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Weekly administration of vincristine, cyclophosphamide, mitoxantrone and bleomycin (VEMB) in the treatment of elderly aggressive non Hodgkin's lymphoma

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Abstract

Background and Objective. **Aim of the study was to assess the efficacy of VEMB, a short-lasting therapeutic regimen (50 days) which alternates two myelotoxic drugs (cyclophosphamide and mitoxantrone) every week with two less hematologically toxic drugs (vincristine and bleomycin) in the treatment of aggressive NHL in the elderly (over 70).**

Design and Methods. **Between November 1994 and March 1996, 37 patients aged more than 70 years, with highly or moderately malignant NHL (according to the Working Formulation) have been enrolled into the study. The stage of the disease ranged between II and IV according to Ann Arbor. Mean age was 77 years; 14 patients (38%) had stage IV; 19 patients (51%) had LDH higher than normal; 26 patients (70%) had extranodal and 9 patients (24%) had bulky disease at time of diagnosis.**

Results. **Sixty-two percent of patients achieved a complete and 22% a partial remission. Non-responders amounted to 5%. Four patients (11%) died during the therapy. Nine patients (24%) experienced grade III-IV neutropenia. The most frequently observed event was mild neurotoxicity (43% of cases). The overall survival rate at 30 months was 55%. DFS at 24 months was 66%.**

Interpretation and Conclusions. **VEMB is a therapeutic regimen whose efficacy is comparable to that of the other derived MACOP-B therapeutic regimens used in the elderly NHL. It has proved to have a good feasibility, though the number of toxic deaths should not be neglected.**

Key words: non Hodgkin's lymphoma, chemotherapy, dose intensity, elderly

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Since the introduction of anthracycline-containing regimens the prognosis of highly or moderately malignant non-Hodgkin lymphomas has markedly improved, with about 50% of patients projected to be cured.[1]

However, these encouraging results have been obtained mostly in patients aged less than 65 years of age at time of diagnosis. In the past older patients have been usually excluded by aggressive treatments considered extremely toxic. In fact, regardless the increasing incidence of NHL in the elderly (up to 40% of aggressive NHL occur in patients aged more than 65 years), only a small number of highly selected patients have been treated with the best available therapies and at full planned doses.[2,3]

In addition, different recent studies have shown that in patients with NHL age should be regarded as an unfavorable prognostic factor.[4,5]

Over the last few years some specific protocols have been designed for elderly patients; in particular, the Vancouver group designed a weekly administration of cytostatic drugs: LD-ACOP-B,[6] VABE[6] and P/DOCE.[7] P-VEBEC,[8] P-VABEC[9] and VNCOP-B[10] have also been designed according to the same model. On the other hand VMP,[11] developed by the Aviano group, prefers the oral administration of chemotherapeutic drugs.

Essentially, such regimens aim at reducing toxicity in patients who, because of age and the frequently concurrent diseases, show less tolerance for the treatment.

In 1994, our cooperative group (*Gruppo Italiano per lo Studio dei Linfomi* [GISL]) designed a new protocol, called VEMB, which alternates two myelotoxic drugs (mitoxantrone and cyclophosphamide) with two drugs having low bone-marrow toxicity (vincristine and bleomycin). The aim is to deliver a satisfactory drug amount, while at the same time allow for a better recovery in subjects with reduced bone-marrow reserves. Mitoxantrone was chosen as an alternative to doxorubicin because of the reported lower incidence of cardiotoxicity.[12]

Materials and Methods

Between November 1994 and March 1996, 37 patients with newly-diagnosed NHL of high or inter-

mediate grade according to the Working Formulation,[13] were enrolled in the study by 10 different Italian onco-hematological centers. None of patients had undergone previous treatments.

The eligibility criteria were as follows:

- age above 70 years;
- histological diagnosis of aggressive NHL (D to H categories according to the Working Formulation);
- Ann Arbor[14] stage II to IV;
- performance status 0 to 3 (according to ECOG);
- normal liver, heart, renal and respiratory functions;
- HIV negativity.

