original paper

PROBABILITY OF CURE IN ELDERLY HODGKIN'S DISEASE PATIENTS

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ABSTRACT

Background. **Elderly Hodgkin's disease patients have a poor prognosis. The question arises whether these patients need aggressive treatment or a palliative strategy. So far, as a consequence of the scarcity of trials designed for them, useful information can be obtained only by retrospective analyses.**

Methods. **We retrospectively studied clinical data from 567 patients recorded from 1982 to 1989 in the Piemonte Hodgkin's Disease Register (PHDR). The 65 patients over 65 years of age were compared to younger ones. We analyzed the role of disease independently of confounding variables, mainly inadequacy of staging and/or treatment, comorbidity and toxicity.**

Results. **In the elderly comorbidity was as high as 35%. Forty elderly patients (60%) entered a suboptimal plan with a low degree of aggressivity, which was different from the usual PHDR protocol. Elderly patients also had a high proportion of subsequent protocol interruptions (25%). Chemotherapy dose intensity was negatively affected by advanced age ($p < 0.01$ after both 3 and 6 courses of chemotherapy). Toxic deaths were significantly higher in elderly patients than in younger ones (14% vs 1%; $p < 0.05$). CR rates, overall survival (OS), disease-specific survival (DSS) and event free survival (EFS) were all significantly influenced by age ($p < 0.01$). Relapse-free survival (RFS) in patients achieving CR did not differ according to age class (77% vs 60%; p = ns). RFS was better in elderly patients entering the PHDR protocols than in those following an alternative plan (75% vs 54%; $p = 0.04$); however, elderly patients treated according to PHDR guidelines showed a higher incidence of toxic deaths than those treated less aggressively (23% vs 8%). The two groups had similar EFS (36% vs 24%; p = ns).**

Conclusions. **Elderly patients who achieve CR can have good RFS and cure is possible, but the toxic cost of conventional strategies is unacceptable and selected strategies still must be found.**

Key words: Hodgkin's disease, elderly, chemotherapy, prognosis

Advanced age has been considered an unfavorable prognostic feature for patients with Hodgkin's disease.[1,2] Elderly patients are usually excluded from clinical trials; therefore the cut-off point for prognostic evaluation is usually between forty and fifty years.[3-5] The role of age has not been clearly explained by the authors who have dealt with patients over 65 or 70 years old.[6-9] In fact, the independent prognostic value of age may be biased by other factors, difficult to control in large retrospective studies. Poor results in elderly patients may be explained by either more aggressive disease or a series of treatment-relat-

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Received on July 27, 1993; accepted December 6, 1993.

ed variables, such as incomplete staging procedures, reduced chemotherapy dose intensities, decreased compliance and increased toxicity.

When all causes of death are grouped together, an age-related difference in survival may be forecasted. The question arises whether a curative approach is better than a palliative one in the elderly. Therefore the best end point to assess is overall chance of cure, i.e. the percentage of patients achieving stable complete remission, while taking into account the relative toxic cost.

The present study is focused on a group of 65 elderly patients, out of a total of 567 Hodgkin's disease patients, whose clinical data were prospectively collected in the Piemonte Hodgkin's Disease Register (PHDR). In order to answer the question of curability in elderly patients, our analysis considered confounding factors, mainly treatment-related variables: adequacy of staging and treatment plan, drug dose intensity and toxic-related deaths.

Materials and methods

Patients and treatments

From January, 1982 to December, 1989, 567 untreated Hodgkin's disease patients were staged and treated at the 14 Institutions contributing to the Piemonte Hodgkin's Disease Register. From an epidemiological analysis, it was found that this number of non selected patients represented about 80% of all Hodgkin's patients treated in Piemonte during these 8 years. The major aims of the PHDR are to collect epidemiological data in Piemonte and to permit quality control analysis. During the period under examination, two different clinical protocols were proposed:

1. HO82 (from January, 1982 to December, 1985)

Staging procedures included conventional biochemistry, chest X-ray, lymphangiogram and bone marrow biopsy in all patients. Abdominal CT scan and/or ultrasound were not routinely performed. Peritoneoscopy with liver biopsy was carried out in those patients with clinical/laboratory uncertainty regarding liver involvement. Staging laparotomy with splenectomy was mandatory only for those stage I A or II A patients who were to be treated with radiotherapy alone. A mediastinal mass greater than one third of the thoracic diameter was defined as bulky mediastinal disease. The following treatment guidelines were proposed:

a. *stage IA or IIA without bulky mediastinal mass*: staging laparotomy followed by subtotal nodal irradiation (STNI), or 3 courses of MOPP chemotherapy followed by STNI without laparosplenectomy, according to the primary physician.
b. *stage IIIA without bulky mediastinal mass*: 3 courses of MOPP followed by total nodal irradiation (TNI).
c. *any stage other than IV with bulky mediastinal mass and/or B symptoms*: 6 courses of MOPP followed by TNI in stage III and STNI in stage II.
d. *stage IV*: MOPP alternated with ABVD for a total of 9/12 courses.

