PROGNOSTIC VARIABLES AND RESULTS OF SALVAGE TREATMENT IN HODGKIN'S DISEASE

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Treatment results and prognostic variables were studied in 549 adult patients with Hodgkin's disease after first-line and salvage treatment. After first-line treatment, 479 out of 549 patients (87%) achieved complete remission (CR). During a mean observation time of 74 months, 99 patients (21%) relapsed. Sixty-nine patients (70% of relapsed patients) achieved a second CR. Variables predicting poor response (< CR) and shortened survival after first-line treatment were advanced disease, B-symptoms and age >60 years. In relapsing patients, age >60 years, relapse within 12 months and non-CR after relapse treatment predicted a poor prognosis, and none of these patients were alive after 10 years. Localized disease at diagnosis and relapse, and relapse later than 24 months predicted a good prognosis with 10-year survival after relapse of 68% and 57%, respectively. Patients with a second relapse had 5-year survival of 28% and 10-year survival of 14%. Based on the prognostic variables at first-line treatment and at relapse, selection of patients to more intensive treatment is discussed.

Results of salvage treatment in Hodgkin's disease depend on age, stage of the disease and the time elapsed between first-line therapy and relapse (1–8). Of patients who relapsed after radiotherapy only for stage I or II disease, 50–70% obtained complete remission (CR) after salvage chemotherapy, with durable remission in 50–70% of cases. The reported results are good even in patients with stages III and IV disease who relapsed more than one year after first-line treatment. CR rates as high as 85% are reported, with 5-year relapse-free and overall survival of 83% and 67%, respectively (7–13). In contrast, poor results are reported after salvage chemotherapy in patients with initially advanced disease who relapse within the first year after first-line treatment. In this group only 33% obtained CR with a long-term overall survival rate of approximately 10% (13).

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Variables predicting prognosis at diagnosis may be helpful in selecting patients with poor prognosis who might need more intensive treatment (14–18). Proctor et al. (19) introduced a prognostic index for selecting such patients (19–22). There is, however, no general agreement on which of the prognostic variables are the most important ones in Hodgkin's disease. Prognostic variables recorded at diagnosis are not necessarily applicable at first relapse, i.e. as predictors of second remission. We are here reporting the results of a retrospective study of prognostic variables at first-line and second-line treatment of Hodgkin's disease from a single institution covering more than 50% of Hodgkin's disease patients diagnosed in Norway between January 1980 and December 1991. The aim of the study was to present the results of relapse treatment and the criteria for selecting patients with poor prognosis to more intensive treatment.

Material and Methods

Patients

Five hundred and forty-nine consecutive adults started treatment for Hodgkin's disease at The Norwegian Ra-

Table 1

Clinical details at diagnosis in 549 patients treated in 1980–1991

	No.	%
Age groups		
15–39 years	339	62
40–59 years	112	20
60+ years	98	18
Sex: male	340	62
Histology		
Nodular sclerosis	229	42
Lymphocyte predominant	136	25
Mixed cellularity	158	29
Lymphocyte depleted	12	2
Unclassified	14	3
Initial stage		
IA	123	22
IB	13	2
IIA	130	24
IIB	47	9
All stages I and II	313	57
IIA	76	14
IIIB	52	9
IVA	25	5
IVB	83	15
All stages III and IV	236	43
Bulky disease	216	39
Observation time, months	74	(1–171)
Median age, (range)	34	(15–86)

dium Hospital between January 1980 and December 1991. The clinical details are presented in Table 1. Most of the patients were young, 339 (62%) being between 15 and 39 years, and 451 (82%) between 15 and 59 years of age. For analysis of remission rates and survival, patients <60 years were compared with the older age group. All biopsies were examined and classified according to the Rye nomenclature by one experienced pathologist (RL). Histological subgroups comprised nodular sclerosis or lymphocyte predominant type in 365 patients (67%). Three hundred and thirteen patients (57%) had stage I or II, and 236 patients (43%) had stage III or IV disease. Two hundred and thirty-six patients (39%) had bulky disease.

