Early positron emission tomography (PET) restaging: a predictive final response in Hodgkin’s disease patients

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Background: It is important to distinguish between responders to standard treatment and non-responders Hodgkin’s disease (HD) patients.

Patients and Methods: Between June 2003–September 2004, in our institute, 40 newly-diagnosed patients with advanced stage HD were consecutively treated with ABVD chemotherapy for six cycles. All these patients underwent staging/restaging: computed tomography (CT) and positron emission tomography (PET) at time 0, PET after two cycles, CT and PET after four and six cycles.

Results: After two cycles (PET-2), the PET was negative in 28/40 (70%), positive in 8/40 (20%), and minimal residual uptake (MRU) was present in the remaining four (10%) patients. After treatment, among eight patients who were PET-2+, seven showed refractory disease and one had relapse after 3 months. All four patients with MRU at the PET-2 became PET− during the further four cycles and, after treatment, three were in complete response (CR) and one relapsed after 5 months. All 28 PET negative patients at the PET-2 remained PET negative and all of them were in CR after treatment.

Conclusions: The PET use for early (after two cycles) response assessment in HD patients is a significant step forward and has the potential to help physicians make crucial decisions about further treatment.

Key words: chemotherapy, early response, HD, PET

introduction

During the decade that followed the first cure claims, techniques were improved, high energy radiotherapy was refined, multiple chemotherapy was first used and quality assurance methods were introduced in Hodgkin’s disease (HD) treatment.

One current problem is how to delineate early in their treatment, those HD patients in whom the chances of cure by conventional treatment are low and for whom an intensification of chemotherapy with bone marrow progenitors autograft is justified. Age in these patients is of prognostic significance, but elderly patients are not good candidates for aggressive therapy modalities. Other factors of poor prognosis are large total tumour burden and associated indicators with it, namely number of involved extranodal organs, elevated ESR, advanced clinical stage, and bulky disease [1].

In the last few years, the fluorodeoxyglucose (FDG)-positron emission tomography (PET) has shown a number of potential advantages in refining and improving the management of HD. PET, based on the increased glucose metabolism of tumour cells, plays a significant role in the initial staging [2–5], in the evaluation of residual masses after therapy [6–12], and in the monitoring of therapy response early in the course of treatment regimens [13–17]. In all such cases, the accuracy of PET for ensuing treatment response is greater than that of a conventional computed tomography (CT) scan.

In the initial stages, the combined PET-CT scan can improve accuracy by increasing the certainty of diagnosis in an otherwise unclear situation. In the evaluation of residual masses after therapy, a high negative predictive value of PET has been consistently reported, clearly showing the ability of PET to identify patients with an excellent prognosis. In addition to a large body of evidence confirming the potential role of PET, including both dedicated and coincidence PET systems, recent data from HD staging and monitoring have tended to confirm that PET should be used as early as possible to predict the response to therapy [18, 19]. It is highly important to identify HD patients with insufficient response to treatment and potentially with poorer clinical outcome. When changing treatment to improve patient response where refractory, or reduce the relapse risk in particular high-risk patients, seems fundamental to therapeutic success.

In what follows, we examined the predictive value of such early evaluation for the clinical response rate and disease-free survival in 40 HD patients in care at our institute.
patients and methods

patients

Forty consecutive histologically verified HD patients with advanced stage (IIB–IVB) who were scheduled to undergo chemotherapy were included in our study prospectively between June 2003 and September 2004. The patients’ characteristics are listed in Table 1. All patients gave fully informed verbal consent.

baseline evaluation. Routine staging methods at diagnosis included clinical examination, laboratory screening, chest X-ray, computed tomography (CT) of chest and abdomen and bone marrow biopsy. All patients were also evaluated by PET at diagnosis.

early treatment evaluation. Early evaluation by PET was scheduled to be performed after two cycles of polychemotherapy. Complete restaging with conventional imaging was not done at this time but PET images were correlated with baseline in all patients.

end of treatment evaluation. One month after completion of therapy (after four and six cycles of chemotherapy), all patients were re-evaluated by clinical examination, CT scan and PET. Figure 1 schematically summarises patient management.

treatment

Treatment was given according to institute protocols. All patients received an ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) regimen at standard doses for six cycles.