The diagnostic procedures to get access to the study included the histological diagnosis and the standard staging investigations, which were as follows:

- physical examination;
- complete hematological and biochemical screening;
- chest and abdominal CT-scan;
- bone-marrow biopsy;

Additional instrumental examinations were carried out only if clinical indications were specified.

Therapeutic regimen

VEMB was administered as follows:

- cyclophosphamide 350 mg/m^2 i.v. and mitoxantrone 10 mg/m^2 i.v. at days 1, 15, 29, 43.
- vincristine 1.4 mg/m^2 i.v. (maximum dose 2 mg) and bleomycin 5 mg/m^2 i.v. at days 8, 22, 36, 50;
- oral prednisone 50 mg at days 1-15, then 50 mg at alternating days.

No dose reduction was specified based on myelotoxicity. Regular administration of vincristine 1 mg was recommended in case of neurotoxicity > grade 1.

The use of growth factors was allowed though not specified.

Response

The re-staging investigations at the end of therapy included a reassessment of the sites involved at the onset of the disease and, in all cases, a chest and abdominal CT-scan.

Complete remission (CR) meant complete disappearance of the clinical and radiological signs of the disease for at least four weeks after the end of therapy. Partial remission (PR) meant the disappearance of at least 50% of the measurable lesions. Patients with a response of less than 50% were classified as non-responders (NR). Recurrences were defined as the presence of NHL in patients who had been in complete remission for at least four weeks.

Survival was measured from the time of diagnosis to the last observation. DFS for patients in complete remission was calculated from the time of the last therapy to the date of the last observation or of the relapse. The OS and DFS curves were drawn according to Kaplan and Meyer's method.[15]

Dose intensity

The dose intensity (DI) analysis was performed according to the method proposed by Hryniuk and Bush.[16] For patients completing the planned 8 courses of chemotherapy, the DI of each drug was considered together with the amount of each drug, normalized to the body surface area, administered during the first 50 days, 50 days was the time required to complete the therapy.

For patients who received less than 8 courses of chemotherapy because of early death or disease progression, DI was expressed as the ratio of the actually delivered dose to the dose prescribed in the regimen over the same time frame. Vincristine was excluded from the calculation of DI, since a dose reduction was specified by the protocol in case of neurotoxicity, even of grade I.

Results

Table 1 summarizes the main characteristics of the 37 enrolled patients.

The mean age was 77 years (range 70-86); 19 patients (51%) had LDH above upper normal limit and 14 (38%) were in stage IV. Extranodal localization was quite frequent: it was found in 26 patients (70%); 9 patients (25%) had a bulky disease.

Table 2 summarizes therapeutic results. Twenty-three patients (62%) had complete remission and 8 (22%) partial remission, with an overall response rate of 84%. The role of radiation therapy was neglectable since it was used in one case only (to consolidate a CR which had been already obtained with VEMB).

Six failures were observed: 4 early deaths due to therapy-related toxicity and 2 cases with less than partial response. Three patients died during induction therapy for fatal infections (septic shock, 1; pulmonary infection, 2): all these patients had multiple negative prognostic factors at diagnosis; none of them had a significant neutropenia when the infection occurred. One patient (with gastric localization) died from gastric hemorrhage. The 2 patients who failed to obtain a major response died for disease progression 4 and 8 months after diagnosis, respectively.

Out of the 8 patients with PR, one achieved CR with salvage therapy.

After a median follow-up of 17 months, OS at 30 months was equal to 55% (Figure 1). Actuarial DFS at 24 months was 66% with 16/23 patients in CCR (Figure 2). Six out of 7 patients who relapsed had a recurrence within the first year from the end of treatment.

Finally, 2 patients died for reasons unrelated to lymphoma (stroke, 1; acute heart failure, 1) at the age of 82 and 80 respectively.

Toxicity and dose intensity

The side effects, assessed according to the WHO scale, are summarized in Table 3. VEMB was generally well tolerated. The most frequent side effect (43% of cases) was mild neurotoxicity (mainly in the form

Table 1. Clinical features at diagnosis of the 37 patients studied.

