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The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: a subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL)

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Background: [^{18}F]fluorodeoxyglucose-positron emission tomography (PET) is emerging as a strong diagnostic and prognostic tool in follicular lymphoma (FL) patients.

Patients and methods: In a subset analysis of the FOLL05 trial (NCT00774826), we investigated the prognostic role of post-induction PET (PI-PET) scan. Patients were eligible to this study if they had a PI-PET scan carried out within 3 months from the end of induction immunochemotherapy. Progression-free survival (PFS) was the primary study end point.

Results: A total of 202 patients were eligible and analysed for this study. The median age was 55 years (range 33–75). Overall, PI-PET was defined as positive in 49 (24%) patients. Conventional response assessment with CT scan was substantially modified by PET: 15% (22/145) of patients considered as having a complete response (CR) after CT were considered as having partial response (PR) after PI-PET and 53% (30/57) patients considered as having a PR after CT were considered as a CR after PI-PET. With a median follow-up of 34 months, the 3-year PFS was 66% and 35%, respectively, for patients with negative and positive PI-PET ($P < 0.001$). At multivariate analysis, PI-PET (hazard ratio 2.57, 95% confidence interval 1.52–4.34, $P < 0.001$) was independent of conventional response, FLIPI and treatment arm. Also, the prognostic role of PI-PET was maintained within each FLIPI risk group.

Conclusions: In FL patients, PI-PET substantially modifies response assessment and is strongly predictive for the risk of progression. PET should be considered in further updates of response criteria.

Key words: FDG-PET, follicular lymphoma, prognosis

introduction

Follicular lymphoma (FL) is the most common indolent B-cell lymphoma and accounts for 10%–20% of all lymphomas in western countries [1]. The availability of rituximab has substantially changed FL therapeutic approaches. Several trials have clearly demonstrated that the addition of rituximab to chemotherapy can prolong survival when compared with chemotherapy alone [2–5]. Also, the benefit of maintenance therapy has been recently suggested [6].

Although the outcome of patients with FL has clearly improved, heterogeneity in patients' outcome still remains. Currently, FLIPI and FLIPI2 are the most widely used prognostic systems [7, 8]. In addition, several biological factors as, for

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example, highly sensitive polymerase chain reaction-based analysis, have been suggested as relevant prognostic factors [9]. So far, however, none of the current available prognostic factors has been used to guide clinical decisions in FL.

[^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET) has recently emerged as a powerful functional imaging tool in staging and response assessment in Hodgkin's lymphoma and diffuse large B-cell lymphoma [10, 11]. Although FL is considered as an FDG avid disease, the literature concerning the role of PET in FL was scarce for many years and this tool was not recommended as a routine procedure [11]. Recently, FDG-PET was shown to add details in the staging [12] and to be an independent prognostic factor for lymphoma progression and survival when used at the end of induction immunochemotherapy (ICT) in patients with FL [13, 14].

In 2005, the Fondazione Italiana Linfomi (FIL) started the prospective randomized phase III trial named FOLL05 that compared R-CVP, R-CHOP and R-FM for patients with newly diagnosed stage II/IV FL [15]. Although PET was not included among diagnostic and response assessment procedures, several patients underwent PET scan after initial ICT. Therefore, we retrospectively investigated the prognostic role of PET scan carried out after initial ICT in patients with advanced stage, active FL.

patients and methods

inclusion and exclusion criteria

The present study was designed as a subset analysis of FL patients enrolled in the phase III trial FOLL05 (NCT00774826), in which patients were randomized to receive R-CVP, R-CHOP or R-FM (rituximab, fludarabine and mitoxantrone) [15]. The FOLL05 study was conducted among 60 institutions in Italy and accrual completed on September 2010 with the enrolment of 534 patients. According to the FOLL05 trial, no maintenance therapy with rituximab or any other agent was allowed. This study was submitted and approved by ethic committee and patients were required to sign for informed consent.

In order to be considered for this current study, patients were required to be fully eligible and randomized in the FOLL05 trial, that is to be between 18 and 75 years, have Ann Arbor stage II to IV, previously untreated and have active disease defined according to published criteria [15]. For the purposes of this study, patients should have available data on post-induction PET (PI-PET). PET scanning was not included among FOLL05 study procedures but was allowed if the facility was available at the participating institution. None of the FOLL05 results was based on PET results. To be included in the present study, PI-PET had to be carried out from 10 days to 3 months after the last cycle of induction treatment.

