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Background: For patients with peripheral T-cell lymphoma (PTCL), the value of 18fluoro-deoxyglucose positron emission tomography (FDG-PET) scans for assessing prognosis and response to treatment remains unclear. The utility of FDG-PET, in addition to conventional radiology, was examined as a planned exploratory end point in the pivotal phase 2 trial of romidepsin for the treatment of relapsed/refractory PTCL.

Patients and methods: Patients received romidepsin at a dose of 14 mg/m^2 on days 1, 8, and 15 of 28-day cycles. The primary end point was the rate of confirmed/unconfirmed complete response (CR/CRu) as assessed by International Workshop Criteria (IWC) using conventional radiology. For the exploratory PET end point, patients with at least baseline FDG-PET scans were assessed by IWC + PET criteria.

Results: Of 130 patients, 110 had baseline FDG-PET scans, and 105 were PET positive at baseline. The use of IWC + PET criteria increased the objective response rate to 30% compared with 26% by conventional radiology. Durations of response were well differentiated by both conventional radiology response criteria [CR/CRu versus partial response (PR), $P = 0.0001$] and PET status (negative versus positive, $P < 0.0001$). Patients who achieved CR/CRu had prolonged progression-free survival (PFS, median 25.9 months) compared with other response groups ($P = 0.0007$). Patients who achieved PR or stable disease (SD) had similar PFS (median 7.2 and 6.3 months, respectively, $P = 0.6427$). When grouping PR and SD patients by PET status, patients with PET-negative versus PET-positive disease had a median PFS of 18.2 versus 7.1 months ($P = 0.0923$).

Conclusion(s): Routine use of FDG-PET does not obviate conventional staging, but may aid in determining prognosis and refine response assessments for patients with PTCL, particularly for those who do not achieve CR/CRu by conventional staging. The optimal way to incorporate FDG-PET scans for patients with PTCL remains to be determined.

Trial registration: NCT00426764.

Key words: romidepsin, peripheral T-cell lymphoma, positron emission tomography, radiology, histone deacetylase inhibitor

introduction

Romidepsin is a potent, bicyclic, class 1 histone deacetylase inhibitor [1–3] approved in 2009 by the US Food and Drug

Administration for treatment of patients with cutaneous T-cell lymphoma who received at least one prior systemic therapy, and in 2011 for treatment of patients with peripheral T-cell lymphoma (PTCL) who received at least one prior therapy [4]. Supportive data for the PTCL approval came from two phase 2, single-arm trials for patients with relapsed/refractory PTCL,

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which demonstrated overall response rates (ORR) of 38% (17/45; NCI-1312) [5] and 25% (33/130; GPI-06–0002) [6], including complete response rates of 18% [5] and 15% [6], respectively. Many responses were durable on continuous therapy, with a median duration of response (DOR) of 28 months (median follow-up, 22.3 months) and the longest response ongoing at 48 months [7].

PTCL is an uncommon form of non-Hodgkin lymphoma (NHL) typically associated with poor prognosis [8–10]. This heterogeneous group of diseases is often marked by aggressive clinical behavior, relatively poor responses to chemotherapy, high relapse rates, and poor long-term survival when compared with the more common B-cell lymphomas (BCLs) [8–10]. Currently, there are no universal standards of care for most subtypes. Only a minority of patients with PTCL achieve sufficient responses and are eligible to undergo stem-cell transplant (SCT) [11]. In a recent population-based study, the median time from diagnosis to relapse or progression following first-line therapy for PTCL ($n = 153$) was only 6.7 months and the median overall and progression-free survival (OS, PFS) for patients with relapsed/refractory disease who did not receive SCT were 5.5 and 3.1 months, respectively [12].