PET scans

To optimise FDG uptake in normal and neoplastic tissue, patients were asked to fast for at least 6 h before undergoing PET examination; no patient had a history of diabetes. Fluorine-18 fluorodeoxyglucose (FDG) was produced in our radiopharmacy using standard synthesis techniques. Each patient was i.v. injected with about 6 MBq kg⁻¹ of FDG; PET scan was carried out 70–90 min after tracer injection. Before PET scanning patients were encouraged to void in order to minimise activity in the bladder. FDG-PET scans were carried out using a dedicated tomograph (Advance NX, General Electrics Medical Systems, Milwaukee, USA). Emission scans were acquired for 4 min at every table positron; 2-min transmission scans were also recorded in all patients. Overall, about six bed positions were required for each patient, with a total scan time of about 40 min. Images were reconstructed with segmented attenuation correction. PET images were evaluated on the basis of image visual inspection by three experienced readers. Areas of focal uptake were interpreted as positive for lymphoma unless they were at the sites of known accumulation, including the kidney and bladder, gastrointestinal tract, skeletal areas showing symmetric joint uptake (especially within the shoulder) were considered as due to arthritis.

evaluations of response and statistical analysis

Conventional restaging evaluations were performed after four and six cycles of chemotherapy; they included clinical examination, CT scan, laboratory screening, and bone marrow biopsy if bone marrow was involved at baseline and classified according to the Cheson criteria [20]. PET restaging evaluations were scored as negative, minimal residual uptake (MRU), or positive [21]. Negative was defined as no evidence of disease. Minimal residual uptake was defined as low-grade uptake of FDG (just above

<table>
<thead>
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<th>Number of patients</th>
<th>40</th>
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<tbody>
<tr>
<td>Age (Years)</td>
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<tr>
<td>Median</td>
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</tr>
<tr>
<td>Range</td>
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</tr>
<tr>
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<tr>
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</tr>
<tr>
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<td></td>
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<tr>
<td>II</td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>15</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
</tr>
<tr>
<td>Extranodal disease (No/Yes)</td>
<td>32/8</td>
</tr>
<tr>
<td>Buly disease (No/Yes)</td>
<td>24/16</td>
</tr>
<tr>
<td>Histological type</td>
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<tr>
<td>NS</td>
<td>30</td>
</tr>
<tr>
<td>MC</td>
<td>1</td>
</tr>
<tr>
<td>CHL</td>
<td>8</td>
</tr>
<tr>
<td>NPL</td>
<td>1</td>
</tr>
</tbody>
</table>

NS, Nodular sclerosis; MC, Mixed cellularity; CHL, Classical Hodgkin lymphoma; NPL, Nodular lymphocyte predominance.

Figure 1. Flow-chart of the study.
background) in a focus within an area of previously noted disease. Positive was defined as increased uptake suspicious for malignant disease.

All patients were followed during the outcome with a median follow-up of 18 months (range, 12–27 months). The statistical significance of differences observed were assessed by the log-rank test.

**results**

**PET evaluations**

Table 2 reports early and later PET restaging results during and after therapy. After two ABVD cycles (PET-2 evaluation), the early PET was negative in 28 of 40 (70%) patients, positive in 8 of 40 (20%) patients, and MRU in the remaining 4 (10%) patients.

At the restaging after four cycles of ABVD (PET-4 evaluation), 7 of 8 of the patients with PET-2 positive still showed PET positivity and in the last patient the PET had changed from positive to MRU. At the same time, only two of the initial four MRU patients showed persisting MRU and the other two patients became PET negative; finally, at PET-4 evaluation 30 patients were PET negative including the 28 already negative at the PET-2 evaluation and two patients who presented a PET negativisation from the MRU result at the PET-2 evaluation.

At the end of the six cycles of treatment (PET-6 evaluation), 32 patients were PET negative including the 30 PET negative patients at the PET-4 evaluation and two patients who showed MRU at the PET-4 (both were also MRU at the PET-2 evaluation). In addition, at this final restaging, only one patient had MRU (this was the patient with PET positive at the PET-2 evaluation) and the remaining seven were still PET positive.

**response**

Of the patients who proved to be PET positive or MRU at the time of PET-2 evaluation, all but one had a negative CT at the CT-4 evaluation.

On the basis of the early PET-2 evaluation, of the eight patients who were PET positive seven showed refractory disease (with persistent PET positive, CT positivity after an initial reduction at the CT-4 evaluation and disease appearance in other new sites) (case example in Figure 2 A-B-C) and one (the patient with PET-2 positive, then PET-4 MRU, and with persistent PET-6 MRU) had HD relapse (with B symptoms, PET positive and CT positive) 3 months after the end of treatment. All four patients with MRU at the PET-2 evaluation became PET negative during the further four cycles of ABVD and, at the end of chemotherapeutic treatment, 3 of 4 were in complete response and the remaining one (one of the two patients who changed from MRU to negative at the PET-6 evaluation) had a relapse of the disease 5 months after the last cycle of ABVD (case example in Figure 2 D-E-F). All 28 patients with PET negative at the PET-2 evaluation remained PET negative and all of them were in complete response after treatment.

Both relapsing patients underwent biopsy which histologically confirmed the HD relapse.

Comparing the 28 PET negative subset versus the 8 PET positive subset at the PET-2 evaluation, we observed no disease progression/early relapse (within one year of the end of the treatment) versus 8 of 8 (100%) progressions/early relapses ($P < 0.00000$).

