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Original Paper

Hodgkin's Disease in Patients Older Than 70 Years of Age: a Registry-based Analysis

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Between 1973 and 1993, 529 patients aged 15 years and over with Hodgkin's disease (HD) were entered into a lymphoma registry. Twenty-eight cases (1 only diagnosed at autopsy) of histologically proven HD in patients aged 70 years or older were identified. The distribution of sex, 'B' symptoms, histology and stage was not significantly different from that of younger patients, except for the fact that there were no patients aged 70 years or older with lymphocyte predominant HD. Nineteen patients were treated radically, 5 patients palliatively and 4 patients received no radiotherapy or chemotherapy. Three of the 14 patients treated with chemotherapy achieved the planned dose intensity. The cause-specific 5-year survival was 75% for patients aged 15–69 years and 28% for patients aged 70 years and over (logrank x^2=43.7, $P < 0.00001$). The younger and older groups treated with radical intent had complete response rates of 97% and 74%, respectively (logrank x^2=17.91, $P < 0.00001$) and relapse rates at 5 years of 27% and 56%, respectively (logrank x^2=4.86, $P = 0.0275$). The main reason for the poorer prognosis of patients aged 70 years and over was the increasing difficulty of chemotherapy delivery associated with advancing age. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

HODGKIN'S DISEASE (HD) has long been thought to have a bimodal age distribution, the first peak occurring in the third decade and the second after the sixth decade [1]. Patients presenting within the first incidence peak have a generally good prognosis. Thereafter, increasing age is associated with a progressively poorer prognosis, particularly after 50 years of age [2].

Previous studies have examined the reasons for the poorer prognosis in elderly patients with HD. Some authors have suggested that HD is in some ways a different disease in the elderly, making it less responsive to treatment [3–7]. Elderly patients with HD have been found to have a higher incidence of B symptoms, advanced stage and more aggressive histological subtypes, as well as a poor response to treatment. It has also been suggested that the immune response of the host to Hodgkin's disease is impaired in the elderly. This based on the progressive decline in T-cell function with age, which is exaggerated in those with HD. This loss of 'host-versus-disease' response may be expected to lead to an increased relapse rate of HD in the elderly [8]. Alternatively, it has been suggested that the poor response to treatment and hence the poor prognosis is due to a failure to deliver adequate treatment rather than to the disease being intrinsically different or to the immune response being impaired [9–13]. However, many of these studies were undertaken prior to the advent of immunohistochemistry, which has increased the accuracy of the diagnosis of HD, and elderly patients were defined as those greater than 50 or 60 years of age. Very little information is available about HD in patients beyond 70 years of age. As the population continues to age, the number of cases of HD presenting in the elderly will also increase. Physicians will need to be aware of the characteristics of the disease in the elderly. We, therefore, present a registry-based analysis of the character-

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istics of immunohistologically-confirmed HD in patients 70 years and over.

PATIENTS AND METHODS

All patients with a histologically-confirmed diagnosis of lymphoma occurring in the Nottinghamshire area (population 1.1 million) have been entered into a lymphoma registry without exclusion. The registry includes all patients diagnosed since January 1973. The information has been obtained from hospital records, the three departments of histopathology (University Hospital and City Hospital, Nottingham, and King's Mill Centre, Sutton in Ashfield) and Trent Regional Cancer Registration. The registry was reviewed and all the patients aged 70 years and over with a diagnosis of HD were identified.

The histological material was reviewed in all cases by three pathologists (IHL, DJ, FD). Histology slides and paraffin blocks were obtained from the files of the pathology departments at the above three hospitals. Repeat H and E-stained sections were cut and immunohistochemistry was performed, using a standard streptavidin–biotin complex method. The panel of antibodies used on each case included CD20, CD3, CD45RO (UCHL1), kappa and lambda light chains, CD15 and CD30 (all antisera supplied by Dako), with additional antibodies used when indicated. Cases of HD were subtyped according to the Rye classification. Only those cases where the diagnosis was confirmed were evaluated. Case notes were obtained and the following registry data confirmed: age, sex, presence of 'B' symptoms, Rye histological classification, Ann Arbor stage, and the type of treatment employed, if any. Treatment was defined to be of either radical or palliative intent. Palliative treatment was defined as anything less than standard chemotherapy (e.g. mustine/vincristine/procarbazine/prednisolone (MOPP) [14] or chlorambucil/vinblastine/procarbazine/prednisolone (ChlVPP) [15], or radiotherapy given other than radically (35–40 Gy in 20 fractions to patients with stage 1A or IIA disease). Information was obtained about treatment intensity, response to treatment (complete response was defined as survival beyond 120 days with no clinical evidence of residual disease), duration of survival from diagnosis and cause of death.

