; GC, germinal center; CT, computed tomography; CR2, second complete remission; PMLBCL, primary mediastinal large B-cell lymphoma; HIR, high-intermediate risk; DOD, dead of disease; HR, high risk; PMBL, primary mediastinal B-cell lymphoma; NHL, non-Hodgkin's lymphoma; N/R, not recorded; PF, progression-free.

Final FDG-PET Scan Results

Because of biopsy-proven disease at interim evaluation, five patients received a consolidative transplantation after three cycles of ICE. We evaluated outcome on the basis of final FDG-PET scan results at 4 to 6 weeks after ICE, or 90 to 100 days after transplantation for these five patients. There was no difference in outcome for patients with FDG-PET–negative versus residual FDG-PET–positive disease ($P = .70$).

Prognostic Factors

Associations between reported clinical and biologic prognostic factors and PFS were calculated by univariate analysis. There was no outcome difference with any of the single IPI risk factors: age ($P = .97$), performance status ($P = .38$), stage ($P = .16$), lactate dehydrogenase ($P = .56$), or two or more extranodal sites ($P = .74$). The same was true of the full IPI model (five factors), the revised IPI model,[19] and the aaIPI score used for study enrollment.

The cell of origin (germinal center *v* non-germinal center) as determined by immunohistochemistry did not affect PFS. We specifically included patients with PMBL, a cohort that typically presents with bulky nodal disease and an unusual relapse pattern. This had no impact on PFS or OS data (Fig 2D). Neither bone marrow involvement nor tumor bulk of $\geq$ 10 cm correlated with outcome.

The only statistically significant pretreatment factor was the proliferation marker Ki-67, of which 87 samples were available. Forty-nine (89%) of the 55 patients whose tumors had less than 80% proliferation rate were progression free at the end of the follow-up period versus 22 (69%) of 32 patients whose Ki-67 expression was $\geq$ 80% ($P = .002$).

Table 3. Correlation Between SUV and Biopsy Result

	Highest SUV at Biopsy Site (Interim PET scan)			Ratio SUV*		
Biopsy Result	Median	Minimum	Maximum	Median	Minimum	Maximum
Negative (n = 33)	3.4	1.5	11.5	1.46	−0.2	3
Positive (n = 5)	5.4	2	14	1.3	0.2	1.7
P (Wilcoxon test)		.25			.36	

NOTE. Thirty-eight patients had a repeat biopsy after interim restaging FDG-PET scan was positive.
Abbreviations: SUV, standard uptake value; PET, positron emission tomography.
*Ratio SUV = log (initial highest SUV at biopsy site/interim highest SUV at biopsy site).

DISCUSSION

The ability to predict an unfavorable outcome early in the course of DLBCL therapy has important clinical and research implications. FDG-PET is well established for staging and restaging of DLBCL and Hodgkin's lymphoma and has recently been incorporated into the International Workshop Criteria for determining response.[20] A negative interim restaging FDG-PET scan has also been associated with an excellent outcome. However, because of inconsistent results in patients with interim FDG-PET–positive scans as well as the need to improve therapy for patients who are eligible for transplantation and who have multiple IPI factors, we conducted this risk-adapted clinical trial for patients with LIR, HIR, and HR DLBCL.

As in other reports, a negative interim restaging FDG-PET scan in our study was associated with an excellent outcome: 87% of these patients are progression free. Only eight (13%) of 59 patients with a negative test relapsed after R-CHOPac followed by ICE consolidation. Unexpectedly, of the 38 patients with positive interim restaging FDG-PET scans, only five (13%) had biopsy-confirming active DLBCL. The remaining patients had negative biopsies. Two patients who had a negative interim biopsy underwent a repeat biopsy at the conclusion of therapy for persistent FDG-positive disease at the same site that demonstrated active DLBCL; thus, in these patients, interim biopsies likely missed the viable tumor. Sampling error in other patients cannot be entirely excluded; however, if biopsies consistently failed to identify tumor, outcomes would differ between patients with FDG-positive residual disease and those with complete resolution of FDG positivity at interim restaging. This was not the case.