All data on baseline features, treatment details, response and follow-up were retrieved from the original FOLL05 data set.

PET results

For the purpose of this study, data were obtained on all PET scans carried out before (baseline PET: B-PET), and at the end of induction ICT (PI-PET). All local PET reports were centralized at the FIL datacentre; a positive or negative PI-PET was defined by the local investigators interpretation of the nuclear physician's scan report that was based on a visual qualitative assessment; no data were available on functional findings [10]. All the centres were included in FIL network of nuclear medicine that adhere to stringent quality criteria and undergo periodic quality assessment. A positive or negative PET scan was defined on the original report and reviewed by SL, AV and QM blinded of patient outcome and discussed with the nuclear physician in uncertain cases. We considered as positive all lesions that were described in the local report. Cases not clearly positive or negative were defined as inconclusive and excluded from subsequent analyses. All PET scans were PET/CT.

end point definition

The primary end point was progression-free survival (PFS), which was calculated as the time from the date of first treatment until the date of lymphoma progression, relapse, death from any cause and last follow-up visit. Secondary end points included response rates, disease-free survival (DFS) and overall survival (OS). Response was defined according to 1999 international criteria and based on the use of CT scan only [16]. DFS was calculated for those achieving complete (CR) or partial remission (PR) according to conventional assessment and was defined as time from the date of remission until relapse, death or last contact. OS was calculated for all patients as time from the date of diagnosis until death, or last follow-up visit.

statistical analysis

Standard descriptive analyses were carried out. For a crude association analysis, categorical data were analysed using the χ^2 or Fisher's exact test (two-sided). Cohen's κ-statistic was used to verify agreement between PET and CT results. The level of agreement was defined by Koch Landis scale. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate Cox regression analyses were conducted to verify the prognostic role of PI-PET regarding PFS and DFS, adjusted for relevant prognostic clinical variables and treatment arm. OS was only analysed with univariate analysis due to the low number of events. Two-tailed P-values of <0.05 were considered statistically significant. Statistical analysis was carried out with SPSS software (version 18.0, Chicago, IL).

results

Two hundred and forty-four out of 534 patients enrolled in the FOLL05 trial had a PI-PET carried out and were initially identified for this study. Among them, 10 patients were subsequently excluded because they were considered ineligible for the FOLL05 study, and 4 patients, because PET was carried out after clinical progression. From the remaining 230 patients, 21 patients were excluded because PI-PET was carried out outside the admitted time range of the study and additional 7 patients were excluded because of inconclusive results for PI-PET. A total of 155 patients also had an available B-PET. Outcome analysis was carried out on all 202 cases, regardless if they had undergone a baseline PET or not, because of the high sensitivity of PET scans at diagnosis and similarly to what was done in a similar study [13].

Baseline patients' characteristics are shown in Table 1. The median age was 56 years (range 33–75). After a median follow-up of 34 months (range 7–66), the 3-year PFS, DFS and OS for the study population was 60% [95% confidence interval (CI) 51%–67%], 53% (95% CI 43%–62%) and 99% (95% CI 94%–100%), respectively. Clinical characteristics of the study population did not differ from that of the FOLL05 study. Also, no difference was found in response rates assessed by CT scan-only for patients in this study compared with patients enrolled in the FOLL05 (CR rate, 72% versus 69%, $P = 0.62$) and no difference

Table 1. Baseline characteristics, treatment and response assessment of all patients and according to post-induction positron emission tomography results (PI-PET)

	All patients, $n = 202$ (%)	PI-PET negative, $n = 153$ (76%)	PI-PET positive, $n = 49$ (24%)	P-value
Age >60	65 (32)	46 (30)	19 (39)	0.29
Male sex	96 (48)	79 (52)	17 (35)	0.05
Ann Arbor stage III–IV	186 (92)	142 (93)	44 (90)	0.54
Hemoglobin <12g/dl	31 (15)	18 (12)	13 (26)	0.02
ECOG PS ≥ 2	9 (5)	7 (5)	2 (4)	1.0
Bulky disease (>6 cm)	64 (32)	45 (29)	19 (39)	0.22
BM involvement	102 (51)	75 (49)	27 (55)	0.51
Increased B2-microglobulin	85 (42)	63 (41)	22 (45)	0.74
Increased LDH	42 (21)	28 (18)	14 (29)	0.29
FLIPI 3–5	71 (35)	51 (33)	20 (41)	0.39
First treatment				
R-CVP	66 (33)	51 (33)	15 (31)	0.78
R-CHOP	62 (30)	48 (32)	14 (29)	
R-FM	74 (37)	54 (35)	20 (40)	

