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Original article

Index of pretreatment intensity predicts outcome of high-dose chemotherapy and autologous progenitor cell transplantation in chemosensitive relapse of Hodgkin's disease

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Summary

Purpose: To identify prognostic factors in patients with chemosensitive relapsed Hodgkin's disease treated by high-dose chemotherapy with autologous progenitor cell transplantation (HDC) and to compare the duration of treatment-free remission prior to HDC with the progression-free survival after HDC in individual patients.

Patients and methods: Forty-five consecutive patients were analyzed retrospectively. We devised an index of pretreatment intensity (IPTI) based number of different chemo- and radiotherapy regimens given between diagnosis and HDC and on the duration of disease.

Results: With a median follow-up of 47 months the post-transplant event-free survival (EFS) was 44% and the overall survival (OAS) was 62% at four years. The IPTI allowed to discriminate between a low and a high-risk group with a four-year post-transplant EFS of 66% and 11% and a OAS of 87% and 28%, respectively (P = 0.0001). Of the 39 patients with sufficient follow-up after HDC, post-transplant EFS lasted on average $\geqslant$18.5 months longer than the pretransplant treatment-free remission.

Conclusions: HDC with the CBV regimen confers significant benefit to patients with chemosensitive relapsed Hodgkin's disease. The IPTI may help to select patients with a good response to HDC and to identify poor prognosis patients suitable for experimental protocols or palliative care only.

Key words: ABMT, high-dose therapy, Hodgkin's disease, PBSCT, prognostic factor

Introduction

High-dose chemotherapy and autologous progenitor cell transplantation (HDC) has gained wide acceptance for patients with a relapse of Hodgkin's disease after adequate systemic therapy [1–3]. The only randomized trial [4] comparing conventional dose with HDC had to be terminated early because of a significant advantage for the high-dose arm and the unwillingness of patients to accept conventional therapy. Because of the current impossibility for further randomized studies, alternative methods to determine a possible benefit of HDC need to be developed. Yuen et al. [2] demonstrated a superior event free survival with HDC compared to conventional salvage therapy using a matched case control study. An alternative way would be to compare the evolution of the disease prior to and after HDC for each individual patient. Progression-free survival tends to become shorter after each successfully treated relapse. Progression-free survival after HDC lasting longer than the last treatment-free remission prior to salvage therapy would therefore indicate a benefit of HDC.

Beside looking for a potential benefit of HDC it would also be important to identify patients for whom HDC is ineffective and thus could be treated with new experimental approaches or palliative therapy only. So far, no widely accepted parameters to identify risk groups exist. Conventional risk factors as determined at initial presentation or at relapse do not seem to significantly influence the post-transplant course of disease [5–7]. Many such factors have yielded prognostic power only in a minority of the studies. Horning et al. [3] and Reece et al. [8] described different risk scores using the presence or absence of several factors to identify a good prognosis group. However, the patients of the poor prognosis group still had a progression-free survival of 41% at four years in one study [3]. The ability to ever achieve a complete remission [5] is a notoriously soft endpoint, since it is influenced by the stringency of response evaluation. The number of pre-transplant chemotherapy regimens [9, 10] and duration of the last treatment-free pre-transplant remission [2, 11, 12] have not been found relevant in all studies. After failing to identify disease related prognostic factors in our patients with often multiple chemosensitive relapses of Hodgkin's disease treated with HDC, we hypothesized that survival after HDC might depend on the aggressiveness of the disease, which might be best reflected by an index of pretreatment intensity (IPTI) based on the number of chemotherapy or radiotherapy regimens before HDC *and* the time elapsed from the first therapy to HDC.

