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Original

The prognostic value of ^{18}F-FDG PET-CT in the management of Hodgkin's lymphoma: preliminary results of a prospective study

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Abstract

BACKGROUND: To date, Hodgkin's lymphoma (HL) patients have achieved long-term survival of more than 80%. Unfortunately, longer follow-up has shown serious adverse effects of the treatments used. For this reason, therapeutic strategies are becoming more tailored to the individual patient's prognosis. Pre-treatment risk factors for early-stage and advanced-stage HL are well known indicators of prognosis. Recently, early interim ^{18}F-FDG PET has been shown as a strong and independent predictor of progression-free survival in HL. Our aim was to assess response to therapy by repeating ^{18}F-FDG-PET/CT after four and six chemotherapy cycles.

MATERIAL AND METHODS: We evaluated 21 consecutive patients affected by (HL) and presenting for assessment over a period of three years. All patients underwent initial staging with ^{18}F-FDG-PET/CT along with standard staging procedures. We tailored an individual treatment plan dependent on pre-treatment risk factors and initial ^{18}F-FDG-PET/CT. With the aim of the best definition of response to treatment, we repeated ^{18}F-FDG-PET/CT after two (FDG-PET 2), four (FDG-PET 4) and six (FDG-PET 6) chemotherapy cycles. Chemotherapy was typically given for four cycles in early disease stages and was prolonged to six to eight cycles in advanced disease stages, depending on PET findings.

RESULTS: Our results showed a strong negative predictive value in detecting responders in early stage HL and a positive predictive value in advanced-stage patients. Clinical stage, extra-nodal sites and the positivity of the ^{18}F-FDG-PET/CT performed during chemotherapy were also noted as strong determinants of response to treatment. Moreover, in our series the ^{18}F-FDG-PET/CT data obtained after only two chemotherapy cycles (FDG-PET 2) were the same of those obtained after FDG-PET 4 and FDG-PET 6 controls.

CONCLUSION: The preliminary data of the present study confirm those of previous published studies about the negative predictive value of ^{18}F-FDG-PET/CT performed after four and six chemotherapy cycles, which contributed to the decision to stop treatment and to avoid radiotherapy in HL patients. Nonetheless, our preliminary data seems to suggest that only the ^{18}F-FDG-PET/CT performed after two cycles of chemotherapy (FDG-PET 2) is able to provide the same prognostic information of the FDG-PET 4 and FDG-PET 6 earlier.

Keywords: Hodgkin's lymphoma, ^{18}F-FDG-PET/CT, prognostic value

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Introduction

The modern combination of chemotherapy and radiotherapy has improved the long-term survival of patients with Hodgkin's lymphoma (HL) to more than 80% in recent decades. However, longer follow-up of these patients has shown serious long-term

adverse effects related to the treatment, including heart and lung disease, and secondary malignancies. In order to reduce these long-term side effects, therapeutic strategies are becoming more tailored to the individual patient's prognosis. The aim of the oncohaematologist is to achieve the highest cure rate with the least morbidity and mortality. Well-established pre-treatment prognostic factors [1] have been shown to predict survival in large cohort studies. Another important predictor of outcome is the response to treatment [2]. Conventional methods for monitoring response to treatment are based on reduction in tumour size documented clinically and with contrast enhanced CT scan (c.e. CT). Recently, early interim ^{18}F-FDG PET has been shown to be a strong and independent predictor of progression-free survival in HL patients [3–9]. In particular, a positive early interim ^{18}F-FDG-PET was found to be highly predictive of disease progression in patients with advanced stage or extra-nodal disease [8].

We present here our preliminary experience with the prognostic value of the ^{18}F-FDG PET/CT in a group of 21 HL patients, with the aim of verifying possible correlations between the pre-treatment risk factors, ^{18}F-FDG-PET performed during chemotherapy compared with the pre-treatment baseline examination, and the treatment outcome.

