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RESULTS OF A LOW AGGRESSIVITY CHEMOTHERAPY REGIMEN (CVP/CEB) IN ELDERLY HODGKIN'S DISEASE PATIENTS

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ABSTRACT

Background. **Hodgkin's disease (HD) after the age of 65 years is uncommon and there are no published data on chemotherapy regimens devised for elderly HD patients.**

Patients and Methods. **From 1990 to 1993, 25 elderly HD patients were treated with the CVP/CEB regimen: chlorambucil 6 mg/sqm p.o. days 1 through 7, vinblastine 6 mg/sqm i.v. on day 1, procarbazine 100 mg/sqm p.o. days 1 through 7, prednisone 30 mg/sqm p.o. days 1 through 7, cyclophosphamide 500 mg./sqm i.v. day 15, etoposide 70 mg/sqm i.v. day 15, bleomycin 10 mg/sqm i.v. day 15. Each course was repeated every 4 weeks. Stage I and II patients were treated with 3 courses followed by involved field radiotherapy, while more advanced stage patients received 6 courses and radiotherapy was limited to bulky areas. The results of the CVP/CEB regimen are retrospectively compared to those of 74 elderly patients treated between 1982 and 1989 and subdivided into the following 2 groups: 32 patients treated according to the same therapy used at that time in younger patients, and 42 patients given alternative low aggressivity or palliative treatment.**

Results. **CVP/CEB is a well-tolerated regimen, with only 1 (4%) toxic death and 2 (8%) protocol violations/interruptions. The CVP/CEB complete remission rate (73%) compares favorably with our previous groups of patients, mainly because of the lower toxic death rate. However, the CVP/CEB relapse-free survival rate is lower than that of patients treated with more aggressive conventional regimens (47% vs. 77%, $p<0.02$). The CVP/CEB overall survival and event-free survival rates are 55% and 32%, respectively, and they are not statistically different from those of patients treated before 1990.**

Conclusions. **CVP/CEB is a well-tolerated low toxicity regimen with a high CR rate. The relapse rate is high and event-free survival is comparable to that of patients treated conventionally. Our results suggest the need for individualized treatment criteria for older patients with HD.**

Key words: Hodgkin's disease, elderly patients, CVP/CEB chemotherapy regimen

The influence of advanced age on the outcome of Hodgkin's disease (HD) is poorly understood.[1] The answers to this problem involve the efficacy and tolerability of antineoplastic chemotherapy in the elderly and the feasibility of alternative, low toxicity treatment regimens.[2,3] The lack of selected trials for elderly Hodgkin's disease patients, in comparison to other hematological malignancies, is a consequence of the scarcity of patients due to the fact that the incidence of HD does not increase with increasing age.[4] We had the opportunity to explore these questions in two different contexts.

First, we had the chance to study retrospectively a non selected population of elderly Hodgkin's disease patients whose data were drawn from the Piemonte Hodgkin's Disease

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Registry (PHDR). This registry has been active since 1982, with the principal aims of collecting epidemiological data from the institutions operating in that region and of performing quality control analysis. During this time three different clinical guidelines have been proposed, but treatment and follow-up data were recorded for all patients independently of age, performance status and treatment plan.

Second, since 1990 we studied prospectively the efficacy and toxicity of a low-dose chemotherapy regimen called CVP/CEB that was devised for older individuals with HD.

Our first retrospective study showed that older patients treated with standard chemotherapy experienced complete remissions (CR) of HD as durable as those of their younger counterparts. However, treatment complications were more common and more severe in the elderly.[5] The results of the new CVP/CEB regimen are analyzed herein and compared with our historical experience.

Patients and Methods

Patients and treatments

The PHDR was established in 1982 for two purposes: epidemiology and quality control. The Piemonte region in northwest Italy has 4,300,000 inhabitants and of these, 17% are over 65. Clinical data for all patients treated in the 21 PHDR co-operating institutions were prospectively collected. In addition to the age of the patients, stage and histology of the disease, the registry recorded coexisting medical conditions, type of treatment, toxicity and outcome.

Since 1982 the PHDR member institutions have adopted uniform staging procedures and treatment plans, while allowing leeway for each practitioner to take the most appropriate course of action in individual cases.

Between 1982 and 1993, 831 cases of HD were reported and of these, 99 patients were 66 years or older.

