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FDG–PET for assessment of early treatment response after four cycles of chemotherapy in patients with advanced-stage Hodgkin's lymphoma has a high negative predictive value

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Background: As positron emission tomography (PET) seems to be a powerful prognostic marker in the treatment of Hodgkin's lymphoma (HL), we analysed the prognostic value of PET after four cycles of combination therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) in patients with advanced-stage HL.

Patients and methods: From January 2004 to March 2007, 50 patients with newly diagnosed HL in clinical stages IIB with large mediastinal mass or extranodal disease, III and IV were treated according to the HD15 protocol of the German Hodgkin Study Group. All patients received a PET scan after four cycles of BEACOPP (PET-4).

Results: Of the overall group, 14 of 50 patients had a positive PET-4 while 36 had a negative PET-4. At a median observation time of 25 months, 2 of the 14 patients with a positive PET-4 had progressed or relapsed, while there was no progression or relapse in PET-4-negative patients.

Conclusion: Our results indicate a very good negative predictive value of PET-4 in advanced-stage HL patients treated with BEACOPP.

Key words: BEACOPP, chemotherapy, Hodgkin's lymphoma, PET, response assessment

introduction

Hodgkin's lymphoma (HL) accounts for ~1% of all malignancies and has become the best curable cancers in adults with reported disease-free survival in excess of 80% at 5 years after treatment [1, 2]. Due to the risk of death from second cancers, cardiovascular disease and other late effects after treatment, reduction of toxicity in this group of patients is being evaluated [3]. The aim of ongoing clinical studies is to retain the excellent tumour control while minimising side-effects. Positron emission tomography (PET) might allow response to be assessed early in the course of treatment, thereby avoiding unnecessary further therapy [4, 5].

As PET might provide a means of discriminating between active and inactive HL tissue in residual tumour masses, several studies have investigated the role of PET with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) after completion of therapy in this malignancy [6–8].

More recently, PET has also been evaluated to predict therapy outcome at an earlier stage of treatment, usually after two cycles of chemotherapy [9–11]. Thus, PET might be used as an early predictor of response allowing a risk-adapted treatment strategy [12]. Since $BEACOPP_{escalated}$ not only has rendered the best cure rates reported so far for advanced-stage HL patients [13] but also has more toxicity, this regimen seems well suited to pioneer the best use of PET for response adaption. Here, we report the results of 50 patients treated with combination therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) in whom PET was carried out after four cycles of treatment.

patients and methods

patients

All patients had to have newly diagnosed, histologically proven HL, clinical stage IIB with large mediastinal mass (more than or equal to

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one-third of the maximum thorax diameter) and/or extranodal disease, stage III or IV. Patients had to be between 18 and 60 years of age and free of any concurrent disease precluding protocol treatment. Patients with HL as part of a composite lymphoma, previous malignancy, previous chemo- or radiotherapy, pregnancy or lactation were not eligible. Exclusion criteria for PET were diabetes mellitus and elevated fasting blood sugar level >130 mg/dl.

study design

Forty-four of the 50 enrolled patients were registered and treated within or according to the HD15 trial of the German Hodgkin Study Group (GHSG). These patients had been randomly assigned to the following courses of treatment: eight cycles of $BEACOPP_{escalated}$ ($n = 13$), six cycles of $BEACOPP_{escalated}$ ($n = 16$) or eight cycles of time-condensed $BEACOPP14_{baseline}$ ($n = 15$). Six patients not part of HD15 receiving eight cycles of $BEACOPP_{escalated}$ were also included. PET-4 was carried out after four cycles of BEACOPP in addition to the interim staging examinations as defined in the HD15 protocol.

chemotherapy

$BEACOPP_{escalated}$ was administered in standard doses consisting of cyclophosphamide 1250 mg/m^2 (day 1), adriamycin 35 mg/m^2 (day 1), etoposide 200 mg/m^2 (days 1–3), procarbazine 100 mg/m^2 (days 1–7), prednisone 40 mg/m^2 (days 1–14), vincristine 1.4 mg/m^2 (day 8), bleomycin 10 mg/m^2 (day 8) and granulocyte colony-stimulating factor (from day 8). $BEACOPP_{baseline}$ was given in standard doses consisting of cyclophosphamide 650 mg/m^2 (day 1), adriamycin 25 mg/m^2 (day 1), etoposide 100 mg/m^2 (days 1–3), procarbazine 100 mg/m^2 (days 1–7), prednisone 80 mg/m^2 (days 1–7), vincristine 1.4 mg/m^2 (day 8), bleomycin 10 mg/m^2 (day 8) and granulocyte colony-stimulating factor (from day 8). $BEACOPP_{escalated}$ was repeated on day 22 and time-condensed $BEACOPP_{baseline}$ on day 15 as described [14].

