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HODGKIN'S DISEASE IN NORTHERN SWEDEN 1971–1981

III. The clinical and prognostic impact of age

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Abstract

A retrospective material of 133 patients with Hodgkin's disease treated between 1971 and 1981 was analysed. In part II of this study it was shown that the prognosis was closely associated with age of the patient. In this part some clinical factors, including therapy, were compared between 66 patients less than 50 years of age and 67 patients 50 years or more. The groups differed mainly in the outcome of primary chemotherapy. Older patients with Hodgkin's disease were particularly vulnerable to chemotherapy, probably as an effect of the disease itself.

Key words: Hodgkin's disease, age, elderly patients, therapy, results of therapy, prognosis.

Considerable interest has been focused on prognostic factors in Hodgkin's disease (HD) and a large number of studies have addressed this subject. Among significant risk factors age is one of the most constantly reported. In some studies age has been the only recognized prognostic factor (1, 2), while others have reported age together with other variables such as stage, histologic subtype, constitutional symptoms, bulky disease or number of involved sites (3–5). In a few studies age was not found to be a relevant risk factor (6, 7).

In part II of the present study (8) we reported an analysis of prognostic factors in a series of 133 patients with a high mean age (48 years), probably reflecting a low degree of primary selection. A clearly worse prognosis was found for elderly patients compared to the younger. In fact, age turned out to be the only factor with an independent, statistically significant bearing on prognosis.

The treatment of elderly patients represents a considerable clinical problem. Treatment strategies have largely been based on the encouraging experiences gained in treating younger patients. However, these strategies are far less successful in the elderly with HD.

Several possible explanations exist for the diverging prognosis in young and elderly patients with HD. In fact, HD may not at all be a homogeneous entity. Etiology and pathogenetic mechanisms may be quite different in young and older patients (9–11).

It has been pointed out (12) that HD in the elderly has a different mode of presentation, more often without lymphadenopathy, with unfavorable histologic subtype, higher stage and more constitutional symptoms, which could be the main explanation for the reduced survival. This view has, however, been questioned by others (13).

The intention of the present study was, on the basis of the previously reported material, to further describe some features of clinical and prognostic relevance. By comparison of younger and elderly patients the aim was to identify clinical factors of importance for the diverging prognosis in these two groups.

Material and Methods

The patient characteristics and the statistical methods were described in part I and II of this study (8, 14). Sixty-six patients were under 50 years of age and 67 were 50 years or more.

Stage classification was performed according to the Ann Arbor staging system (15). A complete blood count, chest roentgenogram and radionuclide scans of spleen and liver were parts of the routine evaluation, together with a bone marrow sample usually obtained by aspiration technique. Among the 67 elderly patients bipedal lymphography was done in 38 and an i.v. pyelogram and/or cavography in 19

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patients. In 18 elderly patients initial staging laparotomy was performed. Karnofsky index was scored retrospectively.

Radiotherapy (RT) was delivered with a telegamma ^{60}Co-unit in the period 1971–1977 and with a 4 MV x-rays from a linear accelerator in 1978–1981. Treatment fields were standard 'mantle-field' for supradiaphragmatic disease and 'inverted Y' for subdiaphragmatic disease. Intended dose was 40 Gy given in daily fractions of 1.5–2.0 Gy for 4–6 weeks. Twenty-four patients less than 60 years were taking part in a randomized study of combined chemotherapy (CT) and RT versus only RT in early stages. Target dose was 25 Gy in the group receiving combined treatment. In a few cases the radiation field was reduced to 'extended field' or even 'involved field', sometimes together with a diminished target dose due to old age or poor general condition.

As CT the MVPP-program described by Nicholson et al. (16) was used during the first year of the study. In 1972 it was replaced by the MOPP-regimen according to DeVita et al. (17), which thereafter was employed as standard CT. A full-length CT program consisted of at least 10 cycles of MOPP with gradually prolonged intervals after the first 6 cycles. Planned versus given doses and interval estimations were based on the first 6 cycles only. The CT schedule was modified in some instances for the same reasons as for RT.

Table 1

Anamnestic illnesses among the 67 elderly patients

Illness	Number
Hypertension	17
Ischemic heart disease	11
Diabetes	7
Ulcus duodeni et ventr.	7
Psychiatric illness	5
Collagenosis	4
Tbc	3
Previous malignancy	3
Prostatic hyperplasia	3
Ischemic cerebral disease	2

Results

Patients

From the records of the 67 elderly patients was noted the presence of other diseases possibly interfering with prognosis (Table 1). Also noted were treatment compliance and tolerance. On presentation 20 patients (30%) had a symptom duration of 1–3 months, 26 patients (39%) 4–6 months, and 21 patients (31%) a duration of more than 6 months. Karnofsky score was 70–100 in 44 patients (66%) and 10–60 in 23 cases (34%).

