Hodgkin's lymphoma in the elderly with special reference to type and intensity of chemotherapy in relation to prognosis

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Background and Objectives. In general, elderly patients with Hodgkin's lymphoma (HL) have a less favorable prognosis than do younger ones. Inadequate therapy, often due to decreased tolerance to treatment, contributes to the poor outcome. This study was undertaken to evaluate potential clinical factors of importance for prognosis with special reference to relative dose intensity (RDI) of chemotherapy (CT).

Design and Methods. Eighty-eight consecutive elderly (>60 years) HL patients diagnosed between 1973-1994 who received up-front CT±radiotherapy (RT) were included (median age 72 years, range 60-92; median follow-up time 78 months, range 49-206). The calculations of RDI of CT were based on Hryniuk's model.

Results. The 5-year overall (OS) and cause-specific (CSS) survival was 39% and 51%, respectively, in patients who received CT±RT. Nine of the 14 patients who only received ≤1 cycle of CT died within 6 months from diagnosis without achieving complete remission (CR). However, the remaining 5 patients in this group survived 14-97+ months. Patients with a RDI >65% had a significantly better OS (p=0.029) and CSS (p=0.024) than those with a RDI ≤ 65%. Patients who received ABVD-based CT with a RDI >65% had a significantly better OS (p=0.0011) than those who were treated with ABVD-based CT with a RDI ≤ 65%, or MOPP-like therapy, irrespective of received RDI.

Interpretation and Conclusions. Prognosis remains heterogeneous and the significance of established prognostic factors is limited in elderly HL patients. Patients who received a low RDI of CT and those receiving non-ABVD-based treatment fared worse. However, also elderly patients can enjoy long-standing complete remission following minimal treatment.

Key words. Hodgkin's lymphoma, elderly, treatment, prognosis, doxorubicin, ABVD.

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In the Western world, a distinguishing epidemiological feature of Hodgkin´s lymphoma (HL) is its bimodal age distribution. One peak occurs in the third decade of life and the second peak around the sixth decade.[1,2] Since the introduction of modern staging procedures and developments in both radiotherapy (RT) and chemotherapy (CT) patients presenting within the first incidence peak generally have a good prognosis. Older age (>50-60 years) has, however, been recognized for many years to be an adverse prognostic factor for survival, both in primary HL and in relapse.[3-11] Yet the causes (and their relative importance) of these less favorable survival rates among older patients remain in part undetermined. Related factors contributing, to a varying extent, to a more dismal prognosis include: a) suboptimal therapy often due to decreased tolerance to treatment; b) comorbid diseases/organ dysfunction; c) inadequate diagnostic and staging procedures; and d) accumulation of certain clinical, biological, and other risk factors associated with a poor response to therapy.[11-13] Many elderly HL patients receive less intensive (schedule/dosing) up-front CT because of treatment-related toxicity.[11] Thus, myelosuppression is known to be one of the major dose-limiting toxicities during induction treatment in elderly patients with both advanced HL and aggressive non-Hodgkin's lymphoma (NHL) leading to a large proportion of patients who cannot receive scheduled CT.[11,14-16] However, as extrapolated from treatment results in various series of patients there seems to be a sub-population of elderly HL patients who have undergone adequate diagnostic and staging procedures and also tolerate intensive treatment. These patients appear to have a complete remission rate and relapse-free and overall survival well comparable to those of younger patients.[17-19]

In the present study the long-term outcome of consecutive elderly (>60 years) HL patients diagnosed during a 20-year-period in a well-defined urban Swedish population was studied. Potential factors of importance for prognosis were evaluated. This retrospective analysis specifically addressed the impact of type and calculated relative dose intensity (RDI) of CT in relation to response and survival. The findings in this population-representative cohort of patients show that the fraction of elderly patients is larger than in most other reported series.[6,20-22] The great heterogeneity in outcome of the elderly with HL is confirmed and the possibilities of optimization of CT in this group are discussed.