Patients and methods

Patient selection

From May 1987 to August 1996, all patients aged 16–60 years with histologically or cytologically proven relapsed Hodgkin's disease were evaluated for inclusion into our study of HDC with autologous progenitor cell support, on the condition they had relapsed after at least one anthracycline-containing chemotherapy regimen, i.e., either after ABVD, alternating MOPP/ABVD, hybrid MOPP-ABV, or a similar regimen given for an appropriate number of cycles. To reduce the tumor volume, all patients underwent conventional salvage regimens prior to HDC. At the time of HDC patients were required to have non-bulky disease (≤ 5 cm in CT-scans) and no bone marrow involvement exceeding 5% of the total marrow. Most patients were initially treated at other institutions and referred to the participating hospitals either before or during conventional salvage therapy. Patients with severe cardiopulmonary, renal, endocrine, neuropsychiatric or infectious disease or lack of informed consent were excluded from HDC. Six patients treated during the study period were not included into the present analysis because they could not receive high-dose chemotherapy: two patients refused HDC. One of them remains in complete remission, the other relapsed with refractory progressive disease. One patient had complications from further conventional salvage therapy precluding HDC, and three patients showed refractory, progressive high-volume disease before HDC could be initiated.

Salvage chemotherapy and harvest of autologous progenitor cells

All patients with relapsed Hodgkin's disease received conventional salvage chemotherapy depending upon pretreatment and consisting either of MOPP, hybrid MOPP-ABV, ABVD, EPOCH or an anthracycline-free regimen containing streptozotocin, mechlorethamine, and DTIC developed at our institution. As soon as at least a minor response to the conventional salvage therapy could be documented progenitor cell harvest was performed, mostly by bone marrow harvest three to four weeks after prior chemotherapy. Peripheral blood progenitor cell (PBPC) were mobilized by chemotherapy and filgrastim in patients with previous pelvic irradiation, bone marrow infiltration, insufficient bone marrow harvest, and as a general policy since 1995. No purging procedures were done prior to progenitor cell retransfusion. CFU-GM counts of $> 2.0 \times 10^4$/kg or CD34+ cells of $> 1.0 \times 10^6$/kg were required.

High-dose chemotherapy, progenitor cell support, and supportive measures

The CBV regimen was used for HDC in all patients and consisted of cyclophosphamide 1500 mg/m^2 at days 1–4, etoposide 300 mg/m^2 at days 1–3 and BCNU 300 mg/m^2 at day 1. Hyperdiuresis and mesna 750 mg/m^2 at days 1–5 were used for uroprotection. Autologous progenitor cells were injected at day 8. Patients presenting with bulky disease at relapse or persistence of a residual mass of unknown dignity, received pre- or post-transplant involved field irradiation, if not precluded by previous radiotherapy. With the exception of the first two patients prophylactic cotrimoxazole was given three times weekly for three months after HDC. Fever > 38 °C was treated with antibiotics, amphothericine-B and aciclovir according to institutional guide lines. All blood products were irradiated with 1500 cGy. Leukocyte-depleted erythrocytes were given and single donor platelet concentrates were used restrictively according to published hospital guidelines [13]. The first 12 patients were treated without colony stimulating factors Thereafter, filgrastim was started the day after progenitor cell retransfusion and given until recovery of absolute neutrophil counts to $> 1.0 \times 10^9$/l for three consecutive days [14].

Risk factors, definitions of intervals and response, and statistics

Patient's charts were reviewed (by JLM or WL) and risk factors present at diagnosis and at the last pre-transplant relapse recorded. Disease duration was calculated as the time from diagnosis to retransfusion of the autologous progenitor cells. The duration of the last pre-transplant remission (PTR) was calculated from the last day of prior therapy to the day of confirmed pre-transplant relapse. Post-transplant event-free survival (EFS) was calculated from the day of progenitor cell retransfusion to either the day of confirmed relapse, death due to causes other than tumor progression or the last control. The overall survival after HDC (OAS) was calculated from the date of progenitor cell retransfusion to the date of death due to any cause or the date of the last control. Probabilities of EFS and OAS were calculated using the method of Kaplan–Meier [15]. Survival differences between subgroups were analyzed by the log-rank test. Pretransplant remission duration was compared to the post-transplant EFS by the two-tailed paired t-test.

