Taylor&Francis
healthsciences

Patients above Sixty Years of Age with Hodgkin's Lymphoma Treated with a New Strategy

Gunilla Enblad, Anita Gustavsson, Christer Sundström and Bengt Glimelius, for the Swedish Lymphoma Study Group

From the Departments of Oncology, Radiology and Clinical Immunology (G. Enblad, B. Glimelius) and Genetics and Pathology (C. Sundström), Uppsala University Hospital and the Department of Oncology (A. Gustavsson), Lund University Hospital, Lund, Sweden

Correspondence to: Gunilla Enblad, Department of Oncology, Radiology and Clinical immunology, Section of Oncology, Uppsala University Hospital, SE-751 85 Uppsala, Sweden. Fax: +46 18 6115 528. E-mail: gunilla.enblad@onkologi.uu.se

Acta Oncologica Vol. 41, No. 7/8, pp. 659–667, 2002

In the Swedish National Care Programme for Hodgkin's lymphoma (HL) a less intensive chemotherapy regimen with individualized dosing (LVPP/OEPA) was introduced in 1989. In total, 139 patients, 77 between 1985 and 1988 and 62 between 1989 and 1992, were studied. Mean ages were 72 and 71 years, respectively. One hundred and nineteen patients were treated with curative intention, 63 (82%) between 1985 and 1988 vs. 56 (90%) between 1989 and 1992 ($p = 0.11$). All patients (13 vs. 20) treated with radiotherapy only achieved a complete remission (CR). The CR rates (67% vs. 65%) for patients treated with 6–8 cycles of chemotherapy were also similar in the two time periods. The 5-year survival rate was 45% in the period 1985–1988 and 48% in 1989–1992. The survival of elderly HL patients was thus not improved from 1985–1988 to 1989–1992. Thus efforts to improve the chemotherapy regimen with individualized dosing did not change the outcome. Many patients experienced myelosuppression and opportunistic infections that may have contributed to the poor treatment results.

Received 18 January 2002
Accepted 22 August 2002

Despite a good prognosis for young patients with Hodgkin's lymphoma (HL), elderly patients have a poor outcome. Age is an adverse prognostic factor in most studies including sufficient numbers of elderly patients. The decline in survival starts in patients above the age of 40 years but is most pronounced above the age of 60 years (1–10). The problem is numerically great, since patients above the age of 60 comprise about one-third, or more, of the HL patients in Western countries (1, 3, 4, 9), although the incidence has decreased, probably owing to a more accurate distinction between HL and the non-Hodgkin's lymphomas (NHL). Elderly patients with HL often have a different presentation, having more advanced disease and less often mediastinal engagement (8). There is also a difference in the distribution of cases in different histopathological subgroups between young and old patients. Elderly patients usually have mixed cellularity (MC) or a lymphocytic depletion (LD) histopathology (9) and are more likely to express Epstein-Barr virus (EBV) in the tumour cells (11–14). This cannot explain the poor prognosis, since MC has only a slightly poorer (12) prognosis, and EBV-positive HL might have a slightly better prognosis (14, 15). No other tumour biological differences between young and elderly HL patients have been found (16, 17). In most studies comprising elderly HL patients, the number of erroneous diagnoses is great (9). However, the poor prognosis remains, also after histopathological re-examination (9).

No reliable prognostic instrument has been described for elderly patients with HL. Recently, a prognostic score has been developed for patients younger than 65 years with advanced HL (18) and shown to be applicable also to lower stages (19).

In Sweden all HL patients in five out of six healthcare regions are reported to a National Care Programme (NCP) for HL. The programme was started in 1985 and it was soon noted that the outcome for patients above the age of 60 years was very poor. When the reasons for this were evaluated, poor tolerance to the intensive chemotherapy seemed to be a major cause, but radiotherapy was well tolerated (9). This led to an amendment of the NCP for elderly patients, valid since 1989. The aim of this study was to evaluate the results of this amendment in two of the Swedish healthcare regions after a prolonged follow-up. Another aim was to apply the International Prognostic Score (IPS) for HL to this elderly patient group.

 ISSN 0284-186X

MATERIAL AND METHODS

National Care Programme (NCP) for HL

Information about histopathology, staging, intention to treat, treatment, relapses and survival is continuously registered in the programme. The registry did not originally include histopathological re-examination or laboratory data. Such data have been retrospectively included, whenever possible. The principles and general results of the NCP have been described (5, 20). The staging procedures and the principles for evaluating staging accuracy are described in Table 1. The recommended treatment between 1985 and 1988 was: Adult patients (16–60 years) in clinical (CS) and pathological (PS) stages IA and PS IIA were treated with radiotherapy (RT) only (mantle field or inverted Y-field, 40 Gy). Patients with CS IIA, and more advanced stages were treated with 6–8 courses of chemotherapy (CT), mainly MOPP/ABVD. Patients with bulky disease in stages CS and PS IA and PS IIA and patients in PS IIB received two courses of CT before RT (mantle field or inverted Y-field, 40 Gy) and patients with bulky disease in advanced stages received additional involved-field RT (30 Gy). For patients above 60 years of age, the treatment recommendations were basically the same as those for younger adults when the treatment was given with curative intention. The following two exceptions were included: mantle field RT was changed to 2 cycles of CT followed by involved field RT, and staging laparotomy was not used.