radiotherapy

Local radiotherapy (30 Gy) was restricted to those patients who had a partial remission (PR) with residual mass ≥2.5 cm after chemotherapy and who were positive in the PET carried out after completion of six to eight cycles of BEACOPP (PET-6/8). All these patients were centrally reviewed by the PET panel of the GHSG in Cologne, Germany, before the start of radiotherapy.

positron emission tomography

PET with FDG was positive if focal or diffuse uptake was seen above background in a location incompatible with normal anatomy or physiology, without a specific standardised uptake cut-off value. In accordance with international guidelines for PET at the conclusion of therapy, a mild and diffusely increased uptake at the site of the residual mass with an intensity lower or equal to the mediastinal blood pool was judged PET negative [5, 15] in both, PET-4 and PET-6/8 scans. PET-4 scanning was carried out as close as possible to the fifth cycle of chemotherapy and PET-6/8 within 2–6 weeks of the last application of chemotherapy.

statistical analysis

The analysis set for this study comprised all patients recruited at one centre (Prague) who had started treatment not later than March 2007. The cut-off date was chosen to ensure that a high proportion of the target population had completed treatment, PET monitoring and at least 12-month follow-up after completion of therapy. The positive predictive value (PPV) and the negative predictive value (NPV) were calculated from the results of patients with progression, relapse or treatment failure of any cause 12 months after PET-4. A 95% confidence interval (CI) for the NPV was calculated using the normal approximation to the binomial distribution: $v \pm 1.96\sqrt{v(1-v)/n}$, where v = NPV and n = total number of cases. Kaplan–Meier analysis and the log-rank test were used to compare PFS values of different patient subgroups.

results

patients

From January 2004 to March 2007, 50 patients underwent PET scanning after four cycles of BEACOPP (PET-4) and 49 patients after completion of chemotherapy (PET-6/8). Forty-nine patients were in remission in response to first- or second-line therapy at the time of analysis, and one patient died due to therapy-associated toxicity in the last cycle of chemotherapy. Forty-three patients had also had a PET for initial staging and these were all positive. Patient characteristics are shown in Table 1.

predictive value of PET after four cycles of BEACOPP

After four cycles of BEACOPP, 36 of the 50 patients had a negative PET-4 scan. Further treatment was given according to the specific HD15 protocol and no patient with a negative PET-4 qualified for additional radiotherapy. There was no

Table 1. Patient characteristics

Characteristics	Analysis set ($n = 50$)	
	n	%
Age group (years)		
16, 20	2	4
20, 30	26	52
30, 40	15	30
40, 50	6	12
50, 60	1	2
Sex		
Female	30	60
Male	20	40
Stage		
IIB	11	22
IIIA	5	10
IIIB	14	28
IVA	3	6
IVB	17	34
Reference histology		
Un	2	4
NS cHL	38	76
MC cHL	8	16
LD cHL	2	4
International prognostic index		
0–1	23	46
2–3	17	34
4–7	10	20
Large mediastinal mass		
	29	58

Un, unconfirmed Hodgkin's lymphoma; cHL, classical Hodgkin's lymphoma; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion.

progression or relapse in PET-4-negative patients, but one PET-4-negative patient died in the last cycle of chemotherapy due to acute toxicity of treatment (bleomycin-induced pneumonitis), resulting in an NPV of 97% (95% CI 94% to 100%) of PET-4. Fourteen of the overall group of 50 patients had a positive PET-4 and seven of these underwent additional radiotherapy after showing a PET-6/8-positive PR ≥2.5 cm following chemotherapy. Additional two patients with a positive PET-4 and a positive PET-6/8 progressed or relapsed within 1 year and underwent salvage therapy with high-dose chemotherapy and stem-cell support. In contrast to the NPV, the calculation of the PPV is based on a treatment with BEACOPP ± radiotherapy (PPV = 14%, 95% CI 12% to 16%). Beside these findings, no other statistically significant difference was found between the PFS values of the PET-4-positive and PET-4-negative groups (Figure 1).

predictive value of PET after chemotherapy

After completion of chemotherapy, 40 of 49 patients achieved a negative PET-6/8. Of these 40 patients, 35 had a negative PET-4 and five had a positive PET-4. Although none of these 40 patients received radiotherapy or any other additional therapy, no patient progressed or relapsed during the 12-month observation period starting at the post-chemo PET-6/8 (NPV 100%) (Figure 2). All nine PET-6/8-positive patients were PET-4 positive. Seven of them underwent additional radiotherapy. The two remaining PET-6/8-positive patients showed early progression or relapsed. As for the PET after four cycles of BEACOPP, the calculation of the PPV is based on a treatment with BEACOPP ± radiotherapy in contrast to PET-negative patients where radiotherapy was omitted (PPV 22%, 95% CI 18% to 26%).

predictive value of a large mediastinal mass

Twenty-nine of the overall group of 50 patients had a large mediastinal mass at the initial staging. Thirteen of these were PET positive after four cycles of chemotherapy (PET-4) and nine stayed PET positive after six to eight cycles of chemotherapy (PET-6/8) of whom two had progressed (Figure 3).

