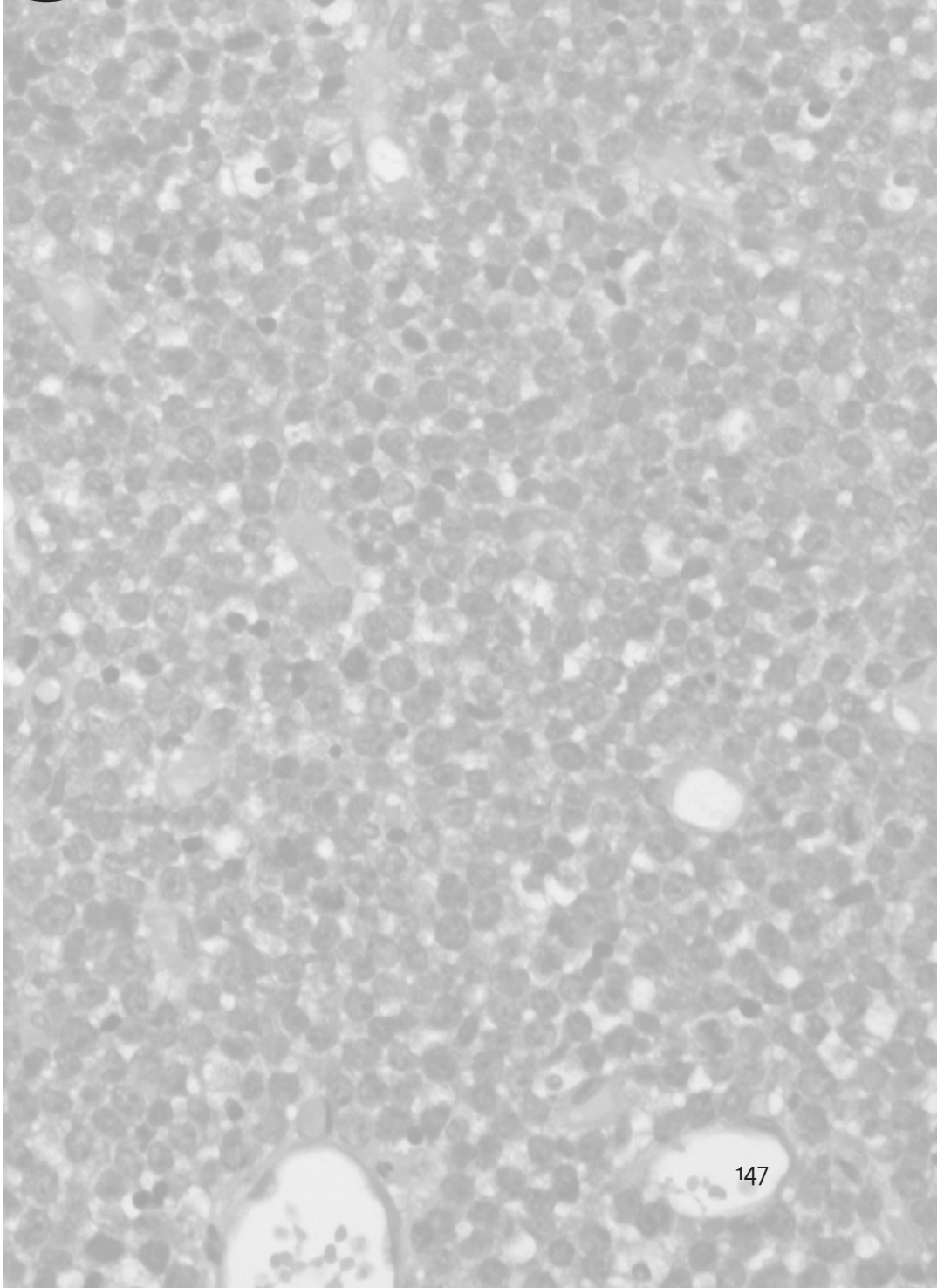


5 Relapsed lymphoma



5.1

Secondary IPI and outcome after autologous stem cell transplantation in chemosensitive patients with relapsed or primary refractory lymphoma

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Background and objective

High-dose chemotherapy and autologous stem cell transplantation (ASCT) may cure a subset of patients with relapsed diffuse large B-cell lymphoma (DLBCL). We evaluated the predictive value of the secondary International prognostic Index of various different non-Hodgkin lymphoma (NHL) subtypes in chemosensitive ASCT patients.

Design and Methods

Data from all 88 consecutive patients with relapsed (n=55) or primary refractory (n=33) NHL who were still chemosensitive and underwent ASCT in our institute between 1989-2002 were analysed.

Results

Median age was 50 years, range 18-64. NHL diagnoses were DLBCL (41), follicular (16), mantle cell (12), peripheral T-cell (12), anaplastic large cell (5), other lymphoma (2). The secondary age-adjusted IPI (saa-IPI) was low in 19%, low-intermediate in 27%, high-intermediate in 42%, and high-risk in 12%, and appeared highly predictive for outcome. After a median follow-up of 76 (range 4-152) months for survivors, 3-year overall survival was 87%, 66% or 28% ($p<.01$) for patients with saa-IPI 0, 1 or 2/3 factors, and progression free survival 80%, 52% or 28% ($p<.01$), respectively. In multivariate analysis, outcome was not different for primary refractory vs relapsed lymphoma nor for lymphoma subtype.

Conclusion

The saa-IPI is highly predictive for outcome in chemosensitive NHL patients treated with ASCT, irrespective of the type of histology and relapse status.