In the amendment introduced in 1989, the following changes for patients above the age of 60 years were stated. An equally thorough staging procedure was stressed. Patients in stage IA were recommended RT alone, but with reduced volumes (less than mantle field). Patients in stage IB were recommended 2 cycles of CT before RT, as for stage IA. Patients in stage IIA were recommended RT alone in cases with only two adjacent sites involved and no bulky disease. In all other instances, 2 cycles of CT followed by RT were recommended. Patients with stages IIB–IV were recommended to be treated with 6–8 cycles of CT followed by RT in cases of bulky disease or slow regression of the tumour. In this amendment bulky disease was defined as a tumour mass greater then 5 cm, not 10 cm as in younger patients. A new CT regimen, LVPP/OEPA, was introduced having a span of doses from about 50% up to 100% of the doses that should have been used in young patients. The starting dose was at the decision of the treating physician with a demand to escalate the doses if well tolerated (Table 2). Complete remission (CR) was defined as disappearance of all disease and partial remission (PR) as a reduction of more than 50% of all known tumour mass.

A simplified model for determining the treatment intensity was used for patients planned to have 6–8 courses of CT (9). In short, group A received 80% or more of the intended highest dose of CT with no or only minor delay (at most 20% prolongation of the treatment time); group B received 40–80% of the planned dose of CT or more than 20% prolongation of the treatment time; and group C received less than 40% of the planned dose of CT.

Table 1

Staging procedures and definitions of the accuracy of the staging procedures

Investigation	Staging accuracy		
	Adequate	Acceptable	Inadequate
Clinical history	+	+	–
Physical examination	+	+	–
ENT examination	+	–	–
Bone-marrow biopsy	+	+	–
Chest x-ray	+	+	–
CT thorax	+	–	–
CT abdomen	+	+[a]	–
US abdomen	+	+[a]	–
Laparotomy	<60 years	<60 years	

[a] At least one of the abdominal imaging techniques should be performed in order to be considered acceptable.

Table 2

The LVPP/OEPA regimen

	Dose range mg/m^2	Maximum dose (mg)	Schedule
LVPP			
Chlorambucil	4–6	10	P.O. d 1–14
Vinblastine	4–6	10	I.V. d 1
Procarbazin	50–75		P.O. d 1–14
Prednisone	15–25	50	P.O. d 1–14
OEPA			
Vincristine	1.0–1.4	2.0	I.V. d 29
Etoposide	50–100		I.V. d 29
Etoposide	100–200		P.O. d 30,31
Prednisone	15–25	50	P.O. d 1–14
Adriamycin	15–25		I.V. d 29, 42

Patients

All patients above the age of 60 years with a newly diagnosed HL, registered in the NCP between 1985 and 1992 in the Uppsala/Örebro and Southern Sweden healthcare regions were included in the study. These two regions were chosen because the registration was complete. Patients diagnosed between 1985 and 1988 were compared with those diagnosed between 1989 and 1992. In all, 184 patients were registered, 70 patients from the southern region and 114 from the Uppsala/Örebro region. All diagnostic specimens were re-evaluated by one of the authors (CS) using the REAL-classification (21). Stage at diagnosis was determined according to the Ann Arbor principles (22). Thirty-nine patients were considered not to be HL

cases (34 NHL, 1 cancer and in 4 cases a cytologic diagnosis only was performed, which could not be re-evaluated). In 12 cases, the original material could not be found. Eight of those were considered as HL and were included in the material because of a thorough description of HL and the immunohistochemistry results in the original pathology report supporting the diagnosis, whereas four cases were considered not to be HL. In two cases there was no clinical information available and they were excluded, leaving 139 patients included in the study, 77 diagnosed between 1985 and 1988 and 62 between 1989 and 1992. Eighty-one patients were from the Uppsala/Örebro region and 58 from the southern region. There were no significant differences in any clinical parameters or outcome between the patients from the two regions and they are therefore analysed together.

Laboratory data were collected from the patients' files, whenever possible. In total, 6 or 7 of the factors included in the IPS (18) could be retrieved in 108 (78%) patients and those patients were included in the evaluation of the IPS.

The mean and median ages were 72 and 71 years, respectively (range 60–91). There were 81 (58%) men and 58 (42%) women. The clinical characteristics are presented in Table 3. The median follow-up for living patients was 110 months.

Table 3

Clinical characteristics of the included patients

Characteristic	1985–1988	1989–1992	Total
Total no.	77	62	139
Median age (range)	71 (61–91)	71 (60–88)	71 (60–91)
Male (%)	44 (57)	37 (60)	81 (58)
Female (%)	33 (43)	25 (40)	58 (42)
Histopathology			
NS	38 (49)	36 (58)	74 (53)
MC	32 (42)	21 (34)	53 (38)
LD	4	3	7
LRCHL	1	1	2
LP nodular	2		2
Unclassifiable			1
Stage (%)			
I	15 (19)	24 (39)	39 (28)
II	21 (27)	12 (19)	33 (24)
III	24 (31)	13 (21)	37 (27)
IV	17 (22)	13 (21)	30 (22)
B-symptoms (%)	41 (53)	25 (40)	66
No B-symptoms (%)	36 (47)	37 (60)	73
Bulky disease	11 (14)	4 (6)	15
Extranodal disease	17 (22)	14 (23)	31
Staging accuracy (%)			
Adequate	41 (53)	30 (48)	71 (51)
Acceptable	7 (9)	4 (6)	11 (8)
Inadequate	28 (36)	27 (44)	55 (40)

Abbreviations: NS = nodular sclerosis; MC = mixed cellularity; LD = lymphocytic depletion; LRCHL = lymphocyte rich classical Hodgkin's lymphoma; LP nodular = lymphocytic predominance.