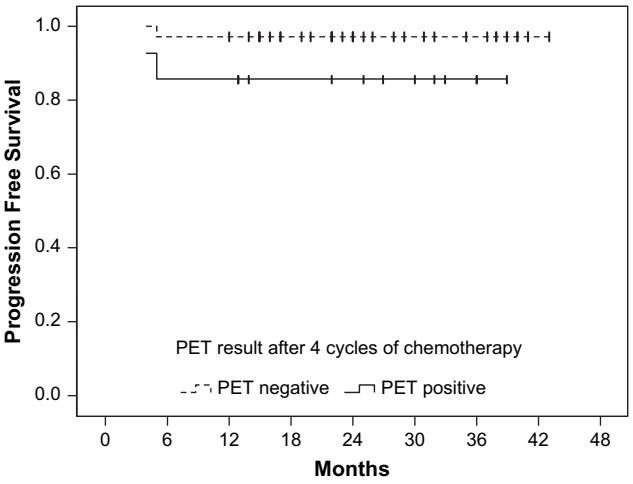

Figure 1. Positron emission tomography (PET) after four cycles of chemotherapy. Kaplan–Meier curves of PET-4-negative and -positive patients. No significant intergroup difference.

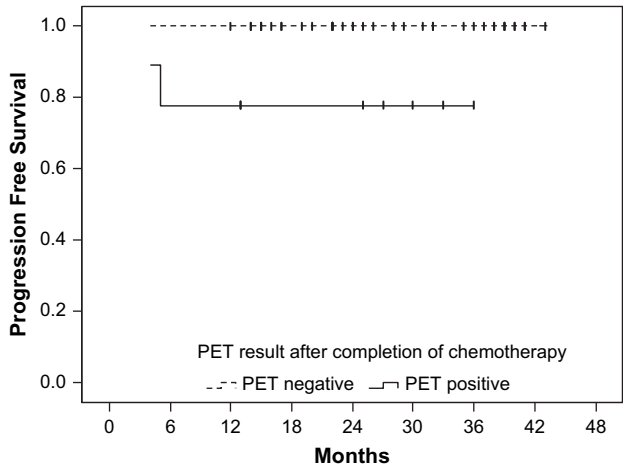

Figure 2. Positron emission tomography (PET) after completion of chemotherapy. Kaplan–Meier curves of PET-6/8-negative and -positive patients. The *P*-value calculation was not possible, as all values for PET-6/8-negative patients are censored.

discussion

The following findings emerge from the analysis of 50 advanced-stage HL patients in whom during chemotherapy with BEACOPP a PET was carried out after the fourth cycle of treatment:

(i) A negative PET scan after four cycles of BEACOPP-based chemotherapy (PET-4) is a strong predictor for successful chemotherapy.
(ii) Omitting radiotherapy in PET-negative patients after completion of BEACOPP-based chemotherapy did not worsen the outcome in our cohort.
(iii) A large mediastinal tumour is a well-known risk factor, which still requires intensive treatment.

Most of the available data on the prognostic value of PET to date have been generated from doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) or similar regimens. However, the evidence presented so far [9–11, 16] has been limited due to the small size of the patient groups studied, the different stages of patients enrolled and the heterogeneous treatment received before PET. The impact of a positive PET remains unclear, although a higher risk of progression or relapse is signalled [17] and the NPV of PET is encouraging [18]. The present analysis was carried out to gain some information on how many patients will be PET positive or negative when receiving BEACOPP and to get some idea on the impact of PET-4 in this setting. On the basis of the results presented here, it can be assumed that about two-thirds of patients will be PET negative after four cycles of BEACOPP and one-third will be PET positive.

