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Prognosis of High Dose Chemotherapy/ Autologous Bone Marrow Transplantation Candidates not Receiving This Treatment after Failure of Primary Therapy of Hodgkin's Disease

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In a multicenter study on the therapy of Hodgkin's disease, in 88 out of 297 patients with primary advanced stages IIIB/IV, a failure to the treatment with the alternating chemotherapy COPP/ABVD ± radiation was recorded. The cause of failure was as follows: tumor progression under current therapy (PD) 23/88, partial response at the end of therapy (PR) 28/88, early nodal relapses 13/88, late nodal relapses 16/88, extranodal relapses 7/88, undetermined localization 1/88.36 months after manifestation of the failure to treatment, 45% of all patients were still alive. In cases of primary PD the prognosis was the worst of all. Only 1/23 of these patients received a long-term continuous complete remission (cCR) with the salvage therapy. 11 patients with only a nodal relapse received a cCR with irradiation alone. These cases could be regarded as low risk relapses. For the high risk relapse group (n = 57) an indication for high dose chemotherapy with subsequent autologous bone marrow transplantation (HDC/ABMT) would have been imperative, following the present-day definition. The probability of survival of these patients who, however, only received a conventional salvage therapy was up to 38% (95% confidence interval 22–54%). Comparing these data with the literature our results seem not to be substantially worse than those for patients who underwent HDC/ABMT. Only in a randomized comparison can the decision be made on whether HDC/ABMT would be superior to high dose conventional chemotherapy supported by hematopoietic growth factors. It is suggested that such a therapy study be performed as soon as possible.

KEY WORDS: Hodgkin's lymphoma relapses salvage therapy high dose chemotherapy autologous bone marrow transplantation

INTRODUCTION

Extended field-radiotherapy and the introduction of a combination chemotherapy[9,27] using substances such as mustargen oncovin procarbazine, and prednisone (MOPP) or similar regimens[2,13,47] have made it possible to cure Hodgkin's disease. The alternating application of a non-cross resistant schedule such as ABVD (adriamycin bleomycin vinblastine, and dacarbazine) has further improved the results of advanced stages.[6,24,40] A report from the International Data Base on Hodgkin's disease,[18] considering the courses of Hodgkin's disease in 14.225 patients from 15 international tumor centers from 1960 to 1988,

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Table 2 Treatment failures after CS IIIB/IV HD and COPP/ABVD ± RT as primary therapy

Patients characteristics		
	HD 3—all patients	*Treatment failures*
Age	15–60 years	16–58 years
Median	31 years	38 years
Gender m:f	196/101	58/30
Primary histology		
NS	148 (49.8%)	41 (46.6%)
MC	94 (31.6%)	29 (32.9%)
LD	19 (6.4%)	6 (6.8%)
LP	17 (5.7%)	4 (5.5%)
epitheloid.	10 (3.4%)	6 (6.8%)
unclass.	9 (3.0%)	2 (2.3%)
Initial stage		
III B	157 (52.9%)	49 (55.7%)
IV A	34 (11.4%)	5 (5.7%)
IV B	106 (35.7%)	34 (38.6%)

Table 3 Treatment failures after CS III B/IV HD and COPP/ABVD ± RT as primary therapy

Chemo-salvage therapy	
Regimens:	*Patients no.**
CCNU-etoposide-vindesine-dexamethasone (CEVD)	16
Cyclophosphamide-vincristine-procarbazine-prednisone (COPP)	12
Adriamycin-bleomycin-vinblastine-dacarbazine (ABVD)	9
Ifosfamide-methotrexate-etoposide-prednisone (IMEP)	8
CCNU-etoposide-prednimustine (CEP)	6
Adriamycin-cyclophosphamide (AC)	1
Ifosfamide-methotrexate-etoposide (IMV)	1
Methotrexate-bleomycin	1
Vindesine	1
Vinblastine-bleomycin-cisplatin	1
High dose cytarabine-mitoxantrone (HAM)	1
High dose chemotherapy + autologous BMT	3

*Double nominations possible.