Staging

Staging was performed according to the Ann Arbor nomenclature for clinical staging (23). Bulky disease in the mediastinum was defined as a maximum mediastinal width greater than 1/3 of the widest thoracic diameter. Bulky disease elsewhere was defined as any tumour greater than 6 cm in its largest dimension. Computed tomography (CT) of the chest was performed when chest radiography was negative. CT of the abdomen was done routinely and if negative supplied with lymphangiography. Scan or ultrasound of the liver and spleen was performed in all patients. Diagnostic laparotomy was restricted to the very few cases of supradiaphragmatic stages IA and IIA with normal-sized retroperitoneal lymph nodes and uncertain lymphangiogram, and in patients with possible enlarged spleen. Restaging was performed after first-line treatment and at first and second relapse. The Ann Arbor classification was used for staging and response evaluation (23). Initial stage was stage at diagnosis before first treatment. Relapse stage was stage at first relapse. Patients with an undertermined complete remission were reported as CR.

Treatment

Initial stages I and II. Ninety-six patients with one of the following findings: Infradiaphragmatic disease, B symptoms, a histology of lymphocyte depletion, bulky tumour or 4 sites or more involved, received 4 cycles of combination chemotherapy before radiation to mantle or inverted Y-field. Patients without these characteristics (152 cases) received mantle field only.

Mantle field radiation therapy was given to patients with supradiaphragmatic disease with fractions of 1.8 Gy for 5 days a week to a total dose of 41.4 Gy. Standard blocks were adapted to optimize lung shielding. Since 1987 the lung shields have been made individually. No spinal blocks were used in the mediastinal part of the radiation field. Furthermore, from 1987 subcarinal blocks were adapted after 30.6 Gy if the patient had no evidence of subcarinal disease. Inverted Y-field was given to patients with infradiaphragmatic disease. Fractions of 1.8 Gy were given 5 days a week to a total dose of 41.4 Gy.

Combination chemotherapy to initial stages I and II disease consisted of 4 cycles of MVPP (mustine, vinblastine, procarbazine and prednisone, (24)), ChlVPP (chlorambucil, vinblastine, procarbazine and prednisone, (25)), ABOD (doxorubicin, bleomycin, vincristine and dacarbazine, (26)), or alternating ChlVPP/ABOD (27) before 1988. After 1988, 4 cycles of EBVP (epirubicin, bleomycin, vinblastine and prednisone (28)) were given before irradiation.

Initial stages III and IV. Eight cycles of combination chemotherapy (ChlVPP, ABOD, or alternating ChlVPP/ABOD) were given to 135 patients (57%). Chemotherapy plus involved field radiotherapy 2 Gy × 20 was given to 101 patients (43%) with bulky tumour or residual tumour after chemotherapy only. Young men with a normal sperm count and mobility were offered the opportunity to cryopreserve semen before the start of chemotherapy.

Salvage treatment. Initial stages I and II patients not obtaining CR after first-line treatment or in first relapse had combination chemotherapy with 6-8 cycles of MVPP, ChlVPP, ABVD or alternating ChlVPP/ABOD. Initial stages III and IV patients not obtaining CR or in first relapse had 8 cycles of combination chemotherapy. Most patients who relapsed after first treatment with MVPP or ChlVPP received ABVD or alternating ChlVPP/ABOD. Patients who relapsed after ABVD or alternating ChlVPP/ABOD received ChlVPP. Additional radiotherapy to the involved field was given with a dose of 2 Gy × 20 to

Table 2

Results of first-line treatment

	No.	CR%	Survival 5-year %	FF 1stR* 5-year %
Stages I-II, 15–59 years	260	94	93	84
Stages I-II, >60 years	53	83	58	83
All stages I-II	313	93	87	84
Stages III-IV, 15–59 years	191	87	80	76
Stages III-IV, >60 years	45	47	30	77
All stages III-IV	236	80	70	76
All patients	549	87	80	81

*FF1stR = Freedom from first relapse

patients with bulky tumour or residual tumour after chemotherapy.

Follow-up. The patients were routinely seen for follow-up every 3 months during the first 3 years and every 4 months during the next 2 years. Most patients were seen 2–3 times a year during the next 5 years, and later on once a year. Time to relapse was calculated from time at completion of treatment.

Statistics

The BMDP (PC/90) statistical software was used (29). The survival probabilities were calculated with the Kaplan-Meier product-limit method. The difference between the survival curves was tested by the logrank test (30). Logistic regression analysis was used to characterize those obtaining CR versus non-CR. The prognostic index was calculated using the regression coefficients derived from the Cox regression analysis.

