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Efficacy of the VBM regimen in the treatment of elderly patients with Hodgkin's disease

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ABSTRACT

Background and Objectives. **No specific chemotherapy regimens have yet been recommended for elderly Hodgkin's disease (HD) patients. We investigated the therapeutic efficacy and toxicity of the three-drug-combination VBM (vinblastine, bleomycin, and methotrexate) regimen in a group of 19 elderly HD patients.**

Design and Methods. **Vinblastine (6 mg/m² i.v.), bleomycin (10 mg/m² i.v.) and methotrexate (25 mg/m² i.v.) were administered on days 1 and 8. Chemotherapy was repeated every 28 days for a total of 6 cycles. Local radiotherapy was given only to patients who presented bulky disease at the time of diagnosis. Of the 19 patients, 13 patients had stage II, 2 stage III, and 4 stage IV disease; the median age was 68 years (range 60 to 75).**

Results. **Of the 19 patients, 15 (79%) achieved complete response (CR) and 3 (16%) partial response, while the remaining patient showed no benefit from the treatment. With a median follow-up of 48 months, the estimated 5-year relapse-free survival was 79%, and overall survival was 64%. Hematologic grade 3-4 toxicity was seen in only 1 (5%) patient; no severe non-hematologic side effects or deaths were associated with the administration of the VBM regimen.**

Interpretation and Conclusions. **These preliminary data indicate that the VBM regimen provides a safe and effective therapeutic option for elderly patients with untreated HD.**

Key words: HD, elderly patients, VBM regimen, first-line therapy

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Hodgkin's disease (HD) in the elderly is still considered something of an enigma. Even though HD has a bimodal age-specific incidence curve with an initial peak between 15 and 35 years followed by a much smaller second peak over the age of 50,[1] its incidence does not increase with age.[2] The later peak is not related to socioeconomic status, and there are many reasons to think that the etiology of the disease is different in younger patients and more elderly ones. Only a handful of studies have focused specifically on HD in the elderly.[3-10] In the elderly, HD appears to have distinct clinical and histologic features, and despite the benefits of modern chemotherapy survival has remained generally poor.

Five-year survival is about 80% under the age of 40 years, 63% for patients aged 40 to 60, and only 30-40% over the age of 60.[11] Some of the rare reports in the literature on elderly patients seem to suggest that this highly unfavorable outcome might be explained by the fact that elderly patients ofetn receive less aggressive treatment. The decision to administer milder forms of treatment is frequently dictated by the high toxicity of treatment protocols and/or the less robust general conditions of elderly patients.

In this study we evaluated the clinical characteristics and outcome of 19 elderly patients aged 60-75 years treated with the vinblastine, bleomycin and methotrexate (VBM) regimen[12-15] with/without local radiation therapy.

Design and Methods

Between August 1992 and January 1997, 19 previously untreated HD patients aged 60 years or over were seen at our institute. The criteria for entry included: histologically confirmed diagnosis of HD; stage II-III-IV as outlined by the Ann Arbor staging system;[16] HIV negativity; an ECOG (17) performance status score of 0, 1, or 2; normal hepatic, renal, and cardiac function. During the same time period, two other elderly HD patients were seen, but they were not enrolled in the present study due to an ECOG score of 3.

In all patients, staging was evaluated by bone marrow biopsy (including immunohistochemical analysis) and hematologic and chemical survey, in addition to chest radiograms, abdominal ultrasonogra-

phy and computerized tomography of the chest and abdomen. Lactate dehydrogenase (LDH) concentration was determined in all patients.

Patients' characteristics

The patients' characteristics are shown in Table 1. The median age was 68 years (range 60-75 years); 9 were males and 10 females. Thirteen patients had stage II, 2 had stage III, and 4 had stage IV disease. Systemic symptoms were present in 7 (37%) patients. The bone marrow was involved in three patients. Eight (42%) patients had bulky disease, 5 in nodal sites and 3 in the mediastinum. The extent of mediastinal disease was defined by a mediastinal mass ratio (MMR), calculated by measuring intrathoracic diameter; an MMR that exceeded one-third was considered as bulky. For the other nodal sites, bulky disease was defined as a maximal transverese diameter > 7 cm.

Treatment protocol

All patients were treated with the VBM regimen: vinblastine 6 mg/m^2 i.v. on days 1 and 8, bleomycin 10 mg/m^2 i.v. on days 1 and 8, and methotrexate 25 mg/m^2 i.v. on days 1 and 8. Chemotherapy was administered every 28 days for a total of 6 cycles. Radiotherapy was given to patients who presented with bulky disease at the time of diagnosis only on bulky sites; the tumor dose ranged from 30 (6 patients, including all 3 with massive mediastinum involvement) to 36 Gy (2 patients) over 4-5 weeks using a schedule of 180 cGy/day for 5 days per week.

