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Efficacy of vinorelbine, epirubicin and prednisone combination regimen in pretreated elderly patients with aggressive non-Hodgkin's lymphoma

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Background and Objectives. To assess the efficacy and toxic profile of the NAEPP protocol, a regimen including vinorelbine, epirubicin and prednisone, in a particularly troublesome subset of patients: pretreated elderly patients with aggressive non-Hodgkin's lymphoma (NHL).

Design and Methods. From November 1998 to January 2000, 20 pretreated patients who had all relapsed after first-line VNCOP-B chemotherapy were enrolled in a phase II trial and treated with the NAEPP regimen: vinorelbine (25 mg/m^2 i.v. on days 1 and 8), epirubicin (40 mg/m^2 i.v. on days 1 and 8), and prednisone (40 mg/m^2 on days 1 and 8) with granulocyte colony-stimulating factor administered at 5 μg/kg/day on days 2-5 and days 9-12. Chemotherapy was repeated every 4 weeks for a total of 6 cycles.

Results. Six (30%) patients achieved complete remission (CR) and 7 (35%) had partial responses (PR), giving an overall response rate of 65%. The response rate was not affected either by type of relapse presentation (nodal versus nodal plus extranodal), presence of bulky disease, or time of relapse. No major toxic effects were recorded.

Interpretation and Conclusions. These preliminary data suggest that the NAEPP regimen is an effective combination with a low toxicity profile in elderly pretreated patients with aggressive NHL. Further trials using NAEPP as a consolidation phase following first-line treatment are needed to establish the advantage in terms of CR rate and relapse-free suvival in these patients.

Key words: elderly aggressive NHL, vinorelbine and epirubicin, pretreated patients

Approximately 30% to 40% of patients with aggressive non-Hodgkin's lymphoma (NHL) are over 60 years old.[1,2] Fisher's study,[3] concerning front-line chemotherapy, confirmed that although the gold-standard regimen for elderly patients with aggressive NHL was CHOP, the percentage of deaths from toxicity was higher in these patients, and when the doses were reduced the complete response (CR) rate also decreased. Second and third generation programs appear to be too intensive to be administered to elderly patients without significantly escalating toxicity. Alternatively, new protocols specifically tailored to the tolerance and the biological, rather than calendar, age of patients have been reported to produce functional lymphoma therapy in the elderly.[4-14] In addition, in view of the particular clinical features of aggressive NHL in the elderly, granulocyte colony-stimulating factor (G-CSF) can be included in standard regimens to optimize their feasibility and safety.[15-17] In all these trials, relapse-free survival was between 10% and 30% at 5 years and the majority of relapses occurred in the first 2 years.[4-17]

Since most patients who have relapsed lymphoma have poor performance scores and short survival, it is usually inappropriate to pursue aggressive therapy, and bone marrow transplantation has traditionally been excluded as a treatment modality for elderly patients. On the other hand, it seems important to identify conventional second-line treatments, defined on the basis of the front-line chemotherapy regimen drugs, suitable for elderly patients with aggressive NHL. For this reason, we designed a pilot regimen including vinorelbine, a unique semi-synthetic vinca-alkaloid substituted on the catharantine moiety,[18] because of its lack of cross-resistance with other vinca alkaloids along with its good tolerability even in elderly patients.[19-20] In this report, we summarize the data concerning our experience with the NAEPP regimen (including vinorelbine, epirubicin, and prednisone) plus G-CSF in patients with aggressive NHL in first relapse after a front-line chemotherapy.

Design and Methods

From November 1998 to January 2000, 20 previously treated patients with aggressive NHL and a minimum age of 60 years completed treatment with the NAEPP regimen in our Institute. All these patients, who had been enrolled at our center in a previous multi-center trial, relapsed in first CR after front-line chemotherapy with the VNCOP-B (etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisone, and bleomycin) regimen.[12] Criteria for entry into the study included: histologic diagnosis of aggressive NHL according to the updated Kiel classification (Burkitt's lymphomas and lymphoblastic lymphomas being excluded);[21] stage II-IV as outlined by the Ann Arbor staging system;[22] performance status 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG):[23] normal hepatic, cardiac, and renal functions. At the time of recurrent disease and before further treatment, all patients were restaged by chest X-ray, hematologic and chemical profiles, bone marrow biopsy, measurement of all tumor masses, and computerized tomography of the chest and abdomen. Informed consent was obtained from all patients in accordance with the ethics policy of the institute, and the study was performed in line with the Helsinki declaration.

