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Absolute monocyte count at diagnosis could improve the prognostic role of early FDG-PET in classical Hodgkin lymphoma patients

Recently published international guidelines suggested that positron emission tomography (PET)-computed tomography (CT) could be utilized for response assessment using the Deauville criteria in fluorodeoxyglucose (FDG)-avid lymphomas (Meignan *et al*, 2012). Interim PET (I-PET) scanning seems highly predictive of treatment failure in Hodgkin Lymphoma (HL) patients.

We recently showed that the absolute monocyte count (AMC) has prognostic value in patients with classical HL (cHL) (Tadmor *et al*, 2015). Here, we show that the combined use of I-PET and AMC at diagnosis enables a more accurate projection of patient outcome in cHL.

The present study is an ancillary branch of the analysis reported by Tadmor *et al*, (2015). Patients with histopathological diagnosis of cHL previously enrolled in the Gruppo Italiano Studio Linfomi trials were eligible if data on all clinical and laboratory features and treatments, reported I-PET results, treatment response and follow-up were available. Response was defined according to the revised International Working Group guidelines (Cheson *et al*, 1999). An absolute lymphocyte count $<0.6 \times 10^9/l$ and AMC $>0.75 \times 10^9/l$ were used as cut-off points. I-PET was performed after 2 cycles of treatment. A positive or negative I-PET was defined by the local investigators' interpretation of the nuclear physician's scan report, which was based on a visual qualitative assessment.

The principal end-point of the study was the impact of I-PET and AMC on progression-free survival (PFS); their impact on overall survival (OS) was the secondary end-point. Survival functions were estimated using the Kaplan–Meier method. Statistical comparisons between curves were performed with log-rank test, and the effect of the covariate was reported as hazard ratios (HR), from Cox regression.

All patients had a diagnosis of cHL; 76% of cases had the nodular sclerosis (NS) subtype. Seventy-six patients (64%) were treated with classical ABVD (doxorubicin, bleomycin,

vincristine, dacarbazine), and 23 (19%) and 19 (16%) with the more intensive BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and COPPEBVCAD (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, bleomycin) regimens (Federico *et al*, 2009), respectively. Of the entire cohort, 104 patients (88%) achieved complete remission. Twenty-six patients had a positive I-PET (22%) and 28 (24%) had AMC $>0.75 \times 10^9/l$ at diagnosis.

The median follow-up of the entire cohort was 88 months (range 5–142 months). The estimated 5-year OS was 91% (95% confidence interval [CI]: 84–95%). The 5-year PFS was 80% (95% CI: 71–86%). Patients with positive I-PET showed a worse PFS compared to patients with negative I-PET (51% and 88%, respectively; HR 5.87 [95% CI: 2.56–13.5]). Patients with AMC $>0.75 \times 10^9/l$ at diagnosis had a worse PFS compared to patients with AMC $\leq 0.75 \times 10^9/l$ (58% and 87%, respectively; HR 3.73 [95% CI: 1.61–8.64]). Multiple Cox proportional hazards (PH) regression, adjusted for International Prognostic Score 3–7, confirmed the prognostic role of I-PET (HR 5.32 [95% CI: 2.30–12.3]; $P < 0.001$) and AMC $>0.75 \times 10^9/l$ (HR 3.19 [95% CI: 1.32–7.68]; $P = 0.010$). Figure 1A, B shows the PFS for I-PET and AMC, and Table I shows the uni- and multivariate Cox PH regression for PFS. The prognostic role of I-PET and AMC on OS was also confirmed.

Given the strong predictive value of both I-PET and AMC, we stratified patients by positive or negative I-PET and AMC $>0.75 \times 10^9/l$ or $\leq 0.75 \times 10^9/l$ into 3 groups with different levels of risk. The low risk level (negative I-PET and AMC $\leq 0.75 \times 10^9/l$; $n = 73$, 62%) had a 5-year PFS of 90% (95% CI: 80–96%), the intermediate level (I-PET positive or AMC $>0.75 \times 10^9/l$; $n = 36$, 51%) had a 5-year PFS of 73% (95% CI: 55–85%), and the high risk level (I-PET positive and AMC $>0.75 \times 10^9/l$; $n = 9$, 8%) had a