Table 2

Stage, constitutional symptoms and histologic subgroups in elderly and younger patients

	0–49 years	⩾ 50 years
Stage		
I	14 (21%)	21 (31%)
II	23 (35%)	8 (12%)
III	20 (30%)	23 (34%)
IV	9 (14%)	15 (22%)
B-symptoms		
Present	20 (30%)	39 (58%)
Histology		
LP	13 (20%)	6 (10%)
NS	19 (29%)	11 (18%)
MC	31 (47%)	40 (64%)
LD	3 (4%)	5 (8%)

Abbreviations: LP = lymphocytic predominance; NS = nodular sclerosis; MC = mixed cellularity; LD = lymphocytic depletion.

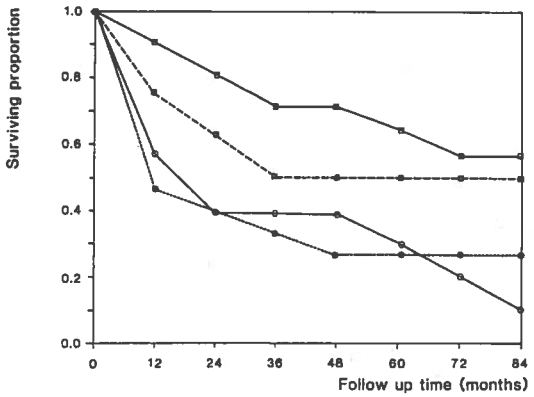

Fig. 1. Life table survival for Ann Arbor stages I-IV in the elderly HD-patients. □— stage I; ■- - - stage II; ○— stage III; ●- - - - stage IV.

Stage II was less frequent among the elderly compared to the younger group (Table 2). Higher stages were more frequent among the elderly in spite of less extensive staging procedures. Constitutional symptoms were almost twice as common in the older age group as in the younger. Survival according to stage is shown in Fig 1.

Histopathology

Tumor histology was mixed cellularity or lymphocytic depletion in 73% of elderly patients compared to 52% in the younger (Table 2). These subtypes are often regarded as adverse prognostic factors. Survival according to histologic subtype is demonstrated in Fig 2.

Therapy

Overall clinical complete remission (CR) rates were 73% for the older age group and 91% for the younger patients,

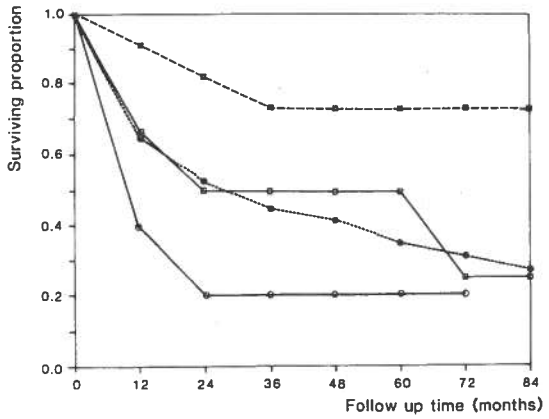

Fig. 2. Life table survival for histologic subgroups according to Lukes-Rye in the elderly HD-patients. □— lymphocytic predominance; ■– – – nodular sclerosis; ●- - - - mixed cellularity; ○— lymphocytic depletion.

Table 3

Relapses and treatment results in elderly versus younger patients

	0–49 years	⩾ 50 years
Relapse rate	21/60 (35%)	21/49 (43%)
Median time to relapse	19 months	9 months
Achieved CR No. 2	14 (67%)	5 (24%)
Alive after relapse	10 (48%)	2 (10%)

with a 5-year survival of 43% (median 34 months) and 82% (median 156 + months) respectively. The relapse rate was the same in both groups, but median time to relapse was shorter and the results of salvage treatment were less advantageous in the older persons (Table 3).

RT alone was delivered to 21 elderly and 29 younger patients respectively. Among those CR was achieved in 19 (90%) of the older and in all of the younger persons. Subsequent relapse occurred in 7 (37%) elderly and in 11 (38%) younger patients. Thus, no major differences were found concerning results of RT.

Among patients receiving CT as the only primary therapy there were considerable differences in the results. CR rates were 20/34 (59%) in the elderly and 13/15 (87%) in the younger group. Relapses were seen in 10 (50%) of the elderly and in 3 (23%) of the younger patients.

Combination of CT and RT was employed in 12 elderly and in 22 young patients. CR was noted in 10 (83%) of the older and 18 (82%) of the younger patients, and relapses in 4 (40%) and 7 (39%) respectively. Consequently, nor with this treatment modality could any major difference be observed between the two age groups.

To further analyse the unsatisfactory results of primary CT in the elderly patients an estimation of the given number of cycles (Table 4) and of the delivered dose during the first 6 cycles (Table 5) was made, together with a calculation of interval times (Table 6). Premature discontinuation of CT was noted in 34 patients in the older group, for reasons listed in Table 7.