International Workshop Criteria (IWC) for NHL [13] employ computed tomography (CT)/magnetic resonance imaging (MRI) scans for assessment of disease stage and response to therapy. IWC + ^{18}fluoro-deoxyglucose positron emission tomography (FDG-PET) scans have been used routinely in the staging and response assessment of patients with select NHL subtypes, such as diffuse large BCL (DLBCL), as well as Hodgkin lymphoma [14]. Response criteria for NHL, which adds FDG-PET determination of disease activity (positive/negative) to the standards of CT/MRI [15, 16], were developed due to recognized limitations with CT/MRI. T-cell and natural killer cell (NK) lymphomas are frequently PET avid at rates similar to BCLs [17–26], and several recent studies suggested that FDG-PET scans may have utility in disease staging in T/NK lymphomas [17–24]. These findings have led to current National Comprehensive Cancer Network guidelines suggesting that both CT and PET scans are essential in monitoring patients with PTCL [27]. However, the utility of PET in terms of response assessments and the predictive value of interim and post-therapy scans remains unclear, particularly in relapsed/refractory patients.

The utility of PET, in addition to standard CT/MRI, was a prospective exploratory end point in the pivotal trial of romidepsin in relapsed/refractory PTCL (GPI-06-0002). Imaging data from all patients underwent independent central review. Herein, an analysis of that exploratory end point is presented, including rates of PET avidity, response assessments by IWC + PET criteria versus standard CT/MRI alone, and the ability of response assessments by PET to predict durability of responses or long-term outcomes, and therefore help to inform treatment decisions.

methods

study design

Study design and eligibility criteria for this prospective, open-label, single-arm, international, phase 2 study of patients with relapsed/refractory PTCL have been previously described [6]. Romidepsin was given at a dosing regimen of 14 mg/m^2 (4 h intravenous injection) on days 1, 8, and 15 of a 28-day cycle for 6 cycles. Patients achieving stable disease (SD) or better could continue to receive treatment beyond 6 cycles. The primary end point was the rate of confirmed/unconfirmed complete response (CR/CRu) as assessed by an independent review committee (IRC) using IWC guidelines for response assessments for NHL [13]. CT scans of the chest, abdomen, and pelvis were carried out within 4 weeks of study entry, on day 22 of every other cycle beginning at cycle 2, and at the final patient visit. If a physical examination indicated palpable nodes, neck CT scans were also carried out. The overall IRC assessment was a two-step process consisting of a central blinded radiology assessment (referred to as IRC radiology review) and review of broader clinical data in conjunction with the IRC radiology review by two independent hematologic oncologists.

FDG-PET exploratory end point

FDG-PET scans were not required at sites in Germany or Poland and were discretionary at all other study sites. Whole body FDG-PET scans were conducted within 4 weeks before study entry and following cycles 2, 4, and 6, unless the patient developed progressive disease (PD). Consistency in PET scanner and imaging techniques were required throughout the study. FDG-PET scans had to be obtained on a dedicated PET scanner using an internal Germanium source for correction attenuation. The injected ^{18}FDG dose was to be between 10 and 15 mCi. Scans were carried out 60 (±15) min following intravenous injection of radiotracer.

For patients with at least a baseline FDG-PET scan, IWC + PET response assessments were conducted by the IRC radiographic reviewers, blinded to the previous CT/MRI scans (supplementary Table S1, available at *Annals of Oncology* online) [15]. Two independent reviewers assessed sites of disease previously indicated on CT by recording persistent pathology, noting any new areas of abnormal uptake, and summarizing the patient as positive or negative for pathology (by visual assessment). As with CT/MRI assessments, discrepancies between reviewers 1 and 2 led to adjudication by a third reviewer who would concur with the findings of reviewer 1 or reviewer 2, and this concurrence would provide the final assessment. For comparisons of PET-positive versus PET-negative patients, best PET response was used for patients with multiple PET scans on treatment.

statistical methods

All descriptive statistical analyses were carried out using SAS statistical software version 9 or higher (SAS Institute, Cary, NC), unless otherwise noted. Time-to-event data were summarized using the Kaplan–Meier methods. *P*-values were assessed using log-rank tests.

results

Of the 131 patients enrolled, 130 had histologically confirmed PTCL by central review and 1 was found to have DLBCL [6]. At baseline, this patient population was heavily pretreated and entered the study at a median of third-line therapy [6]. By overall IRC assessment, the ORR was 25% (33/130), including 15% (19/130) with CR/CRu; these response rates were the same in the IRC radiology review (Table 1).