Statistical methods

Univariate survival analysis was performed using the method of Kaplan and Meier [16] with corresponding Logrank [16] significance testing.

Multivariate analysis, using the Cox proportional hazard model [16] was applied to both the elderly and younger groups separately, with age, gender, symptoms, histology, stage and treatment intent as the potential predictor covariates. ESR (erythrocyte sedimentation rate) and disease bulk were excluded from this test because of the frequency of the missing data. The analysis was performed using a forward selection technique, using the likelihood ratio test as the determinant factor for inclusion in progressive models, and cause-specific survival to determine the interval and event criteria. Cause-specific survival refers to survival in which deaths from Hodgkin's disease are recorded as events. Patients dying of other causes were censored at the time of death.

All analyses were accomplished using the SPSS statistical software package.

RESULTS

Between 1973 and 1993, 529 patients with HD were entered in the lymphoma registry. Of these, there were 53 patients aged 70 years and over. Following case note review, it was evident that 2 cases of non-Hodgkin's lymphoma (NHL) had been entered inadvertently. In 6 cases the patients' records were untraceable and in a further 6 the original slides or histological blocks could not be traced.

Histological review of the remaining 39 cases led to a change in diagnosis in 11. Ten were classified as NHL (peripheral T-cell, 7; high-grade B cell, 2; and T-cell rich, B cell 1). These had originally been classified as 'mixed cellularity', 6; lymphocyte depleted, 1 and 3 as H.D-unclassifiable, 1. One further case of mixed cellularity disease was reclassified as a carcinoma. Overall, 50% of those originally classified as mixed cellularity HD had a revision in their diagnosis. The remaining 28 cases represented 5.6% (28/504) of the cases of HD on the registry (7.3% (37/504) if a similar proportion of the 12 without notes or slides were, in fact, HD). Of these, one case was diagnosed only at autopsy. The histology of 149 of the 529 patients with HD stages IA and IIA treated by radiotherapy alone has been previously reviewed (paper in preparation). The histology was only changed in 8% of patients (12 to NHL, 1 to reactive). Although the histology of the remaining 332 patients with HD has not been reviewed a change of greater than 8% in diagnosis is unlikely.

The distribution of histological subtype in both the young and elderly groups is given in Table 1. The distribution of clinical stage was as follows: Stage I 26%, Stage II 31%, Stage III 30%, Stage IV 14% for patients under 70 years, and Stage I 15%, Stage II 31%, Stage III 39% and Stage IV 15% for patients aged 70 years and over.

The ages of the 28 patients at diagnosis ranged from 70 to 89 years. Thirteen were aged 70–74 years, 7 were aged 75–79 years, 6 were aged 80–84 years and 2 were aged 85–89 years. Of these, 15 were male and 13 were female (ratio 1.15:1). The male:female ratio of the remaining patients with HD under 70 years of age was 1.93:1. In Nottinghamshire, the male:female ratio is 1:1.66 in those greater than 70 years [17]. Correcting for the excess of elderly women in the area produces a male:female ratio of 1.92:1 in the elderly HD group. This is virtually identical to that of the younger HD group (Table 2). 'B' symptoms were present in 30% and 33.3% of the young and elderly HD groups, respectively.

Treatment

Of the 27 patients diagnosed before death, 3 patients received no treatment for HD, 5 patients were treated palliatively (radiotherapy, 2; chemotherapy, 3) and 19 patients (70%) were treated radically (radiotherapy, 5; chemother-

Table 1. Distribution of histological subtype in Hodgkin's disease

Age of patients	LP	NS	MC	LD	U
Under 70 years (%) ($n = 476$)	10	62	23	5	0
70 years and over (%) ($n = 28$)	0	63	26	11	4

LP, lymphocyte predominant; NS, nodular sclerosing; MC, mixed celullarity; LD, lymphocyte depleted; U, unclassifiable