Material and methods

We homogeneously evaluated 21 consecutive patients with newly diagnosed HL who underwent in-therapy assessment with ^{18}F-FDG-PET/CT since January 2004. All patients underwent initial staging with ^{18}F-FDG-PET/CT examinations (FDG-PET 1) along with standard staging work-up procedures including contrast enhanced CT (c.e. CT). ^{18}F-FDG PET/CT was repeated after two (FDG-PET 2) and four cycles of chemotherapy (FDG-PET 4), and after completion of six cycles of chemotherapy (FDG-PET 6). Treatment protocol was decided at baseline:

1. Patients with classic HL and advanced disease (stage IIB–IV) were treated with six courses of ABVD. Chemotherapy was typically given for four cycles in early disease stages while it was prolonged to six to eight cycles in advanced disease stages depending on PET findings. In detail, Chemotherapy was stopped in the presence of a completely negative FDG-PET 4; otherwise, two more courses were given until the achievement of a completely negative FDG-PET 6. In addition, the results of the FDG-PET after 6–8 cycles of chemotherapy were used to decide on further courses of radiotherapy in bulky disease.
2. Patients with early stage classic HL (I–IIA) were treated with chemo-radiotherapy in the presence of at least one of the following adverse prognostic factors: bulky disease, erythrocyte sedimentation rate $>$ 40 mm, more than three nodal basins involved and the presence of sub-diaphragmatic disease. Radiotherapy alone was limited to stage I with no adverse prognostic factors.
3. Patients with nodular lymphocyte predominance were treated as classic HL at first presentation, while four weekly courses of monoclonal antibody anti-CD20 (rituximab) were given when relapse was demonstrated at an early stage.

The patients were followed-up for a period of 4–28 months (median follow-up =17 months).

Whole-body ^{18}F-FDG PET/CT was performed by a hybrid scanner (GE Discovery LS, General Electric Medical Systems, Milwaukee, WI, USA) with the following procedure: *(a)* each patient fasted for at least six hours and was intravenously injected with 5.5 MBq /Kg ^{18}F-FDG; *(b)* the time elapsed between injection and scanning was 60-90 min; *(c)* each patient was scanned from the base of the skull to the mid-thigh, with an acquisition time of four minutes per bed position with attenuation correction performed using CT (120 keV) X-rays. The energy of the annihilation quanta was 0.51 MeV.

For the purposes of the present study, ^{18}F-FDG PET/CT examinations were interpreted visually by two skilled nuclear medicine physicians (D.R., L.R.) blinded of clinical patient data; in cases of discrepancy, final diagnosis was reached by consensus.

Results

Fifteen patients (71.4%) demonstrated negative FDG-PET 2 and FDG-PET 4 controls after the first-line chemotherapy. Of those, 14/15 patients (93.3%) had a negative FDG-PET 6 control and are currently in complete disease remission. Only one patient (patient 2, Table 1), who was FDG-PET 2 and FDG-PET 4 negative, experienced early relapse and successive refractory responses to salvage high-dose chemotherapy.

Six patients (28.6%) were FDG-PET 2 and FDG-PET 4 positive. In these patients, persistent disease was proven by traditional methods, and they were treated by second-line chemotherapy. Furthermore, three of them with evidence of persistent bulky disease at ^{18}F-FDG PET/CT underwent successful radiotherapy. Finally, one no-responder patient was successfully treated by bone marrow transplantation. A new post-treatment ^{18}F-FDG PET/CT control was negative in all these six patients and they remained in disease-remission during subsequent follow-up.

It is worth noting that all patients affected by nodular lymphocyte predominance histotype had negative FDG-PET 2 and FDG-PET 4 controls, while the three patients affected by stage III and IV B all presented with International Prognostic Score (IPS) $\geq$ 3, with two of them showing a positive FDG-PET 2 and FDG-PET 4 control.

It has to be pointed out that in this prospective study we performed serial PET controls every two chemotherapy cycles. However, it is likely that in early stage responder patients, a PET scan obtained after two cycles of chemotherapy is sufficient for obtaining prognostic indications. On the other hand, we found performing a PET scan control after six or eight cycles of chemotherapy very useful in advanced-stage disease patients to decide when to stop treatment.