Design and Methods

Patients' characteristics

Consecutive elderly (>60 years) patients with newly diagnosed HL during the years 1973-1994 in the Stockholm area were included in this study (n=147). Elderly patients accounted for 26% of the total number of patients with primary HL (n=566; 16-95 years) diagnosed in the same region during the study period. Fifty-four (37%) patients received up-front RT alone, 88 (60%) received up-front multiagent CT±RT, 3 (2%) underwent surgery, and 2 (1%) patients received no anti-tumor treatment at all. This study is restricted to patients who received up-front CT±RT. There were 40 men and 48 women with a median age at diagnosis of 72 years (range 60-92 years). The median observation time at follow-up for surviving patients was 78 months (range 49-206 months). Clinical characteristics in relation to the chemotherapy given are shown in Table 1. The study was approved by the Karolinska ethics committee.

Diagnostic and staging procedures

Diagnostic biopsies were reviewed to confirm the diagnosis and classified according to the REAL nomenclature (Table 1).[23] When necessary, complementary immunostainings for CD15, CD30, CD20, LN-1, CD79a, CD3, UCHL-1, and EMA (avidin-biotin-peroxidase complex technique) were performed.[24] Besides a thorough physical examination the following investigations were performed: chest X-ray, computed tomographic scanning of the chest (when clinically indicated) and abdomen. Computed tomographic scanning was introduced in the late 1970s and eventually replaced liver and spleen scans and lymphangiography. Bone marrow involvement was assessed by bone marrow biopsies and aspirates. Bulky disease was defined as a mediastinal mass with a diameter exceeding 1/3 of the maximal mediastinal width or any tumor manifestation with a diameter of >10 cm. Laboratory tests were performed according to standard methods. The Ann Arbor staging classification[25] was used to describe the extent of disease. For further details see previous reports.[12,26-30]

Treatment and response criteria

Details of treatment have been described previously.[12,24,26,29] In short, patients with limited disease (stage I-II/III) were given RT. Two patients were included in a study open between 1974-1979 regarding the value of early splenectomy in intermediate-stage patients aged 18-65 years and received total nodal irradiation.[27] During this period, patients with stage IIIB-IV disease were given MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) or CCNU-OPP (1-(2-chloroethyl)3-cyclohexyl-1-nitrosourea

Table 1. Patients' characteristics; N (%).

	MOPP-like chemotherapy	*ABVD-based chemotherapy*	*Other chemotherapy*
Number of patients	46 (100)	39 (100)	3 (100)
Sex			
Male	22 (48)	16 (41)	2 (67)
Female	24 (52)	23 (59)	1 (33)
Age			
60-69 years	17 (37)	16 (41)	1 (33)
70-79 years	18 (39)	17 (44)	1 (33)
80-89 years	10 (22)	6 (15)	0 (0)
90-years	1 (2)	0 (0)	1 (33)
Clinical stage			
I	5 (11)	2 (5)	1 (33)
II	8 (17)	11 (29)	0 (0)
III	22 (48)	13 (33)	2 (67)
IV	11 (24)	13 (33)	0 (0)
B-symptoms			
Yes	31 (67)	23 (59)	2 (67)
No	15 (33)	16 (41)	1 (33)
Bulky disease			
Yes	1 (2)	1 (3)	0 (0)
No	45 (98)	38 (97)	3 (100)
Histopathology			
LP	6 (13)	3 (7)	0 (0)
NS	7 (15)	8 (21)	0 (0)
MC	18 (39)	18 (47)	1 (33)
LD	9 (20)	3 (7)	2 (67)
Unclassified	6 (13)	7 (18)	0 (0)
Distribution of patients according to IPS factors			
1	5 (11)	3 (7)	0 (0)
2	10 (22)	7 (18)	1 (33)
3	15 (33)	16 (41)	1 (33)
4	12 (26)	11 (29)	1 (33)
5	3 (6)	2 (5)	0 (0)
6	1 (2)	0 (0)	0 (0)
7	0 (0)	0 (0)	0 (0)

LP: lymphocyte predominance; NS: nodular sclerosis; MC: mixed cellularity; LD: lymphocyte depletion; IPS: International Prognostic Score.[33]

(CCNU), vincristine, procarbazine, and prednisone) CT. From 1979, the planned curative treatment in most elderly patients with stage IIB-IV disease was 3-4 full cycles of MOPP/ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), or ABVD alone (6-8 cycles), with irradiation given to bulky disease.[30] Doxorubicin (25 mg/m^2) was sometimes substituted by mitoxantrone (5 mg/m^2) in patients with cardiac disease. Complete remission (CR) corresponded to complete regression of all palpable or histologically documented tumors and resolution of all radiographic and biochemical abnormalities due to HL for a minimum of three months.