Patient evaluation and response criteria

Patients were re-evaluated prior to the start of each cycle of therapy. In particular, on day 1 of each cycle, physical examination, blood count and biochemistry were always performed. Bone marrow biopsy and radiographic studies of areas of involvement were repeated after the fourth cycle and/or at the completion of the six cycles of treatment. These studies were also repeated in the presence of any change in clinical status. Complete response (CR) and partial response (PR) were defined according to the International Working Group Recommendations.[18] Patients with progressive disease were considered as having no response and received no further therapy. Overall survival (OS) was measured from entry into the protocol until death. Relapse-free survival (RFS) was calculated from the date of response until relapse or death. OS and RFS curves were calculated according to the Kaplan and Meier method.[19] Standard ECOG[17] toxicity criteria were used.

Table 1. Patients' characteristics.

Age (years)	
median	68
range	60-75
Sex M/F	9/10
Symptoms A/B	12/7
Satge	
II	13
III	2
IV	4
Histology*	
LP	1
NS	10
MC	6
LD	2
LDH: normal/elevated	16/3
Bulky disease: No/Yes	11/8

**LP= lymphocyte predominance; NS= nodular sclerosis; MC= mixed cellularity; LD= lymphocyte depletion.*

Table 2. Response rates of 19 elderly HD patients.

	No. of pts	*CR (%)*	*PR (%)*	*CR + PR (%)*
All patients	19	15 (79)	3 (16)	18 (95)
Age				
60-69 yrs	13	10 (77)	2 (15)	12 (92)
≥70 yrs	6	5 (83)	1 (17)	6 (100)
Stage				
II	13	13 (100)	0	13 (100)
III	2	0	2 (100)	2 (100)
IV	4	2 (50)	1 (25)	3 (75)
Histology				
LP	1	0	1 (100)	1 (100)
NS	10	10 (100)	0	10 (100)
MC	6	5 (83)	1 (17)	6 (100)
LD	2	0	1 (50)	1 (50)
Bulky				
No	11	9 (82)	2 (18)	11 (100)
Yes	8	6 (75)	1 (12.5)	7 (87.5)
Hasenclever Prognostic Score				
≤3	12	11 (92)	1 (8)	12 (100)
>3	7	4 (57)	2 (29)	6 (86)

Results

Of the 19 patients,15 (79%) fulfilled the criteria for CR and 3 (16%) for PR, giving an overall response rate of 95%. The remaining patient (5%) did not respond to the therapy. The responses are reported in Table 2 with respect to various clinical and biological features. Of the 15 patients who obtained a CR, 12 (80%) are still in remission after a follow-up of 12 to 72 months (median: 48 months); the median duration of CR is 30 months. Three CR patients relapsed at 6, 12, and 22 months. Of these, all presented with stage II disease, two had mixed cellularity subtype and one the nodular sclerosis subtype; two had bulky disease. The ages of the three relapsed patients were 60, 65, and 71 years. Two of these three patients obtained a second continuous CR after second-line chemotherapy, the duration of response currently being 24 and 27 months. The third died of disease progression. The OS (Figure 1) at 84 months was 64%; Figure 2 shows a projected RFS at 72 months (median 30 months) of 79%. So far, as many as 5 patients have died, all due to disease progression: one of the 3 who relapsed, the only one who never responded to the VBM regimen and all 3 patients who obtained PR.

With respect to histology, the overall response rates in the nodular sclerosis and the mixed cellularity sub-

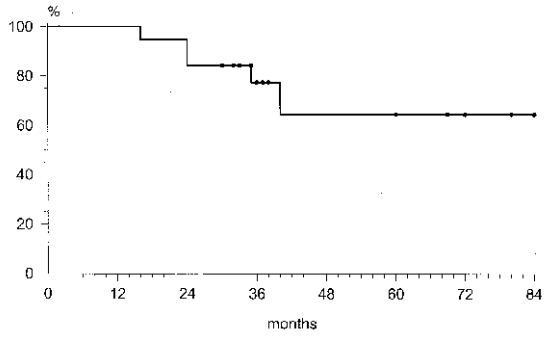

Figure 1. The overall survival of 19 patients.

