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The Prognostic Significance of Age in Patients with Advanced Hodgkin's Disease

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Abstract—*One hundred and forty-eight patients with Stage III and IV Hodgkin's disease, treated at a single institution, were studied to investigate the importance of age as a prognostic pre-study factor. The median age of the patients was* 30 (2–81). *All patients received combination chemotherapy. The overall response rate was* 85%. *The median survival is not reached with a median follow-up time of* 9.6 *years. Age was found to be the dominant prognostic discriminant with younger patients having a better survival. Factors which were significant in a univariate analysis were performance status (PS), stage, weight loss, histology and liver involvement. In a stepwise logistic regression model, however, only age and PS remained independent significant prognostic discriminants. It is concluded that even in the absence of serious concomitant disease, such as heart disease, age is the single most important prognostic variable.*

INTRODUCTION

THE MAJORITY of patients with Stage III and IV Hodgkin's disease (HD) given adequate chemotherapy are now cured. Although cure rates for patients with Stage III or IV disease are now given as 60–70% [1] there remain patients who are not cured. It is therefore particularly important to investigate the importance of disease and patient discriminants that would predict the curability of this disease.

Age has been reported to be of prognostic significance in patients with advanced HD [2–9] and to retain prognosic significance in multivariate regression models that allow for other prognostic discriminants [5]. Two major publications did not confirm a prognostic significance for age [1, 10].

A study of the importance of age as a prognostically significant pre-study factor was undertaken at the Department of Medical Oncology of the University of Pretoria.

MATERIALS AND METHODS

Data on 148 patients with Stage III or IV HD seen at the Department of Medical Oncology, University of Pretoria, from 1968 to 1986 were analyzed. All the data used in the present analysis were prospectively recorded at the start of treatment. All patients were required to have biopsy-proven Stage III or IV HD (Ann Arbor criteria) [11] with either clinical or pathologic staging. Patients had to have tumor measurable by either physical examination and/or lymphangiography, and/or X-rays, radioisotope scans and ultrasound scans. Patients had adequate bone marrow function (leukocytes more than 4000; platelets more than 100,000) except in the presence of documented bone marrow involvement. Adequate renal function was required with normal serum creatinine and urea levels. Bone marrow biopsies were performed. Patients with any serious medical condition which would preclude aggressive chemotherapy were excluded from the sudy. All patients gave written informed consent.

The median age of the patients was 30 years (2–81). Fifteen per cent of the patients were younger than 16 years, 36% between 16 and 30 years, 25% between 31 and 50 years, 15% between 51 and 65 while 9% were older than 65. Age distribution by stage of disease are given in Table 1. Sixty-two per cent were males. Seventeen per cent of patients had a performance status (PS) [12] of 0, 48% a PS of 1, 16% a PS of 2, 13% a PS of 3 while 6% had a PS of 4.

Weight loss in excess of 10% was documented in 45% of patients prior to treatment while night

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Table 1. *Age distribution within stage of disease*

Age groups	Stage III (%)	Stage IV (%)
<16	7.4	4.9
16–30	15.3	21.5
31–50	9.8	15.3
51–65	7.4	7.9
>65	3.1	7.4

sweats and fever were documented in 52% and 37% respectively. Four per cent of patients had Stage IIIA disease, 37.9% Stage IIIB while 70.8% and 47.3% had Stage IVA or IVB disease respectively. Among the Stage IV patients, 24.4% had bone marrow infiltration, 20.9% lung infiltration, 77.9% liver involvement and 16.2% other organ infiltration including meningeal, gastrointestinal and gynaecologic.

Histologic subtypes were lymphocytic predominant (11%), nodular sclerosing (32%), mixed cellularity (45%), lymphocyte depleted (9%) and unclassified (3%). The relation between the incidence of histology and age is given in Table 2.

All patients received combination chemotherapy and 17 patients received consolidation radiotherapy. The different chemotherapy treatments include: MOPP (27.7%), Bleo-MOPP (18.2%), BCVPP (19.6%), MOPP-ABVD (5.5%), BOPP (10.2%), COPP (9.5%), MVPP (4.7%), CVPP (2.7%) and OPP/COPP (2.1%).

Statistical analysis

Associations between all the above variables were investigated using the chi-square or Fisher's exact tests [13]. Survival analysis was performed using the generalized Wilcoxon (Breslow) [14] and the generalized Savage [15] tests. All variables significantly associated with prognosis as determined by the Breslow and generalized Savage tests were entered into a stepwise logistic regression model.

RESULTS

Among the 148 patients studied an overall response rate of 85% was obtained with a complete remission rate of 70%. The present median follow-up time is 9.6 years and a median survival time has not been reached with 62% of patients alive.

Investigation of the association between the different variables seen as an univariable value showed age over 50 to be significantly related to PS, histology, weight loss and response to treatment but not to sex, stage, fever or night sweats.