Introduction

The prognosis of aggressive non-Hodgkin's lymphoma in relapse is poor. High-dose chemotherapy with autologous stem cell transplantation (ASCT) may improve both progression free survival (PFS) and overall survival (OS) in patients with relapsed disease. Approximately 50% of patients with relapse still have disease responding to second-line chemotherapy. Subsequent high-dose therapy and ASCT may cure approximately half of those chemosensitive patients. Ultimately, only 25% of patients with relapse/refractory disease after first-line treatment will long-term survivors.¹⁻⁵ The determination and validation of selection criteria for those patients who might benefit from high-dose therapy and ASCT still remains a challenge. Thus far, response to chemotherapy preceding

high-dose treatment and ASCT has been the most important predictive factor for final outcome.⁵ The International Prognostic Index (IPI)⁶ is a powerful tool to predict response and survival in patients with aggressive lymphoma at initial diagnosis. The IPI at relapse, here referred to as secondary IPI (s-IPI) also has an important predictive value for outcome after ASCT. Because most patients, subjected to high dose chemotherapy, are below the age of 60 years, the use of the (secondary) age-adjusted IPI (saa-IPI) is more practical. The predictive value of the saa-IPI was analysed for the first time in the PARMA trial,⁵ which included 215 patients with aggressive NHL in relapse, who were randomised between further conventional treatment or high dose chemotherapy with ASCT if they had chemosensitive disease as proven by at least a partial remission after two courses of conventional second-line treatment. In the PARMA trial, the IPI at relapse was of prognostic significance when all patients were taken into account. However, its significance disappeared when only chemosensitive patients treated with ASCT were considered.⁷ Next, Moscovitz et al.⁸ confirmed the importance of the s-IPI at relapse in a series of 51 patients of whom 34 were transplanted. Recently, Hamlin et al.⁹ addressed the value of the saa-IPI in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), treated with ICE chemotherapy followed by HDT/ASCT. In this study, saa-IPI at the initiation of second-line therapy was predictive for PFS and OS of all patients, including chemosensitive patients of whom the large majority (91%) underwent transplantation.

Because chemosensitivity is the first selection criterion for subsequent high-dose therapy and ASCT, we wondered whether – in addition to the DLBCL category – the saa-IPI could also be applied to patients with chemosensitive relapse of other categories of NHL, eg, transformed follicular lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma and even (untransformed) follicular lymphoma. Therefore, we analysed the outcome in relation to the saa-IPI of all patients with relapsed and primary refractory NHL, who were chemosensitive and subsequently had been treated with ASCT in our institution in the period 1989-2002, allowing for sufficient follow-up of all patients.

Patients and methods

All consecutive patients with relapsed chemosensitive NHL who were subsequently treated with high-dose therapy and ASCT in our hospital between 1989 and 2002 were investigated. The database was closed at September 2004.

Patients were routinely re-staged according to standard procedures including confirmation of active disease by biopsy, whole-body CT-scanning and bone marrow biopsy before starting re-induction treatment. Patient with central nervous system involvement were excluded. Stage at relapse/progression was clas-

sified according to the Cotswolds modification of the Ann Arbor staging system.¹⁰ All representative histologic specimen including those at first diagnosis were reviewed and converted into the World Health Organisation classification.¹¹

Treatment was either within randomised trials (HOVON-studies) or according to local protocols (Table 1). Most patients received the DHAP regimen (dexamethasone, cisplatin, and cytarabine) followed by the VIM regimen (etoposide, ifosfamide, and methotrexate) as re-induction chemotherapy at 3 to 4 weekly intervals.¹² Subsequently, patients were evaluated for response including whole body CT-scan, and bone marrow biopsy if initially involved. Patients with documented complete or partial responses¹³ were defined as having chemotherapy-sensitive disease and proceeded with an additional cycle of DHAP followed by high-dose chemotherapy and ASCT. Bone marrow or peripheral blood stem cells were harvested during re-induction chemotherapy according to standard methods as previously published.¹² Patients received the myeloablative BEAM regimen (carmustine, etoposide, cytarabine and melfalan)¹² followed by reinfusion of the stem cell graft. Ten patients with initial bulky site in PR (n = 6) or CR (n = 4) after ASCT received additional involved field radiotherapy.

The relevant clinical data were extracted from the medical records. The saa-IPI was calculated at time of initiation of salvage therapy. Only four patients (3 DLBCL, 1 peripheral T-cell lymphoma) had incomplete saa-IPI data. Serum LDH, clinical stage and WHO performance status were available in, respectively 87 (99%), 84 (96%), and 84 (96%) of the 88 patients. Data analysis was performed using SAS software, version 8.0 (SAS-Institute inc., Cary, North Carolina, USA). Survival curves were computed from date of stem cell re-infusion until date of last follow-up or event, according to the method of Kaplan and Meier.¹⁴ Events were defined as overall mortality; relapse or progression of NHL, and death from lymphoma. Univariate and multivariate analyses with Cox regression were performed to explore additional factors of possible significance for OS and PFS. In univariate analysis, the following variables were tested: saa-IPI and each IPI factor separately; histology type, de novo *versus* transformed disease; response to first-line therapy: responsive disease (PR/CR more than 3 months duration after first-line therapy) *versus* primary progressive disease (all others); number of prior treatments.

Variables with a p value <0.1 at univariate analysis, including saa-IPI were also tested in a multivariate Cox regression model

Results

Between January 1989 and January 2002, 88 patients with relapsed or primary refractory NHL reached at least a partial response to salvage chemotherapy and subsequently received high dose chemotherapy followed by ASCT.