Response evaluation prior and three months after HDC was done by CT-scans. The notoriously difficult distinction between partial remission (PR) and complete remission with residual disease of unknown significance (CRu) was pragmatically solved as follows: Patients without clinical and laboratory signs of active Hodgkin's disease and with residual masses of < 5 cm were retrospectively considered to be in complete response (CR) at the time of examination, if the residual mass remained unchanged or had decreased without further therapy at the following examinations. Any notion of tumor progression after any degree of response was used to define a relapse. Patients were evaluated clinically and with appropriate radiographic exams at regular intervals not distinct from those used after first-line therapy (approximately every three months for the first year, at least every six months for the second and third year and at least once during the following years).

Index of pretreatment intensity

To quantify the aggressiveness of disease we chose an index of pretreatment intensity (IPTI) which is based on the number of chemotherapy or radiotherapy regimens before HDC *and* the time elapsed from the first therapy to HDC. The number of regimens was defined as follows: Number of different chemotherapy regimens (No. R_{CTx}) and of temporally separated radiation therapies (No. R_{RTx}) given since diagnosis. The IPTI was calculated by dividing the number of regimens by the time elapsed from the first therapy to HDC measured in years:

IPTI = (No. R_{CTx} + No. R_{RTx})/Time (measured in fractions of years) from the date of diagnosis to the date of HDC

The cut-off values for the IPTI were modeled to best discriminate between either two or three patient groups of similar size.

As an example, a first-line regimen with MOPP-ABV hybrid (counted as one regimen) followed by a salvage regimen for relapse before HDC two years after diagnosis gives an IPTI of 1.0 ($R_{CTx} = 2$). The IPTI would rise to 1.5, if a consolidating radiotherapy to the mediastinum had been added ($R_{CTx} = 2$, $R_{RTx} = 1$) within the same time, but would drop to 0.33, had the time elapsed from the first therapy to HDC been six years with a number of two regimens. MOPP-ABV hybrid, planned sequential or alternating MOPP/ABVD or similar multidrug regimen were counted as only one regimen. However, if a patient received an adequate number of MOPP cycles and had to be treated after a treatment-free interval for relapse with the same or a different single regimen, the number of treatments was defined as 2. Irradiation with a mantle field or a mantle field with extension to involved areas including cervical or splenic lymph nodes was counted as one therapy. None of our patients received subtotal nodal irradiation, but we suggest to count such an extensive treatment as two regimens.

Table 1 Patients characteristics.

No. of patients	45
Age	
Median	34 years
Range	18–60 years
Sex	
Female	15 patients
Male	30 patients
Number of relapses prior to HDC	1 in 25 patients, 2 in 13 patients, 3- in 7 patients
No. of chemotherapy regimen prior to HDC	2 in 27 patients, 3–6 in 18 patients
Radiotherapy regimen during pretreatment	None in 12 patients, 1 in 20 patient 2 in 9 patients, 3–4 in 4 patients
Radiotherapy after HDC	6 patients (2 patients with pre-tran plant radiotherapy)
Total therapies (CTx+RTx) prior to HDC	
Mean	3.8
Range	2–9