Using Breslow and generalized Savage models, age was significantly associated with survival with a median survival not reached in patients less than 50 years of age and a median survival of 2.7 years in patients over 50 ($P < 0.0001$). Among the 15% of patients who are between 51 and 65 years of age the median survival was 4.7 years while for the 9% of patients who were over 65 years of age, the median survival was 1.4 years (Fig. 1).

Table 2. *Histologic subtypes related to age*

Histologic subtypes	Age ≤50 (%)	Age >50 (%)
Lymphocyte predominant	9.09	14.29
Nodular sclerosing	38.84	16.67
Mixed cellularity	41.32	42.86
Lymphocyte depleted	8.26	16.67
Unclassifiable	2.48	9.52

$P < 0.003$.

Table 3. *Survival—age with single variables*

	Age groups	Median survival (years)	*P*-value Breslow/generalized Savage
Sex:			
Male	≤50	NR	<0.0002/<0.00001
	>50	2.7	
Female	≤50	NR	<0.0002/<0.0005
	>50	2.0	
PS:			
0–1	≤50	NR	<0.02/<0.009
	>50	9.1	
2–3	≤50	NR	<0.0007/<0.0001
	>50	1.1	
4	≤50	Sample size	
	>50	too small	
Stage:			
III	≤50	NR	<0.05/<0.01
	>50	7.5	
IV	≤50	NR	<0.0001/<0.0001
	>50	1.7	
Histology:			
LP	≤50	NR	<0.0001/<0.0001
	>50	1.6	
NS	≤50	NR	<0.6/<0.9
	>50	NR	
M	≤50	NR	<0.0001/<0.0001
	>50	4.1	
LD	≤50	2.0	<0.7/<0.9
	>50	1.6	
Symptoms:			
Absent	≤50	11.9	<0.6/<0.7
	>50	NR	
Present	≤50	NR	<0.0/<0.0
	>50	1.7	

NR = not reached; NS = nodular sclerosing; LD = lymphocyte depleted; LP = lymphocyte predominant; M = mixed cellularity.

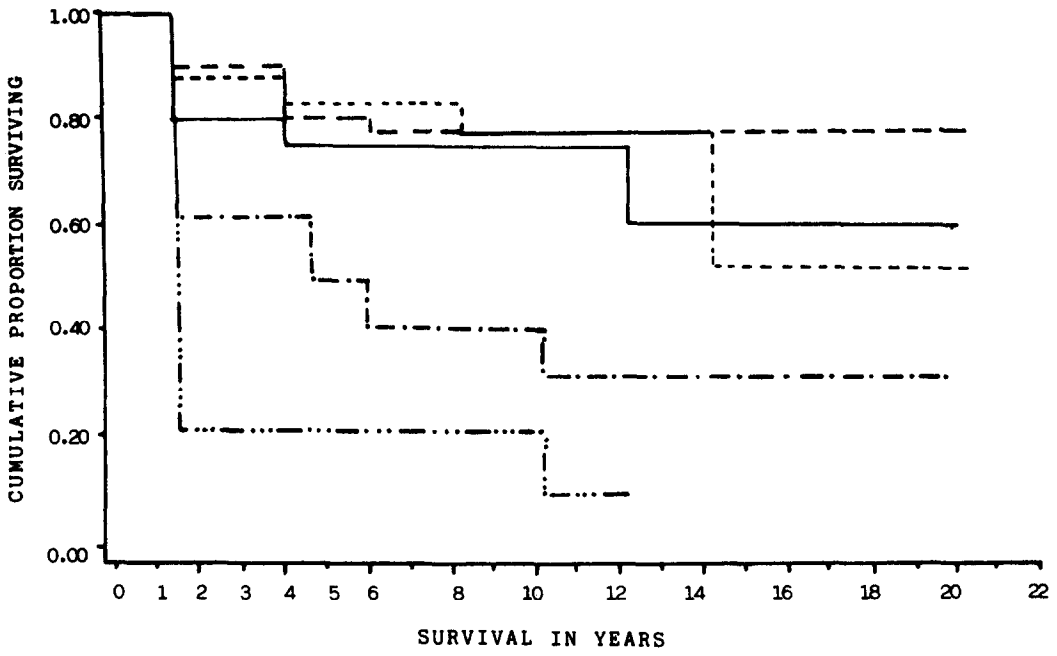

Fig. 1. *Survival by age in advanced HD.* ——— <16; - - - - - 16–30; ----- 31–50; -.-.- 51–65; -...-...- >65. $P<0.0001$.

PS, weight loss, liver involvement, stage and histology were all found separately to be significantly associated with survival, whereas sex, fever, night sweats, bone marrow, lung or other organ infiltration had no statistically significant influence on survival in this group of patients.

Using both the Breslow and generalized Savage tests the single most significant prognostic factors were investigated relative to age (Table 3): males less than or equal to 50 had a significant better survival than males over 50 years as did females less than or equal to 50 compared to females over 50 years of age.