Table 1. **Characteristics of 88 patients with chemosensitive relapsed/progressive NHL treated with ablative therapy and autologous stem cell transplantation between 1998-2001.**

Characteristic	#Patients (%)
Median age (range)	50 (18-64)
Male/female	60/28 (68%/32%)
Histology	
– Diffuse large B-cell lymphoma	41 (47%)
– de novo DLBCL	33 (38%)
– transformed from follicular lymphoma	8 (9%)
– Follicular grade 3	4 (5%)
– Follicular lymphoma grade 1-2	12 (14%)
– Mantle cell lymphoma	12 (14%)
– Anaplastic large cell lymphoma	5 (6%)
– Peripheral T-cell lymphoma	12 (13%)
– Burkitt lymphoma	1 (1%)
– Unclassifiable B-cell lymphoma	1 (1%)
Response to 1st line treatment	
– CR/PR \geq 3 months	55 (62%)
– CR/PR < 3 months	20 (23%)
– No change/Progression	13 (15%)
No. of treatments before re-induction chemotherapy prior to ablative therapy and ASCT (<i>at least one regimen was doxorubicin-containing</i>)	
– 1	47 (54%)
– 2	17 (19%)
– 3 or 4	24 (27%)
Re-induction chemotherapy before ASCT	
– DHAP-VIM-DHAP	54 (61%)
– ProMace-MOPP	17 (19%)
– Mini-BEAM	6 (7%)
– Other	11 (13%)
Age adjusted IPI at relapse (saa-IPI) (n=84)	
– Low (0)	16 (19%)
– Low-intermediate (1)	23 (27%)
– High-intermediate (2)	35 (42%)
– High (3)	10 (12%)

The main characteristics of the 88 chemosensitive patients are given in Table 1. DLBCL was the most frequent histological type; eight patients had follicular lymphoma transformed into DLBCL. All patients had completed at least one full anthracycline-based regimen of combination chemotherapy prior to re-induction chemotherapy, 46% had completed more than one prior regimen. A total of 55 (62%) patients had relapsed disease, whereas 33 (38%) patients had primary refractory disease. The saa-IPI distribution for low (0 factors), low-intermediate (1 factor), high-intermediate (2 factors) and high-risk (3 factors) patients (excluding 4 patients with incomplete data) was 19%, 27%, 42% and 12% respectively.

Median follow-up after ASCT for surviving patients was 76 months (4 to 152 months). Progression or relapse after ASCT occurred in 45 patients, of whom 36 died of progressive lymphoma. Four patients died within the first 90 days from treatment-related toxicity (infectious complications during (prolonged) aplasia). Three-yr OS and PFS for all patients was 48% and 43% respectively. No differences were observed between patients in CR or PR at restaging after re-induction therapy, before ablative therapy and ASCT.

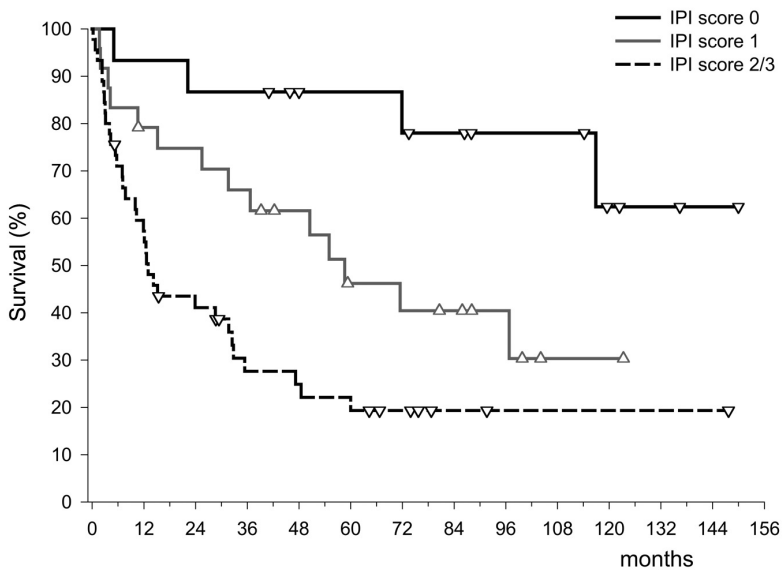


Figure 1. **Overall survival of chemosensitive relapsed NHL patients treated with high-dose chemotherapy and ASCT according to the saa-IPI (excluding 4 patients with incomplete data).**

Three year estimates: saa-IPI 0 (n=16) 87%, saa-IPI 1 (n=23) 66%, saa-IPI 2/3 (n=45) 28%, log rank $p < .01$. Triangles indicate time of censoring of patients in each stratum.

All individual saa-IPI risk factors: LDH, performance score and to a lesser degree stage, correlated with PFS and OS. For patients with saa-IPI 0, 1 or 2/3 factors, 3-yr PFS estimates were 80%, 52% and 28% respectively ($p < .01$); OS estimates were 87%, 66% and 28% respectively ($p < .01$) (Figure 1). Although the survival curve of the 33 patients with primary refractory NHL showed a rapid decline during the first months (Wilcoxon test; $p = .02$), ultimately, OS was not significantly different from 55 patients who relapsed after initial response (Log rank test; $p = .33$) (Figure 2). The 3-yr OS estimates were 38% versus 53%, respectively, whereas at 5-years these were 38% versus 37%. In univariate analysis, histology (DLBCL v. follicular lymphoma v. peripheral T-cell lymphoma (anaplastic large cell excluded) v. mantel cell lymphoma) did not have prognostic impact on outcome, although numbers of various subsets obviously were rather small. Neither did outcome of patients with early relapse (<1 yr) versus late relapse (>1 yr) (3-yr OS 46% versus 51%; $p = .50$). In multivariate analysis, saa-IPI remained as strong predictive factor for PFS and OS (Table 2).