Results

Patient characteristics

All 45 consecutive patients with relapsed Hodgkin's disease treated with HDC at our institution were analyzed. Patient demographics and therapy prior to HDC are summarized in Table 1. Including conventionally dosed salvage therapy, an average of 2.7 chemotherapy regimens (range 2–6) was given. Radiotherapy prior to HDC was given to 33 of the 45 patients. Radiotherapy was applied twice in nine patients and three or four times in four patients. Altogether the average number of regimens prior to HDC was 3.8 (range 2–9). Twenty-five patients had one relapse, 13 patients had two relapses, three patients had three relapses, and two patients each had four or five relapses prior to salvage therapy. The median duration of the last treatment-free pre-transplant remission (PTR) was 6.3 months (range 0–52 months). The median interval from diagnosis to HDC was 39 months (range 9–198 months). The median calculated index of pretreatment intensity (IPTI) was 1.12 (range 0.24–6.73). At the time of HDC 14 patients had achieved a PR and 25 patients a CR with (5) or without (20) residual mass of unknown significance of maximally 2–5 cm in diameter. Five patients had discernible signs of tumor regrowth after achieving a PR early during conventionally dosed salvage and were transplanted because they still had low volume disease as defined by our entry criteria and barely fulfilled the progressive disease criteria of 25% increase in diameter from the time of best response. These patients were termed to be refractory. The median time of follow-up from the date of progenitor cell retransfusion to the last control (cut-off date: October 15, 1996) was 47 months (range 2–104 months).

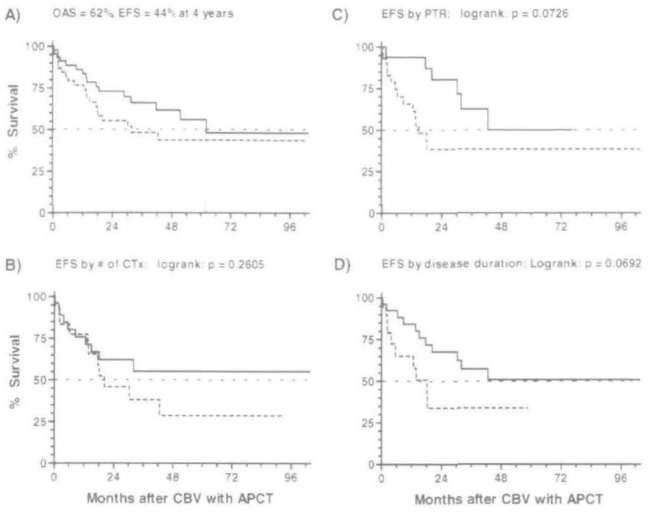

Figure 1. In *Graph A* the Kaplan–Meier estimates of post-transplant overall survival (OAS, solid line) and event-free survival (EFS, dotted line) are shown for all 45 patients with relapsed Hodgkin's disease. The median post-transplant OAS is 62.3 months, the median EFS 32.0 months. OAS at 36 and 48 months is 66.0% and 61.6% respectively. The corresponding post-transplant EFS values are 48.1% and 43.7%.

Graph B depicts the EFS for 27 patients with two chemotherapy regimens prior to HDC (solid line) and for 18 patients with three or more regimens (dotted line, P = n s.).

Graph C shows the EFS for patients with long pre-transplant remission duration (PTR $\geq$ 12 months, solid line, n = 16) or short PTR (< 12 months, dotted line, n = 29, P = 0.073).

Graph D shows the EFS for 26 patients with an interval from diagnosis to HDC of $\geq$ 30 months (solid line) and for those 19 with < 30 months (dotted line, P = 0.069).

Response to high-dose chemotherapy and early toxicity

Response to high-dose chemotherapy was assessed at three months: Twenty-five patients remained at CRu or CR, 13 patients in PR converted to CRu or CR, one patient had no change and five patients had tumor progression. One patient who did not receive prophylactic cotrimoxazole died in CR of *Pneumocystis carinii* pneumonia before hematologic recovery. All other patients had complete and timely hematologic recovery.

Survival after high-dose chemotherapy and late toxicity

The post-transplant event-free survival (EFS) at four years was 44 ± 9% and the overall survival (OAS) 62 ± 9% (Figure 1A). Seventeen patients have relapsed with and 12 patients have died of Hodgkin's disease. Three patients died of possible late toxicity, including respiratory syncytial viral pneumonia, chronic aggressive hepatitis B, and sudden death with a history of ventricular arrhythmias.