Table 4 Treatment failures after CS/PS IIIB/IV HD and COPP/ABVD ± as primary therapy

Subgroups		
		n
Progression under therapy (PRO)		23
Partial remission at the end of primary therapy (PR)		28
Relapse after CR (REL)		37
Extranodal (REL-E)	7	
Early nodal relapse (REL ≤ 12 mo)	13	
Late nodal relapse (REL > 12 mo)	16	
Relapse with unclass. loc.	1	
Total		88

vere accompanying medical illnesses, or a Karnofsky index below 70%.

The probability of survival of these HDC/ABMT candidates was then evaluated from this time onwards. Estimation of the probability of survival was performed by applying the method of Kaplan and Meier. For statistical comparisons the Logrank test was used.

RESULTS

In March 1991, the treatment results of all 297 patients, treated with the HD3 protocol, were available. 88 patients failed to primary treatment. As it can be seen in Table 2, the patients with relapsed HD do not noticeably differ from the overall group of patients in the HD3 trial. 23 patients were progressing under treatment, in 28 patients only a partial response was present, and a relapse occured in 37 patients (Table 4). In the following, these cases have been designated as failures to primary therapy. The salvage therapy regimens actually applied are shown in Table 3. In 21 patients, radiation therapy alone was given. It is known that two patients have kept themselves away from a tumorspecific therapy, and that they had turned to alternative methods of therapy. High dose chemotherapy with the combinations HAM (high dose Alexan Mitoxantrone) and/or CVB (Cyclophosphamide + Vepeside + BCNU), followed by an autologous bone marrow transplantation, was performed in three patients. From the group failing to primary treatment, 33 out of 88 patients (37%) achieved a complete remission after the treatment of the relapse. The results obtained with salvage therapy are represented in Table 5. After a median follow-up of 28 months, in 22 patients a long-term ongoing complete remission could be found. A partial response was present in three patients. In 18 patients the disease was progressing. 41 patients have died. The survival curve of the overall group of failures can be seen from Figure 1. It becomes discernible that only 45% of these patients are still alive. If the patterns of failure such as tumor progression (PRO), partial response (PR) and relapse (REL) are separated, a striking difference in the survival curves are evident (Figure 2). The curve for those

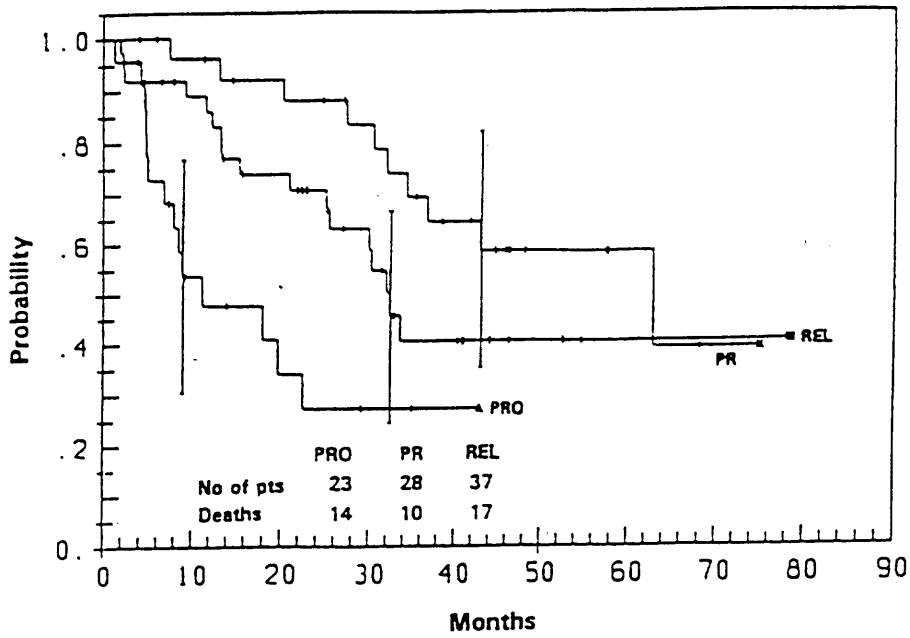

Figure 2 Treatment failures after CS IIIB/IV HD and COPP/ABVD ± RT as primary therapy. Survival after failure of primary treatment according to type of failure.