Of 130 patients, 110 had baseline FDG-PET scans; this population was used for the additional analyses presented. In total, 105 patients (95%) were PET-positive at baseline. The five remaining PET-negative patients had diagnoses of PTCL-not otherwise specified (PTCL-NOS, $n = 3$), angioimmunoblastic T-cell lymphoma (AITL, $n = 1$), and subcutaneous panniculitis-like T-cell lymphoma ($n = 1$). For patients with baseline FDG-PET scans, response rates based on overall IRC review were similar to those based

Table 1. Response rates by independent review committee radiology review (CT/MRI) or exploratory (IWC + FDG-PET) analysis

Best response category, n (%)	CT/MRI		IWC + FDG-PET (n = 110[b])
	All patients (n = 130[a])	Patients with baseline PET scan (n = 110[b])	
Objective disease response (CR/CRu + PR)	33 (25)	29 (26)	33 (30)
Complete response (CR/CRu)	20 (15)	16 (15)	22 (20)
CR	18 (14)	14 (13)	22 (20)
CRu	2 (2)	2 (2)	0
PR	13 (10)	13 (12)	11 (10)
Stable disease	37 (29)	32 (29)	19 (17)
Progressive disease/not evaluable[c]	60 (46)	49 (45)	58 (53)

Patients with baseline FDG-PET scans who were evaluable for response by CT/MRI were not evaluable for response by FDG-PET if no post-baseline scan was available.

[a]All patients with histologically confirmed PTCL.

[b]Patients with baseline FDG-PET scan.

[c]Patients with insufficient data to determine response were included as non-responders in this analysis.

CR, complete response; CRu, unconfirmed complete response; CT, computed tomography; FDG-PET, [18]fluoro-deoxyglucose positron emission tomography; IRC, independent review committee; IWC, International Workshop Criteria; MRI, magnetic resonance imaging; PR, partial response.

on radiology assessments alone, with 26% ORR including 15% CR/CRu (Table 1).

The use of IWC + PET criteria for response assessment increased rates to 30% ORR including 20% CR (Table 1). The quality of response was improved in three patients [partial response (PR)→CR; 2 PTCL-NOS, 1 AITL] and reduced in three patients (CR→PR; 2 PTCL-NOS, 1 AITL), with seven additional patients identified as responders [SD→PR or CR; 4 PTCL-NOS, 2 AITL, 1 anaplastic lymphoma kinase-negative anaplastic large cell lymphoma (ALCL)] and only one patient no longer identified as a responder (PR→PD; PTCL-NOS) (supplementary Table S2, available at *Annals of Oncology* online). For seven of the nine patients who were in PR or SD via CT/MRI assessment, but were in CR with PET, adjudication for either the CT/MRI or PET assessments was required. For the patients whose response was decreased with PET, the reductions were due to additional activity found in lesions also detected by CT scans or new lesions not detected by CT, in areas of the body that were imaged by CT, rather than due to additional body areas imaged by PET.

By CT/MRI, 47 of 110 patients (43%) had ≥1 extranodal lesion at baseline (by-lesion assessments not done by PET). Of the 17 patients with shifts in response assessment with the addition of PET (supplementary Table S1, available at *Annals of Oncology* online), 9 (53%) had extranodal lesions at baseline. Of those nine, four and five had an increase and decrease in best response with PET, respectively. For the eight patients without extranodal lesions at baseline and a shift in response, five and three had an increase and decrease in best response with PET, respectively.