To quantify the possible merits of high-dose chemotherapy, we compared the post-transplant EFS to the last pre-transplant remission duration for each individual patient as shown in Figure 2. Six patients with no evidence of disease were not evaluable for this comparison, because their time of follow-up had not yet exceeded the duration of pre-transplant remission. In the remaining 39 patients, the median post-transplant EFS

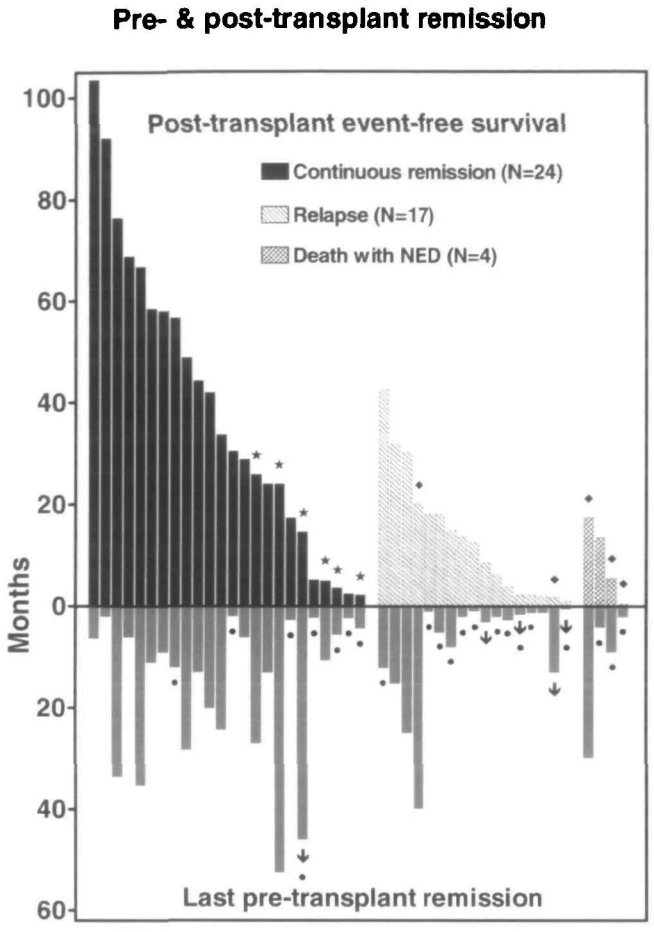

Figure 2. In this graph post-transplant event-free survival (EFS) is compared with the duration of the last treatment-free pre-transplant remission (PTR) of each patient. NED = no evidence of disease. '★' denotes the six patients in continuos CR with an insufficient follow-up, i.e., an EFS still shorter than their PTR, '◆' marks the two relapsed patients and the three patients deceased with NED and an EFS shorter than their PTR, '●' highlights the poor prognosis patients with an IPTI ⩾ 1.2, and '⬇' indicates the five patients with tumor regrowth prior to HDC. Median EFS for the 39 patients with a post-transplant follow-up longer than the PTR is 18.2 months, whereas their median PTR was 6.0 months (paired *t*-test: $P = 0.0005$).

was ⩾18.2 months comparing favorably with the median duration of the pre-transplant remission of 6.0 months ($P = 0.00005$, average: ⩾28.9 vs. 10.4 months). Thirty four patients (87%) had a post-transplant EFS that was longer than their last pre-transplant remission. The average value after subtraction of each patient's duration of the pretransplant remission from the post-transplant EFS was ⩾18.5 months (median: ⩾11.8 months). The average of the ratios of post-transplant EFS over PTR of the individual patients was ⩾ 5.4 with a median ratio of ⩾ 2.3.