Statistical methods

Chi-squared analyses were performed to compare differences in proportions and HL-specific survival was defined as the time from diagnosis to death from or with HL. Patients who died from other causes without any evidence of HL were censored after their deaths. Survival analyses were done with the log-rank test and uni- and multivariate analyses using Cox's proportional hazards model. All factors were first tested univariately and then with a multivariate technique including only the variables with significant univariate correlations ($p < 0.05$).

RESULTS

The survival rate of patients accepted as HL was statistically significantly better than that of those who were not accepted ($p = 0.002$) (Fig. 1).

Stage and accuracy of the staging

There was no difference in the accuracy of the staging procedures between 1985 and 1988 and 1989 and 1992, 54% were adequately staged between 1985 and 1988 and 49% between 1989 and 1992 ($p = 0.63$). There were somewhat more patients in stage III in 1985–1988 and slightly more patients in stage I in 1989–1992 ($p = 0.08$). Furthermore, B-symptoms tended to be more frequent in 1985–1988 (53% vs. 39% ($p = 0.13$)) (see Table 2). Fifteen (11%) patients presented with bulky disease, whereas 31 (22%) patients had extranodal disease. Bone marrow was the most common extranodal presentation and was present in 9 (6%) patients, followed by the liver in 7 (5%) patients.

Treatment

In total, 119 (86%) patients were treated with curative intention, 63/77 (82%) in the period between 1985 and 1988 and 56/62 (90%) between 1989 and 1992 ($p = 0.11$). The mean ages of these patients were 72 and 70 years, respectively. The treatment and treatment results are summarized in Table 4.

Radiotherapy. Thirty-six (27%) patients were treated with primary RT, 13 (17%) with curative and 3 with palliative intention between 1985 and 1988, and 20 (32%), all with curative intention between 1989 and 1992. Twenty-nine patients were in stage IA and 7 in stage IIA disease, and 1 patient had bulky disease. There was no difference in stage distribution between the two time periods. Twenty-nine patients received approximately 40 Gy, and 1 patient 56 Gy (simultaneous breast cancer with lymph node metastases and HL in the axilla). The radiation fields could be summarized into four groups: mantle field or inverted Y (4 patients), reduced mantle field, i.e. exclusion of lower mediastinum and one axilla (5 patients), mini-mantle field (12 patients) and involved field only (15 patients). There were no differences in the type of radiation fields used between 1985–1988 and 1989–1992. All

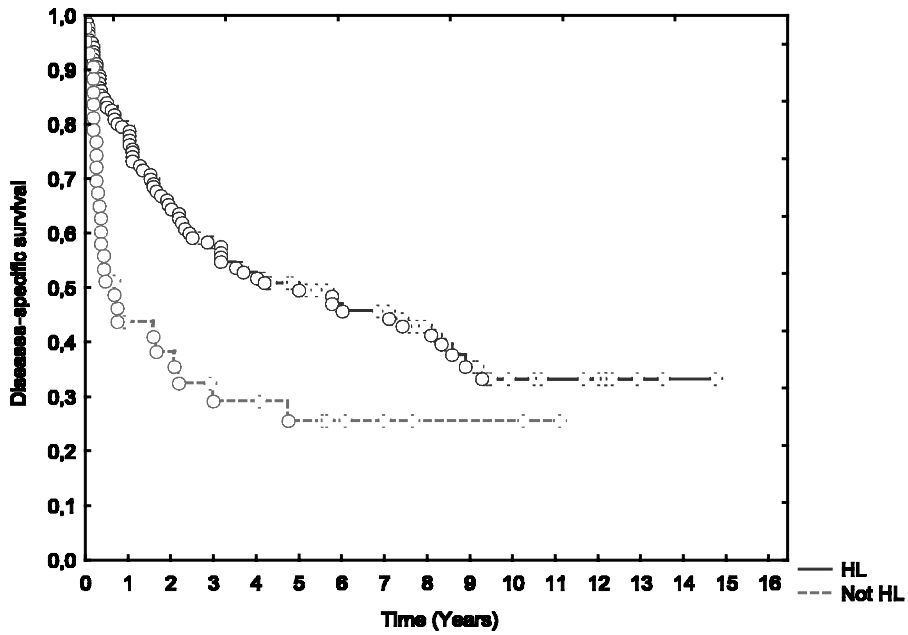

Fig. 1. Disease-specific survival of patients diagnosed with Hodgkin's lymphoma (HL) after histopathological re-evaluation vs. those not accepted as HL ($p = 0.002$).

patients treated with curative intention achieved CR (Table 4). Patients treated with primary RT between 1989 and 1992 tended to have a better survival time, but the difference was not statistically significant ($p = 0.16$) (Fig. 2).