Discussion

Modern treatment regimens for early-stage HL show very high cure and survival rates. As cure rates have improved over the years, late adverse effects of treatment have become a matter of increasing concern. In both early and advanced HL, further risk-adapted therapy is being introduced to achieve high cure rates with minimal long-term morbidity and mortality. In the case of advanced-stage HL, where the prognosis is less favourable, efforts have also concentrated on intensifying chemotherapy to improve the chances of cure [10]. Primary refractory disease and

Table 1. Clinical characteristics and ^{18}F-FDG PET/CT results in our patient series

No.	Patients (sex, age)	Histological type	Clinical stage	IPS*	Bulky	Extra–nodal disease	FDG-PET 2**
1.	FR, F, 18 y	Nod. sclerosis	IVB	3	+	+ (lung, liver)	+
2.	BR, F, 35 y	Nod. sclerosis	IVB	3	–	+ (lung, liver)	–
3.	MG, M, 56 y	Nod. sclerosis	IIIB	4	+	–	+
4.	BN, F, 30 y	Nod. sclerosis	IIB	0	–	–	–
5.	BE, F, 28 y	Nod. sclerosis	IIB	2	+	–	+
6.	SS, M, 27 y	Nod. sclerosis	IIB	2	–	–	+
7.	AF, F, 29 y	Nod. sclerosis	IIB	2	+	–	–
8.	EB, M, 55 y	Nod. sclerosis	IIB	3	+	–	–
9.	VE, F, 28 y	Nod. sclerosis	IIB	0	+	–	–
10.	PC, M, 45 y	Nod. sclerosis	IIA (unfavourable)	2	–	–	+
11.	RG, F, 48 y	Nod. sclerosis	IIA (favourable)	2	–	–	+
12.	NB, M, 48 y	Mixed cellularity	IIA (favourable)	2	–	–	–
13.	DG, M, 40 y	Nod. lymph. predominance	IIA (relapse, favourable)	2	–	–	–
14.	RC, M, 25 y	Nod. lymph. predominance	IIA (relapse, favourable)	2	–	–	–
15.	CD, M, 25 y	Nod. lymph. predominance	IIA (favourable)	2	–	–	–
16.	AM, F, 23 y	Nod. lymph. predominance	IIA (favourable)	1	–	–	–
17.	GT, M, 32 y	Nod. lymph. predominance	IIIB	2	+	–	–
18.	LT, M, 33 y	Nod. lymph. predominance	IIA (favourable)	2	–	–	–
19.	FR, F, 20 y	Nod. lymph. predominance	IIA (favourable)	1	–	–	–
20.	CM, F, 28 y	Nod. lymph. predominance	IIA (favourable)	1	–	–	–
21.	GZ, F, 34 y	Nod. lymph. predominance	IIA (favourable)	1	–	–	–

*IPS — International Prognostic Score; **FDG-PET 2 — ^{18}F-FDG PET/CT results after two cycles of chemotherapy

early relapse have the worst prognosis with conventional chemotherapy. Salvage high-dose chemotherapy with haematopoietic stem cell transplantation improves the outcome of both groups [11]. Risk-adapted therapy depends on reliable prognostic stratification as early as possible during treatment. While the prognosis can be estimated using well-established and validated pre-treatment prognostic indices [1], response to treatment is the most important single prognostic factor for the individual patient [8]. Early interim ^{18}F-FDG PET has recently been found to be a major indicator of response to treatment in retrospective and prospective studies [8, 12–15]. In particular, early interim ^{18}F-FDG PET was stronger than all pre-treatment prognostic factors when evaluated independently in univariate regression analyses, with clinical stage and extra-nodal disease also showing considerable prognostic strength. In multivariate regression analyses, an early ^{18}F-FDG PET control was shown to be an independent stronger predictor of progression-free survival (PFS) than clinical-stage and extra-nodal disease [8]. Moreover, the negative predictive value in detecting responders of early interim ^{18}F-FDG PET has been reported to be high in early stage patients, while the positive predictive value in predicting patients with persistent disease is high in advanced-stage patients [8, 12]. Early ^{18}F-FDG PET control during chemotherapy may help risk-adapted treatment strategies by selecting good-prognosis HL patients for less intensive and less morbid treatment, while worse-prognosis patients destined to have short term progression or relapse may be designated for early treatment intensification [8, 10, 13–15].