Relative dose intensity of chemotherapy

The effects of dose intensity of CT were assessed in relation to outcome by calculating the RDI based on Hryniuk's model.[31-33] The following drugs and projected doses were used in the RDI calculations: mechlorethamine 6 mg/m^2 (maximum 10 mg/day) days 1 and 8 (MOPP), cyclophosphamide 1000 mg/day days 1 and 10 (COPP), CCNU 80 mg/m^2 day 1 (CCNU-OPP), doxorubicin 25 mg/m^2 days 1 and 15 (ABVD), mechlorethamine 6 mg/m^2 (maximum 10 mg/day) days 1 and 8 and doxorubicin 25 mg/m^2 days 28 and 42 (MOPP/ABVD). For patients who received MOPP/ABVD the RDI was based on the mean value of the combined relative mechlorethamine and doxorubicin doses. The above alkylating agents and anthracyclines/anthracenedione were chosen for the RDI calculations because of their well documented anti-tumor effect associated with a dose-limiting myelotoxicity.[31,32] To calculate dose intensity, the total milligrams administered were divided by the total number of weeks of treatment.[33] The calculated RDI values were based on the initial two cycles of CT for each patient. Individuals who received ≤ 1 cycle of CT (n=14) were excluded from RDI calculations. Since the follow-up period was dependent on duration of treatment, the analyses of the prognostic impact of RDI were performed after an observation period of 60 days from start of administration of CT.[34,35]

Factors related to outcome

In patients with advanced disease (stage IIB-IV) who were treated with CT±RT the following clinical factors were assessed in relation to the end-points of overall, cause-specific, and disease-free survival: International Prognostic Score[36] and its component factors [age (≥ 45 vs <45 years), sex (male vs female), stage (IV vs I-III), serum albumin (<40 g/L vs ≥ 40 g/L), hemoglobin (<105 g/L vs ≥105 g/L), white blood cell (WBC) count (≥15×10^9/L vs <15×10^9/L), lymphocyte counts (<0.6×10^9 /L vs ≥0.6×10^9/L, or <8% vs ≥8% of WBC counts)], histopathology, bone/bone marrow involvement or not, and constitutional (B-symptoms) symptoms or not. Serum albumin and hemoglobin levels, age, WBC and lymphocyte counts

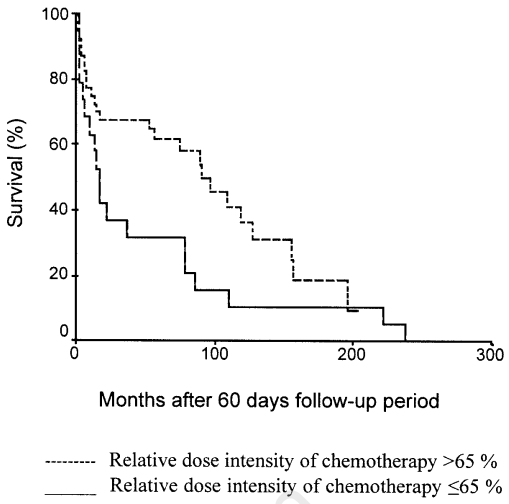

Figure 1. Overall survival in relation to relative dose intensity of chemotherapy (n=59).

were also tested as continuous variables. The prognostic power of each factor was assessed and compared in a multivariate analysis. An analysis including all patients irrespective of stage and treatment was also performed with the same design as described above.