Seven (54%) of the 13 patients treated with curative intention in the first time period suffered relapses, with a median time to relapse of 23 months (range 9–85). All relapses occurred outside the radiation fields. All but two were treated with reduced mantle field or involved field. Two were treated with CT at relapse, the others palliatively, or nor at all. All seven patients died of HL. Seven (35%) of the 20 patients treated with curative intention between 1989 and 1992 relapsed, median 35 months (range 13–46) from diagnosis. All relapses again occurred outside the radiation fields in patients who were treated with reduced mantle field or involved field. Five patients were treated with CT and one has achieved a second CR.

Primary combined therapy. Six patients were treated with primary combined limited CT and RT (Table 4). The single patient treated in the first period (stage IIA) failed to achieve a CR after 4 cycles of ChlVPP and RT. Five patients were treated between 1989 and 1992, 2 in stage IA, 2 in stage IIA and one in stage IIIA, bulky disease. The last patients had a simultaneous hypopharyngeal carcinoma T3N0M0. Four received 2–4 cycles of LVPP/OEPA and one 3 cycles of MOPP. All achieved a CR and none of these patients had relapses.

Primary chemotherapy. Forty-nine patients (64%) were treated with CT with curative intention between 1985 and 1988 and 31 (50%) between 1989 and 1992. The mean age was 70 years in both groups. There was no significant difference between patients in the two time periods regarding stage distribution or presence of B-symptoms. The regimens chosen are presented in Table 5. The mean number of cycles given was 5.5 in 1985–1988 and 6.0 in

Table 4

Results of treatment given with curative intention

Treatment	85–88			89–92		
	Total No.	CR (%)	Relapse 1 (%)	Total No.	CR (%)	Relapse 1 (%)
RT	13	13 (100)	7 (54)	20	20 (100)	7 (35)
CT	49	33 (67)	13 (39)	31	20 (65)	10 (50)
Comb.	1	0	0	5	5	0
Total	63	46 (73)	20 (43)	56	45 (80)	17 (32)

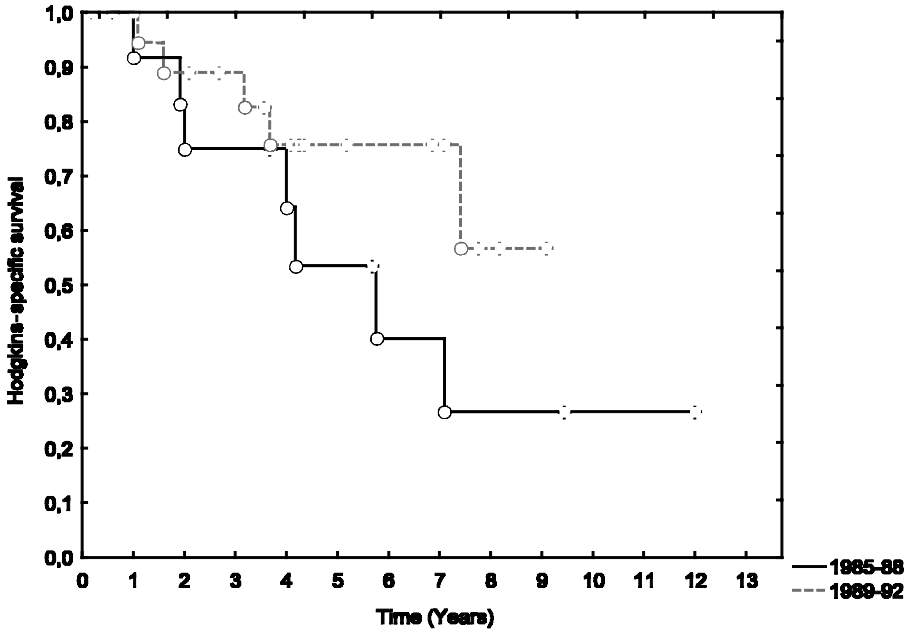

Fig. 2. Hodgkin's lymphoma-specific survival of patients treated with primary radiotherapy with curative intention ($p = 0.16$).

1989–1992 ($p = 0.39$). In total, 10 patients received one course only, 8 in the first period and 2 in the second. The reason for this limited treatment was bone marrow toxicity and death as a result of infection in 5 patients, death from rapid disease progression in 3 patients, death due to acute myocardial infarction in one patient, and in one case, patient refusal. Ten patients received additional RT, 5 in each time period. The reason for the RT was bulky disease or slowly responding disease.

The dose intensity achieved was somewhat higher in 1989–1992 as compared with 1985–1988, 21 (68%) and 22 (45%) patients, ($p = 0.09$), respectively, had received more than 80% of the planned dose with no or minor prolongation. In 1985–1988, 33/49 (67%) of the patients achieved a CR as compared with 20/31 (64%) in the second time period. When LVPP/OEPA and MOPP/ABVD were compared, regardless of year of administration, no significant differences were seen. In the LVPP/OEPA regimen, different dose levels were introduced and a possibility to increase the doses was stressed if treatment started at a lower level and the tolerability was good. Twenty patients were treated with LVPP/OEPA as the primary CT. Most of the patients started at the highest dose level, and none of the patients was subjected to dose escalation. Instead, most patients had dose reductions, because of bone-marrow toxicity.