The patients' characteristics are summarized in Table 1. Their median age was 73 years (range, 65 to 80 years); 12 patients were males and 8 females. The bulk of palpable lymph nodes was defined by the largest dimension of the single largest lymph node or conglomerate node mass in each region of involvement. A node or nodal mass had to be 10 cm or greater to be recorded as bulky. Three patients had bulky disease. Sixteen patients had nodal disease presentation only. Four patients had extranodal disease associated with nodal presentation. The extranodal sites involved were: spleen (2 cases), lung (1 case) and tonsil (1 case). The median relapse time from the initial CR (after VNCOP-B) was 12 months (range 8 to 18 months).

Treatment protocol

Intravenous vinorelbine was administered on days 1 and 8 of the treatment over 20 minutes; the dose was 25 mg/m^2. Epirubicin was infused at a dose of 40 mg/m^2 on days 1 and 8; prednisone was given at a dose of 40 mg/m^2 on days 1 and 8. The treatment cycle was repeated every 28 days for a total of six courses. G-CSF was administered subcutaneously at 5 μg/kg/day on days 2-5 and days 9-12. All cycles were delivered in an outpatient setting. Antiemetic prophylaxis was not obligatory: nausea and vomiting were routinely treated when necessary.

Evaluation of response

CR was defined as the complete disappearance of signs and symptoms due to lymphoma for at least 6 weeks. Partial response (PR) was defined as a reduction of at least 50% in the product of the largest perpendicular diameters of all measurable lesions for a duration of at least 6 weeks. Disease progression was considered to be present when there was clear evidence of advancing disease, despite continuation of the treatment. Patients were evaluated by monthly history taking and physical examination, complete blood counts, and chemistry profiles. All signs, symptoms or laboratory abnormalities were assessed using ECOG criteria[24] for toxicities. One month after completion of the last course of therapy, clinical and pathologic evaluations were undertaken by repeating radiographic investigations, and bone marrow and/or liver biopsies that had been positive before treatment.

Table 1. Characteristics of 20 elderly patients with aggressive NHL.

Age (years)	
Median	73
Range	65-80
Sex (male/female)	12/8
Symptoms (no/yes)	13/7
Stage	
II	5
III	9
IV	6
Disease presentation:	
Nodal	16
Nodal + extranodal	4
Bulky disease:	
Present	3
Absent	17
Histology	
Diffuse large B-cell	15
Peripheral T-cell	3
Anaplastic large cell	2

Results

Response

The therapeutic results are shown in Table 2. Major responses (CR + PR) were seen in 13 out of 20 (65%) patients, with 6 (30%) CR and 7 (35%) PR. As regards the histologic subset of diffuse large B-cell lymphoma, 10/15 (67%) patients had response, with 5 (33.5%) CR and 5 (33.5%) PR. Among the 3 peripheral T-cell lymphoma patients, only 1 (33.5%) patient responded obtaining a PR. Both anaplastic large cell lymphoma patients achieved a response, 1 (50%) a CR and 1 (50%) a PR. The overall response rates of the patients who had relapsed at < 12 months or > 12 months, were 55% (5/9; 2 CR and 3 PR) and 73% (8/11; 4 CR and 4 PR), respectively (n.s.). The response rate was not affected either by type of relapse presentation (nodal vs. nodal plus extranodal) or by presence of bulky disease. The influence exerted by performance status and lactate dehydrogenase (LDH) on the response rate is detailed in Table 2. Of the remaining 7 (35%) patients who did not respond, 2 died of NHL and the other 5 are still alive with the disease. As regards the relapse-free interval, 2 out

Table 2. Response of 20 elderly patients with aggressive NHL to the NAEPP regimen.