Characteristics	*No.*	*%*
Median age: 77 years (range 70-86)		
Sex		
Male	20	54
Female	17	46
Stage		
II	14	38
III	9	24
IV	14	38
Histology		
D	1	3
E	1	3
F	14	38
G	14	38
H	7	18
Extranodal disease		
Yes	26	70
No	11	30
Bulky		
Yes	9	24
No	28	76
LDH		
Normal	18	49
Elevated	19	51
Performance status (ECOG)		
0-1	26	70
2-3	11	30

Table 2. Response.

Type of response	No.	%
CR	23	62
PR	8	22
NR*	6	16

**Including 4 patients died during induction therapy due to toxicity.*

Table 3. Hematological and clinical toxicity.

Side effect	*WHO (1-2)*	*WHO (3-4)*
Anemia	1 (3%)	1 (3%)
Neutropenia	15 (41%)	9 (24%)
Infections	5 (14%)	4(11%)*
Mucositis	6 (16%)	1 (3%)
Neurotoxicity	16 (43%)	0 (0%)

**including 3 patients died during induction.*

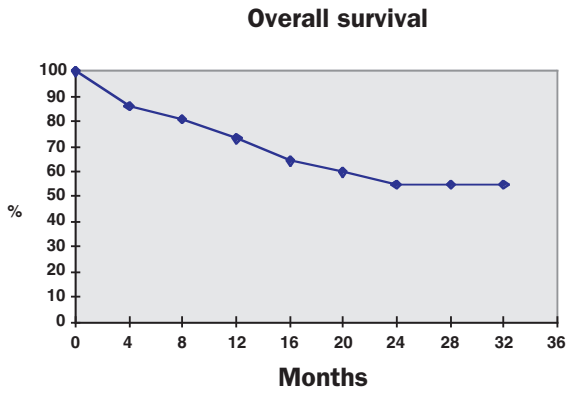

Figure 1. Overall survival of 37 patients treated with VEMB.

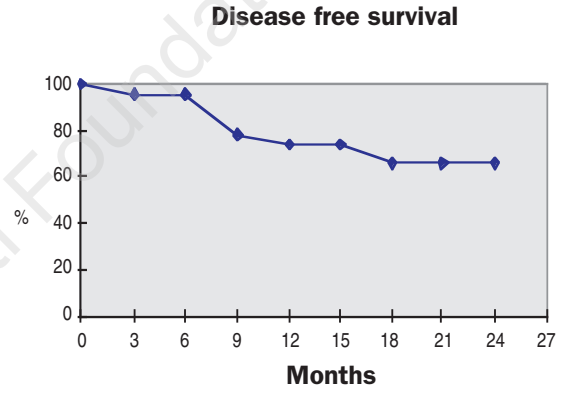

Figure 2. Disease-free survival of 23 CRs treated with VEMB.

of constipation), but no severe neurotoxicity has been observed. Severe toxicity was found with significant frequency only at the hemopoietic level (neutropenia stage 3-4 in 24% of cases). However, it did not prevent 16 patients (43%) from completing therapy within the 50 expected days, so that the mean treatment completion time was 58 days (range 50-85).

The data to calculate DI were available for 36 patients. They received 98%, 97% and 100% of the planned dose of cyclophosphamide, mitoxantrone and bleomycin, respectively. In most cases it was preferred to postpone treatment rather than reducing drug dosage. Considering both the administered drug dosage and the time required to complete therapy as planned, the actual delivered DI was 90% for the whole group.

Prognostic factors

Table 4 summarizes the analysis of the main prognostic factors with respect to response and survival.

The prognostic factors positively affecting CR resulted the stage of the disease (p = 0.002) and the absence of bone marrow involvement (p = 0.01). Concerning the overall survival rate, the only significantly positive factor was the female gender (p = 0.003), with good balance between the main prognostic factors and gender.

Discussion

Most studies[4,17,18] agree on the fact that elderly patients with aggressive NHL have a worse prognosis than younger patients with the same conditions. This would depend on the higher incidence of concurrent diseases and on the resulting inability of adopting an aggressive therapeutic regimen or completing it within the required timing or in an adequate dosage.