Two different guidelines were proposed for patients with advanced stage disease (stage IIB to IV). First, between 1982 and 1985, stage IIB and III patients were treated with 6 courses of MOPP according to the original schedule reported by De Vita,[6] with extended field irradiation (subtotal nodal irradiation in stage II B and total nodal irradiation in stage III B). Stage IV patients received 9 courses of an alternated MOPP-ABVD regimen,[7] with irradiation limited to bulky areas. Second, since 1986, the hybrid MOPP/ABVD (MAMA) as originally proposed by Viviani *et al.*[8] was administered to stage IIB, III and IV patients, with irradiation limited to bulky areas. The number of courses given was based on the early response to chemotherapy; individuals entering CR after the first 3 cycles received a total of 6 courses, while patients achieving CR between the fourth and sixth cycle underwent 3 more courses for a total of nine.

Between 1982 and 1989, elderly patients were treated the same way as younger ones or according to the judgement of the individual practitioners. In January 1990 we began to study the CVP/CEB regimen prospectively in people aged 66 and older. All patients had a diagnosis of HD and were staged with a chemical panel, thoracic and abdominal CT and bilateral bone marrow biopsy. A mass of 10 cm. or more on physical examination or CT and/or a mediastinal mass greater than one third of the thoracic diameter were defined as bulky disease. Staging was repeated after 3 and 6 courses of treatment. Chemotherapy was administered every 28 days and included: chlorambucil 6 mg/sqm p.o. days 1 through 7, vinblastine 6 mg/sqm i.v. on day 1, procarbazine 100 mg/sqm p.o. days 1 through 7, prednisone 30 mg/sqm p.o. days 1 through 7, cyclophosphamide 500 mg/sqm i.v. day 15, etoposide 70 mg/sqm i.v. day 15, bleomycin 10 mg/sqm i.v. day 15. Patients with stages IA and IIA disease received three courses of CVP/CEB followed by involved field irradiation. Patients with more advanced disease received at least 6 courses of CVP/CEB and radiotherapy to areas of bulky disease; slow responding patients were given two more courses after achieving CR, for a maximum of 8 courses for patients entering CR at the end of the sixth course.

Eligibility criteria included age over 65, diagnosis of HD confirmed histologically, no previous chemotherapy or radiotherapy for HD, and creatinine level below 2. Concomitant morbidi-

ty was evaluated and patients were excluded if, in the investigators' opinion, they were unsuitable for even low-dose chemotherapy. From 1990 to 1993, 25 elderly patients were treated according to the CVP/CEB protocol.

In this report, the patients have been subdivided into three groups:

Group A: 32 patients treated between 1982 and 1989 according to the protocol used at that time in younger individuals.

Group B: 42 patients treated between 1982 and 1989 who received suboptimal doses of chemotherapy by decision of the attending physician.

Group C: 25 patients treated between 1990 and 1993 with the CVP/CEB protocol for the elderly.

Statistical methods

Staging data were collected at diagnosis for all patients. The file was updated for follow-up information twice a year. The file data for the present study was updated in December 1995. Early deaths were included as failure in the evaluation of both final complete remission (CR) and overall survival (OS). The relapse-free survival (RFS) curves were plotted only for patients achieving CR. Patients dying while in CR of causes unrelated to Hodgkin's disease were considered as censored in computing RFS. In the event-free survival (EFS) curves, any type of unfavorable event (failure to achieve CR, relapse, toxic death) was considered a failure.

In order to compare the CVP/CEB dose intensity to that of conventional chemotherapy regimens, the method of Hryniuk and Bush[9] was used to calculate the average intended dose intensity of each chemotherapy regimen. A hypothetical combination that would use all ten drugs in full doses was used as a reference standard according to the method proposed by De Vita *et al.*[10] and the dose intensity of each regimen was expressed as a decimal fraction of the average of the drug doses in the theoretical ten-drug combination. Prednisone was excluded from this count and the drug doses of the MOPP and ABVD schedules were considered standard full doses of the seven drugs included in these two regimens. The CVPP,[11] ChlVPP[12] and EVA[13] schedules were considered as standard full dose models of cyclophosphamide, chlorambucil and etoposide, respectively.

The actual dose intensity of each cytotoxic drug was calculated as mg/sqm/week, according to the method of Hryniuk and Bush,[9] after 3 and 6 courses of chemotherapy. 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) chemotherapy courses was used as an indicator of drug delivery adequacy.