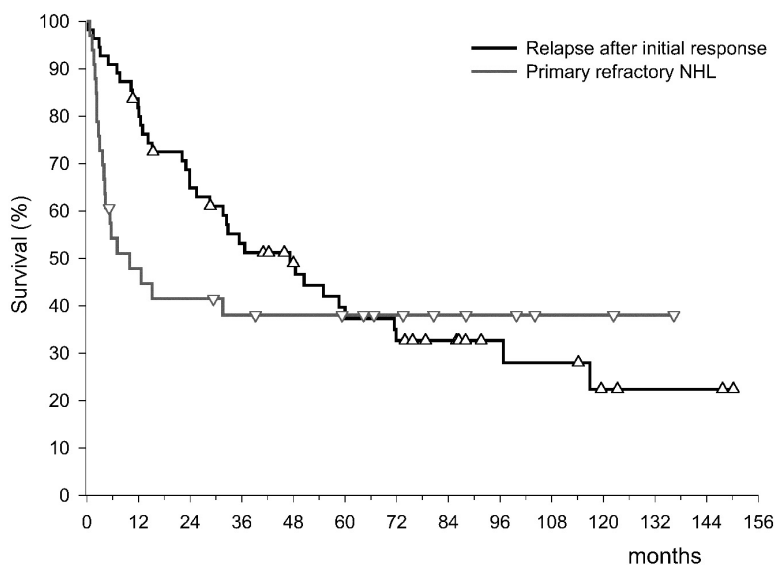


Figure 2. **Overall survival of 88 patients with NHL treated with ASCT according to response to frontline chemotherapy.** 55 patients suffered from relapse after initial response; 33 patients were primary refractory to initial treatment (including progressive disease, no change and relapse within 3 months after completion of frontline chemotherapy).

Log rank test, $p = .33$; Wilcoxon test, $p = .02$ (this gives additional weight to early effects). Triangles indicate time of censoring of patients in each stratum.

Table 2. Factors of prognostic significance for overall survival and progression-free survival in chemosensitive NHL patients treated with ASCT.

Progression-free survival Risk factor	Univariate*			Multivariate		
	HR	95% CI	P	HR	95% CI	P
WHO PS (0-1 vs. 2-4)	2.5	1.4-4.4	<.01	1.9	1.1-3.3	.03
Stage (I-II vs. III-IV)	1.7	0.9-3.1	.08			.16
LDH > ULN	1.8	1.1-3.1	.03	1.8	1.0-3.2	.04
saa-IPI 0	1.0		.04**			
saa-IPI 1	1.1	0.5-2.5		1.1	0.5-2.5	.85
saa-IPI 2	2.0	0.9-4.1		2.0	0.9-4.2	.07
saa-IPI 3	3.0	1.2-7.6		3.0	1.2-7.6	.02

Overall survival Risk factor	Univariate*			Multivariate		
	HR	95% CI	P	HR	95% CI	P
WHO PS (0-1 vs. 2-4)	2.5	1.4-4.4	<.01	2.3	1.3-4.0	<.01
Stage (I-II vs. III-IV)	1.7	0.9-3.1	.08	1.4	0.7- 2.5	.3
LDH > ULN	2.3	1.4-4.0	<.01	2.3	1.3-4.1	<.01
saa-IPI 0	1.0		<.01**			
saa-IPI 1	1.6	0.7-4.0	.03	1.6	0.7- 4.0	.2
saa-IPI 2	3.1	1.4-7.0	<.01	3.1	1.4-6.9	<.01
saa-IPI 3	4.2	1.6-11.2	<.01	4.2	1.6 -11.2	<.01

* Only factors $p < .1$ are shown; ** Composite IPI variable.

WHO PS = WHO performance score; saa-IPI = secondary age-adjusted International Prognostic risk Index; ULN = upper limit of normal.

Discussion

The results presented in this study confirm that the secondary aa-IPI at relapse is the most important factor for outcome in chemosensitive NHL patients treated with high-dose chemotherapy followed by ASCT, and this may even be the case irrespective of histologic type. This implies that one should wonder whether ASCT is a good option for patients with two or three adverse factors at the initiation of salvage chemotherapy, even in case of chemosensitive disease. On the other hand, as our data and those of others⁹ show, patients with low risk (no adverse factors) and chemosensitive disease have an excellent chance for prolonged survival and even cure after ASCT.

In the analysis of patients included in the PARMA trial, the saa-IPI correlated well with response and OS for all patients initially included. However, after ran-

domisation, including only chemosensitive patients, the IPI at relapse had lost its predictive significance in the group of 54 patients subsequently treated with high-dose chemotherapy and ASCT. This was attributed to the survival benefit of ASCT in patients with IPI intermediate and high-risk.⁷ However, relatively few patients in that study had poor risk features, as only four patients had high and 14 had high-intermediate risk profiles. This might explain why no significant difference was observed. The fraction of saa-IPI poor-risk patients in our study and that of Hamlin et al.⁹ was larger.

In the PARMA trial an analysis was made by dividing patient groups in early and late relapse, using a cut-off of one year after first-line treatment. Time to relapse less or more than one year after first-line treatment was of independent prognostic value for survival in patients with relapsed NHL.¹⁵ We did not observe a survival difference between patients with early or late relapse.

We treated 33 primary refractory patients with ASCT who were still sensitive to second-line chemotherapy. Although it is generally assumed that only a small subset of primary refractory patients benefit from ASCT,¹⁶ this treatment modality is more widely applied than in the past.^{9,17,18} Our data support the notion that primary refractory patients should be offered ASCT, provided they have a fair saa-IPI status at initiation of second-line chemotherapy and show evidence of chemosensitive disease at subsequent treatment.