PS, performance status; BM: bone marrow; FLIPI, follicular lymphoma international prognostic index; LDH, lactic dehydrogenase; R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone; R-FM, rituximab, fludarabine and mitoxantrone.

was found in PFS (58% versus 61%, $P = 0.61$) between the two groups, indicating no response-selection bias.

conventional and PET-based response assessment

According to conventional response criteria (CT only), 145 patients achieved CR (72%) and 48 (24%) patients achieved PR, with an overall response rate of 96%; 9 (4%) patients had stable disease/progressive disease. Forty-seven (23%) patients among those who achieved a CR were classified as CRu.

PI-PET was carried out at a median of 36 days (range 10–92) after the last dose of ICT. Overall, PI-PET was defined as negative in 153 (76%), and positive in 49 (24%) patients. PI-PET positivity was referred to lymph node or nodal areas in 40 (82%) cases; in 14 cases, PI-PET positivity was described at extranodal sites and was the only residual site in 9 cases: among these cases, bone was the most frequent site (4 cases). Comparison of baseline characteristics, treatment and response assessment according to PI-PET is shown in Table 1. No difference regarding baseline and prognostic characteristics was found between positive and negative PI-PET patients, except for an increased proportion of patients with hemoglobin level <12 g/dl and of female patients in the group of positive PI-PET. Agreement rate between PET and CT was 74% with κ-value of 0.336 (fair agreement). Using PI-PET, 30 out of the 57 patients not classified as CR according to CT were converted into CR (53%) and 22 out of the 145 classified as CR, were reclassified into PR (15%). The frequency of positive PI-PET increased from the categories of poorer responses to those of better responses (Table 2). Among CRu patients, 19% (9/47) were PI-PET positive. No difference in terms of PI-PET results was found between CR and CRu cases ($P = 0.45$).

Table 2. Results of post-induction positron emission tomography by CT response in 202 patients with evaluable post-induction positron emission tomography (PI-PET)

	CR, $n = 145$ (%)	PR, $n = 48$ (%)	SD/PD, $n = 9$ (%)
PI-PET negative	123 (85)	27 (56)	3 (33)
PI-PET positive	22 (15)	21 (44)	6 (67)

Pearson's χ^2 test = $P < 0.001$; test for trend Cochran–Armitage $P < 0.001$.
CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; PI-PET: post-induction PET.

analysis of survival

PFS and DFS. Patients who presented a negative PI-PET had a significantly superior PFS (3-year: 66%; 95% CI 57%–74%) than those who presented a positive PI-PET [35%; 95% CI 18%–52%; hazard ratio (HR) 2.59, 95% CI 1.59–4.24] ($P < 0.001$). The median PFS was 29 months for patients with a positive PI-PET and not attained for negative PI-PET, respectively (Figure 1). Also, patients who showed a negative PI-PET had a significantly superior 3-year DFS of 57% (95% CI 46%–67%) compared with 36% (95CI 19%–54%) of those who presented a positive PI-PET (HR 2.26: 95% CI 1.34–3.80) ($P = 0.002$). The median DFS was 45 and 24 months between patients with a negative and positive PI-PET, respectively. By using the conventional response criteria (CT only), patients achieving CR had a better 3-year PFS when compared with those achieving less than CR (3-year PFS: 63%, 95% CI 53%–72% versus 51%, 95% CI 35%–64%;