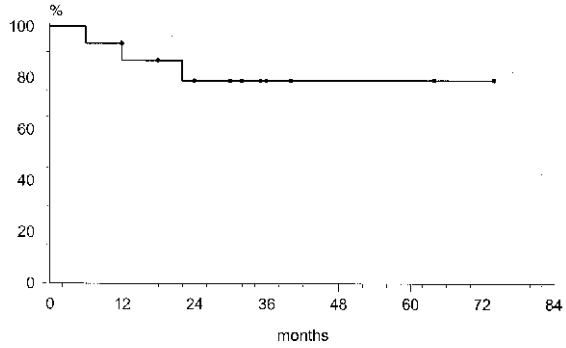

Figure 2. The relapse-free survival of 15 CR patients.

sets were both 100%, and the CR rates were 100% and 83%, respectively. With regard to stage, CR was achieved by 13 (100%) stage II patients, 0 stage III patients, and 2 (50%) stage IV patients (Table 2). Finally, with respect to the Hasenclever Prognostic Score,[20] CR was achieved by 12/13 (92%) patients with a score <3 and 4/7 (57%) patients with a score >3 (Table 2) and notably all patients who relapsed belonged to the latter subgroup. No relationship was observed between response and age (60-69-year and ≥ 70 age cohorts) or bulky disease at presentation (Table 2).

Toxic effects

The VBM regimen was well tolerated in general, and all the patients who responded completed therapy. No deaths from toxicity related to chemotherapy were recorded. Hematologic side effects were present in 6 (31.5%) patients, while toxicity ≥ 3 according to ECOG scale was observed only in 1 (5%) patient. Both neutropenia and thrombocytopenia were usually of short duration (3-8 days) and only 5/114 (4.5%) courses were temporarily postponed for one week. Neither transfusions, nor dose reductions, nor administration of growth factors were ever required. Non-hematologic toxicities were rare and generally mild. Nausea/vomiting was the major non-hematologic side effect. No pulmonary (even in patients receiving radiotherapy to the mediastinum), cardiac, neurologic, or renal toxicity was observed. Transient grade 1-2 hepatic toxicity was recorded in 5 patients who developed abnormal levels of SGOT and SGPT.

Discussion

Some imperatives in the management of HD in young adults are currently changing. In particular the dose intensity of radiotherapy and the size of the radiation fields are being reduced, and shorter courses of chemotherapy are being introduced in early stages of the disease. However, these treatment strategies, based on data obtained from younger HD patients, cannot automatically be transferred to elderly ones, for whom the prognosis of the disease is intrinsically worse and still variable, to such an extent that it is not easy to find uniform agreement on where to put the age cut-off firmly defining such a subgroup. Furthermore, in the elderly it is necessary to consider individual profiles of comorbidity, as well as the possibility that combined modality therapy might be poorly tolerated. A few reports have stated that elderly patients may do as well as younger patients if adequate therapy is given.[21] Nevertheless, it is hard to find chemotherapy regimens that have been consistently recommended for this relatively neglected subset of patients and in practice most investigators have adopted the same multiagent schedules commonly used in the younger population, with ad hoc modifications in order to avoid unacceptable toxicity. Well-tolerated, less aggressive chemotherapy protocols such as CVP/CEB have failed to provide adequate RFS or OS rates.[9] In a Swedish national study, elderly patients who received conventional MOPP or MOPP/ABVD treatment with a curative intent had a disease-specific 5-year survival of just over 40%.[22]

In our study, we treated elderly HD patients with the VBM regimen, a novel and potentially less toxic chemotherapy designed by investigators in Stanford[12] for treatment of early-stage HD in combination with radiation therapy. To our knowledge, this is the first specific study on the efficacy of this regimen in elderly untreated HD patients. Our results show a very encouraging overall response rate of 95%, with a 79% CR rate. As far as it concerns the main histologic subtypes, VBM proved effective in both the nodular sclerosis and mixed cellularity subsets. The regimen seemed more effective in stage II disease than in stage III-IV, as well as in patients with a low rather than high Hasenclever score. Since we followed stringent criteria for the definition of response, the results obtained do appear to be durable, with a projected RFS of 79% at 5 years. These figures are particularly encouraging in the light of the limited toxicity exerted by the VBM regimen in our elderly patients. Apart from sporadic hematologic toxicity, no severe toxic side effects were recorded. Pulmonary toxicity was not observed, probably because only three patients required local radiation therapy for bulky mediastinal involvement.

In conclusion, this preliminary study strongly suggests that the VBM regimen provides a much needed

therapeutic option for untreated elderly HD patients. With this appropriately tailored chemotherapeutic regimen, the use of involved field radiotherapy can be limited to sites of bulky disease. More extensive clinical trials could test the efficacy of aggressive formulations for stage III-IV patients, with the adoption of strategies for reducing toxicity, such as the administration of hematopoietic growth factors, amifostine and cardioprotective agents.