Table 5

Chemotherapy regimens given with curative intention

Regimen	1985–1988	1989–1992
MOPP/ABVD	16	3
LVPP/OEPA	0	20
ChlVPP	11	5
MOPP	19	3
CHOP	1	1
ABVD	1	0
OPEC	1	0
Total	49	31

There were also no significant differences in toxicity between the time periods when all regimens were considered. In all, 14 treatment-related deaths were seen, 9 between 1985 and 1988 and 5 between 1989 and 1992 ($p = 0.86$). Serious infectious complications were reported in 15 and 13 patients, respectively ($p = 0.26$). Many infectious complications were opportunistic infections, e.g. pneumocystis carinii, deep fungal infections and herpes zoster. Neurotoxicity was reported in 10 and 8 patients, respectively ($p = 0.51$).

Thirteen (39%) of the 33 patients treated with curative intention who reached a CR between 1985 and 1988 suffered relapses. Two were treated with RT and one patient is in continuous CR (CCR). The others were treated with CT or palliatively but subsequently died of HL. Ten (50%) out of 20 complete responders treated with curative intention between 1989 and 1992 have suffered relapses. Three were treated with RT and one is in CCR. The others were treated with CT or palliatively and all subsequently died of HL. There was no difference in survival rate between 1985 and 1988 as compared with 1989 and 1992 (Fig. 3).

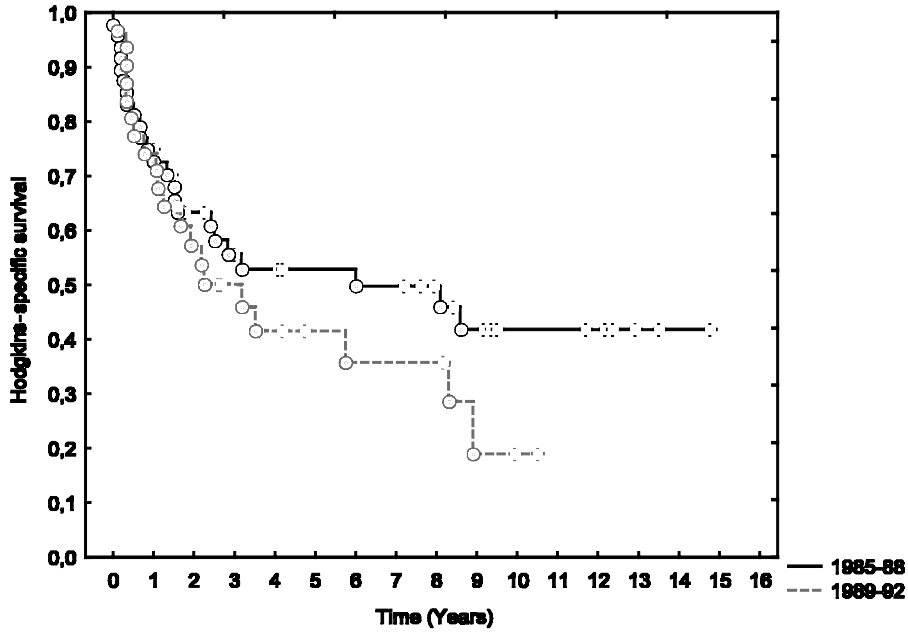

Fig. 3. Hodgkin's lymphoma-specific survival of patients treated with primary chemotherapy with curative intention (p = 0.26).

The international prognostic score

In 108 patients, ≥ 6 factors included in the IPS could be identified (Table 6). The most prevalent prognostic factors were male sex and low S-albumin. The latter was seen in about two-thirds of the patients. Twenty-nine percent of the patients had an IPS ≥ 4 (age + ≥ 3 factors) and a poorer survival rate, although not statistically significant when analysed with the log rank test (p = 0.10), but when analysed with an alternative test, Gehan's Wilcoxon test, the difference was statistically significant (p = 0.02) (Fig. 4). No other cut-off level discriminated better for prognosis.

Survival in all patients

When survival was analysed in all patients and in those treated with curative intention, there was no difference between patients treated between 1985 and 1988 and those

Table 6

The international prognostic score

Factor	All patients (n = 118)		Patients treated with curative intention (n = 94)	
	Frequency (%)	Missing (%)	Frequency (%)	Missing (%)
Age > 45 years	118 (100)		94 (100)	
Male sex	62 (57)		66 (67)	
Stage IV	24 (22)		22 (22)	
S-Albumin < 40 g/L	71 (66)	16 (15)	66 (67)	11 (11)
B-Hb < 105g/L	22 (20)		22 (22)	
WBC > 15×10^9/L	8 (7)	1	8 (8)	1 (1)
Lymphocytes < 0.6×10^9/l	7 (6)	26 (24)	6 (6)	25 (26)
No. of risk factors				
0	0		0	
1	11 (10)		9 (9)	
2	36 (33)		31 (32)	
3	32 (30)		29 (30)	
4	22 (20)		22 (22)	
5	6 (6)		6 (6)	
6	1 (1)		1 (1)	
7	0		0	