Factors predicting post-transplant outcome

Tentative analysis of disease-related prognostic parameters like age, sex, histology, tumor bulk, extranodal involvement, stage, and B-symptoms at diagnosis or relapse showed no significant discriminating power in our small series of patients (data not shown). Most conventional treatment-related factors were not discriminating good and poor prognosis patients as shown in Table 2. Only patients refractory to salvage therapy did significantly worse ($P = 0.0004$). The number of pre-transplant chemotherapies failed to significantly influence post-transplant EFS (Figure 1B). Patients with a duration of the last treatment-free pre-transplant remission of ⩾12 months showed a trend for better post-transplant EFS ($P = 0.073$, Figure 1C). A disease duration from diagnosis to HDC of ⩾30 months was associated with a trend for better EFS ($P = 0.069$, Figure 1D).

The only powerful predictor of post-transplant survival was the index of pretreatment intensity (IPTI). Using a two-tier division (IPTI < 1.2 or ⩾1.2) the EFS at four years after HDC was 66% for the good risk group and 11% for the poor risk group ($P = 0.0001$) (Figure 3). Post-transplant overall survival showed a plateau at 87% for the good risk group and was 28% at four years for the poor risk group with no patient surviving more than 62 months ($P < 0.0001$). The results were practically identical, when the five patients with questionable chemosensitivity were excluded (EFS: 72% vs. 12%, OAS: 90% vs. 27%, $P \leqslant 0.0001$).

Table 2. Kaplan–Meier survival estimates and prognostic factors (univariate analysis).

Potential risk factors	No. of patients	EFS at 4 years	Log-rank test
No. of chemo- and radiation therapies > 4			
Yes	22	44%	
No	23	44%	$P = 0.6665$
No. of chemotherapy regimen > 2			
Yes	18	29%	
No	27	55%	$P = 0.2605$
Last pre-transplant remission < 12 months			
Yes	29	39%	
No	16	50%	$P = 0.0726$
Time from diagnosis to HDC < 30 months			
Yes	19	34%	
No	26	51%	$P = 0.0692$
Refractory to salvage therapy			
Yes	5	20%	
No	40	48%	$P = 0.0004$
Index of pretreatment intensity (IPTI) > 1.2			
Yes	21	11%	
No	24	66%	$P = 0.0003$
Index of pretreatment intensity (IPTI) > 1.2 (with the five refractory patients excluded)			
Yes	19	12%	
No	21	72%	$P = 0.0001$
Post-transplant event-free survival for all patients	45	48%	
Kaplan–Meier estimates of median survival for all 45 patients	Event-free survival = 32 months Overall survival = 62 months		
Follow-up since high-dose chemotherapy	Median = 47, range = 2–104 months		

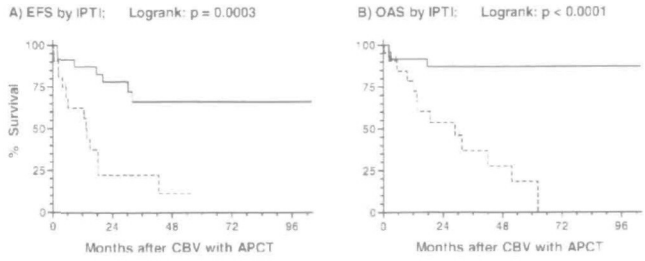

Figure 3. The Kaplan–Meier estimates of post-transplant event-free (*graph A*) and overall (*graph B*) survival are depicted as a function of the index of pretreatment intensity (IPTI). The good risk group (IPTI < 1.2, solid lines, $n = 24$) shows a significantly better survival (log-rank test $P = 0.0003$ (for EFS) and $P < 0.0001$ for OAS) than the high-risk group (IPTI ≥ 1.2, dotted lines, $n = 21$). Similar results were obtained after exclusion of the five patients with discernible signs of tumor regrowth prior to HDC ($P = 0.0001$ for EFS and $P < 0.0001$ for OAS, graphs not shown, see Table 2).