Potential implications for clinical practice

The VBM regimen is a safe and effective option for untreated elderly patients with Hodgkin's disease.

Contributiona and Acknowledgments

PLZ designed the study and wrote the paper. MM, FG, MT, PA and VS were involved in clinical assessment of the patients. MB helped PLZ with the data analysis interpretation and the writing of the paper. EB and AG performed the radiotherapy treatment when needed. LB and ST critically revised the paper and gave the final approval for its submission.

The actual order in which they appear listed reflects the decreasing (quantitative and qualitative) involvement in the whole process, except for the directors of the institutions involved, who are listed at the end of the authors' list.

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Disclosures

Conflict of interest: none.

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References

1. Medeiros LJ, Greiner TC. Hodgkin's disease. Cancer 1995; 75:357-69.
2. La Vecchia C, Levi F, Lucchini F, Kayes B, Boyle P. Hodgkin's disease mortality in Europe. Br J Cancer 1991; 64:723-34.
3. Austin-Seymour MM, Hoppe RT, Cox RS, Rosenberg SA, Kaplan HS. Hodgkin's disease in patients over sixty years old. Ann Intern Med 1984; 100:13-8.
4. Walker A, Schoenfeld ER, Lowman JT, Mettlin CJ, MacMillan J, Grufferman JS. Survival of the older patient compared with the younger patient with Hodgkin's disease. Influence of histologic type, staging, and treatment. Cancer 1990; 65:1635-40.
5. Guinee VF, Giacco GG, Durand M, et al. The prognosis of Hodgkin's disease in older adults. J Clin Oncol 1991; 9:947-53.
6. Eghbali H, Hoerni-Simon G, de Mascarel I, Durand M, Chauvergne J, Hoerni B. Hodgkin's disease in the elderly: A series of 30 patients aged older than 70 years. Cancer 1984; 53:2191-93.
7. Bosi A, Ponticelli P, Casini C, et al. Clinical data and therapeutic approach in elderly patients with Hodgkin's disease. Haematologica 1989; 74:463-73.
8. Diaz-Pavon JR, Cabanillas F, Majlis A, Hagemeister FB. Outcome of Hodgkin's disease in elderly patients. Hematol Oncol 1995; 13:19-27.
9. Levis A, Depaoli L, Bertini M, et al. Results of a low aggressivity chemotherapy regimen (CVP/CEB) in elderly Hodgkin's disease patients. Haematologica 1996; 81:450-6.
10. Levis A, Depaoli L, Urgesi A, et al. Probability of cure in elderly Hodgkin's disease patients. Haematologica 1994; 79:46-54.
11. Mir R, Anderson J, Strauchen J, et al. Hodgkin's disease in patients 60 years of age or older. Histologic and clinical features of advanced-stage disease. The Cancer and Leukemia Group B. Cancer 1993; 71:1857-66.
12. Horning SJ, Hoppe RT, Hancock SL, Rosenberg SA. Vinblastine, bleomycin, and methotrexate: an effective adjuvant in favorable Hodgkin's disease. J Clin Oncol 1988; 6:1822-31.
13. Bates NP, Williams MV, Bessel EM, Vaughan Hudson G, Vaughan Hudson B. Efficacy and toxicity of vinblastine, bleomycin, and methotrexate with involved-field radiotherapy in clinical stage IA and IIA Hodgkin's disease: a British National Lymphoma Investigation pilot study. J Clin Oncol 1994; 12:288-96.
14. Gobbi PG, Pierasca C, Frassoldati A, et al. Vinblastine, bleomycin, and methotrexate chemotherapy plus extended-field radiotherapy in early, favorably presenting, clinically staged Hodgkin's patients: the Gruppo Italiano per lo Studio dei Linfomi Experience. J Clin Oncol 1996; 14:527-33.
15. Horning SJ, Hoppe RT, Mason J, et al. Stanford-Kaiser Permanente G1 study for clinical stage I to IIA Hodgkin's disease : subtotal lymphoid irradiation versus vinblastine, methotrexate, and bleomycin chemotherapy and regional irradiation. J Clin Oncol 1997; 15:1736-44.
16. Carbone PP, Kaplan HS, Musshof K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971; 31:1860-1.
17. Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-55.
18. Cheson B, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 1999; 17:1244-53.
19. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-81.
20. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998; 339:1506-14.
21. Specht L, Nissen NI. Hodgkin's disease and age. Eur J Haematol 1989; 43:127-35.
22. Glimelius B, Enblad G, Kalkner M, et al. Treatment of Hodgkin's disease: the Swedish National Care Programme experience. Leuk Lymphoma 1996; 21:71-7.