Table 2. Sex distribution in Hodgkin's disease

	Males	Ratio	Females
1. Patients under 70 years	314	1.94 : 1.00	162
2. Patients aged 70 years and over	15	1.15 : 1.00	13
3. Population aged 70 years and over in Nottinghamshire	33 438	1.00 : 1.66	55573
4. Patients aged 70 years and over corrected using (3) above	15	1.92 : 1.00	7.8

apy, 14). In only 3 (21%) of the 14 patients treated radically with chemotherapy was the planned dose intensity achieved. In 6 patients, treatment cycles were delayed and in 5 patients there was dose reduction as well as treatment delay. In 7 of these 11 patients, the reason for delay/dose reduction was myelosuppression in 2 patients, non-neutropenic infection and in 2 patients, peripheral neuropathy. The 5 patients treated with radiotherapy experienced no delays, and so only 8 of the 27 patients received treatment as planned.

Response and survival

Of the 19 patients treated radically with either chemotherapy or radiotherapy, a complete response (CR) was achieved in 14 (74%) and a partial response (PR) in 4 (21%). Patients with HD under 70 years of age achieved a complete response in 351 of 362 (97%) evaluable patients (logrank x^2=17.9, $P < 0.00001$). Once CR was achieved, the relapse rate at 5 years was 56% for patients 70 years and over compared with 27% for those aged under 70 years (logrank x^2=4.86, $P = 0.0275$). The median cause-specific survival of the elderly groups 16.1 months (CI 5.7–26.4 months) with a 5-year survival of 28% (Figure 1). In comparison, in those under 70 years of age, the cause-specific survival at 5 years was 75% (logrank x^2=43.7, $P < 0.00001$). Survival was strongly influenced by achievement of a complete clinical response. For those patients aged 70 years and over who achieved a complete response, the overall and cause-specific median survivals were 21.6 months and 124.4 months, respectively, and the overall and cause-specific 5-year survival rates were 35.7% and 52.5%, respectively. Those who failed to achieve a complete response had overall and cause-specific median survivals of 11.8 months with no 5-year survivors (overall survival logrank x^2=5.80, $P = 0.016$; cause-specific survival logrank x^2=12.64, $P = 0.0004$).

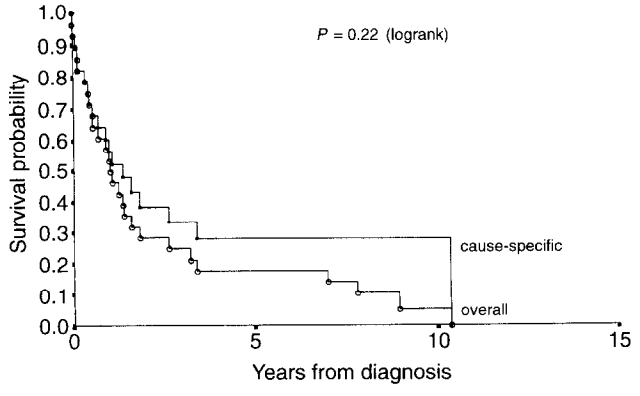

Figure 1. Overall and cause-specific survival in 28 patients with Hodgkin's disease aged 70 years and over.

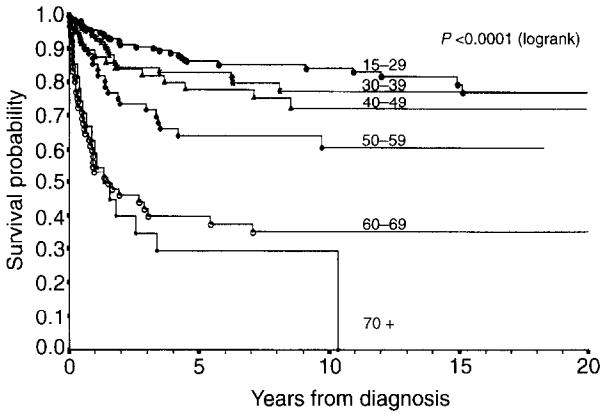

Figure 2. Cause-specific survival of 504 patients with Hodgkin's disease aged 15–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years and 70 years and over.

Univariate and multivariate analysis

The prognostic factors found to be significant for the younger HD group by univariate and multivariate analysis, namely age (Figure 2), histology, stage and B symptoms, were also examined in the elderly group, along with histology, sex and treatment intent. At the univariate level (Table 3), treatment intent was the only significant prognostic factor in the elderly group. At the multivariate level (Table 4), sex and treatment intent were of prognostic significance, in that female patients and patients treated radically had a more favourable prognosis.