Discussion

At least since the only randomized study of high-dose chemotherapy with autologous progenitor cell support (HDC) of Linch et al. [4] the strategy of HDC has become accepted routine therapy at many centers [1–3]. Our survival data support the use of high-dose chemotherapy with CBV and progenitor cell transplantation as salvage therapy for patients with relapsed Hodgkin's disease. The OAS of 62% and the EFS of 44% at four years are similar to the findings of many other studies studies [2–5, 10, 12, 16–19]. The mortality rate of 2.2% and no death since routine use of prophylactic cotrimoxazole compares favorably with published studies. This might be attributed to the moderate dose (300 mg/sqm) of BCNU used or possibly to the faster hematologic recovery with hematopoietic growth factors and or peripheral progenitor cell support [14, 20, 21] used in 73% of the patients.

Although HDC is generally accepted for the treatment of relapsed Hodgkin's disease, its benefits need to be better defined. We attempted to do this comparing the evolution of the disease prior to and after HDC for each individual patient. Event-free survival after HDC lasting longer than the last treatment-free remission prior to salvage therapy might substantiate the benefit of HDC in this disease. In 34 of 39 patients with sufficient follow-up, the event-free survival after HDC surpasses the duration of the pretransplant remission. The ≥ 18.5 months longer duration of the post-transplant remission than the pretransplant remission duration represents a finding in support of a benefit of HDC in relapsed Hodgkin's disease.

For whom does HDC work and for whom it doesn't? It is well known that patients with progressive disease prior to HDC despite extensive conventional pretreatment do very poorly [2, 10, 12, 17, 22], a fact that can be confirmed in our series as well, since only one of the five patients termed refractory achieved a CR with a post-transplant EFS of over 12 months duration. Besides that, data concerning prognostic factors for post-transplant survival by different authors are conflicting. Factors established at the time of initial presentation rarely showed prognostic power in this setting. Our series may be too small to identify prognostic factors. On the other hand, if a factor can be found only after analysis of hundreds of patients, they may not be clinically useful because of only modest differences in survival. The duration of the first or last treatment-free pre-transplant remission (PTR) has been proposed as good prognostic factor [2, 11, 12, 22], but discriminates long-term post-transplant event-free survival (EFS) rather poorly in our series of heavily pretreated patients and would certainly not have been good enough to deny a patient undergoing HDC. An explanation can be easily found in the fact that the duration of PTR as prognostic parameter does not consider the amount of treatment required to achieve this remission. Turning to the number of different therapeutic regimes [9, 10] does not solve the problem either, because the numbers can be equally high in patients with a long history of ever relapsing and ever responding Hodgkin's disease and those with minimally responsive, rapidly progressing disease requiring frequent changes of the treatment regimen. This would be in line with the observation, that patients with a higher number of relapses did better than those with HDC after the first relapse in one study [10]. We therefore developed an index of pretreatment intensity (IPTI) taking into consideration both the number of the therapies given *and* disease duration. The proposed index can be easily calculated with the knowledge of a summary of the patient's history and quantifies the aggressiveness of the disease by our therapeutic activity to cope with it.

Using our index of pretreatment intensity one can clearly state that the CBV-regimen as used in our series of heavily pretreated patients is insufficient to really help those roughly 35% with the most aggressive disease. The EFS of our poor prognostic group is 11% at four years even for patients responsive to conventional salvage therapy. On the other hand, EFS remains at 66% after 4 years for the good prognostic group. In our hands, i.e., with our referral pattern and our mode of patient selection for HDC, the proposed index is much more powerful than any other proposed risk factor such as bulk at presentation or residual mass at HDC [3, 12], female sex [10], partial *versus* complete remission prior to HDC [22, 23], performance status [9, 11, 24] or B-symptoms [8], different locations of extranodal disease disease [3, 8, 24–26] and even age [27].

If the index of pretreatment intensity (IPTI) as proposed in our study is confirmed in larger series or among registry data, we would have an easily applicable and effective tool to identify those patients with relapsed Hodgkin's disease who benefit most from HDC and autologous progenitor cell support. Patients not likely to significantly benefit from conventional HDC could be offered new experimental programs or palliative care only.

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