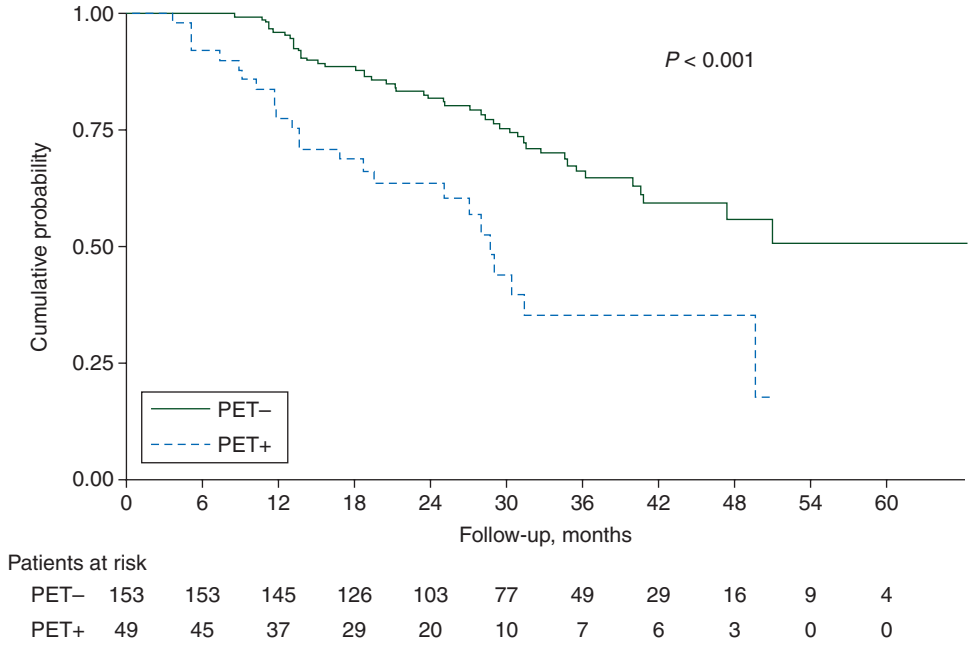

Figure 1. Progression-free survival in 202 patients with follicular lymphoma according to post-induction positron emission tomography.

Table 3. Multivariate Cox analysis for progression-free survival (PFS) and disease-free survival (DFS) in patients evaluated by PI-PET

	PFS (n = 202)			DFS (n = 193)		
	HR	95% CI	P-value	HR	95% CI	P-value
PI-PET +	2.57	1.52–4.34	<0.001	2.23	1.28–3.92	0.005
FLIPI 3–5	1.80	1.13–2.89	0.014	2.07	1.27–3.37	0.003
Response <CR (CT only)	1.17	0.70–1.95	0.549	1.18	0.67–2.06	0.565
R-CVP[a]	1.84	1.15–2.95	0.011	2.08	1.27–3.39	0.003

HR, hazard ratio; CI, confidence interval; PI-PET, post-induction PET ; FLIPI, follicular lymphoma prognostic index; CR, complete remission; CT, computed tomography; R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone; R-FM, rituximab, fludarabine and mitoxantrone.
[a]R-CVP versus (R-CHOP and R-FM).

P = 0.049), respectively. Comparing PI-PET and CT response, the prognostic role of PI-PET was more relevant for patients classified as PR, while no differences were observed comparing patients in CR versus CRu (data not shown). Multivariate Cox regression analyses for PFS and DFS were carried out in order to verify the prognostic role of PI-PET adjusted by relevant prognostic factors and treatment arm. In the final multivariate Cox regression analysis, PI-PET was an independent prognostic factor for PFS and DFS, along with FLIPI and conventional response and type of ICT (Table 3).

Finally, combining the information of FLIPI and PI-PET, the information of PI-PET allowed the identification of different risk groups within each FLIPI risk group (supplementary Figure S1, available at *Annals of Oncology* online).

overall survival

At the time of the analysis, six patients died: three in the negative post-induction PET group and three in the positive post-induction PET group. The causes of death were disease progression in four patients and secondary neoplasia in two. The 3-year OS for all the 202 patients was 99% (95% CI 94%–100%).

discussion

The present study shows that PI-PET can influence response assessment and represents a robust and independent prognostic factor in predicting PFS and DFS in patients with FL treated with ICT. Overall, for the 76% of patients who had a negative PI-PET, a 3-year PFS of 66% was foreseen, unlike the unsatisfactory 35% 3-year PFS observed for the remaining 24% of patients with a positive PI-PET. Noteworthy, the predictive power of PI-PET was not influenced by other well-known relevant clinical prognostic factors, including type of ICT, conventional response and FLIPI. Finally, PI-PET was prognostic, even within each FLIPI risk group (scores 0–2 versus 3–5).