All curves were plotted according to the Kaplan-Meier method.[14] Differences between curves were assessed for significance with the generalized Wilcoxon method.[15]

Results

The demographic characteristics of our patients are summarized in Table 1. The age of group A was significantly different from the age of group B. This suggests the possibility that the majority of the oldest patients had been treated with suboptimal chemotherapy until 1989. The prevalence of concomitant morbid conditions and the percentage of stage IV cases were not significantly different among the three groups of patients. Group C showed a higher prevalence of bulky disease, of B symptoms and of NS histology. These differences may be explained by the natural variations in the clinical manifestations of a rare disease over a relatively short period of time.

Concomitant morbid conditions were distributed among the three groups as follows:

- 5 patients in group A: two coronary artery disease, one ischemic cerebrovascular disease, one liver cirrhosis and one chronic renal failure.
- 10 patients in group B: three chronic obstructive lung disease, three chronic heart failure, two diabetes and two liver cirrhosis.
- 5 patients in group C: two chronic obstructive lung disease, two liver cirrhosis and 1 coronary artery disease.

The CVP/CEB average dose intensity relative to a hypothetical ten-drug combination employing each drug as it would be used in full

		Groups A	B	C	p value A vs. B	A vs. C	B vs. C
Number of patients		32	42	25			
Age: median		71	74	72	0.01	n.s.	n.s.
range		66-83	66-89	66-82			
Sex: male		18 (56%)	25 (60%)	14 (56%)	n.s.	n.s.	n.s.
female		14 (44%)	17 (40%)	11 (44%)			
Concomitant morbidity		5 (16 %)	10 (23 %)	5 (20 %)	n.s.	n.s.	n.s.
Stage: II + III		26 (81 %)	36 (86 %)	19 (76 %)	n.s.	n.s.	n.s.
IV		6 (19%)	6 (14%)	6 (24 %)			
Histology:	LP + NS	12 (37 %)	12 (29 %)	12 (55 %)	n.s.	n.s.	0.04
	MC + LD	20 (63 %)	30 (71 %)	10 (45 %)			
B symptoms		14 (44 %)	16 (38 %)	17 (68 %)	n.s.	n.s.	0.01
Bulky disease		3 (9 %)	3 (7 %)	9 (36 %)	n.s.	0.02	0.03

Table 1. Clinical features at diagnosis according to treatment modalities: group A = the same regimen proposed at the time for younger patients; group B = alternative low aggressivity strategy; group C = CVP/CEB regimen; n.s.= not significant.

	Groups A	B	C	p value A vs. B	A vs. C	B vs. C
RDI3	0.67	0.67	0.79	n.s.	0.03	n.s.
RDI6	0.62	0.56	0.78	n.s.	0.04	n.s.
Toxic deaths during induction	6 (19 %)	5 (12 %)	1 (4 %)	n.s.	0.05	n.s.
Protocol interruption/violation	6 (19 %)	13 (31 %)	2 (8 %)	n.s.	n.s.	0.03
CR rate	62 %	65 %	73 %	n.s.	n.s.	n.s.

Table 2. Results in elderly patients by treatment modalities: group A = the same regimen proposed at the time for younger patients; group B = alternative low aggressivity strategy; group C = CVP/CEB regimen. RDI3 and RDI6 = mean actual relative dose intensity after 3 and 6 courses of chemotherapy; CR = complete remission; n.s. = not significant.

dose was calculated to be 0.27. This is inferior to the dose intensity of conventional chemotherapy regimens used in younger patients: 0.4 for ABVD, 0.35 for alternated and hybrid MOPP-ABVD, and 0.3 for MOPP.

Table 2 reports the actual relative dose intensity of treatment, the incidence of toxic deaths, protocol violations and CRs. Not unexpectedly, the relative dose intensity at 3 and 6 courses was higher for patients in group C than for those in group A: RDI3 and RDI6 were, respectively, 0.67 and 0.62 in group A, as compared to 0.79 and 0.78 in group C ($p<0.05$). Treatment interruptions and/or major protocol violations were more frequent in groups A and B (19% and 31%, respectively) than in group C (8%). The CVP/CEB toxic death rate during induction therapy was lower than that of patients aggressively treated: 4% in group C vs. 19% in group A ($p=0.05$). Neutropenia played a major role in increasing the toxic risk of aggressively treated patients, as demonstrated by the high proportion of deaths due to severe infections in group A: more than the 50% of all deaths during induction. Five patients in group C died within six months of beginning treatment. One toxic death was due to sepsis, three more deaths were directly related to HD progression, the last one was due to heart failure and was considered HD and treatment unrelated. Of special interest, the final CR rate was similar among the three groups: 62%, 65% and 73% for groups A, B and C, respectively.