ASCT was applied in 16 chemosensitive patients with relapsed follicular lymphoma and eight patients with follicular lymphoma transformed into DLBCL, resulting in OS similar to *de novo* relapsed DLBCL. Although ASCT offers improved OS and PFS compared with conventional therapy in patients with relapsed follicular lymphoma,¹⁹ data of ASCT in transformed lymphoma are sparse. The recent study of Hamlin et al.,⁹ which focused on DLBCL, also included transformed follicular lymphoma or discordant lymphoma patients. Although a separate analysis on the outcome of these subgroups was not presented. Chen et al.²⁰ reported a median survival of 58 months from histological transformation in 35 patients with transformed lymphoma treated with ASCT and a 5-year overall survival rate of 37%. Although lead-time bias must be considered, this prolonged survival appears significantly better than the median survival rates of less than one year for transformed lymphoma patients treated with conventional chemotherapy.²⁰ The European Bone Marrow Transplantation registry reported on 50 patients with transformed lymphoma treated with ASCT with a 5-year OS of 51%. In concurrence with our data, no difference in survival was observed when comparing matched patients with low-grade or *de novo* high- or intermediate grade lymphoma.²¹ Taken together, these data suggest that patients with chemosensitive transformed follicular lymphoma *and* a favourable saa-IPI profile, might benefit from ASCT.

The overriding impact of saa-IP on outcome was evident in all histological subgroups, even those with relatively small numbers of patients. For instance, of twelve patients with relapsed mantle cell lymphoma, six remained disease-free; five of those had saa-IP score 0-1. Of twelve patients with peripheral T-cell lymphoma all 3 patients with saa-IPI score 0-1 remained disease-free, while 7 of 9 patients with saa-IP 2-3 progressed.

In conclusion: saa-IPI is one of the most important predictive factors for outcome of ASCT in patients with relapsed or primary refractory NHL who are still sensitive to reinduction chemotherapy prior to ASCT. This holds true not only for patients with DLBCL, but also for other categories, such as (transformed) follicular lymphoma. Patients with zero or one adverse factor have an excellent long-term outcome, whereas patients with two or three adverse factors – despite chemosensitivity upon reinduction chemotherapy – have such a poor prognosis that additional or other therapy is warranted.

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5.2

Predictive value of early ^{18}F -fluorodeoxyglucose positron emission tomography in chemosensitive relapsed lymphoma

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¹⁸F-fluoro-deoxyglucose (FDG) positron emission tomography (PET) might be a better tool than computer tomography (CT) in predicting long-term treatment outcome in patients with relapsed chemosensitive lymphoma who are candidates for autologous stem cell transplantation (ASCT).

We studied patients with recurrent or persistent aggressive Non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD), who were treated with three courses of second-line induction chemotherapy (DHAP-VIM-DHAP), followed by myelo-ablative therapy and ASCT if chemosensitive. FDG-PET was performed in parallel to conventional diagnostic methods before start, and after two courses of second-line therapy.

Of 68 relapsed lymphoma patients, 46 chemosensitive patients (33 NHL and 13 HD) were included of whom 39 were transplanted. After DHAP-VIM, the second PET scan was normalised in 15/46 patients; PFS at 2 years was 62% for PET-negative patients versus 32% for PET-positive patients ($p=0.048$). The relative risk for progressive disease in patients with <90% intensity reduction was 2.85 (95% CI: 1.15-7.05, $p=0.018$).

Early FDG-PET may help to predict long-term treatment outcome of ASCT in chemosensitive patients with relapsed lymphoma and identify those patients who need extra or alternative treatment. Disappearance or >90% reduction of intensity of abnormal FDG-uptake after two courses of re-induction therapy was correlated with a favourable outcome.

Introduction

Although a substantial number of patients with aggressive lymphoma may achieve a complete remission after CHOP-like chemotherapy, 40% will relapse within 1-2 years after treatment.¹ Patients with relapsed lymphoma are frequently offered intensive chemotherapy with autologous peripheral stem cell transplantation (ASCT) if the tumour is still responsive to second-line chemotherapy. Unfortunately, approximately half of those responding patients will relapse after ASCT, resulting in an overall survival in relapsed patients treated in this way of only 25-30% at 2 years.² Thus, a substantial number of patients are exposed to intensive treatment with a high degree of morbidity but with limited success. Therefore, it would be useful to have better tools to predict which chemosensitive patients might ultimately benefit from ASCT.

Previous studies have demonstrated that computer tomography (CT) has a low accuracy in predicting therapy outcome in patients with malignant lym-

phoma. A substantial number of patients with a residual mass on post-treatment CT will not relapse. The diameter of the residual mass on CT has been shown not to be predictive.^{3,4} Gallium scintigraphy combined with single-photon emission computerized tomography (SPECT) has a better predictive value than CT. In a study comparing gallium with CT scanning in patients with first-line treatment for malignant lymphoma, 73% of the patients with a positive gallium scan relapsed, whereas only 35% of the patients with a positive CT scan relapsed.⁵ The overall sensitivity of a gallium scan is high; however, its usefulness in abdominal regions is limited as a result of bowel excretion of the radionuclides.

Recently, FDG-PET (positron emission tomography, using ¹⁸F-fluorodeoxyglucose as a tracer) has been introduced for staging^{6,7} and therapy response monitoring in lymphoma patients.⁸⁻¹¹ Retrospective studies in newly diagnosed patients with non-Hodgkin's lymphoma (NHL) have shown that FDG-PET can be predictive for progression free survival (PFS) and overall survival (OS) after two to five cycles of CHOP chemotherapy. Patients who showed disappearance of abnormal FDG-uptake had a significantly better PFS and OS than patients with persisting abnormal FDG uptake after a limited number of CHOP cycles,¹² as well as after induction therapy before up-front autologous stem cell transplantation.¹³ Becherer et al.¹⁴ presented the results of 16 lymphoma patients, suggesting that an abnormal pretransplantation PET might predict relapse after ASCT.