Table 3 summarises the comparative data between PET-2 status and the final clinical results.

**discussion**

Our findings clearly show that the PET scan has a high prognostic value for evaluation of therapy as early as after two cycles of ABVD regimen in HD patients.

The distinction between minimal treatment required to control advanced HD and the maximal tolerated treatment is a fine one. Early prediction of outcome is indispensable to adjust treatment before it is too late. Accurate evaluation of response to therapy is of vital importance in the management of patients with HD. The main endpoint of chemotherapy is the achievement of complete remission, which is associated with a longer progression-free survival and potential cure than is partial remission.

The initial patient and disease characteristics are not ideal prognostic factors for treatment adaptation as they are obtained too early [22]. There is a growing interest among risk-directed approaches in using prognostic factors that predict non response or early relapse.

Over the past few years, several studies have shown that the PET scan has a good predictive value for the post-treatment evaluation of HD patients [13–19]. After the treatment, PET has a high positive and negative predictive value in the assessment of remission and prediction of prognosis.

In our study, the PET result obtained after two cycles of chemotherapy provided valuable information regarding early assessment of therapy response with no cases of refractory disease (non-responder patients) or early relapse (within the first year of ending induction treatment) in patients with no residual FDG uptake compared to 100% refractory disease or early relapse rate in patients with persistent PET positive ($P < 0.00000$). In addition, of the four patients with a PET scan of MRU, one (25%) had an early relapse only 5 months after the last cycle of chemotherapy.

Recently, Hutchings and co-workers [19] reported a role for PET in early prediction during therapy (after two cycles), whether in early and advanced stage HD patients, demonstrating that PET was a strong and independent predictor of progression-free survival. These data have confirmed the previous preliminary published data [13–15] on the value of PET as an early predictive factor. Our data, from our own institute, confirm the Hutchings’ report with particular attention to the statistically significant role of PET in the early identification of refractory HD patients. We also note the potential of PET in cases of MRU, which is another subset of
high-risk potential non responders. In addition, our study shows that the accuracy of PET for early treatment response is greater than that of CT.

The problem of MRU as a distinctive PET situation is quite relevant. The definition of MRU has been introduced by Mikhaeel [21] and then it was usefully applied to identify the patients difficult to categorise as either positive or negative at interim PET. The different evolution of MRU patients has then been confirmed by Hutchings et al. [18] in HD and by Mikhaeel et al. [23] with differences between NHL and HD. Identification of MRU as a distinctive (although not frequent) PET finding corresponds in clinical practice to recognition by nuclear medicine physician of challenging scans to report, which are not clearly attributable to either positive or negative cases. Distinction of a faint increased uptake due to minimal residual disease or to inflammation is sometimes impossible; the introduction of a category with uncertain findings is more acceptable and realistic than necessarily to force the results into two limited categories (positive or negative).

It is now time to develop prospective trials to establish the clinical role of PET in this setting by comparing complete response and disease-free survival rates after randomly assigning HD patients with positive early-treatment PET findings to either continuing standard induction therapy or to switch to a more aggressive approach. Again, patients with a negative PET after two cycles would continue with a full course of their first line therapy while patients with a positive PET after two cycles could be randomised to second line chemotherapy and stem cell transplant without completing a full course of first line treatment. Significant questions remain and should be the subject of further clinical trials. They include: When is the best time to use PET for early response assessment? What is the best method for early response assessment: a quantitative approach (is there a role for the MRU situation?) or

Table 3. Comparison between PET-2 status and final clinical results

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<th>No. of patients</th>
<th>Final clinical result (No. of patients)</th>
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<tbody>
<tr>
<td>Positive</td>
<td>8</td>
<td>refractory 1 early relapse 100%</td>
</tr>
<tr>
<td>MRU</td>
<td>4</td>
<td>early relapse 25%</td>
</tr>
<tr>
<td>Negative</td>
<td>28</td>
<td>refractory/relapse</td>
</tr>
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MRU, minimal residual uptake.

Figure 2. Example of sequential PET findings in two patients. A, B, and C show scans from patient with PET positive at the time of PET-2 evaluation predicting no response. (A) Pretherapeutic scans; (B) PET-2 evaluation; (C) PET-6 evaluation. D, E and F show scans from patient with MRU at the time of PET-2 evaluation. (D) Pretherapeutic scans; (E) PET-2 evaluation; (F) PET positive showing a relapse after 5 months from the end of treatment.

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MRU, minimal residual uptake.
a dichotomous visual method of complete response versus less than complete response? Can we use PET to choose patients who can readily be cured with less than standard therapy? Will survival be better for patients who receive more intensive therapy as a result of a poor response on interim response assessment? Use of early PET response assessment may indeed allow treatments to be more closely tailored to the patient’s disease but without further clinical trials, clinicians will be unsure how best to use this new information.

acknowledgement

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references