There are numerous potential explanations for the number of false-positive scans. FDG as a marker is not highly specific and shows uptake in infectious and inflammatory processes.[21-26] In addition, variation in the induction regimens may have had some effect. Using interim FDG-PET scans may be effective if standard CHOP is administered at 21-day intervals but may have only limited utility when other regimens, including R-CHOP, are given.[27]

All interim biopsies in this study demonstrated some degree of inflammation and/or necrosis. It may be that the timing of the scan affected FDG positivity. When we initiated this study, a position paper by the European Organisation for Research and Treatment of Cancer (EORTC) recommended a time interval of 1 to 2 weeks between completion of a chemotherapy cycle and FDG-PET scan to avoid transient flare at the diseased sites.[28] Seven chemotherapy cycles were administered in our study. The plan was for cycle 1 to begin on day 1, and cycle 2 to begin on day 15. After cycle 4 of R-CHOPac, an FDG-PET scan was ordered so that before administering cycle 1 of ICE, we could decide either to biopsy or to continue chemotherapy. The scan occurred at a median of day 12 in the 2-week period; no patient had the scan before day 10. The final FDG-PET scan was performed at least 4 weeks after ICE therapy.

It is also possible that the use of immunotherapy increased lesion inflammation. Antibody-mediated cellular cytotoxicity and complement activation are important rituximab mechanisms.[29-31] Both processes recruit mediators of inflammation to the tumor site. The greater use of rituximab in the current study compared with use in the prior studies of Spaepen et al (none)[3,5] and Haioun (41%)[6] could have contributed to the high rate of FDG positivity unrelated to tumor activity.

We specifically included patients with PMBL in this study. Although the outcome of PMBL is favorable, long-term disease-free remission rates have been achieved with combined-modality therapy, including radiation to the mediastinum, which was specifically excluded in our study.[32] However, other reports also suggest that with novel treatment programs, radiotherapy can be avoided without compromising outcome.[33] Even excluding patients with PMBL, the fundamental conclusion of this study remains unchanged, ie, that interim FDG-PET scans, as conducted in this protocol, do not predict outcome.

Consolidative therapy may have overcome the adverse outcome expected for patients with FDG-PET–positive disease after R-CHOPac induction therapy. That is, even if there were false-negative biopsies, the results were excellent because ICE effectively eradicated residual DLBCL. However, in our 15-year experience with ICE-based salvage therapy, we have reported that it is unlikely for ICE to overcome disease refractory to R-CHOP to the extent that outcomes are identical to those of patients with a negative interim FDG-PET scan, who presumably have highly chemosensitive disease. Nevertheless, these results compare favorably with standard R-CHOP, R-CHOPE (rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide), and R-EPOCH (r ituximab + etoposide, d oxorubicin, v inristine, c yclophosphamide, and p rednisolone)[34] and have similar PFS rates to R-ACVBP (rituximab + ACVBP) and consolidative transplantation for all patients, as recently reported at the 2009 American Society of Hematology meetings by the Groupe d'Etude des Lymphomes (GELA; Appendix Table A1, onlineonly).

It is likely that some combination of these described factors contributed to rendering the interim FDG-PET–positive scans invalid for predicting treatment outcome. We selected FDG-PET as a tool for interim response evaluation on the basis of prior studies that used this imaging test for patients receiving chemotherapy for DLBCL. However, interim FDG-PET lost its validity as a predictive and prognostic marker because of alterations in trial design, which included introduction of immunochemotherapy, altered timing between treatment and interim scan, and possibly the use of more effective consolidation. Our experience in this study illustrates that a marker of response assessment will be valid only if it is used in a manner nearly identical to the one in which it was established.

This study demonstrates a highly effective strategy for the treatment of advanced-stage DLBCL, one that cured approximately 80% of patients. However, an interim FDG-PET scan did not identify those patients at high risk for a poor outcome. At present, suspected residual active DLBCL on interim restaging FDG-PET scans should be confirmed by biopsy before initiating a change in therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Juweid ME, Stroobants S, Hoekstra OS, et al: Use of positron emission tomography for response assessment of lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 25:571-578, 2007

2. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007

3. Spaepen K, Stroobants S, Dupont P, et al: Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: Is [18F]FDG-PET a valid alternative to conventional diagnostic methods? J Clin Oncol 19:414-419, 2001

4. Jerusalem G, Beguin Y, Fassotte MF, et al: Persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. Haematologica 85: 613-618, 2000

5. Spaepen K, Stroobants S, Dupont P, et al: Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 13:1356-1363, 2002

6. Haioun C, Itti E, Rahmouni A, et al: [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: An early prognostic tool for predicting patient outcome. Blood 106: 1376-1381, 2005

7. Fruchart C, Reman O, Le Stang N, et al: Prognostic value of early 18 fluorodeoxyglucose positron emission tomography and gallium-67 scintigraphy in aggressive lymphoma: A prospective comparative study. Leuk Lymphoma 47:2547-2557, 2006

8. Fisher RI, Gaynor ER, Dahlberg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002-1006, 1993

9. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 329:987-994, 1993

10. Moskowitz CH, Bertino JR, Glassman JR, et al: Ifosfamide, carboplatin, and etoposide: A highly effective cytoreduction and peripheral-blood progenitor stem-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. J Clin Oncol 17:3776-3785, 1999