2. HO86 (from January, 1986 to December, 1989)

The following staging differences were introduced into the HO82 program:

- thoracic and abdominal CT scan for all patients;
- lymphagiogram was omitted in patients with infradiaphragmatic involvement already documented by CT scan.

The treatment plan was changed as follows:

a. *stage IA or IIA without bulky mediastinal involvement*: laparosplenectomy followed by STNI.
b. *stage IA or IIA with bulky mediastinal involvement*: 3 courses of ABVD followed by STNI.
c. *stage III*: 3 courses of ABVD followed by TNI.
d. *stage IV and all patients with B symptoms*: a total of 6/9 courses of 1/2 MOPP - 1/2 ABVD (MAMA) with radiotherapy limited to the sites of initial bulky disease.

MOPP and ABVD were given as originally proposed by De Vita et al.[10] and by Bonadonna et al.,[11] respectively. Drug doses were regulated according to peripheral blood counts. No special protocol was designed for elderly patients. After 3 courses of chemotherapy and on completion of the whole protocol, remission status was assessed and patients were classified as being in:

complete remission (CR): complete disappearance of all pretreatment lesions with no signs or symptoms of active disease;

partial remission (PR): more than a 50% decrease in the size of all measurable pretreatment lesions;

failure (F): no response, disease progression, or less than a 50% decrease in the size of any lesion.

Statistical methods

Data were collected from all patients at diagnosis. Clinical information was recorded, even if staging and therapy protocol had not been regularly followed. The reasons, if any, for choosing an alternative program were also registered. The computer file for data processing was updated in December 1992, with a minimum follow-up period for censored patients of 36 months. Early deaths were included as failures in the evaluation of both final complete remission (CR) and overall survival (OS) time. Patients who died from causes clearly unrelated either to Hodgkin's disease or its treatment were considered to be unrelated deaths and were excluded from the events of disease-specific survival (DSS). Relapse-free survival (RFS) curves were plotted for patients entering CR; patients dying of unrelated causes while in CR were considered as censored in the calculation of RFS. The few patients lost to follow-up during the initial phase of therapy, while having a good performance status, were excluded from analysis of remission and relapse-free survival. Event-free survival (EFS) curves were plotted as an index of overall chance for cure, considering as failure any type of unfavorable event: failure to achieve CR, relapse, toxic death, etc.

After 3 and 6 chemotherapy courses, the actual dose intensity of each cytotoxic drug was calculated as mg/sqm/week, according to the method of Hryniuk and Bush.[12]

The relative dose intensity of each drug was calculated as the ratio between actual and projected dose intensity. The arithmetic mean of relative drug dose intensities after 3 (RDI3) and 6 (RDI6) courses of chemotherapy was used as an indicator of drug delivery adequacy.

Differences among means were evaluated by the T-test. The chi-square test was used to compare two ratios for equivalence. All curves were calculated according to the Kaplan-Meier method.[13] Differences between curves were assessed for significance with the generalized Wilcoxon method.[14]

Table 1. Distribution of clinical features at diagnosis by age group. Percentages in parentheses.

		< 65 y. N = 502		*> 65 y. N = 65*		*p value*
protocol	HO82	237	(47)	28	(43)	n.s.
	HO86	265	(53)	37	(57)	
histology	LP	36	(7)	1	(1)	< 0.01
	NS	281	(56)	19	(29)	
	MC	154	(31)	40	(62)	
	LD	20	(4)	3	(5)	
	Unknown	11	(2)	2	(3)	
symptoms	A	308	(61)	38	(59)	n.s.
	B	194	(39)	27	(41)	
stage	I and II	301	(60)	37	(57)	n.s.
	III	107	(21)	18	(28)	
	IV	94	(19)	10	(15)	
mediastinal adenopathies						
	absent	210	(42)	54	(83)	< 0.01
	non bulky	180	(36)	10	(15)	
	bulky	112	(22)	1	(2)	
infradiaphragmatic stage II		55	(11)	16	(25)	< 0.01

Results

Study population

The median age of the 65 elderly patients was 72 years (range 66-80). The clinical features at diagnosis are listed in Table 1 and compared with those of younger patients enrolled during the same period. Elderly patients had a significantly higher incidence of mixed cellularity histology (62 vs 31%; $p < 0.01$). The older group was also more likely to show infradiaphragmatic presentation (25 vs 11%; $p < 0.01$) and an absence of intrathoracic involvement (83 vs 42%; $p < 0.01$). There was no significant difference in stage or B symptoms between young and elderly patients.