The actuarial 5-year RFS rate was significantly higher ($p<0.05$) for patients in group A than for those in the other two groups: 79% in group A, as compared to only 55% in groups B and C, respectively (Figure 1). The differences in RFS became apparent after the first year of CR. OS (Figure 2) and EFS (Figure 3) were similar for

the three groups. The high incidence of treatment-related mortality in group A and of concomitant morbid conditions in group B may account in part for this similarity. In group C, the RFS and the EFS were not significantly influenced by the presence of B symptoms and/or bulky disease.

Discussion

Our study demonstrates that age is not a contraindication for aggressive treatment of HD. Those older patients who were treated with MOPP or MAMA at full dose experienced the most durable CRs; 79% of those patients who experienced a CR are still free of disease 7 years later. Authors agree that elderly patients who achieved CR with an adequate conventional treatment have the same disease-free survival and chance of cure as young patients.[5,16,17] However, in our experience only 62% of conventionally treated patients entered CR and 6 patients (19%) died of some toxic complication during induction. Moreover, the conventional chemotherapy schedule was difficult to follow in elderly patients, as demonstrated by the low mean actual relative dose intensity of drugs calculated after 3 and 6 courses of chemotherapy (RDI3 and RDI6 less than 0.70). The real problem is therefore that it is difficult to achieve CR as a consequence of the high toxicity that elderly patients suffer when treated with conventional strategies.[5,18,19]

On the other hand, our study confirms that low aggressivity chemotherapy may obtain a high CR rate in older individuals with HD. The toxic death rate was reduced to 12% in patients entering *ab initio* a suboptimal treatment strategy (group B) but, as expected, this advantage was unfavorably offset by a high relapse rate. The major aim of our original CVP/CEB pilot study was to design a low toxicity regimen that could induce a high percentage of stable CR. In order to reduce toxicity and improve patient compliance, invasive staging procedures and antracycline cardiotoxicity were avoided. The CVP/CEB average intended dose intensity (0.27) is lower than that of conventional regimens, but this is favorably balanced in part by better adherence to time and dose schedule (RDI3 and RDI6 superior to 0.75). CVP/CEB is a well-tolerated low toxicity regimen, as documented by the low percentage of both toxic deaths and treatment interruptions and the high actual relative drug dose intensity. Unfortunately, the high CVP/CEB CR rate (73%) is unfavorably offset by the high relapse rate. This failure rate might be a result of the high percentage of patients with B symptoms and/or bulky disease in group C, even though the small number of patients made it impossible to demonstrate any relationship between B symptoms or bulky disease and RFS. As a consequence of the high relapse rate, the CVP/CEB final cure rate expressed by event-free survival (Figure 3) is no better than that of group A or B. However, the

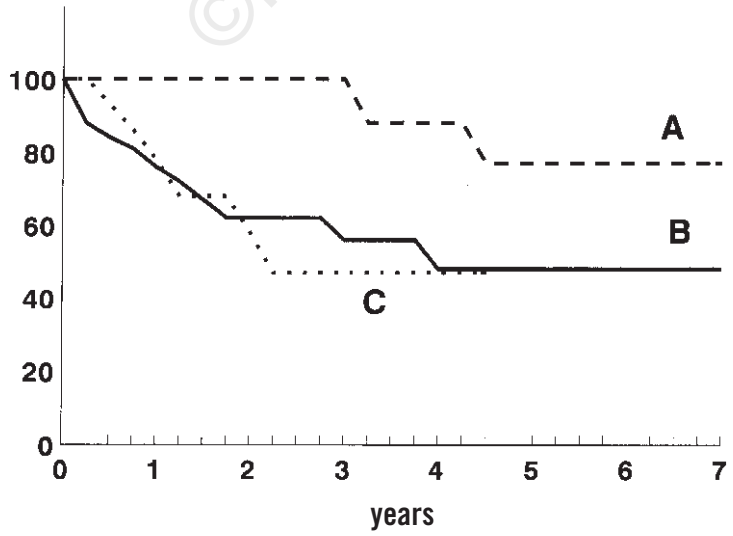

Figure 1. Relapse-free survival of patients entering complete remission according to treatment modalities: group A = the same regimen proposed at the time for younger patients; group B = alternative low aggressivity strategy; group C = CVP/CEB regimen (A vs. B, p=0.02; A vs. C, p<0.01; B vs. C, p=not significant).