11. Kewalramani T, Zelenetz AD, Nimer SD, et al: Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 103:3684-3688, 2004

12. Moskowitz CH, Glassman JR, Wuest D, et al: Factors affecting mobilization of peripheral blood progenitor cells in patients with lymphoma. Clin Cancer Res 4:311-316, 1998

13. Gallamini A, Hutchings M, Rigacci L, 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 25:3746-3752, 2007

14. Hutchings M, Loft A, Hansen M, et al: FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 107:52-59, 2006

15. Youden WJ: Index for rating diagnostic tests. Cancer 3:32-35, 1950

16. Coffin M, Sukhatme S: Receiver operating characteristic studies and measurement errors. Biometrics 53:823-837, 1997

17. Perkins NJ, Schisterman EF: The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol 163:670-675, 2006

18. Mazumdar M, Glassman JR: Categorizing a prognostic variable: Review of methods, code for easy implementation and applications to decision-making about cancer treatments. Stat Med 19:113-132, 2000

19. Sehn LH, Berry B, Chhanabhai M, et al: The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 109:1857-1861, 2007

20. Juweid ME, Wiseman GA, Vose JM, et al: Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. J Clin Oncol 23:4652-4661, 2005

21. Weinblatt ME, Zanzi I, Belakhlef A, et al: False-positive FDG-PET imaging of the thymus of a child with Hodgkin's disease. J Nucl Med 38:888-890, 1997

22. Ford CD, Gabor F, Morgan R, et al: False-positive restaging PET scans involving the spleen in two patients with aggressive non-Hodgkin lymphoma. Clin Nucl Med 31:391-393, 2006

23. Inoue Y, Tamaki H, Yamagami T, et al: False-positive FDG-PET findings due to bone metastasis from prostate cancer in staging of non-Hodgkin's lymphoma. Eur J Haematol 79:88-90, 2007

24. Belakhlef A, Jani C, Church C, et al: Fat necrosis mimicking B-cell lymphoma: A PET/CT and FDG study. Clin Nucl Med 33:271-272, 2008

25. Focosi D, Caracciolo F, Galimberti S, et al: False positive PET scanning caused by inactivated influenza virus vaccination during complete remission from anaplastic T-cell lymphoma. Ann Hematol 87:343-344, 2008

26. Zhao S, Kuge Y, Kohanawa M, et al: Extensive FDG uptake and its modification with corticosteroid

in a granuloma rat model: An experimental study for differentiating granuloma from tumors. Eur J Nucl Med Mol Imaging 34:2096-2105, 2007

27. Han HS, Escalon MP, Hsiao B, et al: High incidence of false-positive PET scans in patients with aggressive non-Hodgkin's lymphoma treated with rituximab-containing regimens. Ann Oncol 20: 309-318, 2009

28. Young H, Baum R, Cremerius U, et al: Measurement of clinical and subclinical tumour responsex using [18F]-fluorodeoxyglucose and positron emission tomography: Review and 1999 EORTC recommendations—European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 35:1773-1782, 1999

29. Cartron G, Watier H, Golay J, et al: From the bench to the bedside: Ways to improve rituximab efficacy. Blood 104:2635-2642, 2004

30. Smith MR: Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene 22:7359-7368, 2003

31. Maloney DG: Preclinical and phase I and II trials of rituximab. Semin Oncol 26:74-78, 1999

32. Zinzani PL, Martelli M, Bendandi M, et al: Primary mediastinal large B-cell lymphoma with sclerosis: A clinical study of 89 patients treated with MACOP-B chemotherapy and radiation therapy. Haematologica 86:187-191, 2001

33. Wilson WH, Grossbard ML, Pittaluga S, et al: Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: A pharmacodynamic approach with high efficacy. Blood 99:2685-2693, 2002

34. Sehn LH, Donaldson J, Chhanabhai M, et al: Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 23:5027-5033, 2005

35. Coiffier B, Lepage E, Brière J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. N Engl J Med 346:235-242, 2002

36. Wilson WH, Dunleavy K, Pittaluga S, et al: Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol 26:2717-2724, 2008

37. Pfreundschuh M, Trümper L, Kloess M, et al: Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: Results of the NHL-B1 trial of the DSHNHL. Blood 104:626-633, 2004

38. Pfreundschuh M, Trümper L, Kloess M, et al: Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL. Blood 104:634-641, 2004

39. Pfreundschuh M, Schubert J, Ziepert M, et al: Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: A randomised controlled trial (RICOVER-60). Lancet Oncol 9:105-116, 2008