In view of these results, we studied the predictive value of FDG-PET in patients with relapsed chemosensitive lymphoma in the early phase of second-line chemotherapy before ASCT.

Our results demonstrated that the disappearance of lymphoma lesions on early FDG-PET correlates with a favourable outcome.

Patients and methods

Patients and treatment

Between January 1999 and January 2002, consecutive patients with histologically proven relapse or progression of either aggressive NHL after or during CHOP-like therapy (cyclophosphamide, adriamycin, vincristin and prednisone),¹ or Hodgkin's disease failing first-line ABVD therapy (adriamycin, bleomycin, vinblastin and dacarbazine),¹⁵ or MOPP/ABV therapy (mechlorethamine, oncovin, procarbazine, prednisone, adriamycin, bleomycin and vinblastin),¹⁶ were eligible for this study. A reference pathologist from our lymphoma working group confirmed the histology of all biopsies. All included patients gave informed consent. The medical ethics committee of our hospital approved the protocol.

After conventional restaging, patients were treated with second-line chemotherapy consisting of DHAP-VIM (dexamethasone, cytarabine, cisplatin)

followed by etoposide, iphosphamide and methotrexate).¹⁷ Patients who were responsive to DHAP-VIM, based on conventional diagnostic methods, were subsequently eligible for a second DHAP course with stem cell mobilisation followed by BEAM (carmustine, etoposide, cytarabine and melphalan) therapy and ASCT.¹⁷ These chemosensitive patients were included in this analysis. All patients had a follow-up of at least 6 months after ASCT.

Positron Emission Tomography

Whole body FDG-PET was performed before and after treatment with DHAP-VIM. The subjects received 400 MBq FDG intravenously and were scanned from the mid-thigh to the crown upwards, starting 90 minutes after injection. Time per bed position was 8 minutes. Interleaved protocol (ETTE) scans were used to correct for attenuation of the FDG signal in most but not all patients.

We used two scanners with an axial FOV of 10.8 cm and a 6 mm resolution (ECAT model 951/31, Siemens/CTI, Knoxville, TN, USA) respectively 5.4 cm and 5 mm resolution (ECAT EXACT HR+, Siemens/CTI, Knoxville, TN, USA). The majority of patients were scanned on the latter machine. Data were reconstructed iteratively into coronal, sagittal, and transverse sections and a three-dimensional rotating maximum intensity projection using standard ECAT software. FDG was synthesised according to Hamacher et al.¹⁸ by a computer controlled-synthesis module. The number of abnormal lesions (visual assessment), the volume of the largest lesions and the intensity of the largest lesions were assessed at each scan using manually set regions of interest. Because of the lack of attenuation corrected data in a number of patients we did not use standard uptake values, but tumour/non-tumour ratios instead. Intensity was assessed using a tumour/non-tumour ratio: the number of counts per abnormal region were compared with those in four standard regions of upper and lower extremities (Intensity-ratio = $(\text{Intensity}_{\text{tumor}} - \text{Intensity}_{\text{background}}) / \text{Intensity}_{\text{background}}$).¹⁹

PET results were evaluated in three ways: persistence of abnormal FDG-lesions after DHAP-VIM (visual analysis), reduction in volume and reduction in intensity compared to the PET scan before treatment.

Computer tomography

CT scans were performed in parallel to FDG-PET scans (at diagnosis of relapse/progression of lymphoma and after 2 courses of induction chemotherapy), allowing a maximal interval of 2 weeks between the two diagnostic methods. CT scanning was performed after oral and intravenous contrast. Slice thickness varied from 0.5 cm in the neck region to 1.0 cm in thorax and abdomen.

The number of enlarged lymph nodes was counted and the diameter of the largest lesions was measured in two perpendicular dimensions. After restaging, remission status was assessed, using standardised response criteria according to the International Working Group recommendations.²⁰

Statistics

The aim of this study was to evaluate the value of FDG-PET in assessing progression free survival for responding patients after second-line chemotherapy who were subsequently treated with myelo-ablative therapy followed by stem cell reinfusion. Time to progression was calculated from the date of the second PET scan until progressive disease was documented. Progressive disease was defined as tumour progression according to the International Working Group recommendations.²⁰ For PFS, events were defined as progressive disease or death from lymphoma.

PFS was calculated using Kaplan-Meier analysis, and comparison between groups was performed using a log-rank test. The predictive value of CT and FDG-PET was determined by a Chi-square test and expressed as relative risk. A P value smaller than 0.05 was considered to be statistically significant. Data analysis was performed using the SPSS 10.0 software packet (SPSS, Chicago IL, USA).

Results

Between January 1999 and January 2002, a total of 68 consecutive patients were treated for relapsed or refractory lymphoma in our department. Fifty-five patients consented to participate in our study. Eighty-four per cent of the patients had chemosensitive disease based on conventional diagnostic methods and were included in the analysis: 33 patients with NHL (64% diffuse large cell B-cell lymphoma) and 13 with HD. The patient characteristics are shown in Table 1. The median age was 52 years (range, 21 to 65 years). One patient had progressed during first-line chemotherapy. The other 45 patients had relapsed after first-line therapy with a median disease-free interval between first-line chemotherapy and relapse of 6 months (1-172 months). At relapse or progression, 63% of the patients presented with stage III-IV disease. Lactate dehydrogenase (LDH) was increased in 21 out of 46 NHL patients.