Results

The results of first-line treatment of 549 patients are shown in Table 2. The best results are obtained in younger patients with initial stages I and II disease with a CR rate of 94% and 5-year survival of 93%. Seventy patients (13%) did not obtain CR after first-line treatment.

Of 479 patients in CR after first-line treatment, 99 patients (21%) relapsed. Biopsy of the first relapse was performed in 32 patients. In 20 patients (62%) the histologic subgroup of relapse was unchanged, and in 7 patients (23%) the relapse was unclassified Hodgkin's disease. Histological transformation from nodular sclerosis or lymphocyte predominant type to mixed cellularity or lymphocyte depleted type was observed in 5 patients (15%).

Sixty-eight patients who were treated at first-line with radiotherapy alone or combined chemotherapy and radiotherapy had relapse. Five of these relapses occurred solely within and 13 both within and outside the irradiated field. Fifty patients (74%) had relapse outside the radiation field only. The prognosis was not influenced by relapse site, as 5 years' survival after relapse was 64% and 62% respectively after relapse within or outside the radiation field.

As shown in Table 3, 12 patients relapsed during the first year after first-line treatment. These patients had similar responses to salvage therapy as patients with later relapses. The survival, however, was much shorter. Most of the relapses occurred during the next 4 years with approximately 20 relapses per year. During the first 5 years, relapses were equally distributed in old and new sites. After 5 years only 10 patients had relapsed, and all at new sites.

The results of second-line treatment in relation to initial stage and age are shown in Fig. 1. The survival was significantly shorter in advanced disease compared with

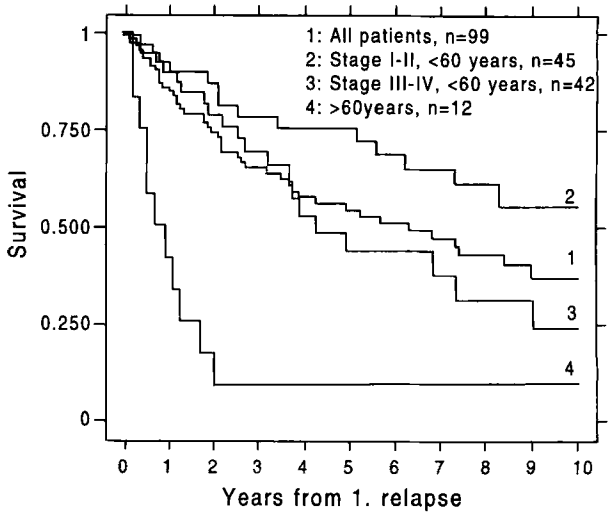

Fig. 1. Survival after first relapse in relation to initial stage and age.

Table 3

The influence of time to first relapse upon site of relapse and results of second-line treatment

Time to relapse Months	No.	Site of relapse			CR		Overall survival 5-year %
		Old	New	Old/new	No.	%	
1–12	12	6	5	1	8	67	28
13–59	77	32	33	12	53	69	59
60–	10	0	10	0	7	70	
Total	99	38	48	13			

localized disease. Patients >60 years old had generally a poor response to second-line treatment.

Non-complete responders to second-line treatment had an extremely poor prognosis, as only 8 patients (26%) were alive after 2 years and none after 5 years. Of the 70 patients who achieved a second CR, 21 patients (30%) had a second relapse. Five patients (24%) had a third CR. Overall survival after a second relapse was 28% and 14% after 5 and 10 years, respectively.

Prognostic variables at diagnosis

To study the impact of various variables for predicting prognosis at diagnosis, we included age, sex, initial stage, A/B symptoms, primary histology, mediastinal involvement, bulky disease, combined bulky disease and mediastinal involvement, ESR and haemoglobin concentration in a logistic regression analysis for all patients. The prediction variables for patients not obtaining CR and shortened overall survival after first-line treatment were advanced initial stage, B-symptoms and age >60 years. Using the regression coefficients from analysis of overall survival, a prognostic index was calculated:

Stages I-II (=1), stages III-IV (=2) × 0.45 +

B-symptoms no (=1), yes (=2) × 0.56 +

Age <60 years (=1), >60 years (=2) × 1.81.

Survival curves based on the prognostic index are presented in Fig. 2.