Although FL has been always described as an FDG-avid disease [17], the prognostic role of PET in FL has only recently

been analysed. In one large retrospective study carried out on 122 patients from the PRIMA trial, Trotman et al. [13] showed that, at a median follow-up of 42 months, the 26% of patients with a positive PET after induction ICT had a significantly inferior PFS of 32.9% compared with the 70.7% in those remaining PET negative. More recently, a prospective study on 121 patients conducted by the Lysa group with the specific aim of investigating the role of PET in response assessment after R-CHOP showed that 2-year PFS was 61% in positive PET (24% of cases) and 87% for those with negative PET [14].

The present study is the largest one investigating the role of PET in response assessment after induction ICT in patients with FL. Similar to Trotman's study, we conducted a retrospective subset analysis of a randomized trial, treatment was not homogenous, and PET assessment was based on local interpretation. Unlike the Trotman study, in our series, none of the patients was treated with maintenance rituximab, which was not allowed in the original FOLL05 design. Among the three studies, the Lysa group study was the only prospective one. It included centralization of PET scans for review and the results were reported using the Deauville five-point scale. As with our study, patients did not receive maintenance after ICT. Notwithstanding the methodological differences, the results of the three studies are absolutely superimposable. The rate of PET positivity was very similar, being 24%, 26% and 24% in our study, the Trotman's and Lysa experience, respectively. Likewise, the magnitude of the increased risk of progression determined by post-induction result was very similar as well as the observed PFS. Finally, the prognostic role of PET was independent of relevant known prognostic factors, including FLIPI, in all three studies. In addition, OS was also investigated as a secondary end point and PI-PET confirmed to be predictive in the Trotman and Lysa trials. In our analysis, we were not able to analyse OS as an end point due to the low number of events [13, 14].

Similar to other lymphoma subtypes, a relevant question is how PET response assessment should be evaluated in patients with FL. Looking at the results of the three largest studies, it does not seem that the methodology used to define response really matters when identifying patients with different prognosis. However, in order to provide comparable results, methodology must be standardized and reproducible. As clearly shown in the Lysa study, the Deauville score with a cut-off at 4 seems to provide excellent results, both in terms of reproducibility and accuracy [14].

Our results confirm that the incorporation of PI-PET in response assessment [11] is suitable and should be considered in further updates of response criteria. However, with available data on the use of PI-PET for response assessment, some relevant questions should be answered. First, most of available data on the prognostic role of PI-PET come from patients treated with R-CHOP or R-CVP who are not treated with maintenance therapy; PI-PET results should then be carefully applied to chemotherapy regimens different from R-CHOP or R-CVP, including R-bendamustine, and, most important, other novel promising treatment modalities (R-lenalidomide, or drugs targeting the B-cell-receptor pathway). Regarding maintenance, available data do not allow to define if the prolonged use of rituximab has an impact on outcome if they achieve a negative PI-PET. Looking at the poor PFS of patients with positive PI-PET, however, it seems reasonable to consider these patients as affected by high-risk FL and define appropriate clinical trials to investigate the role of more aggressive approaches than simple rituximab maintenance therapy, considering the use of radioimmunotherapy, or the anticipation of salvage conventional therapies or of investigational new drugs. Finally, in FL, FDG-PET results should also be compared and integrated with results from molecular assessment of minimal residual disease that has been shown to be prognostic in several studies [9]. So far, no data are available comparing PET and MRD analysis in the same patients, and such studies are strongly warranted.

In conclusion, based on the results of our study, we confirmed that PI-PET improves response assessment in patients with FL treated with conventional immunochemotherapy and strongly support its inclusion in response criteria for FL similarly to Hodgkin lymphoma and DLBCL. Based on the prognostic role of PET response, future studies should be designed to assess if with a PET-driven approach, it will be possible to further improve patients' outcome, aiming in particular at improving the high risk of progression observed for PET-positive patients.

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disclosures

The authors have declared no conflicts of interest.

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Preference for involvement in treatment decisions and request for prognostic information in newly diagnosed patients with higher-risk myelodysplastic syndromes†

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Background: The main objective of this study was to assess preferences for involvement in treatment decisions and requests for prognostic information in newly diagnosed higher-risk myelodysplastic syndrome (MDS) patients.

Patient and methods: This was a prospective cohort observational study that consecutively enrolled MDS patients with an international prognostic scoring system (IPSS) risk category of intermediate-2 or high risk (summarized as 'higher risk'). The control preference scale was used to assess patient preferences for involvement in treatment decisions, and whether a request by patients for prognostic information during consultation was made, was also recorded. All of the patients were surveyed at the time of diagnosis before receiving treatment. Univariate and multivariate analyses were

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