Table 1. **Characteristics of patients with chemosensitive relapsed lymphoma.**

Characteristic	#Patients (N=46)	Median (range)
Sex (male/female)	29/17	
Age (years)		52 (21-65)
Resistant disease (n)	1	
Recurrent disease (n) with DFI (months)	45	6 (1-172)
HD	13	
NHL	33	
- DLBCL	23	
- MCL	5	
- FL grade III	2	
- PTCL	2	
- ALCL	1	
Stage at relapse		
- I and II	17	
- III and IV	29	

HD = Hodgkin's disease; NHL = non-Hodgkin's lymphoma; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; FL = follicular lymphoma; PTCL = peripheral T-cell lymphoma; ALCL = anaplastic large (T-)cell lymphoma; DFI = disease-free interval between last treatment and relapse.

Treatment and outcome

After two courses of induction chemotherapy (DHAP-VIM), 46 patients had responsive disease according to conventional diagnostic methods and were selected for a second DHAP course with stem cell mobilisation followed by BEAM and ASCT. Forty-four patients received the second DHAP course; two patients did not receive the second DHAP course because of heart failure (n=1) and failure to collect stem cells (n=1). Of the 44 patients who received the second DHAP course, five showed clinical signs of progression before transplantation after the second DHAP course. They received palliative treatment or other rescue treatments. The seven patients who went off protocol were considered as failures in the PFS analysis.

Ultimately, 25/46 (54%) patients progressed (3/13 HD and 22/33 NHL patients). Median time to progression was 5 (range, 1-16) months. Median follow-up for those who did not progress (n=21) was 24 (8-43) months after the second PET scan.

CT and outcome

Because we selected chemosensitive patients on the basis of conventional diagnostic methods, all CT responses after DHAP-VIM demonstrated at least a

50% reduction of lymphoma lesions. Residual masses after DHAP-VIM were found in 33/46 (72%) of the patients. However, the presence of residual mass did not correlate with outcome after ASCT: median PFS for patients with a residual mass was 20 months versus 18 months without a residual mass (not significant, NS).

PET and outcome

A visual assessment of PET response identified persistent abnormal FDG uptake after DHAP-VIM in lesions previously shown to be involved by lymphoma (PET-positive) in 31/46 (67%) patients. Twenty (65%) of these 31 PET-positive patients showed progressive disease after PET. In 15/46 patients, all abnormal lesions disappeared (PET-negative). Five (33%) of the PET-negative patients progressed during follow-up. At the time of writing, 11 PET-positive (35%) and 10 PET-negative patients (66%) are still in remission after a median follow-up of 20 months. Persistence of abnormal FDG-uptake correlated with poorer prognosis. PET-positive patients had a relative risk of 2.59 (95% CI: 1.01-6.90, $p=0.048$) for progressive disease. The PFS at 2 years was 32% (95% CI: 15-48) for PET-positive patients versus 62% (95% CI: 36-88) for PET-negative patients (Figure 1).

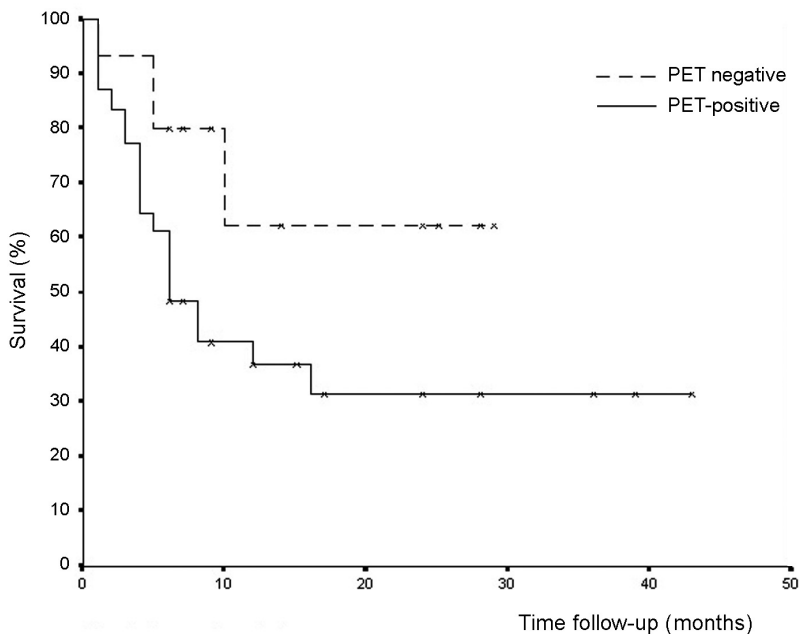


Figure 1. **PET-positive and PET-negative patients and PFS in 46 chemosensitive relapsed lymphoma patients.** Kaplan-Meier curve showing cumulative progression free survival (PFS) of 15 PET-negative patients and 31 PET-positive patients (RR 2.59, 95%CI 1.01-6.90, $p=0.048$).

To determine whether additional PET characteristics were of importance for long-term PFS, the reduction in tumour volume and intensity of PET scans after DHAP-VIM were investigated in 40/46 patients. The remaining six patients could not be assessed because of the absence of a pre-treatment PET scan.

A reduction in tumour volume of less than 90% was observed in 16/40 patients. Eleven (69%) of those 16 patients showed progressive disease versus ten (42%) of the 24 patients in whom the PET scan showed more than 90% volume reduction. Overall PFS analysis showed no significant difference between these two groups.