Comparison of young versus elderly patients

Treatment profiles and results by age group are summarized in Table 2; 397 (79%) young patients entered the program suggested by the PHDR, as compared to only 26 (40%) elderly patients. Independently of initial choice, a subsequent violation of the original plan was needed in 33 (12%) young and in 16 (25%) elderly patients ($p = 0.06$). In the older group, difficulty in following the planned treatment was mainly due to a high incidence of poor hematological tolerance (11 patients = 17%). For this group of 11 patients treatment modification consisted of treatment interruption before the last planned chemotherapy course (9 patients), or of a reduction in radiation fields (2 patients). Protocol violations secondary to disease progression consisted of a shift to salvage chemotherapy regimens and were similar in the two age groups (6% vs 8%; p = ns).

Mean relative drug dose intensities of patients entering a chemotherapy program were influenced by age: 86 vs 65% after 3 courses of chemotherapy and 75 vs. 47% after 6 courses of chemotherapy ($p<0.01$).

CR rates were significantly higher in younger patients than in the older ones: 82 vs 67% ($p < 0.01$). Actuarial 8-year OS rate was, as expected, better in the younger group (72 vs 46%; $p < 0.01$). Moreover, survival differences were maintained even when deaths not related to Hodgkin's disease were counted as censored in the DSS curves (76 vs 50%; $p < 0.01$). The chance of cure expressed by the EFS curves was clearly affected by age (68 vs 41%; $p < 0.01$). However, there was no difference in RFS rates between complete responders in the two age groups (77 vs 60%; p = ns), as shown in Figure 1.

Other concurrent diseases requiring specific treatment and/or reducing the performance status were present in 23 (35%) elderly patients. The incidence of toxic deaths during induction therapy was higher in elderly patients than in the younger ones: 14 vs 1%; $p < 0.01$. The nine deaths considered to be related to induction

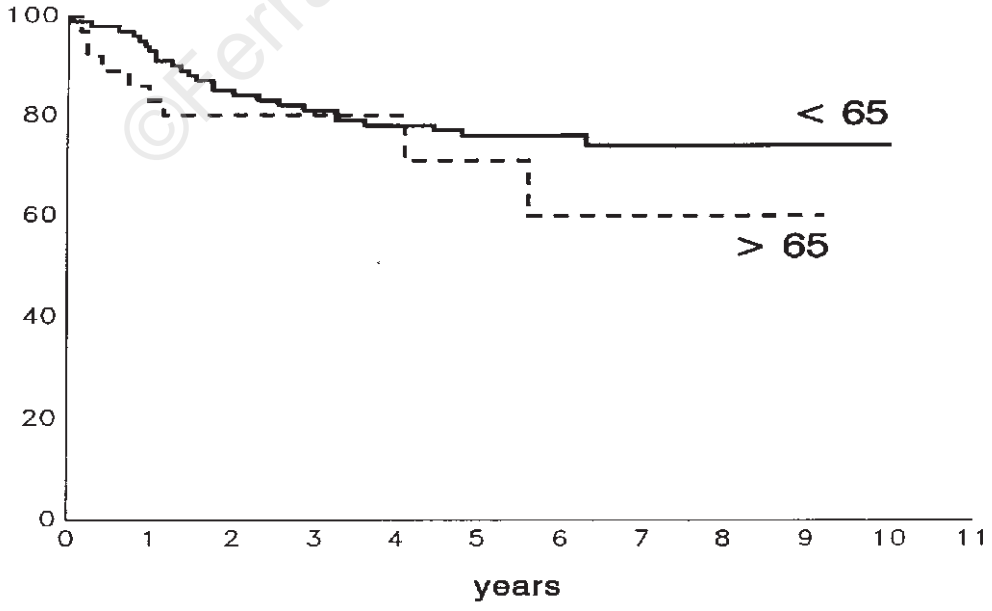

Figure 1. Relapse-free survival of patients who achieved CR, according to age.
Patients under 65 years of age (——) versus patients over 65 years old (- - -); p = n.s.

treatment in the older group were distributed as follows: 1 heart failure, 5 neutropenic sepsis, 2 hepatic comas, 1 cachexia. Comorbidity was higher in the group of patients who subsequently suffered toxic death (6/9 = 66%) than in the remaining 56 patients (17/56 = 30%). Clinical outcome in the elderly was not affected by histological subtype, and the 43 patients who showed mixed cellularity or lymphocyte depletion disease did not fare worse than the 20 with more favorable histology.