DISCUSSION

The 28 patients aged 70 years and over with histologically confirmed HD have been identified in a population from

Table 3. Univariate analysis summary

Covariate	Age group	Chi-square significance	Category
Stage	<70	0.00001	I
			II
			III
			IV
Histology	<70	0.0823	
Symptoms	<70	0.00001	'A'
			'B'
Gender	<70	0.1244	
Age	<70	0.00001	15–29
			30–39
			40–49
			50–59
			60–69
Stage	≥70	0.2799	
Histology	≥70	0.8698	
Symptoms	≥70	0.8418	
Gender	≥70	0.1841	Male
			Female
Age	≥70	0.0510	70–79
			80 plus
Treatment intent	≥70	0.0001	Palliative
			Radical

Table 4. Multivariate analysis summary

Covariate	Age group	Chi-square significance	Category	β value	Significance
Stage	<70	0.0001	I	−1.18	0.01
			II	−0.40	0.28
			III	0.43	0.16
			IV	–	–
Histology	<70	(0.1847)			
Symptoms	<70	0.0088	'A'	−0.64	0.01
			'B'		–
Gender	<70	(0.4583)			
Age	<70	0.00001	Continuous (years)	0.0432	0.001
Stage	≥70	(0.6291)			
Histology	≥70	(0.7053)			
Symptoms	≥70	(0.9936)			
Gender	≥70	0.0313	Male	1.32	0.03
			Female	–	–
Age	≥70	(0.8408)			
Treatment intent	≥70	0.0008	Palliative	4.15	0.001
			Radical	–	

Significance values in brackets not included in final model.

which all patients with HD are entered in a lymphoma registry. Thus it is likely to represent the true pattern of HD in the community and does not suffer from referral bias. Only 5% of patients with HD are aged 70 years or over, in comparison to 35% of patients with NHL [18] in the Nottinghamshire lymphoma registry. This result is similar to that of other reports [4, 19].

The majority of reports of HD in the elderly have been published prior to the advent of immunohistochemical techniques which have improved the accuracy of lymphoma identification. The distribution of histological subtype of HD has also been reported to be different in the elderly, with an excess of mixed cellularity (MC) and lymphocyte depleted (LD) forms [3–7]. The routine use of immunohistochemical techniques has led to a reduced incidence of HD in the elderly and a reduction in the proportion of patients with MC and LD subtypes [20]. In our study, the majority of diagnostic revisions occurred in patients previously classified as having mixed cellularity HD. The distribution of sex, B symptoms, histological subtypes and stage was not significantly different between the young and elderly HD groups, except for the fact that in the elderly group there were no patients with lymphocyte predominant HD. In particular, although there were nearly as many female (13) as male patients (15) in the elderly group, the true male:female ratio was 2:1 once allowance had been made for the male:female ratio of the whole population over 70 years of age (M:F = 1:1.8)(Table 2).

In several other studies [12, 13, 19, 21, 22] of HD in the elderly, different characteristics or prognostic factors in patients aged 70 years or greater have also not been found. However, in our study, in spite of the similar patient characteristics, in the elderly group only treatment intent and patient sex were of prognostic significance at the multivariate level (treatment intent at the univariate level).

Age at diagnosis of HD is the more important prognostic factor (Figure 2), with the survival worsening with each decade of age. In this study, after the age of 60 years, the cause-specific 10-year survival was only 36% for patients aged 60–69 years and 28% for patients aged 70 years and over. Although female patients aged 70 years and over had a better prognosis, the major adverse prognostic factor is treatment intent, with patients treated with radical intent having a better prognosis. Even with those treated with radical intent, only a minority (21%) of those treated with chemotherapy achieved the planned dose intensity. Consequently, not only was there a lower CR rate in those aged 70 years and over (74% in comparison with 97% in those aged 15–69 years), but the relapse rate was higher (56% compared with 27% in the younger age group).

The factors predicting relapse have previously been reported to be bulk disease and inadequate treatment delivery but not age [23].

Although it is possible that the deteriorating T-cell function in the elderly is partly responsible for this higher relapse rate, the main reason must be the inadequate dose-intensity of chemotherapy. Therefore, when treating HD in the elderly, ways need to be found (perhaps with colony stimulating factors) to deliver therapy without dose reduction or delay.

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