Statistical methods

Cause-specific survival was defined as the time from diagnosis to death from HL or death judged to be related to treatment of the disease (infections, certain second malignancies [non-Hodgkin´s lymphoma n=1, myelodysplastic syndrome n=1] and cardiovascular events).[30] Overall survival was defined as the time from diagnosis to death, irrespective of cause. In the RDI analysis (see above), cause-specific and overall survival were calculated from the first day of treatment +60 days.[34,35] In patients with complete remission, disease-free survival was defined as the time from last day of treatment to relapse or death from HL or death related to treatment of the disease (*see above*). Survival curves were constructed by the Kaplan-Meier procedure.[37] Differences in prognostic prediction of categorical factors with regard to overall and cause-specific survival were calculated by Gehan's Wilcoxon test.[38] Cox regression analyses were used for univariate analyses of continuous factors and for multivariate analyses.[39]

Results

Outcome

The CR rate was 49% (43/88). The 5-year overall and cause-specific survival rates were 39% and 51%, respectively. Nine of the 14 patients who received ≤ 1 cycle of CT died within 6 months from diagnosis without achieving CR. However, the remaining 5

patients in this group survived 14-97+ months. Two of these patients (overall survival 83 and 97+ months) received additional RT. An additional 15 (17%) patients had to be excluded from the RDI calculations (*see below*) due to lack of detailed information regarding the CT they had received. The impact of RDI in the final study cohort (n=59) was investigated as follows: the patients were arbitrarily divided into three groups (each consisting of 1/3 of the patients) with low (range 27-64%), intermediate (65-80%), and high (81-112%) RDI values. Patients with intermediate and high RDI values did not differ with regard to response to treatment and clinical outcome and were thus grouped together and compared to those with low RDI values, i.e. RDI >65% vs ≤ 65%. Patients with RDI >65% had a significantly better overall (p=0.029 Figure 1) and cause-specific (p=0.024) survival than those with RDI ≤ 65%. When tested in multivariate analysis, RDI added significant prognostic information to that achieved by the remaining factors under study (see below). In addition, RDI >65% predicted a higher CR rate when tested as described above (χ^2 test, p=0.024). Twenty-nine percent of patients with RDI >65% as compared to 50% of patients with RDI ≤ 65% died within 24 months after the 60-day follow-up period. A majority (92%) of patients treated with ABVD-based (MOPP/ABVD or ABVD) CT had a RDI value >65% while the corresponding figure for patients treated with MOPP-like (MOPP, COPP, or CCNU-OPP) therapy was 24% (p<0.001). Patients who received ABVD-based CT with a RDI >65% had a significantly better overall survival (p=0.0011) than those who were treated with ABVD-based CT with a RDI ≤ 65%, or MOPP-like therapy, irrespective of RDI value (Figure 2). RDI or type of CT did not predict disease-free survival. Outcomes in relation to RDI analyses were also examined according to year of diagnosis, which was not found to have any influence on the results.

Predictors of outcome at diagnosis

In univariate analysis, only low albumin was associated with inferior overall survival (p<0.001) when the IPS cut-off values were applied.[33] When the factors were tested as continuous variables with the same design as described above in a Cox proportional hazards regression analysis, low albumin (p=0.028) and increasing age (p<0.001) predicted an inferior overall survival. Patients aged 60-69 years at diagnosis had a significantly better overall survival than did patients ≥70 years (p=0.002) which is shown graphically in Figure 3. None of these factors was associated with disease-free survival.

Treatment and prognosis at relapse

Six of 43 (14%) patients achieving complete remission (age: 63-82 years; stage: IIIA-IVB) relapsed during the observation period (median time to relapse: 16 months; range 6-30 months). One patient had rapidly progressive disease and survived only 2 weeks after relapse. Five patients received rescue treatment: CT (n=4; MOPP or mitoguazone, ifosfamide, methotrexate, etoposide [MIME]) or RT (n=1). The survival times in these five patients were 3-51+ (3; 10; 11; 45; and 51+) months from established relapse. Three died from HL or infections judged to be related to treatment of the disease while one patient died of a cerebral hemorrhage.

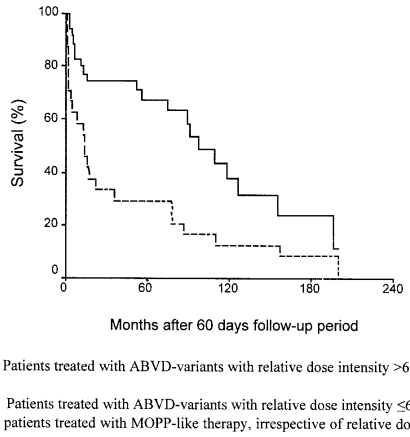

Figure 2. Overall survival in relation to type and relative dose intensity of chemotherapy (n=59).