Another factor affecting the expected number of patients in randomised treatment protocols might be the interpretation of PET scans. To ensure high consistency, we used the same

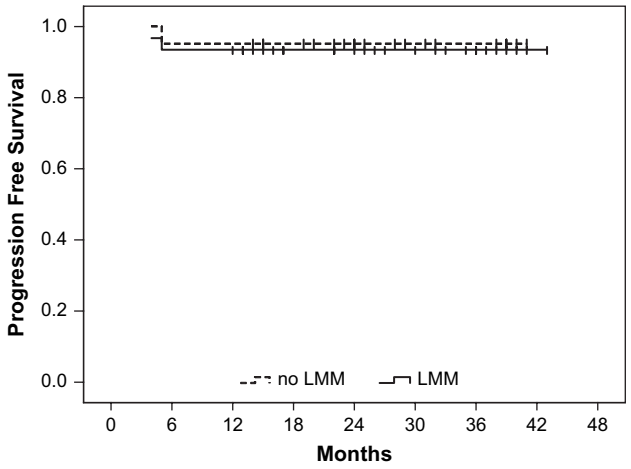

Figure 3. Large mediastinal mass (LMM). Kaplan–Meier curves of patients with/without LMM. No significant intergroup difference.

criteria for PET-4 and PET-6/8 interpretation. A PET result was rated as positive when residual masses had an uptake higher than the mediastinal blood pool structures as recommended for the interpretation of PET at the end of therapy [5, 15]. This is in contrast to recent observations suggesting this to be classified as minimal residual uptake (MRU) and thus being PET negative [16]. Especially for reading of interim scans, a more liberal PET interpretation is discussed [17]. Mikhaeel et al. [19] have demonstrated that the prognostic value of MRU differed in non-HL patients with early as opposed to advanced stages of the disease while Hutchings et al. [10] found early progression at the end of therapy in one of nine early interim MRU HL patients. The HD15 trial focussed on advanced HL patients and required a stringent interpretation of MRU as radiotherapy was omitted in PET-negative patients. To compare the predictive value of PET-4 and PET-6/8 and as PET-4 might become the end-of-treatment PET in future studies, the use of the same criteria for interpretation is essential. The criteria used for PET interpretation will be further analysed in future studies, as foreseen in the HD18 trial of the GHSG. The difference in progression-free survival between different treatment groups can be expected to be small; to minimise additional variables, a central PET review must be carried out, as the interpretation of PET is an evolving field with centre-to-centre variation.

The high predictive value of PET after completion of chemotherapy [6–8] has led to the idea of using PET to monitor therapy and allow early alteration of treatment plans. Hutchings et al. [10] retrospectively assessed the prognostic value of PET after two to three cycles of ABVD in 85 HL patients and found that particularly in advanced stages, PET had a strong predictive value with all six PET-positive patients relapsing within 2 years. Zinzani et al. [20] reported results obtained after two cycles of ABVD in 40 HL patients: all 28 PET-negative patients reached complete response. In a further study by Hutchings et al. [9], 58 of 61 PET-negative HL patients were progression free after two cycles of ABVD at a median follow-up of 23 months, while 13 of 16 PET-positive patients relapsed or died. Only advanced-stage HL patients underwent PET after two cycles of ABVD in the study by Gallamini et al. [11]: at a mean follow-up of 1 year, 18 of 20 PET-positive patients had progressed or relapsed, while 85 of 88 PET-negative patients remained in complete remission. Nearly all trials reported have examined the value of PET in HL patients after one or two cycles of ABVD. So far, none of these trials made therapeutic decisions on the basis of this early interim PET.

Since BEACOPP is the most effective treatment of advanced-stage HL [13], this regimen is an obvious candidate for better individually tailoring the intensity of treatment. However, little information is available on the prognostic value of early PET for therapy stratification after BEACOPP. In a study reported by Dann et al. [12], unfavourable and advanced-stage HL treatment was adapted on the basis of PET results after two cycles of $BEACOPP_{escalated}$. In PET-positive patients, therapy was continued with four cycles of $BEACOPP_{escalated}$ while PET-negative patients were switched to four cycles of $BEACOPP_{baseline}$. At a follow-up of 12 months, 42 of 43 PET-negative and 8 of 11 PET-positive patients survived event free.

These results are very similar to the results obtained after four cycles of BEACOPP as presented here. The NPV of early PET in our study was high even if only 50 patients in total were included. The only failure in this group was related to therapy-associated toxicity in the eighth cycle of chemotherapy. In contrast to the study by Picardi et al. [21], the outcome for PET-negative patients after chemotherapy with or without residual lymphoma tissue was even better than the outcome for PET-positive patients with residual tissue, even though they were irradiated. A possible reason for this is the effectivity of BEACOPP chemotherapy. However, our data like most other studies published on this topic so far must be interpreted with care due to the small number of patients included. Whether a negative PET after chemotherapy with BEACOPP justifies abandoning radiotherapy even in patients with a large mediastinal mass can only be answered by larger studies such as the prospectively randomised HD15 trial of the GHSG. First results have shown an NPV of 94% at 12 months for PET-negative patients after chemotherapy, even though they received no additional radiotherapy [18].

In summary, the results presented here suggest that PET-4 might also be a good prognostic discriminator for advanced-stage HL patients treated with BEACOPP. The high NPV of an interim PET might allow a significant reduction of toxicity while maintaining high cure rates to be proven in future trials.

funding

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