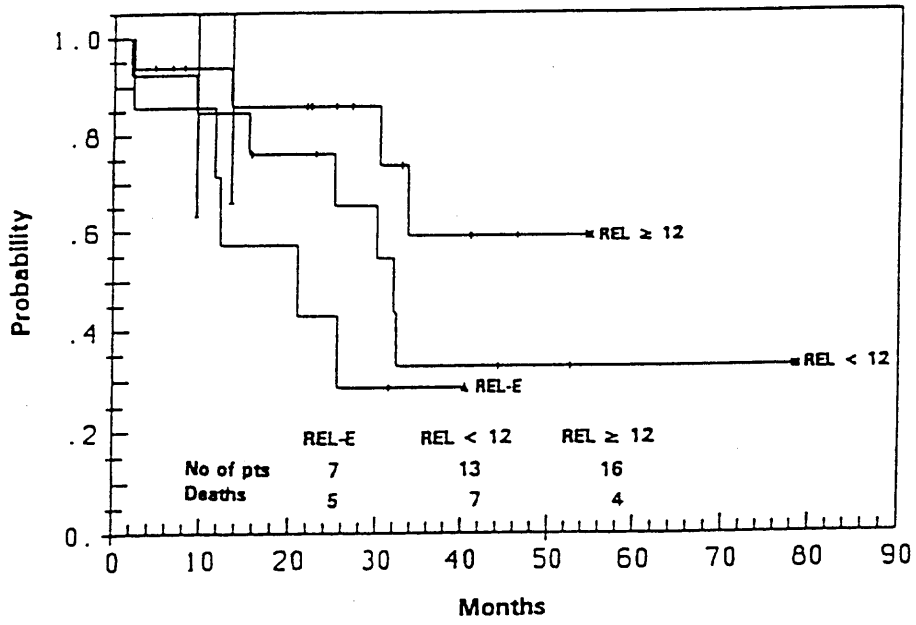

Figure 3 Treatment failures after CS IIIB/IV HD and COPP/ABVD ± RT as primary therapy. Survival after relapse as primary treatment failure.

response at the end of the initial therapy, tumor progression developed in 11 cases afterwards. These patients also have been classified as candidates for HDC/ABMT. In addition to that, relapsed patients were also included after a preceding complete remission, unless the relapse was diagnosed as an exclusively nodal recurrence which could be turned into a long-term ongoing response by radiotherapy alone.

36 patients out of 57 patients for whom the hypothetical indication was established had died at the time

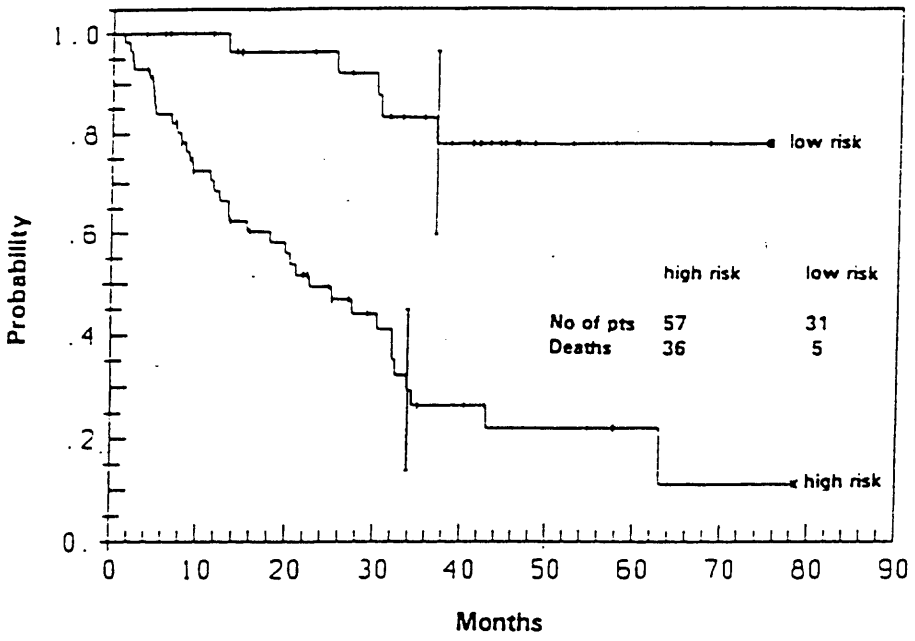

Figure 5 Treatment failures after CS IIIB/IV HD and COPP/ABVD ± RT as primary therapy. Survival of patients with treatment failures according to risk factors.