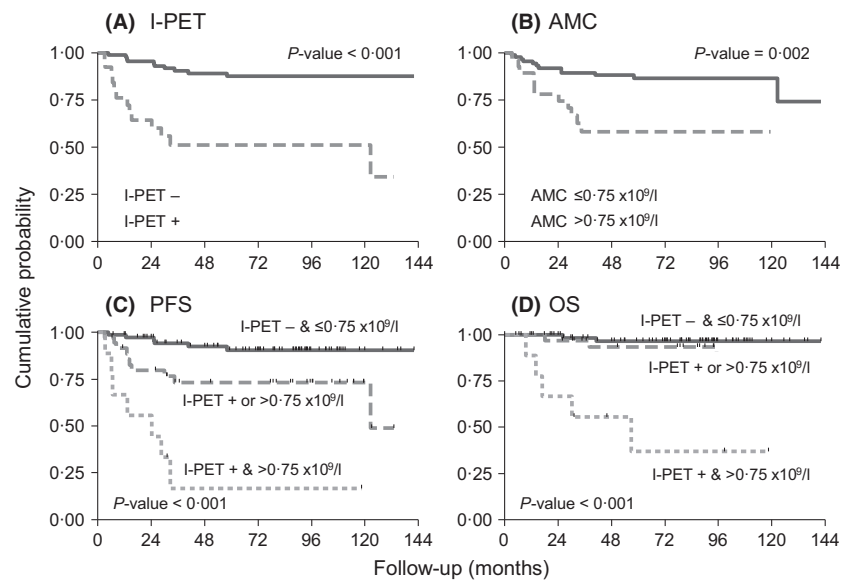


Fig 1. (A) Progression-free survival (PFS) stratified by interim- positron emission tomography (PET); (B) PFS stratified by absolute monocyte count (AMC); (C) PFS stratified by combined interim-PET and AMC; (D) overall survival (OS) stratified by combined interim-PET and AMC.

Table 1. Uni- and multivariate Cox proportional hazard regression for progression-free survival (PFS).

		5-year PFS (%)	HR	95% CI	P-value
Univariate					
I-PET	Negative	88	1.00		
	Positive	51	5.87	2.56–13.5	<0.001
AMC	$\leq 0.75 \times 10^9/l$	87	1.00		
	$> 0.75 \times 10^9/l$	58	3.73	1.61–8.64	0.002
LMR	> 2.1	82	1.00		
	≤ 2.1	77	1.51	0.67–3.43	0.320
Stage	I–IIA	93	1.00		
	IIB–IV	78	3.08	0.41–22.9	0.272
IPS	0–2	83	1.00		
	3–7	74	1.65	0.72–3.76	0.236
Histology	NS	79	1.00		
	Other	81	1.08	0.43–2.75	0.864
Multivariate					
I-PET	No		1.00		
	Yes		5.32	2.30–12.3	<0.001
AMC	$\leq 0.75 \times 10^9/l$		1.00		
	$> 0.75 \times 10^9/l$		3.19	1.32–7.68	0.010
IPS	0–2		1.00		
	3–7		1.09	0.46–2.61	0.839

I-PET, interim positron emission tomography; AMC, absolute monocyte count; LMR, lymphocyte to monocyte ratio; NS, nodular sclerosis; HR, hazard ratio; CI, confidence interval.

5-year PFS of 17% (95% CI: 1–49%). The log-rank test between the intermediate and low levels and between the high and intermediate levels were significant ($P = 0.007$, $P = 0.001$, respectively). For OS, the difference between the intermediate and low risk levels tended to narrow ($P = 0.232$), while the difference between the high and intermediate levels was significantly different ($P < 0.001$).

Figure 1C, D shows the PFS and OS stratified by risk group. The test for trend in PFS and OS was significant ($P < 0.001$).

The rationale for using AMC as a prognostic parameter in cHL is relevant because immunohistochemical and molecular data, including the gene expression profile, have identified a key role for monocytes and macrophages in the biology of cHL (Steidl *et al*, 2010; Porrata *et al*, 2012; Tan *et al*, 2012; Koh *et al*, 2015; Tadmor *et al*, 2015). It might therefore be possible that AMC is associated with the number of tumour-associated macrophages (TAMs) in the microenvironment. If so, then it could be considered as a biomarker of reactive cells that is easily detectable in peripheral blood. The FDG-PET scan is currently considered the most precise staging method and may also be used to provide an early prediction of treatment efficacy.

There is a strong suggestion that reactive cells are responsible for the increased FDG uptake at baseline, as they account for 99% of Hodgkin tumours (Gallamini, 2010). Furthermore, early responses to treatment have been suggested to demonstrate the elimination of reactive cells, or at least the disappearance of their activity, and are indirect surrogates of tumour chemo-sensitivity (Gallamini & Kostakoglu, 2012). Thus, the FDG-PET scan could be considered a biomarker of the extent and activity of the tumour microenvironment.

However, in clinical practice, patients with negative I-PET can rapidly progress during induction treatment, while other patients with positive I-PET may eventually achieve a CR. Therefore, there is a need to further improve the predictive power of I-PET. By combining the AMC at diagnosis with the I-PET results, we showed that it is possible to increase the discriminatory power of I-PET alone in identifying cHL patients with poor PFS and OS. We are fully aware that our study has many weaknesses, such as its retrospective nature,

the small number of patients and the lack of use of the Deauville criteria. However, our results suggest that it is possible to further improve the already high predictive power of PET by combining it with a simple and inexpensive surrogate biomarker of reactive cells that are easily detectable in peripheral blood.

Authors Contribution

AB, LM, RM, SP, TT and SS: conception and design of the study, interpretation of the data, final approval of the version to be published. LM, RM and PF: statistical analysis, data collection, interpretation of data, and creation of tables and figures. AB, LM, RM, PF, TT and SS wrote the manuscript. AB, SP, MCC, CB, PG, LB, PM, MF and SS have participated in the data recording, and the interpretation of the data. All authors contributed critically to the drafting of the article and approved the final version. The authors report no potential conflicts of interest.

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