Prognostic variables at first relapse

As shown in Fig. 1, the prognosis for patients >60 years old after first relapse was poor with only 8% alive after 5 years. We therefore excluded patients >60 years old from further analyses of prognostic variables. The influence of initial stage and relapse stage upon overall survival is shown in Fig. 3. Patients with initial stage I or II disease had a longer overall survival after relapse if the relapse stage was I or II (5-year 83% and 10-year 68%) compared with relapse stage III or IV (5-year 58% and 10-year 29%). Patients with initial stage III or IV had shorter survival, especially if the patient had relapse stage III or IV (5-year 35% and 10-year 21%).

The influence of time to relapse upon overall survival is shown in Fig. 4. Only 9 patients <60 years old relapsed

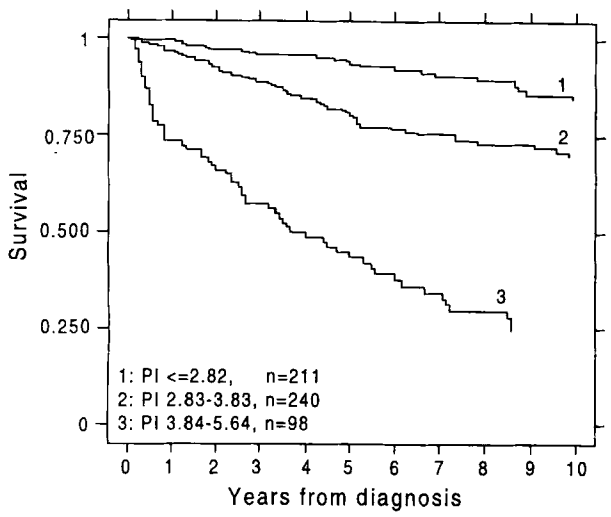

Fig. 2. Overall survival according to prognostic index based upon initial age, A/B symptoms and stage. 1. Good prognosis group. No. 211, 2. Intermediate prognosis group. No. 240, 3. Poor prognosis group. No. 98.

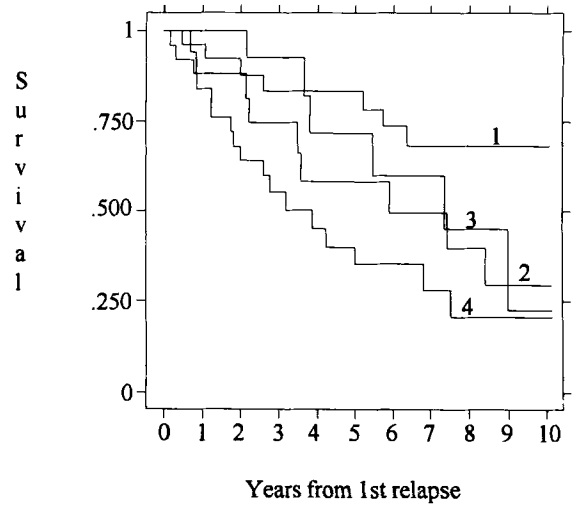

Fig. 3. Overall survival in relation to initial and relapse stage in patients aged 15–59 years. 1, Intitial and relapse stage I/II. No. 27, 2. Initial stage I/II and relapse stage III/IV. No. 18, 3. Initial stage III/IV and relapse stage I/II. No. 17, 4. Initial and relapse stage III/IV. No. 25.

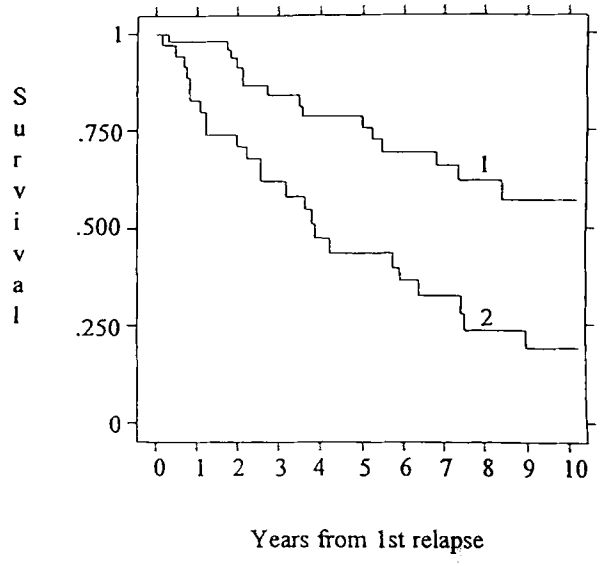

Fig. 4. Overall survival in relation to time to relapse in patients aged 15–59 years. 1. Relapse after 24 months. No. 52, 2. Relapse before 24 months. No. 35.