In the past, since CHOP was regarded as the gold standard in the therapy of aggressive NHL, attempts were made at adapting this therapeutic regimen to the elderly population with an aim at reducing its toxic effects as much as possible.[19,20]

Other groups[21,22] preferred to use CHOP at full doses based on the assumption that inadequate treatment of chemoresponsive neoplasias is worse than chemotherapy-induced toxicity.

Since the early 90's, attempts have been made at using chemotherapeutic regimens specially designed for the elderly, giving priority to one or more of the following guidelines: 1) greater use of the oral cytotoxic therapy, such as VMP[11] and PEN;[23] 2) use of less toxic drugs, similar to those already used (e.g. mitoxantrone to reduce cardiotoxicity);[24] and 3) short-lasting therapy.[25]

With an aim to treat the elderly patients with shorter therapeutic courses, several MACOP-B-derived regimens have been used. Initially the Vancouver group kept to the 12 original weeks (LD-ACOP-B and VABE)[6] which were then reduced to 8 (P/DOCE).[7] Similar regimens were used by other groups (P-VEBEC,[8] P-VABEC[9] and VNCOP-B[10]). All required 8 weeks of treatment.

Table 4. Prognostic factors.

	Response	*OS*
Stage (II-III vs IV)	p = 0.002	NS
Age (< 75 vs >75)	NS	NS
Sex (F vs M)	NS	p = 0.003
Symptoms (A vs B)	NS	NS
Bone marrow (NEG vs POS)	p = 0.01	NS
LDH (NORM vs HIGH)	NS	NS
Bulky (NEG vs POS)	NS	NS
Performance status (ECOG 0-1 vs 2-3)	NS	NS
Dose intensity (> 0.9 vs < 0.9)	NS	NS

OS: overall survival.

Also VEMB, whose results are described in this report, should be included in this last group of regimens: the CR rate (62%), the OS (55% at 30 months) and DFS (66% at 24 months) are comparable to the results obtained with other regimens of the same type. These results seem to be significant in light of the fact that the mean age (77 years) of the patients enrolled in our group is the highest of all published studies.

The recorded toxicity should also be taken into consideration, especially because of the quite high number of toxic deaths (11%) which is comparable to the mortality rate found with CHOP.[24] Among the side-effects, the most frequent one (43%) was neurotoxicity-induced constipation, most likely related to the frequent administration of vincristine. Myelotoxicity was also acceptable (neutropenia stage 3-4 in 24% of cases), considering that the use of growth factors was not planned.

The satisfactory actual DI for the whole group has confirmed that the VEMB regimen is quite feasible.

The relatively low number of patients enrolled in the study does not allow to draw any final conclusions for the statistical analysis of prognostic factors; in such a view, one should probably also consider the significantly favorable prognosis for female patients. In agreement with other studies,[8,17,26] however, one should also point to the negative role of bone marrow localization and of the advanced stage of the disease in influencing the possibility of reaching the CR.

In conclusion, even if the case series do not overlap in terms of age and number of enrolled patients, the results obtained with VEMB are comparable to those of the other therapeutic MACOP-B-derived regimens and can be favorably compared with the previously described regimens, especially CHOP. On the basis of the described results, a randomized prospective study on a MACOP-B-derived regimen and CHOP seems to be desirable. Such study should, apart from the clinical results, also consider the quality of life before, during and after therapy since this seems to be particularly important in patients with limited life expectancy. Furthermore, even if not using complex procedures which are difficult to implement, one should carry out, as accurately as possible, an assessment of the concurrent diseases since they are factors which may affect the good feasibility of a chemotherapeutic regimen in the elderly.[27]

Contributions and Acknowledgments

FM designed and coordinated the study. MF and PA were responsible for statistical analysis. FI collected data. CS, EI, MC, DV, GS and LP followed the patients clinically. All authors contributed to the writing of the paper.

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Disclosures

Conflict of interest: none.

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Manuscript processing

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