By overall IRC (n = 110; median follow-up, 22.6 months), the median DOR (n = 33) was 28 months (range, <1–48+ months); the patient whose response was noted as <1 month discontinued to receive an SCT. Other reasons for early discontinuation (DOR <12 months at the time of censoring) included PD (n = 11), patient decision (n = 4), adverse event (n = 3), physician decision (n = 2), and SCT (n = 2). For responding patients,

DOR were well differentiated by both conventional radiology response criteria (CR/CRu versus PR; P = 0.0001) and PET status (negative versus positive; P < 0.0001; Figure 1). Of those who became PET-negative during the study, 11 first did so at cycle 2, two patients at cycle 4, 5 patients at cycle 6, and 1 patient at cycle 8. Patients who achieved early PET-negative status (cycle 2) had prolonged DOR compared with those who remained PET-positive at cycle 2, but this difference was not statistically significant (P = 0.1155). For patients who achieved PET-negative status, only one progressed within 12 months of achieving response. Other reasons for early discontinuation included adverse event (n = 1), patient decision (n = 2), SCT (n = 2), and physician decision (n = 1).

Patients who achieved CR/CRu by overall IRC had prolonged PFS (median 25.9 months) compared with other response groups (PR or SD; P = 0.0007; supplementary Table S3, available at *Annals of Oncology* online, Figure 2). The majority (13/16) of patients who achieved CR/CRu were PET-negative with the median PFS not reached; the three patients who achieved CR/CRu but were PET-positive had a median PFS of 9.2 months. Patients who achieved PR or SD by conventional criteria had similar PFS (P = 0.6427). When stratifying PR/SD patients by PET status, patients who achieved PR/SD with PET-negative disease had a notable trend toward prolonged PFS versus those who remained PET-positive (median 18.2 versus 7.1 months, respectively), although the difference was not significant (P = 0.0923).

discussion

In this examination of the prospective FDG-PET exploratory end point in the pivotal study of romidepsin for the treatment of relapsed/refractory PTCL, the vast majority (95%) of patients examined were FDG-PET avid at baseline, confirming previous assessments that T-cell lymphomas are almost universally PET avid [17–26]. The addition of FDG-PET to response assessments modestly increased response rates to 30% ORR including 20%
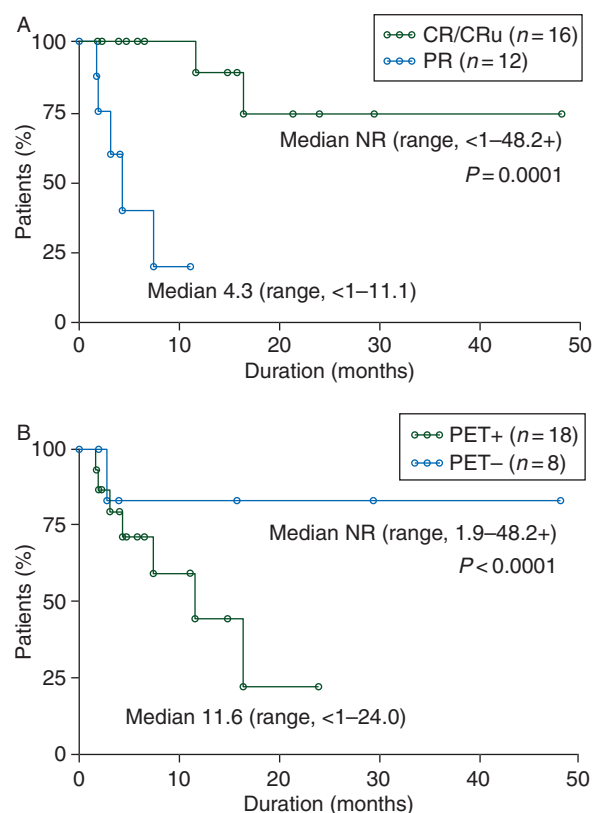
Figure 1. Duration of response [overall independent review committee (IRC)] stratified by (A) radiology response criteria or (B) PET-status for patients with baseline [18]fluoro-deoxyglucose positron emission tomography (FDG-PET) assessment. (A) One patient with best response of partial response by overall IRC and progressive disease by radiology response criteria was excluded from this analysis. (B) Two patients with missing response assessment by FDG-PET were excluded from this analysis. CR/CRu, confirmed/unconfirmed complete response; FDG-PET, [18]fluoro-deoxyglucose positron emission tomography; IRC, independent review committee; NR, not reached; PD, progressive disease; PR, partial response.
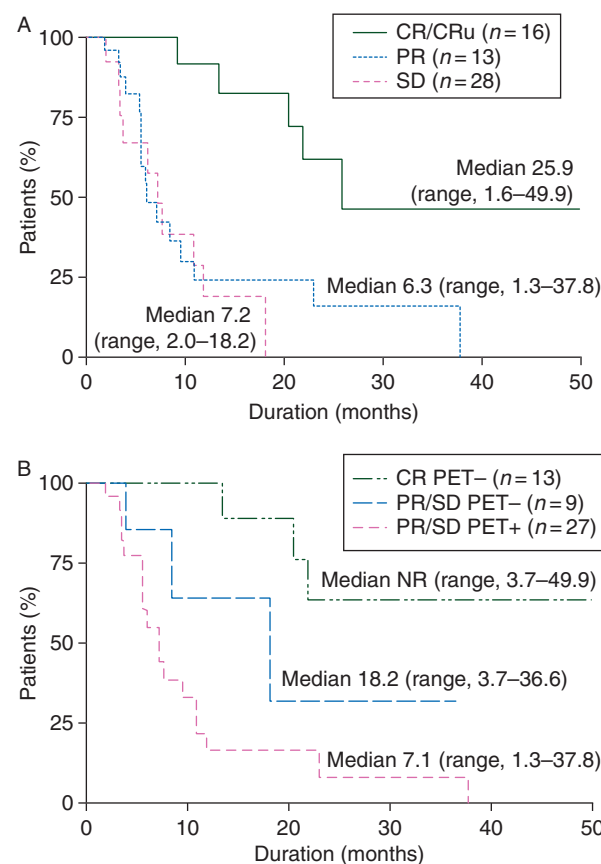