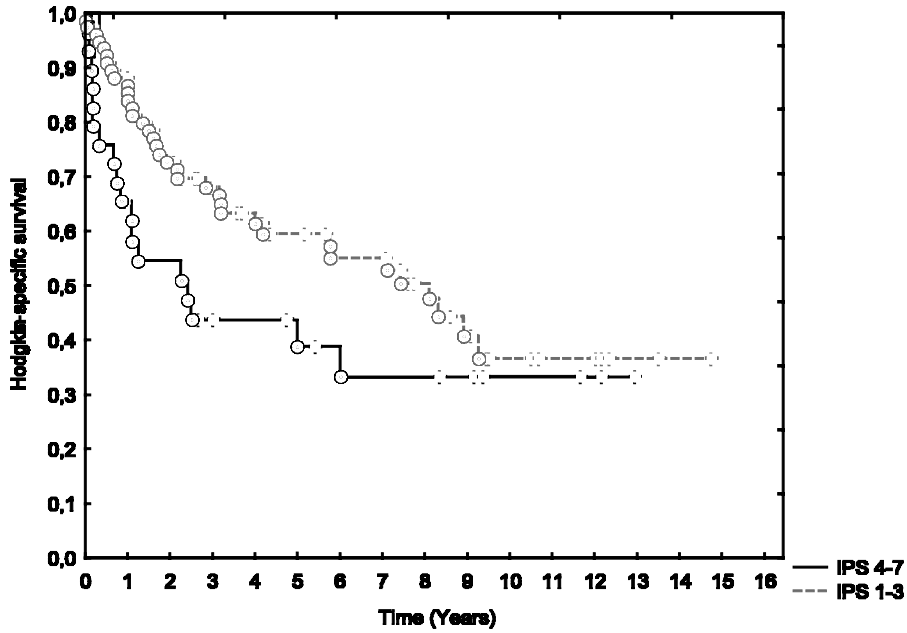

Fig. 4. Hodgkin's lymphoma-specific survival of patients with an International Prognostic Score (IPS) of 1–3 vs. >4 ($p = 0.10$ with the log-rank test and $p = 0.02$ with Gehan's Wilcoxon test).

treated between 1989 and 1992 (Fig. 5). In univariate analyses, age, B-Hb, lymphocyte count and stage III–IV all affected survival significantly. In a multivariate analysis, age was the only statistically significant factor. The importance of age is illustrated in Fig. 6.

DISCUSSION

In the present study we have evaluated the new principles for treatment of elderly patients with HL presented in an amendment of the National Care Programme for HL. The principles are based on the results of a retrospective evalu-

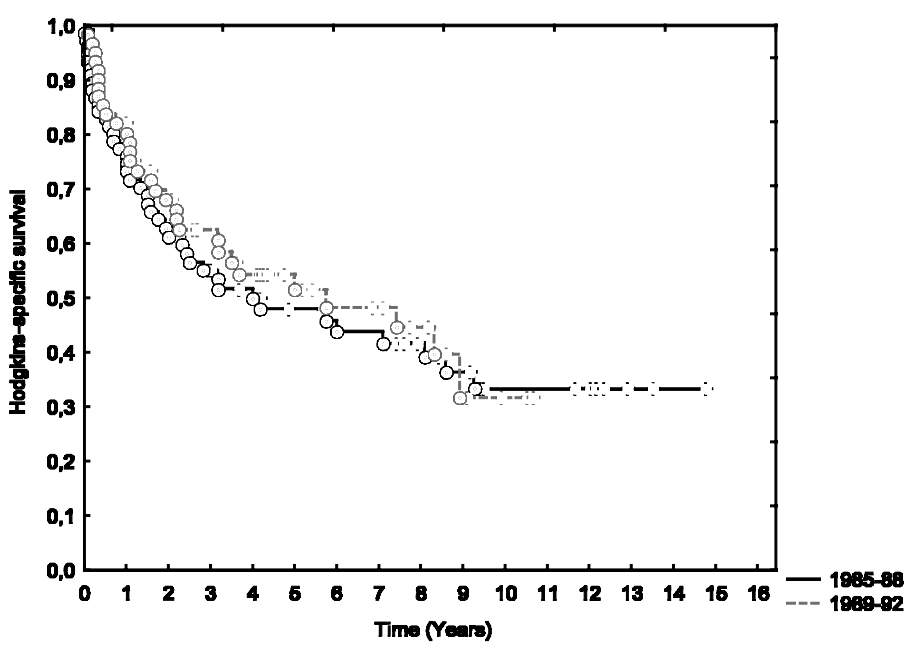

Fig. 5. Hodgkin's lymphoma-specific survival of patients diagnosed between 1985 and 1988 vs. 1989 and 1992.