	CR		CR+PR	
	N.	%	N.	%
All patients	6	30	7	35
Histologic subtype:				
Diffuse large B-cell (15)	5	33	5	67
Peripheral T-cell (3)	/	/	1	33
Anaplastic large cell (2)	1	50	1	50
Timing of relapse:				
≤12 months (9)	2	/	3	55
>12 months (11)	4	36.5	4	73
Performance status:				
0-1 (13)	5	38	9	69
≥2 (7)	1	14	4	57
LDH level:				
normal (12)	5	42	9	75
abnormal (8)	1	12.5	4	50

of 6 (33%) patients who achieved CR had a relapse after 6 and 8 months; the remaining 4 are still in CR after 10, 12, 15, and 16 months. In the PR subset, 2 out of 7 (28%) patients showed disease progression within 6 months.

Side effects

NAEPP treatment was generally well tolerated, and all the patients who responded completed therapy. Overall, only two patients did not complete the treatment plan, and this was because of disease progression. With regard to hematologic toxicity, grade 3-4 neutropenia was recorded following only 4 out of 109 (4%) cycles, and grade 3-4 thrombocytopenia occurred in 2/109 (2%) cycles. Non-hematologic toxicity was minimal. Hair loss was mild to moderate, and no patient experienced complete alopecia. No nausea/vomiting or renal, hepatic or cardiac toxicity was revealed by the clinical and laboratory evaluations. Only one case of mild peripheral neurological toxicity was recorded. No patient died of complications related to the NAEPP regimen.

Discussion

In the context of the increasing incidence of NHL, the aggressive histologic subtype shows a peak in patients over 60 years of age. While anthracyclines (CHOP or CHOP-like regimens) remain a prerequisite for the successful treatment of these patients, there is increasing evidence that specific regimens may be tailored to enhance feasibility and efficacy in elderly patients. Whereas only 10 years ago, elderly patients with aggressive NHL could only receive palliative treatment, principally because most standard regimens had proved to be consistently toxic for this weaker patient subset, it is now possible to obtain CR rates only slightly lower those achieved with younger patients. The next challenge is to extend the relapse-free interval after front-line treatment, which is frequently brief even in the presence of CR. It is likely that, as with younger patients, development of specific second-line treatments including drugs different from those used in front-line treatment could help to offer the real possibility of salvaging a subgroup of these elderly patients. Thus, alternative strategies or new drugs need to be investigated to improve the life expectancy of elderly patients with aggressive NHL. Among the new drugs, vinorelbine has shown good activity in lymphoma[19-20] and has less pronounced side effects than the known vinca alkaloids. We, therefore, decided to combine vinorelbine with an anthracycline, epirubicin, with the aim of increasing therapeutic efficacy while reducing cardiotoxicity.

The present study concerns 20 patients who had all relapsed after initially obtaining CR following front-line treatment with VNCOP-B. Salvage treatment based on the combination of vinorelbine and epirubicin allowed us to obtain 6 (30%) CR, with an overall response rate of 65%. In terms of side effects, mild myelosuppression was observable due to the use of G-CSF. No organ toxicity was recorded. Standard antiemetics were not called for, and no cumulative toxicity patterns were observed. These findings provide confirmation of preliminary data regarding the activity and mild toxicity profile of vinorelbine.

Despite the obvious limitations of the relatively short follow-up and small size of the patient cohort, the present study strongly suggests that the NAEPP regimen can be useful for pretreated elderly NHL patients. Our data also provide support for the utility of developing standardized second-line therapeutic protocols for elderly NHL patients. Thus, in upcoming trials, the NAEPP regimen may be incorporated as a consolidation phase following the initial VNCOP-B protocol. The aims of the consolidation phase would be to achieve further CR among patients who have obtained only PR after induction, and to reduce the risk of relapse among those already in CR. Larger randomized trials are necessary to further explore the therapeutic potential of NAEPP either as front-line treatment or as a consolidation schedule.

Contributions and Acknowledgments

PLZ designed the study and wrote the paper. MB helped PLZ with the data analysis interpretation. MT, VS, EV, PA, LA, and FG were involved in clinical assessment of the patients. ST critically revised the paper and gave the final approval for its submission.

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Disclosures

Conflict of interest: none.

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Manuscript processing

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Potential implications for clinical practice

The NAEPP regimen can be considered as a valuable option for pretreated, elderly patients with aggressive non-Hodgkin's lymphoma.

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