Figure 2. Impact of (A) response category or (B) PET-status + response category on progression-free survival (overall IRC) for patients with baseline FDG-PET assessment. CR, complete response; NR, not reached; PET, position emission tomography; PR, partial response; SD, stable disease.

CR compared with 26% ORR including 15% CR/CRu with CT/MRI alone. The presence of extranodal lesions at baseline did not appear to impact the utility of PET in this patient population.

In a similar phase 2 trial of pralatrexate for relapsed/refractory PTCL, the ORR was 29% (32/109), including 11% (12/109) CR/CRu by IWC criteria (assessed by IRC) [28]. Ninety-three of 109 patients (85%) had a positive PET scan at baseline. When using IWC + PET criteria, ORR slightly decreased to 26% (28/109), and CR increased to 14% (15/109).

Achieving CR/CRu on romidepsin by IRC assessment resulted in prolonged DOR and PFS. DOR and PFS were similar for patients achieving PR or SD, but markedly shorter than for those achieving CR/CRu. However, among those with a best response of PR or SD, achieving PET-negative status on romidepsin predicted a prolonged DOR and PFS regardless of conventional radiology staging. Patients who achieved PET-negative status had DOR and PFS similar to that of patients who achieved CR/CRu by conventional staging. For patients with a best response of PR or SD, PET status appeared to better differentiate PFS ($P = 0.0923$) than conventional response category ($P = 0.6427$).