Role of treatment strategy in elderly patients

A comparison among the elderly patients of both prognostic variables and results according to treatment profile is summarized in Table 3. The mean age of the 26 patients following PHDR guidelines was lower than that of the remaining 39 elderly patients (70 vs 73; $p < 0.01$), while distribution of sex, stage, histology, B symptoms and comorbidity was similar in the two treatment groups. Of the 39 elderly patients who entered an alternative plan, 36 cases (92%) can be considered suboptimally managed (understaged or undertreated) according to PHDR guideline criteria. Of these 39 patients treated out of protocol, 31 (87.7%) had their staging and treatment plan selected with curative intent, even though it was less aggressive than that foreseen by the protocol. The remaining 8 patients (12.3%) were treated with palliative intent: only involved field radiotherapy in stages I and II, and sequential vinblastine in advanced stages.

The incidence of toxic deaths during induction therapy was higher in patients following conventional PHDR guidelines (6/26 = 23%) than in those adhering to an alternative plan (3/39 = 8%), although the difference was not statistically significant. Elderly patients treated according to PHDR guidelines had a better 8-year RFS rate than those entering a less aggressive plan: 75 vs 54%; $p = 0.04$ (Figure 2); however, the 8-year EFS rate was not influenced by the initial treatment option (24 vs 36%; p = ns), as shown in Figure 3.

Discussion

As a result of the recent increase in life expectancy, oncologists are now frequently faced with having to treat elderly patients. Nevertheless, the most appropriate management for this group of patients has still not been defined. Elderly patients are usually excluded from conventional trials, and the need for randomized studies limited to this age group has been suggested.[15, 16] So far, only few

Table 2. Treatment profile and clinical outcome by age group.

	< 65 y.	> 65 y.	p value
initial treatment plan			
a. protocol	397 (79%)	26 (40%)	< 0.02
b. alternative	105 (21%)	31 (48%)	
c. palliative	— —	8 (12%)	
results			
CR	82%	67%	<0.01
RFS	77%	60%	n.s.
OS	72%	46%	<0.01
DSS	76%	50%	<0.01
EFS	68%	41%	<0.01
causes of death			
a. Hodgkin's disease	52	12	
b. toxic deaths			
- during induction	5	9	
- during salvage	8	1	
- second cancer	5	—	
- other later toxicity	5	—	
c. causes not related to HD	4	1	

CR = complete remission rate, RFS = 8-year relapse-free survival rate of patients achieving complete remission, OS = 8-year overall survival rate, DSS = 8-year disease-specific survival, EFS = 8-year event-free survival rate.

preliminary data on treatment strategies tailored to advanced age are available for Hodgkin's disease.[17, 18] This is also a consequence of the low number of elderly patients with this pathology as compared to those with other hematological malignancies, due to the fact that the incidence of Hodgkin's disease in advanced age decreases the older a person gets. In the meantime, preliminary information can only be obtained by retrospective analyses.

The negative impact of age over 65 on prognosis of Hodgkin's disease patients has been reported in many studies.[7, 9] Authors agree that in later life Hodgkin's disease shows peculiar clinical features, and this aspect has been confirmed in our study with regard to histology and frequency of infradiaphragmatic presentation. However, differences in stage or symptoms by age groups were not shown. Some authors[8, 19] suggest that histological subtype at diagnosis may play a role in explaining the poor outcome in the elderly, but, as was the case with Mc Guinee's study,[7] our data showed no prognostic difference on the basis of histology. The varying histological patterns might imply different biological behavior but their role in affecting prognosis remains uncertain, and the disease risk factors are probably similar for younger and older patients.