Table 4

Chemotherapy — number of cycles given in the elderly

Number of cycles	1	2	3–4	4–5	6 or more
Number of patients	6	2	4	7	14

Thus, among the elderly patients CT was delivered with standard or near standard dosage without any marked prolongation of intervals between cycles. However, there was a substantial number of premature disruptions caused mainly by death or general deterioration in this age group. Therapy related complications were also quite frequent, with major infections as the most commonly encountered (Table 8).

Table 6

Chemotherapy — interval between cycles in the elderly (first 1–6 cycles)

Interval (days)	⩽ 35	36–49	50–69	⩾ 70
No. of cycles	96	14	4	2

Table 5

Chemotherapy — given versus planned dose for first 1–6 cycles in the elderly

Given vs planned dose (%)		100	75–99	50–74	25–49
Number of patients	MOPP[1)]	13	17	4	1
	MVPP[2)]	4	6	7	1
	ABVD[3)]	1	3		
	Other	2	3	1	1
Total No.		20	29	12	3
(%)		(31)	(45)	(19)	(5)

[1)]MOPP = Nitrogen mustard, vincristine, procarbazine, prednisone;
[2)]MVPP = Nitrogen mustard, vinblastine, procarbazine, prednisone;
[3)]ABVD = Doxorubicin, bleomycin, vinblastine, dacarbazine.

Table 7

Causes of discontinuations of primary therapy

Deceased	17 patients
Deterioration	6
Bone marrow depression	3
Major neurologic loss	3
Long standing CR	2
Refusal	2
Intercurrent disease	1

Table 8

Therapy-related complications

	No. of patients
Major febrile infection	12
Cerebral	3
Cardiac	3
G-I hemorrhage	3
Trombo-embolic	3
Serious herpes zoster	2
Other	3

Causes of death

Forty-seven of the 67 elderly patients died during the observation period. Autopsy was performed in 21 (45%) of these cases. Based on clinical and post-mortem data the following factors were considered as the main cause of death: HD in 20, therapy related complication in 5 (11 if combinations of causes are included) and intercurrent disease in 8 cases. Corresponding figures for younger patients were 12 deaths, with HD as the main cause in 9, therapy complication in 2 and intercurrent disease in 1 patient.

Thus, intercurrent disease played an important role as cause of death among the older patients and there were more therapy-related deaths in this group as well.

Discussion

Generally, the prognosis in HD is considered to be quite favorable. As shown in several studies (18–20), this statement applies primarily to younger patients, while the outcome is considerably more doubtful in elderly patients. The reasons remain obscure. Different etiologic mechanisms may be existing in HD. By means of epidemiologic evidence it was suggested by MacMahon (9) and by others (10, 11) that HD may be an infectious disease in younger patients and a true neoplastic disease in older persons.

In this material, analysis of the older patient population revealed differences in the results of different therapy modalities. CT as well as RT or combinations of the two were given with a curative intent even in the majority of elderly patients. While RT or combination therapy resulted in quite similar CR rates in young and elderly persons, primary CT alone gave clearly less favorable results in the older category.

Early clinical deterioration and death during primary therapy rather than insufficient intensity of treatment appeared to be the causes for the poor results. It should be noted that therapy is closely linked to clinical stage. Patients receiving CT generally have more advanced disease than those receiving other types of therapy. However, this statement can be applied to young as well as old patients, and thus it cannot possibly explain the differences in results of chemotherapy between the age groups.

The disorder itself may also contribute to a decreased ability to tolerate treatment due to immunological deterioration. The importance of this mechanism may be more pronounced in the older patient with HD than in the younger. There is evidence for reduced cellular immunological defence mechanisms in old age as well as in HD (21–25). These two mechanisms for relative immunodeficiency in older patients with HD may well work together in an additive or even synergistic way. This may lead to a type of 'burnt-out syndrome', which frequently may be observed in older patients with HD.

A large proportion of elderly patients also have concomitant disorders which may affect their ability to tolerate the neoplastic disease and its treatment. To this factor may be added the fact that less regenerative and reparative capacity of normal tissues exists among elderly persons. However, our impression is that patients with HD are more vulnerable and have less tolerance to therapy than persons of corresponding age with other neoplastic diseases, e.g. non-Hodgkin's lymphoma.

In conclusion, this study shows that treatment strategy for older patients with HD in stage III-IV is doubtful when based on experience gained from management of young patients. The strategy by Eghbali (26) seems to be a reasonable compromise. This strategy is based, when possible, on RT with the addition of careful, individually matched CT. However, it may be suspected that even this strategy turns out to be insufficient. We feel that entirely novel types of therapy must be sought for in order to substantially improve the outcome for elderly patients with Hodgkin's disease.

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