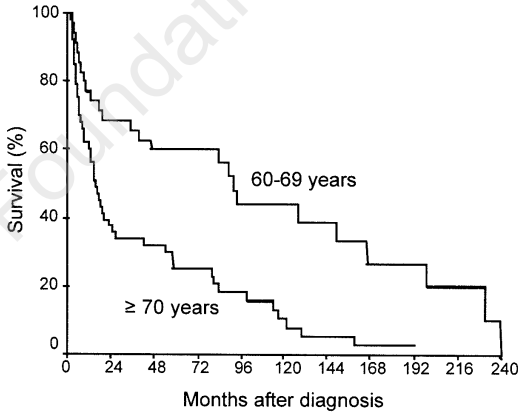

Figure 3. Overall survival in relation to age in patients treated with chemotherapy (n=88).

Discussion

Age has long since been recognized as an important predictor of prognosis in patients with both localized and advanced HL.[40] Thus, both overall survival and time to treatment failure decrease with increasing age. In addition, improvement in outcome following therapeutic achievements introduced during the last decades has been mainly confined to younger patients.[8,19,41–47] In contrast, disease-free

survival following achievement of a CR may not differ significantly dependent on age.[4,46] The age-related decline in overall survival has not been totally consistent and in some reports it has been stated that elderly patients do as well as younger patients provided *adequate* therapy is given.[11] Discrepancies in treatment results of elderly patients obtained in different series are most probably explained by differences in the patients selected.

An estimation of the fraction of elderly patients in clinical cohorts of HL patients is one way to elucidate the degree of patient selection. In the present report 26% of all patients collected during the study period were above the age of 60 years. This is in contrast to most other major clinical series in which the reported fraction of elderly patients varies between 3-20%[6,20-22] with an occasional exception.[6] However, we have previously observed diagnostic and other errors introduced by registry-based patient identification[48] which is why, in this study, we refrained from seeking additional elderly patients reported as HL to the local (and Swedish) cancer registry during the same study period. Thus, we regard this cohort of patients collected after the introduction of effective, wide-field megavoltage radiation and combination CT, in an urban Swedish population as a population-representative series of elderly people with HL. Based on a long-term follow-up certain observations of clinical relevance have been made with a special focus on patients receiving CT. The recorded remission and survival rates are in good accordance with the results of previous reports.[4,6,46] Only 14% of patients relapsed following CT with long-term survival observed in a few patients following rescue treatment. This corroborates the notion that age may not be a significant factor predicting freedom from first and second relapse.

A restricted number of studies focused on dose intensity in relation to prognosis in HL have been published previously.[6,49-53] These studies have often been limited to younger HL patients, mainly treated with MOPP-like therapy. Therefore, one major aim of the present study was to elucidate the prognostic impact of type and intensity of CT in the elderly. As described above, the RDI calculations in this study were based on the initial two cycles for each patient. The specific design used was considered to be adequate since the follow-up period was dependent on duration of treatment.[34,35] The period of 60 days was chosen because of distributional reasons with respect to length of treatment and survival time, the design permitting the RDI to be evaluated in as many patients as possible. Not surprisingly, patients with RDI >65% had significantly better overall and cause-specific survival than remaining patients. Importantly, ABVD-based CT was associated with a better overall survival than was MOPP-like CT. This is partly explained by the fact that significantly more patients treated with ABVD-based therapy had a RDI value exceeding 65% than did patients treated with MOPP-like therapy. These findings corroborate the results of a previously published study showing that the myelosuppression associated with MOPP-like CT necessitates greater reductions in the prescribed doses than those required for ABVD.[54] In addition, the overall survival was significantly better in patients who received up-front ABVD-based treatment with a RDI >65% than in patients given the same CT with a RDI ≤ 65% and patients treated with MOPP-like therapy, *irrespective* of received RDI, again favoring ABVD-based CT. It should be borne in mind that the RDI analysis performed in this study was retrospective in design and the results should therefore be considered exploratory and not conclusive in nature. As for any positive dose-response relationship, it is hard to distinguish cause from effect, i.e., patients complying and receiving full doses do well, or patients who are doing well comply and receive full doses.[54] However, in strong further support for the present findings is an only recently published study by Weekes *et al.* showing a significantly improved survival of elderly (>60 years) patients receiving a doxorubicin-containing regimen in comparison to those receiving chlorambucil-based MOPP-like CT.[55] No analysis of the potential impact of RDI of CT on outcome was performed in that study. It is noteworthy that also in elderly patients long-term disease-free survival can be observed following very brief CT as exemplified by 5 patients who survived 14-97+ months.[26] Granulocyte colony-stimulating factor (G-CSF) was only available for a small number of patients in this series and since G-CSF support has not improved response or survival rates in elderly patients given similar combination CT for aggressive NHL,[14-16] G-CSF treated patients were not analyzed separately.