If the influence of a peculiar biological or clinical presentation is minimized, age-related variables could play a major role in affecting prognosis. Performance status and concurrent cardiac, renal or lung diseases are strictly age-related. A difference in survival due to these factors, which are so closely related to increasing age, should be predicted; however, these variables count for only a small part of the increasing deaths rates, as is demonstrated by the similarity between overall survival and DSS in our series as well as in those of other authors.[7, 8, 19] It could be argued that toxic deaths were included as failures when computing DSS in our analysis. The toxic risk was very high in our patients; this can be at least partially explained by the high incidence (35%) of comorbidity, which reached 66% in the subgroup of patients who suffered toxic death. It might be difficult to separate unrelated deaths from toxic deaths, but in our opinion deaths possibly due to treatment complications during induction chemotherapy cannot be considered independently from Hodgkin's disease, and they have to be counted as an event in DSS (8), even though they are partially dependent on comorbidity and treatment aggressiveness.

Table 3. Features at diagnosis and clinical outcome of elderly patients by treatment strategy.

		protocol	*alternative treatment*	*p value*
# of patients		26	39	
mean age		70.2	73.3	0.004
male sex		14 (54%)	23 (59%)	n.s.
B symptoms		12 (46%)	15 (38%)	n.s.
stage	I + II	11 (24%)	24 (62%)	n.s.
	III	11 (42%)	9 (23%)	
	IV	4 (16%)	6 (15%)	
histology	LP+NS	11 (42%)	11 (28%)	n.s.
	MC+LD	15 (58%)	28 (72%)	
comorbidity		8 (31%)	15 (38%)	n.s.
early toxic deaths		6/26 (23%)	3/39 (8%)	n.s.
RC		61%	71%	n.s.
RFS		75%	54%	0.04
OS		48%	50%	n.s.
EFS		36%	24%	n.s.

CR = complete remission rate, RFS = 8-year relapse-free survival rate of patients achieving complete remission, OS = 8-year overall survival rate, DSS = 8-year disease-specific survival, EFS = 8-year event-free survival rate.

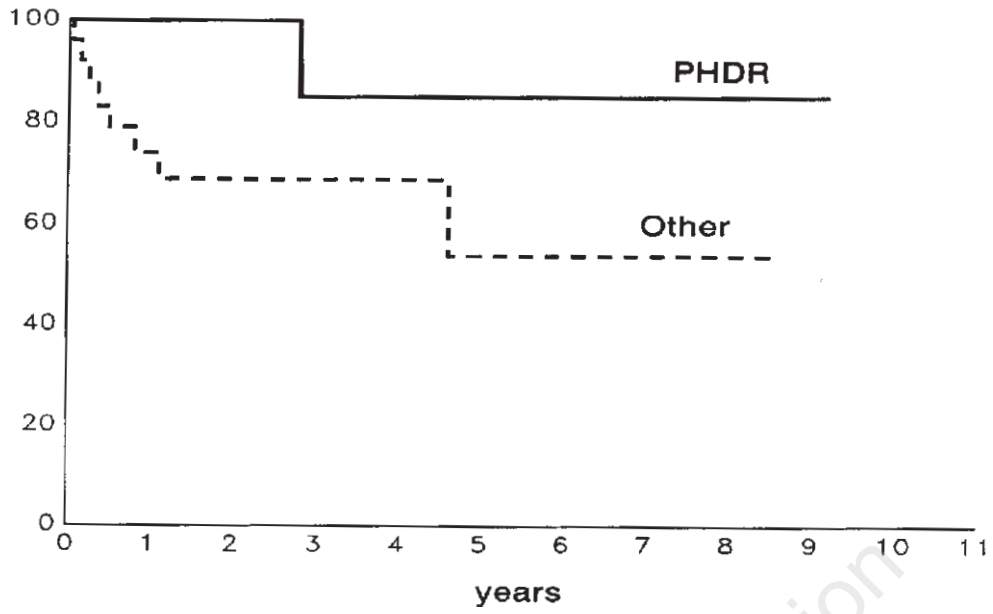

Figure 2. Relapse-free survival of elderly patients who achieved CR, according to treatment plan. PHDR protocol (——) versus a less aggressive plan (- - -); p = 0.04.