during the first 12 months, and none of them were alive after 10 years. We compared the survival data of 35 patients who relapsed during the first 24 months with those of 52 patients with later relapse. Patients who relapsed during the first 24 months had a significantly shorter overall survival after relapse (5-year 44%, 10-year 19%) compared with patients who relapsed after 24 months (5-year 76%, 10-year 57%) ($p = 0.0004$).

Discussion

This retrospective study supports and extends earlier results of prognosis and results of first-line and second-line treatment of Hodgkin's disease (1–21). In our study patients >60 years had a very poor outcome after first relapse. The younger patients with localized disease had a high rate of CR and a high percentage of long-term survival after second-line chemotherapy, as shown by others (1–9). In these reports, the outcome was not influenced by time to first relapse (9). In advanced disease, however, the outcome was poor if the relapse occurred during the first year after the first complete remission (10–14). In one study, Longo et al. (13) observed that half of their relapses after chemotherapy of advanced disease occurred within the first year. In contrast, we found that only 12% of the relapses occurred during the first year irrespective of stage. The CR rates did not differ in patients with an early or late relapse, but the survival was poorer in the former group. The low probability of relapse after 10 years from first-line treatment and the good prognosis at a late relapse are in agreement with other presented results (13). Non-complete responders on second-line treatment and patients with a second relapse have a very poor prognosis.

It might be important to identify patients with poor prognosis at the time of diagnosis in order to intensify the primary treatment, such as high-dose therapy with stem cell support. Such prognostic variables differ from study to study. The most commonly identified variables are the size of mediastinal tumour (16), relapse stage (17), histologic subtype (18), age, ESR and sex (19). Haybittle et al. (20) and Proctor et al. (21) have constructed a prognostic index based upon single prognostic variables. In our material, initial stages III and IV, B-symptoms and age >60 years were predictors of a shortened survival, and a prognostic index based on these variables identified groups of patients with poor, intermediate and good prognosis expressed as overall survival. Age, however, was the most important single variable identifying a good or poor prognostic group. In patients <60 years only small differences were found between the good and poor prognosis groups after first-line treatment. This is in agreement with the experience at Stanford presented by Rosenberg (7) which concludes that most of the classical prognostic variables, with the exception of age, might not be relevant for identification of poor prognostic groups in younger patients with Hodgkin's disease. It is therefore difficult to define solid prognostic variables at first-line treatment, with the exception of age, that identify patients for upfront intensive treatment with stem cell support.

In relapsing patients, it is possible, based upon the presented results, to recognize patient groups with a good and poor prognosis. Patients <60 years old with relapse after 2 years and patients with initial stage and relapse stages I and II belong to a good prognosis group with a 10-year overall survival of 60% and 70%, respectively. In contrast, patients >60 years old, non-complete responders and patients with relapse within 12 months have an extremely poor prognosis with no patients alive after 10 years. In addition, patients with a second relapse belong to this poor prognosis group. We feel that these patients should be considered for more intensive treatment programmes such as high-dose chemotherapy with stem cell support. In addition, patients <60 years old with initial and relapse stage III or IV and initial stage I or II and relapse stage III or IV have a relatively poor prognosis with 5-year survival of 35% and 58% and 10-year survival of 21% and 30%, respectively. For these patients, the results obtained with conventional treatment have to be compared with those obtained after high-dose chemotherapy with stem cell support. As stated by Armitage (31), the results of high-dose chemotherapy with bone marrow transplantation depend upon selection of patients. Actual 4-year, disease-free survival varied from 44% after only one chemotherapy regimen to 21% after 3 or more regimens. It is therefore difficult to evaluate our results of conventional treatment of relapsed stage III or IV patients against published results of high-dose chemotherapy with stem cell support. Only prospective randomized studies with patients observed for a longer period of time may give more information on the best treatment for these patients.

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