The reduction in intensity was less than 90% (median reduction of 27%) in 19/40 (48%) patients. Fourteen (74%) of these 19 patients relapsed versus 7/21 (33%) for patients in whom the PET scan showed intensity reduction. The relative risk for progressive disease in patients with less than 90% intensity reduction was 2.85 (95% CI: 1.15-7.05, $p=0.018$, Figure 2). The PFS at 2 years was 25% (95% CI: 6-45) for patients with an intensity reduction of <90% versus 62% (95% CI: 39-84) for patients with an intensity reduction of 90% or more.

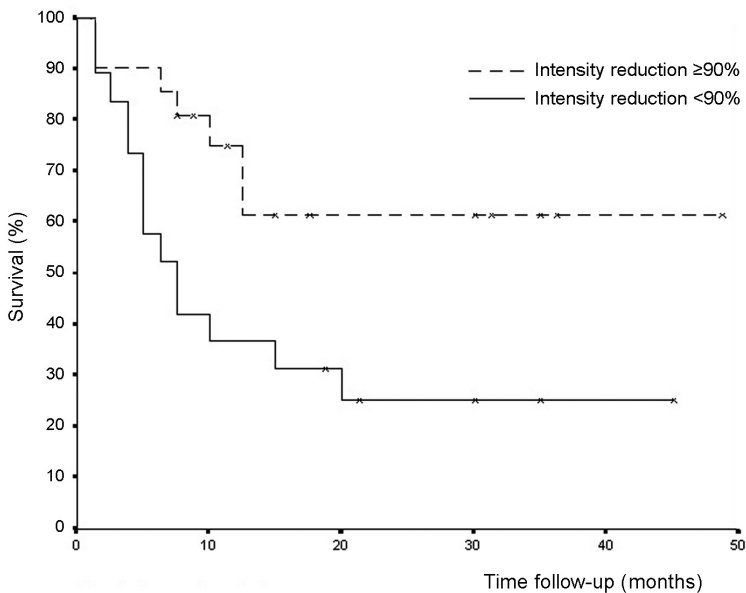


Figure 2. **PET intensity reduction and PFS in 40 chemosensitive relapsed lymphoma patients.** Kaplan-Meier curve showing cumulative progression free survival (PFS) of 21 patients with an intensity reduction of 90% or more and 19 patients with an intensity reduction of less than 90% (RR 2.85, 95%CI 1.15-7.05, $p=0.018$).

Discussion

In the present study, we assessed the predictive value of early FDG-PET for PFS in patients with relapsed chemosensitive lymphoma. Conventional diagnostic methods are not very accurate for the selection of patients who would benefit from highly intensive treatment. The results of our study demonstrate that early FDG-PET may be a better tool for predicting long-term treatment outcome in these patients. Three different methods have been used to evaluate PET responsiveness in conjunction with outcome in terms of PFS. Disappearance of abnormal FDG uptake or more than 90% intensity reduction after two courses of induction chemotherapy correlated with favourable outcome, whereas reduction of PET volume did not correlate with outcome. As not all PET scans were attenuation corrected, we were not able to assess standardised uptake values (SUV) of the abnormal lesions. Reliable intensity assessments were made using standardised tumour/non-tumour ratios. Metabolic changes after chemotherapy have been shown to precede volume reduction of the tumour.²¹ In view of this, our findings may be interpreted as result of early tumour viability reduction occurring before shrinkage of the enlarged lymph node.

Timing of PET is essential for the interpretation of the FDG uptake. Shortly after their administration, chemotherapy, radiotherapy and haematopoietic growth factors (such as granulocyte colony stimulating factor (G-CSF)) may influence the PET scan.²¹ Chemotherapy may suppress FDG uptake (so-called 'flare' phenomenon). Radiotherapy administered shortly before scanning may lead to increased FDG uptake due to local inflammation,²² and use of haematopoietic growth factors may lead to increased FDG uptake in spleen and bone marrow.²³ In our study, a window of three weeks between chemotherapy course and PET was used, while G-CSF was not used before PET scanning.

The second PET evaluation was planned in parallel to conventional diagnostic procedures after two courses of reinduction chemotherapy. This time point is conventionally used for clinical assessment of response. Non-responding patients will not be treated with ASCT and usually will be offered rescue or alternative treatment options at this time point. We do not know whether timing of the PET scan shortly before myeloablative therapy would have led to an even better correlation with outcome. For reasons of patient management, PET scanning just before myeloablative therapy would be unsuitable as a tool of selection. Römer et al.²⁴ showed a continuing decline of FDG uptake from day 7 until day 42 in patients with newly diagnosed lymphoma treated with CHOP-like therapy. Kostakoglu et al.²⁵ stated that FDG-PET after 1 cycle of chemotherapy is better for predicting outcome than post-treatment scanning in lymphoma patients. This again means that chemosensitivity proven by normalisation of FDG-uptake is an important prognostic factor for outcome, which can be useful early during

treatment. At the moment there are few data available addressing this issue in relapsed lymphoma. In keeping with our results, PET scanning within 8 weeks before transplantation appeared to be highly predictive for relapse-free survival in a study of 16 patients with relapsed or non-responsive lymphoma.¹⁴

The predictive value of FDG-PET might be different for Hodgkin's lymphoma and non-Hodgkin's lymphoma, as these are distinct disease entities. In our study only 23% of the patients with Hodgkin's lymphoma relapsed versus 67% of patients with NHL. FDG-PET showed excellent correlation with PFS especially in HD patients. None of the HD patients with normalisation of the PET lesions relapsed after transplantation.

The results presented indicate that PET is a promising tool during the treatment of relapsed lymphoma patients. Patients with a negative PET scan after two courses of re-induction chemotherapy have an excellent outcome after ASCT. This mid-treatment PET scan can be used not only as a predictor for long-term treatment outcome after ASCT, but also to identify patients who may need other or additional therapy.

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