Age under 50 was associated with a better prognosis in PS, stage of disease, histologic subtypes (except for nodular sclerosing and lymphocyte depleted) and absence of symptoms.

In a stepwise logistic regression model only two factors remained independent of significant prognostic statistical significance. Age and PS remained significant prognostic factors with patients younger than 50 having a significantly better prognosis than their older counterparts. When removing patients younger than 16 from the model, age was still significant with the older patients having a poorer prognosis. Prognosis becomes progressively poorer as age increases and patients over 60 have a poorer prognosis than those under 60, also patients above 65 have a poorer prognosis than those under 65.

PS of 0–1 remained statistically significant compared to other performance statusses ($P < 0.008$).

Although stage, weight loss, liver involvement and histology were significant on their own in predicting survival these factors lost their prognostic power in a multivariate analysis.

A dose intensity analysis was not performed in the present study as full dose was planned on all patients studied and dose modification was a *post hoc* and not a prospectively studied factor. Patients who did not do well tolerated treatment less well and had more dose modifications even though an attempt was always made to deliver optimal drug dosage.

No change was seen in prognosis by age groups over time particularly within the various age groups started treatment in 1968 and patients started treatment in 1978 have the same median survival time.

DISCUSSION

In patients with advanced HD without other concomitant diseases, combination chemotherapy is usually given with the hope of cure. Although age is usually documented in reports of treatments of patients with advanced HD, and although age is generally conceded to be of possible prognostic significance, it has received little attention in analysis.

In the present study despite a good overall response rate and a good median survival in younger patients, a poor prognosis with a less than 20% chance of cure was documented in patients over 60 years of age.

HD characteristically has a bimodal age incidence curve with one peak in early adult life and the second sustained increase in incidence in the fifth decade [5, 16–21]. In the present series of previously untreated patients with advanced disease this classic bimodal distribution was not seen, although the first peak as usually described in

early adult life did occur. The median age was 30. Twenty-four per cent were more than 50 and 12% of patients were more than 60. In the Cancer and Leukemia Group B study of age in 385 previously untreated patients with Stage III and IV HD, 53% were more than 40 and 19% were more than 60 years of age [7]. The mean age in a series from Sweden [5] was 47 and 50% of the patients with Stage III and IV disease were more than 50 years of age.

In a study of the clinical features of HD in the elderly, Lokich *et al.* [9] found that 80% of patients over 60 years of age presented with Stage III or IV disease and concluded that there appears to be a direct relationship between age and clinical extent of disease. Furthermore, 26 of these 47 patients had B-symptoms. A higher percentage of elderly patients are reported to have less favorable histologic subtypes of HD [9, 22, 23]. This higher incidence of poorer histologic subtypes is reconfirmed in the present series.

In the present series significant statistical univariate differences between patients over and under 50 included not only histology and weight loss, but also PS. The young patients having significantly better PS.

In the Cancer and Leukemia Group (CALGB) series [7] a significant difference in survival was seen with the oldest group of patients having the shortest median survival, with a median survival of 18 months for patients older than 60, 54 months for those between 40 and 59 and a median not reached for patients under 40 years of age. In the Swedish series [5], patients over 50 had a 5-year survival of 28% as compared to 74% for the remainder. In the study of Lokich *et al.* [9], the median survival for patients over 60 was 15 months for those with Stage III and 3 months for those with Stage IV disease. In the present series with a median follow-up time of more than 9 years the median survival time was not reached for patients younger than 50 while for patients between 51 and 65 it is 56 months and for patients older than 65, 15 months. The survival by age groups in the present series are therefore similar to that of the CALGB series and both groups consist of Stage III or IV patients who received combination chemotherapy.

In analyzing the long term follow-up of MOPP treated patients DeVita *et al.* [1] found that comparing patients less than 30 to those 30 or more years of age the percentage without tumor mortality was not different at either 5 or 10 years. In the ECOG study of BCVPP compared to MOPP patients less than 35 were compared to patients 35 or more years of age but there was no statistical difference [10]. No specific statement was made in either publications about patients above 60 years of age [1, 10].

Of specific importance in the current study of patients with Stage III and IV HD are the results obtained in the multivariate regression model in which the only highly significant prognostic factors were age and PS. Analysis by others have not included PS. When PS and age are taken into account, disease stage, extent of disease, constitutional symptoms and histologic subtypes ceased to be of importance.

In this study patients with serious concomitant diseases which would preclude them from receiving aggressive chemotherapy were not included. It is concluded that even in the absence of other serious diseases (which are more common in the elderly), age is the single most important prognostic measurement at the start of treatment for patients with advanced HD. The only other factor that even approaches the importance of age as a prognostic factor is PS. This finding is of clinical importance as the prognosis becomes progressively poorer as patients become older and for patients over 60 the chances of cure are significantly less than for patients in younger age groups. As the same therapeutic dose intensity was planned for patients irrespective of age, and as the criteria for dose modification was uniformly for all patients studied it would appear justified to consider investigating different treatment approaches for elderly patients with HD.

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