In spite of the relatively small number of cases described in the present study, some conclusions can be made. Firstly, our data have shown a strong negative predictive value in detecting responders of FDG-PET 2 in our early-stage patients. One limitation of our study is the relatively short post-treatment follow-up period, especially for patients at high risk of disease relapse. On the other hand, it should be emphasised that a very early ^{18}F-FDG PET/CT control, obtained after only two courses of chemotherapy (FDG-PET 2), was effective in our early-stage HL patients with a very high negative predictive value. However, in our responder patient group, the FDG-PET 4 control did not add further prognostic information to the FDG-PET 2 control. This information may be useful for the early identification of responders and in planning the most accurate course of treatment.

Some authors have suggested a semi-quantitative interpretation of the FDG-PET exam by measuring the Standardised Uptake Value (SUV) that was found to offer some advantage over a visual exam interpretation [13]. These data were not confirmed in other studies [12].

It can be concluded that in common practice the ^{18}F-FDG PET/CT exam has become very important in establishing a tailored plan of treatment for HL patients. The FDG-PET 2 control is very useful, especially in identifying responder patients, and the FDG-PET 4 control does not appear to add further useful information to this purpose. The persistence of bulky disease at the FDG-PET 2 control leads to the treatment of the patient also with radiotherapy. In contrast, in the case of negative FDG-PET 2, the adjunct of radiotherapy seems useless. Lastly, negativity of the FDG-PET 6 represents an important step to decide subsequent follow-up. These preliminary results need to be confirmed in larger patient series with prolonged follow-up.

Conclusions

Our preliminary data seems to support the impression that the performance of serial PET scans can help in modulating the

treatment of Hodgkin's lymphoma patients through personalisation of the therapeutic schedule, thus avoiding aggressive approaches in early-stage responders.

References

1. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease: International Prognostic Factors Project in advanced Hodgkin's disease. N Engl J Med 1998; 339: 1506–1514.
2. Oza AM, Ganesan TS, Leahy M et al. Patterns of survival in patients with Hodgkin's disease: long follow-up in a single centre. Ann Oncol 1993; 4: 385–392.
3. Jerusalem G, Beguin Y, Fassotte MF et al. Whole-body positron emission tomography using ^{18}F-fluorodeoxyglucose for post-treatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood 1999; 94: 429–433.
4. Jerusalem G, Beguin Y, Fassotte MF et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. Ann Oncol 2003; 14: 123–130.
5. Torizuka T, Nakamura F, Kanno T et al. Early therapy monitoring with FDG-PET in aggressive non-Hodgkin's lymphoma and Hodgkin's lymphoma. Eur J Nucl Med Mol Imaging 2004; 31: 22–28.
6. Reinhardt MJ, Herkel C, Altehoefer C, Finke J. Moser E. Computed tomography and ^{18}F-FDG positron emission tomography for therapy control of Hodgkin's and non-Hodgkin's lymphoma patients: when do we really need FDG-PET? Ann Oncol 2005; 16: 1524–1529.
7. Castellucci P, Zinzani P, Pourdehnad M et al. ^{18}F-FDG PET in malignant lymphoma: significance of positive findings. Eur J Nucl Med Mol Imaging 2005; 32: 749–756.
8. Kostakoglu L, Goldsmith SJ, Leonard JP et al. FDG-PET after 1 cycle of therapy predicts outcome in diffuse large cell lymphoma and classic Hodgkin disease. Cancer 2006; 107: 2678–2687.
9. 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 2006; 107: 52–59.
10. Brepoels L, Stroobants S, Verhoef G. PET and PET/CT for response evaluation in lymphoma: current practice and developments. Leuk Lymphoma 2007; 48: 270–282.
11. Diehl V, Franklin J, Pfreundschuh M et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003; 348: 2386–2395.
12. Dann EJ, Bar-Shalom R, Tamir A et al. Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome. Blood 2007; 109: 905–909.
13. Sweetenham JW, Carella AM, Taghipour G. High-dose therapy and autologous stem-cell transplantation for adult patients with Hodgkin's disease who do not enter remission after induction chemotherapy: results in 175 patients reported to the European Group for Blood and Marrow Transplantation. Lymphoma Working Party. J Clin Oncol 1999; 17: 3101–3109.
14. Hutchings M, Mikhaeel NG, Fields PA, Nunan T, Timothy AR. Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. Ann Oncol 2005; 16: 1160–1168.
15. Gallamini A, Rigacci L, Merli F et al. The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease. Haematologica 2006; 91: 475–481.