these patients only one third will achieve a complete remission under salvage therapy. In our series, the CR rate was 37%.[33,88] After a 28-months follow-up, there was a long-term ongoing CR in 22/88 patients (25%). Using CEVD combination as salvage therapy Pfreundschuh *et al.*[37] from our group published a CR rate of 44% in 32 patients. In all these cases the relapses occurred after COPP/ABVD as induction therapy.

Santoro *et al.*[40] described a complete remission in 40% of his 58 chemotherapeutically pretreated patients with relapse occurring after a combination with CCNU-Etopside-Prednisone. Hagemeister *et al.*[16] published a response rate of 23%, using the MIME scheme for MOPP-resistant relapses. Roach *et al.*[39] found that the tumor burden, measurable as stage of the relapse, is the most predictive factor for the outcome of the disease after salvage therapy. Whilst 90% of the patients with relapse stages IA and IEA achieved a second CR, at relapse stages IIA, IIEA, IIIA a CR was possible in only 60% of the cases.

Only 34% of patients with relapse stage IV with B symptoms achieved a CR. Pooling these data from the literature[11,20,26,39,42,43] it is evident that the prognosis with respect to survival is negatively influenced by the following factors: relapsed stage IV, occurrence of relapse within 12 months after completing the primary therapy carried out in conformity with standards, extranodal manifestations, age more than 45 years, progression under current treatment, bulky disease, B symptoms, poor general conditions.

According to Lohri *et al.*,[26] relapsed HD patients had a 5-year disease-free survival of only 17% in the presence of risk factors in comparison with 82% for those who did not have any risk factors. Our results (Figures 2 and 5), also show impressively how different the courses of failures may be after an initial stage IIIB and IV. Progressions under treatment are difficult to control. With conventional salvage therapy stable CR is rarely obtained. On the contrary late relapses seem to be more favorable than early or extranodal recurrences.

Moreover, the eligibility criteria for HDC/ABMT split the failures into biologically quite different groups, namely, into those with a prognostically unfavourable outcome not responding to salvage therapy (resistant relapse) and those with a therapeutically sensitive relapse. This reveals how crucial selection criteria can be. An insignificantly looking change in these criteria may already have considerable influence on the selection and the distribution of the group of patients and thus may influence survival curves without having any real underlying therapeutic effects.

Nowadays the majority of cooperative groups demand that a so-called chemosensitive relapse must be present in order to accept a patient for HDC/

patients an individualized, non-toxic, cytoreductive treatment is recommended.[32]

CONCLUSIONS

Continuous complete remission must be the aim of the initial therapy of Hodgkin's disease. If we demand cure some extent of therapy-related early and late toxicity has to be accepted. The diagnostic investigation of a relapse must be done as carefully as staging at the first disease manifestation. When a relapse is confirmed and subsequently staged the following therapeutical management is recommended:

1. Relapses, restricted to lymph nodes primarily previously not or insufficiently irradiated have a good prognosis if risk factors are absent. In this instance the treatment of choice is curative radiotherapy.
2. All other relapses are subject to a worse prognosis. As high risk patients they need intensive chemotherapy, preferably within clinical trials for HD relapses, for instance by applying the escalated conventional DEXA-BEAM scheme. Patients who respond to this therapy may undergo HDC/ABMT thereafter or continue on DEXA-BEAM. The question of whether reconstitution of the bone marrow will reveal clear-cut advantages for ABMT compared with high dose conventional chemotherapy supported by haematopoietic growth factors must be clarified in a prospective randomized study comparing these two modalities of treatment.
3. No benefit can be expected for patients undergoing aggressive systemic treatment who have a high risk relapse pattern without responding to preceding conventional chemotherapy. These patients should be treated cytoreductively in a mild manner with palliative intention, alone.

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