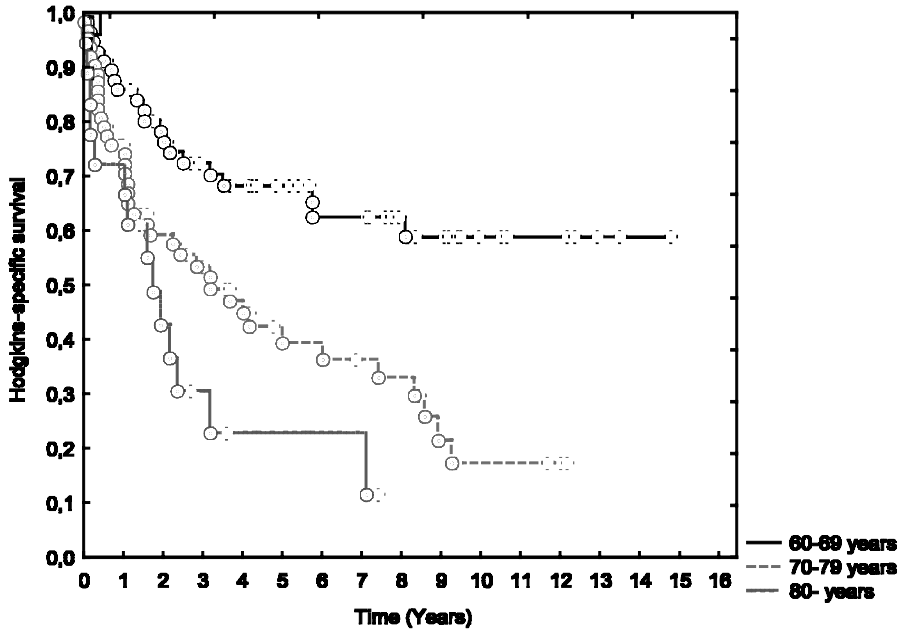

Fig. 6. Hodgkin's lymphoma-specific survival in different age groups ($p = 0.01$).

ation of the staging intensity and treatment results in elderly HL patients in a defined population. In that study, staging was insufficient in too many patients, and they did not tolerate the intensive chemotherapy regimens given to younger patients (9). This resulted in early termination of treatment in many patients, with consequent poor outcome. By administering a lower initial dose of chemotherapy in those with concomitant diseases/poor performance, it was hypothesized that a higher total dose could be given, with a higher cured fraction. A similar approach has been tried by Levis et al. who treated 25 patients above the age of 65 with the CVP/CEB (23). They found a good remission rate but a high relapse rate and a poorer survival time than in patients treated with more aggressive regimens. In contrast, Zinzani et al. reported apparently better results in a group of 19 patients above the age of 60 years treated with the VBM (vinblastine, bleomycin, methotrexate) regimen (24). The overall results of the present study, however, revealed no survival benefit with this approach. In order to draw valid conclusions from non-randomized comparisons, patient selection must be known in great detail. In practice, this requires population-based series where any selection is eliminated after having traced every individual with the diagnosis. The Swedish healthcare system allows this. The advantages of various trial designs and the possibilities of drawing conclusions from population-based studies with complete registration have already been discussed (25). However, the comparison with other studies of HL must be interpreted with caution since the present study has been re-evaluated with modern histopathology excluding patients with NHL and a poor prognosis.

The awareness of the importance of staging and caring also for elderly patients with HL, stressed in the amendment and discussed at repeated meetings, thus did not result in any indication of improved outcome. The hypothesis behind some of the changes in the treatment recommendations may be wrong, or the changes made too small to influence outcome to such an extent that it can be detected in these limited patient series. It was, however, disappointing that staging intensity was not improved, reaching the same standard as that used in young patients (5, 20). The reason for this is difficult to elucidate in retrospect, since the reasons for not performing the recommended staging procedures were not given on the forms. However, it is possible that the importance of adequate staging was not sufficiently stressed in the programme. Of course, the poor staging might contribute to a rather poor prognosis in low-stage patients.

Haematological toxicity was pronounced throughout the entire chemotherapy-treated group and several patients also contracted opportunistic infections. The reasons for poor toleration of chemotherapy among elderly HL patients might be at least partly attributable to circulating tumour necrosis factor (TNF). High TNF-levels predict myelosuppression in patients with lymphoma (26). High levels of TNF are also seen in patients with HL (27). The immune deficiency described in HL patients (28) combined with the myelosuppression caused by TNF might be extra deleterious in elderly HL patients. None of the patients in the present study received G-CSF. In the light of the high prevalence of haematological toxicity, this is a patient

group suitable for this type of support. Opportunistic infections, however, also occurred in periods when the patients were not neutropenic. Since elderly HL patients have an even more pronounced immune deficiency (28) than young patients, they might also benefit from prophylactic antibiotics. Since virtually all patients received the highest dose level up-front, doctors treating lymphoma had either no confidence in starting with a lower dose, or they overestimated the ability of their patients to tolerate the treatment. The idea that elderly patients may do better with a slightly lower initial dose that could be maintained, or even escalated, without much delay in a greater proportion of the patients can thus not be rejected.

Radiotherapy was relatively well tolerated in the retrospective study and the indications for radiotherapy were widened in the amendment. In the second time period, patients treated with RT clearly tended to have a better survival time, although a greater proportion of the patients were treated with RT only, thus excluding that less advanced patients were chosen for RT only. This could imply that RT is an important treatment in this patient group. The role of RT is further stressed by the relatively excellent survival rate found in the group of patients receiving primary combined modality treatment.

The optimal treatment of elderly patients with HL cannot be concluded from this study. We believe that whatever regimen is chosen, a combination of G-CSF and prophylactic antibiotics to prevent opportunistic infections should be considered.

ACKNOWLEDGEMENTS

This study was supported by grants from the Swedish Cancer Society and from the Lions Cancer Research Foundation, Uppsala, Sweden.