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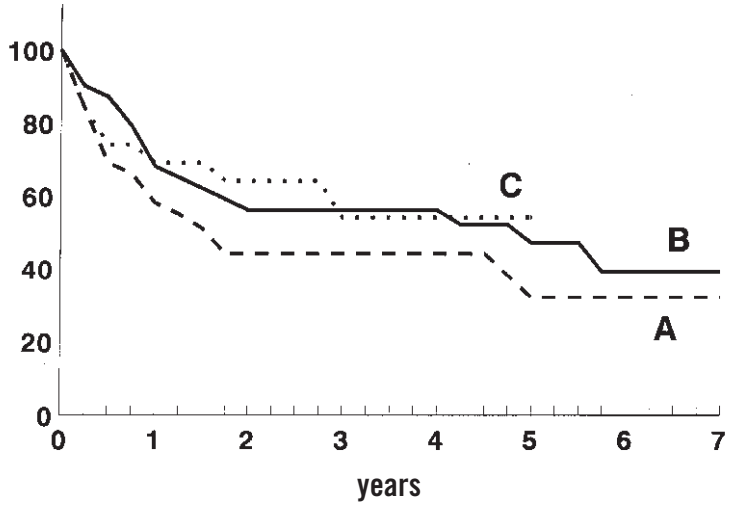

Figure 2. Overall survival of all patients by treatment modalities: group A = the same regimen proposed at the time for younger patients; group B = alternative low aggressivity strategy; group C = CVP/CEB regimen.

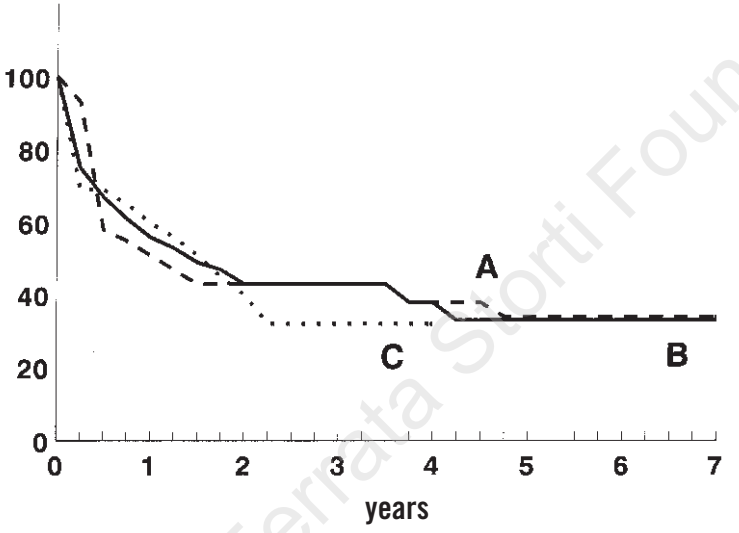

Figure 3. Event-free survival of all patients by treatment modalities: group A = the same regimen proposed at the time for younger patients; group B = alternative low aggressivity strategy; group C = CVP/CEB regimen.

future studies should focus on this issue. Patient life expectancy (LE) may provide some treatment guidelines; naturally, those patients whose LE is shorter than two years are more li ag

rate and quality of life might be profitable to older symptomatic patients with limited life expectancy and poor tolerance to conventional aggressive treatments.

Clearly, these studies emphasize the importance of patient selection in the management of older people with HD. To strike an optimal balance between benefits and risk, it is important to identify those subjects for whom standard chemotherapy involves a high risk of lethal toxicity and those for whom low-dose chemotherapy may provide inadequate control of HD. Treatment personalization is one of the most urgent problems in geriatric oncology, and with a longer LE. The differences in RFS between patient groups A, B, and C became apparent after the first year of CR. LE can be calculated from a patient's age and disease-specific survival from coexisting conditions,[20,21] but unfortunately the determination of life expectancy is still not very accurate.

CVP/CEB or similar low toxicity regimens can improve patient compliance and increase the complete remission rate, but new strategies that offer a better chance of cure are still needed. The difficulty in balancing effectiveness and low toxicity suggests focusing attention on two points: first, better selection of patients that can tolerate

an aggressive approach; second, better treatment support, mainly through the introduction of hematopoietic growth factors. Analogously to what has been suggested for non Hodgkin's lymphomas,[22] randomized co-operative studies are needed to compare conventional versus new low toxicity regimens.

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