Overall, there is a great need to explore biological mechanisms, focusing on age-related changes in pharmacokinetics in relation to multiagent CT, and to gain knowledge in order to be able to explain better the variations in toxicity and response to therapeutic modalities associated with aging.[56,57] The well-established clinical prognostic factors in younger patients (<65 years) with advanced disease[36] were found to be of limited value in predicting outcome in this restricted cohort of elderly patients. This was not unexpected and is in good accordance with several previous efforts over the years to identify patient- and disease-related factors of potential help in predicting prognosis and to choose treatment strategy in the elderly with HL.[36,58-63] Thus, in the above cited study by Weekes *et al.*, event-free survival was not predicted by gender, stage, performance status, lactic dehydrogenase, number of extranodal sites, B symptoms, size of the largest mass, or histologic subtype.[56] In the present study, low albumin and increasing age were the only factors which independently predicted an inferior

overall survival. Thus, patients 60-69 years of age treated with CT±RT survived significantly better than patients ≥70 years. This finding could not solely be explained by attribution of suboptimal treatment in the oldest group since there was no pronounced difference in the RDI values between the two groups (mean RDI 77% vs 71%; $p>0.05$). Other so far unidentified clinical and biological risk factors may further contribute to the poor outcome associated with increasing age.[11-13] In a small cohort of elderly HL patients, we previously observed that long familial life-span of two previous generations predicted superior survival.[64] However *parental* longevity did not predict superior survival in the present series of elderly patients with HL.[65] In conclusion, the present results confirm the lack of apt and clinically useful prognostic factors and illustrate the great heterogeneity in outcome of the elderly with HL. Many factors contribute to a decreased RDI which is strongly associated with a dismal prognosis in this population of patients. ABVD-based CT appears superior to MOPP variants.[54] Long-term survival can be achieved even following minimal CT. When interpreting therapeutic studies of HL in the elderly, one should be aware of the fact that differences in patient selection may be very pronounced. This may be related to type of hospital or health care system, or to geographic and many other factors. In addition, it is well-known that in a rather large proportion of elderly patients (10-20%), HL is diagnosed *post-mortem*.[5,66] Some of these patients might have benefited from a correct diagnosis and a potentially curative treatment.

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Pre-Publication Report & Outcomes of Peer Review

Contributions

OL, CA, UA, BN, CW, AP-MD, GG, MB: conception and design, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

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In the following paragraphs, the Associate Editor summarizes the peer-review process and its outcomes.

What is already known on this topic

Optimal treatment of elderly patients with Hodgkin's lymphoma is not well established. Whether or not those patients benefit from treatments given in younger patients with a curative intent is still a matter of discussion, and many groups have tried to design specific treatments for elderly patients, with often lower doses of chemotherapy or anthracyclines.

What this study adds

This study indicates that classical ABVD or ABVD-like treatment delivered at full dose intensity provides good results in elderly patients. MOPP treatment appears to be inferior to ABVD in this population.

Caveats

This study on relative dose intensity is retrospective, and by nature, cannot formally establish the benefit of full-dose treatment over other approaches. However, it is difficult to plan randomized trials to test such a hypothesis in this category of patients.