It is evident from our data that therapy-related variables, mainly program feasibility and treatment-related toxicity, play an important prognostic role. The percentage of elderly patients who entered a suboptimal treatment protocol was as high as 60% (with a strictly palliative aim in 12% of these cases). Patient age influenced the decision to choose a treatment plan different from the PHDR protocol, but the two groups of patients (aggressively and non aggressively treated) did not differ with regard to other prognostic variables, mainly comorbidity, as shown in Table 3. Moreover, the incidence of dose intensity reductions or of pro-

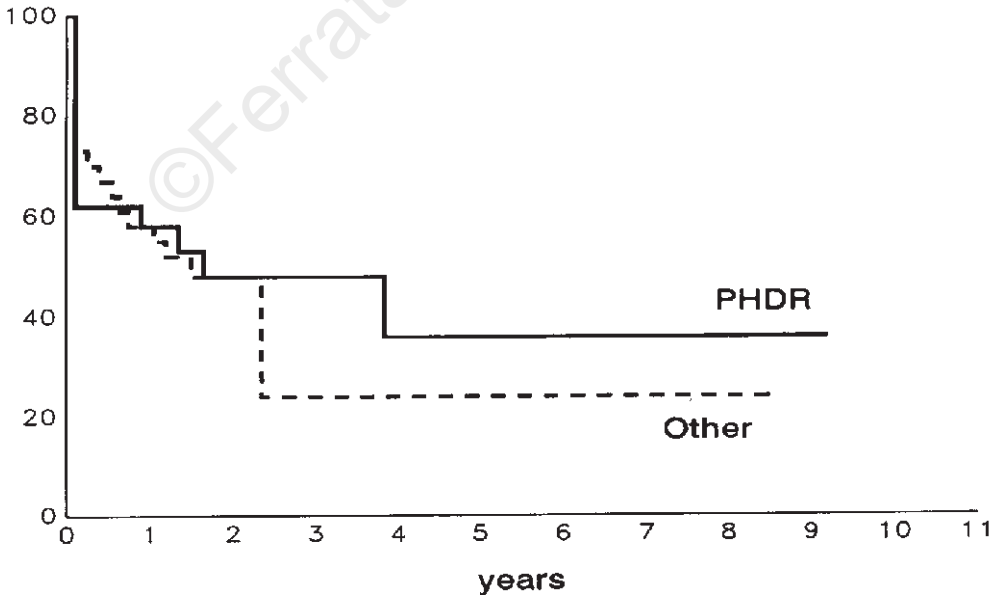

Figure 3. Event-free survival of elderly patients, according to treatment plan. PHDR protocol (——) versus a less aggressive plan (- - -); p = ns.

gram interruptions was very high, independently of initial treatment strategy. Treatment efficacy was therefore highly jeopardized by a suboptimal treatment schedule, and it might be expected that patients inadequately treated cannot be cured. However, our data show that elderly patients achieving complete remission have a relapse rate as high as younger ones (Figure 1). Moreover, elderly patients receiving conventional, adequate treatment showed better RFS than those following a non-aggressive plan (Figure 2). The higher relapse rate for undertreated patients could suggest that an aggressive curative approach might be better than a palliative one, but the chance for cure with conventional treatment plans is reduced, in our experience, by the high incidence of toxic deaths. Therefore patients treated with conventional therapy, in spite of their good RFS, do not have a better EFS than those treated less aggressively (Figure 3).

Therefore we believe that it is possible to cure elderly patients, but the toxic cost of conventional strategies is unacceptable for them. In our experience, chemotherapy-induced neutropenia played a major role in increasing the toxic risk, as was demonstrated by the high percentage of deaths due to severe infections (more than 50% of total toxic deaths). Nowadays, the availability of growth factors could help to reduce the incidence of severe neutropenia and other related septic complications. The safety of growth factors in Hodgkin's disease has already been documented by their use in both conventional chemotherapy regimens[20] and high-dose salvage chemotherapy.[21, 22] The availability of these growth factors might encourage development of curative strategies based on moderately toxic regimens.

Appendix

Institutions cooperating in the PHDR from 1982 to 1989

- Divisione di Ematologia, Ospedale Molinette, Torino
- Cattedra di Ematologia, Università di Torino
- Divisione di Radioterapia, Università di Torino
- Clinica Medica, Università di Torino
- Divisione di Ematologia, Ospedale Mauriziano, Torino
- Sezione di Ematologia, Ospedale S. Croce, Cuneo
- Sezione di Ematologia, Ospedale S. Annunziata, Savigliano
- Divisione di Medicina, Ospedale Civile, Ivrea
- Divisione di Medicina, Ospedale Civile, Asti
- Divisione di Medicina, Ospedale Maggiore, Novara
- Divisione di Medicina, Ospedale Agnelli, Pinerolo
- Divisione di Oncologia, Ospedale Civile, Aosta
- Divisione di Medicina, Ospedale Civile, Borgomanero
- Divisione di Medicina, Ospedale Cottolengo, Torino

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