The predictive value of PET negativity in patients with PTCL or other T/NK lymphomas has been assessed in several studies. In a single-center study of patients with PTCL ($n = 34$) treated in the first line with 6 cycles of CHOP-21 (cyclophosphamide, doxorubicin, vincristine, and prednisone every 3 weeks), prolonged survival was observed for patients with negative versus positive interim PET (after cycle 3; $P = 0.02$) and final PET ($P < 0.0001$) [29]. In a phase 2 study of brentuximab vedotin in patients with relapsed/refractory systemic ALCL ($n = 58$), authors also concluded that interim PET negativity (cycle 4) appeared predictive of longer PFS and OS, although P-values were not provided [30]. Furthermore, in a single-center retrospective study of patients with PTCL ($n = 95$), patients with negative interim PET had superior PFS compared with those with positive interim-PET ($P = 0.03$), but differences in OS did not reach significance ($P = 0.171$) [26]. Alternatively, in a retrospective study of patients with non-cutaneous T/NK lymphomas ($n = 54$), differences in 4-year OS and PFS did not reach significance for patients with negative versus positive interim or final FDG-PET scans [31]. These varied results regarding the predictive ability of interim or final PET status may be in part related to variability in the timing (e.g. definition of interim) and calculation methods for PET status. At the Third International Workshop on Interim Positron Emission Tomography in Lymphoma, results from international validation studies on the

use of the five-point Deauville criteria and change in maximum standardized uptake value (SUV) in Hodgkin lymphoma and DLBCL were discussed, and there was a preliminary consensus on the need to focus on interim PET results for non-DLBCL NHL subtypes [32]. Recent studies seem to have taken note of these recommendations. For example, two studies of patients with newly diagnosed PTCL treated with systemic chemotherapy demonstrated that interim PET score of 4 or 5 by Deauville criteria was significantly predictive of worse survival [33, 34]. One of these studies also derived cutoffs for SUV and metabolic tumor volume assessments that were significantly predictive for survival [34]. As the measurement of PET status in patients with PTCL and other non-DLBCL NHLs become more uniform, the predictive value of interim or final PET status will be better understood.

conclusion

Although FDG-PET does not obviate conventional staging, routine use in this data set of patients with relapsed/refractory PTCL treated with romidepsin appears to aid in prognosis and response assessments, particularly for patients who do not achieve CR/CRu by conventional staging. Many patients with relapsed/refractory PTCL experience poor outcomes and short survival. Using interim FDG-PET assessments to identify patients more likely to have prolonged responses to treatment may aid in making often challenging management decisions such as whether to keep responding patients on a prolonged or maintenance course of therapy or attempt to consolidate a remission with SCT. The optimal protocol for utilization of FDG-PET scans for patients with relapsed/refractory PTCL, including timing of scans, standardization of scan procedure and interpretation, determination of positive versus negative scan result, and utility in patient management remains to be determined, but their routine incorporation in prospective clinical trials will provide data to further define the role of FDG-PET in this patient population and help answer these questions.

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disclosure

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European cancer mortality predictions for the year 2015: does lung cancer have the highest death rate in EU women?

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Background: Cancer mortality statistics for 2015 were projected from the most recent available data for the European Union (EU) and its six more populous countries. Prostate cancer was analysed in detail.

Patients and methods: Population and death certification data from stomach, colorectum, pancreas, lung, breast, uterus, prostate, leukaemias and total cancers were obtained from the World Health Organisation database and Eurostat. Figures were derived for the EU, France, Germany, Italy, Poland, Spain and the UK. Projected 2015 numbers of deaths by age group were obtained by linear regression on estimated numbers of deaths over the most recent time period identified by a joinpoint regression model.

Results: A total of 1 359 100 cancer deaths are predicted in the EU in 2015 (766 200 men and 592 900 women), corresponding to standardised death rates of 138.4/100 000 men and 83.9/100 000 women, falling 7.5% and 6%, respectively, since 2009. In men, predicted rates for the three major cancers (lung, colorectum and prostate) are lower than in 2009, falling 9%, 5% and 12%. Prostate cancer showed predicted falls of 14%, 17% and 9% in the 35–64, 65–74 and 75+ age groups. In women, breast and colorectal cancers had favourable trends (−10% and −8%), but predicted lung cancer rates rise 9% to 14.24/100 000 becoming the cancer with the highest rate, reaching and possibly overtaking breast

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