REFERENCES

1. Guinee VF, Giacco GG, Durand M, et al. The prognosis of Hodgkin's disease in older adults. J Clin Oncol 1991; 9: 947–53.
2. Vaughan Hudson B, MacLennan KA, Easterling MJ, et al. The prognostic significance of age in Hodgkin's disease: examination of 1500 patients (BNLI report no. 23). Clin Radiol 1983; 34: 503–6.
3. Erdkamp FL, Breed WP, Bosch LJ, Winjen JT, Blijham GB. Hodgkin's disease in the elderly. Cancer 1992; 70: 830–4.
4. Walker A, Schoenfeld ER, Lowman JT, et al. Survival of the older patient compared with the younger patient with Hodgkin's disease. Cancer 1990; 65: 1635–40.
5. Glimelius B, Enblad G, Kälkner M, et al. Treatment of Hodgkin's disease: the Swedish National Care Program experience. Leuk Lymphoma 1996; 21: 71–8.
6. Gustavsson A. Hodgkin's disease of the elderly. A different disease? Hematol Oncol 1993; 11 (Suppl 1): 73–7.
7. Sextro M. Difference in clinical presentation and course between adult patients with Hodgkin's disease older and younger than 60 years. Am Soc of Hematol, Dec 1996. Blood 1997; 88 (Suppl 1): 227A (Abstr).
8. Illes A, Vadasz G, Gergely L, Szegedi G. Hodgkin's disease in the elderly: a single institution retrospective study of 40 patients aged 65 or over. Haematologia (Budap) 2000; 30: 263–9.
9. Enblad G, Glimelius B, Sundström C. Treatment outcome in Hodgkin's disease in patients above the age of 60: a population based study. Ann Oncol 1991; 2: 297–302.
10. Brandt L, Kimby E, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in Hodgkin's disease. Acta Oncol 2001; 40: 185–97.
11. Glaser SL, Lin RJ, Stewart SL, et al. Epstein-Barr virus-associated Hodgkin's disease: epidemiological characteristics in international data. Int J Cancer 1997; 70: 375–82.
12. Jarret AF, Armstrong AA, Alexander E. Epidemiology of EBV and Hodgkin's lymphoma. Ann Oncol 1996; 7 (Suppl 4): 5–10.
13. Niedobitek G. The role of Epstein-Barr virus in the pathogenesis of Hodgkin's disease. Ann Oncol 1996; 7 (Suppl 4): 11–7.
14. Enblad G, Sandvej K, Sundström C, Pallesen G, Glimelius B. The proportion of EBV-positive Hodgkin's disease in an unselected population. Acta Oncol 1999; 38: 425–9.
15. Naresh KN, Johnson J, Srinivas V, et al. Epstein-Barr virus association in classical Hodgkin's disease provides survival advantage to patients and correlates with higher expression of proliferation markers in Reed-Sternberg cells. Ann Oncol 2000; 11: 91–6.
16. Morente MM, Piris MA, Abraira V, et al. Adverse clinical outcome in Hodgkin's disease is associated with loss of retinoblastoma protein expression, high Ki 67 proliferation index, and absence of Epstein-Barr virus latent membrane protein 1 expression. Blood 1997; 90: 2429–36.
17. Enblad G, Sundström C, Glimelius B. Immunohistochemical characteristics of Hodgkin and Reed-Sternberg cells in relation to age and clinical outcome. Histopathology 1993; 22: 535–41.
18. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. N Engl J Med 1998; 339: 1506–14.
19. Franklin J, Paulus U, Lieberz, et al. Is the international prognostic score for advanced stage Hodgkin's disease applicable to early stage patients? Ann Oncol 2000; 11: 617–623.
20. Amini R-M, Enblad G, Gustavsson A, et al. Treatment outcome in patients younger than 60 years of advanced stages (IIB–IV) Hodgkin's disease. Eur J Haematol 2000; 65: 379–89.
21. Harris NL, Jaffe ES, Stein H, et al. A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 85: 1361–92.
22. Carbone PP, Kaplan HS, et al. Report on the committee on Hodgkin's disease staging. Cancer Res 1971; 31: 1960–1.
23. Levis A, Depaoli L, Bertini M, et al. Results of a low aggressive chemotherapy regimen (ChlVP/CEB) in elderly Hodgkin's disease patients. Haematologica 1996; 81: 450–6.
24. Zinzani PL, Magagnoli M, Bendandi M, et al. Efficacy of the VBM regimen in the treatment of elderly patients with Hodgkin's disease. Haematologia 2000; 85: 729–32.
25. Nygren P, Glimelius B. The Swedish council of technology assessment in health care (SBU) report on cancer chemotherapy—project objectives, the working process, key definitions and general aspects on cancer trial methodology and interpretation. Acta Oncol 2001; 40: 155–65.
26. Voog E, Warzocha K, Moullet I, et al. Factors that predict chemotherapy-induced myelosuppression in lymphoma patients: role of the tumour necrosis factor ligand-receptor system. J Clin Oncol 2000; 18: 325–31.
27. Vener C, Guffanti A, Pomati M, et al. Soluble cytokine levels correlate with the activity and clinical stage of Hodgkin's disease. Leuk Lymphoma 2000; 37: 333–9.
28. Tullgren O, Grimfors G, Holm G, et al. M. lymphocyte abnormalities predicting a poor prognosis in Hodgkin's disease. Cancer 1991; 68: 768–75.