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.

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

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 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 VABE6 and P/DOCE.7 P-VEBEC,8 P-VABEC9 and VNCOP-B10 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 Formula­
13 were enrolled in the study by 10 different Ital­
ian 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 Formula­
14 stage II to IV;
• cyclophosphamide 350 mg/m² i.v. and mitox­
histological diagnosis of aggressive NHL (D to H
• Ann Arbor stage II to IV;
• performance status 0 to 3 (according to ECOG);
• normal liver, heart, renal and respiratory func­
• 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 screen­
ing;
• 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/m² i.v. and mitox­
antrone 10 mg/m² i.v. at days 1, 15, 29, 43.
• vincristine 1.4 mg/m² i.v. (maximum dose 2 mg)
and bleomycin 5 mg/m² 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 myelo­
toxicity. 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 disap­
ppearance of the clinical and radiological signs of the
disease for at least 4 weeks after the end of ther­
apy. 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 4 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
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 cours­
es of chemotherapy, the DI of each drug was con­sidered together with the amount of each drug, nor­
malized 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 pro­
gression, DI was expressed as the ratio of the actual­
ly delivered dose to the dose prescribed in the regi­
men 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 1.

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 localiza­
tion 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 par­
tial response. Three patients died during induction
therapy for fatal infections (septic shock, 1; pul­
monary 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
due to 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 (Fig­
ure 2). Six out of 7 patients who relapsed had a recur­
cence 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 gener­
ally well tolerated. The most frequent side effect (43% of
cases) was mild neurotoxicity (mainly in the form
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.

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

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

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

Table 2. Response.

<table>
<thead>
<tr>
<th>Type of response</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>23</td>
<td>62</td>
</tr>
<tr>
<td>PR</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>NR*</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

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

Table 3. Hematological and clinical toxicity.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>WHO (1-2)</th>
<th>WHO (3-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16 (41%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Infections</td>
<td>5 (14%)</td>
<td>4(11%)*</td>
</tr>
<tr>
<td>Mucositis</td>
<td>6 (16%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>16 (43%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Including 3 patients died during induction.
The prognostic factors positively affecting CR resulted in 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 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.

Other groups 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 and PEN; 2) use of less toxic drugs, similar to those already used (e.g. mitoxantrone to reduce cardiotoxicity); and 3) short-lasting therapy.

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) which were then reduced to 8 (P/DOCE). Similar regimens were used by other groups (P-VEBEC, P-VABEC and VNCOP-B). All required 8 weeks of treatment.

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. 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, 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.

**Table 4. Prognostic factors.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Response</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage (II-III vs IV)</td>
<td>$p = 0.002$</td>
<td>NS</td>
</tr>
<tr>
<td>Age (&lt; 75 vs ≥75)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (F vs M)</td>
<td>NS</td>
<td>$p = 0.003$</td>
</tr>
<tr>
<td>Symptoms (A vs B)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Bone marrow (NEG vs POS)</td>
<td>$p = 0.01$</td>
<td>NS</td>
</tr>
<tr>
<td>LDH (NORM vs HIGH)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Bulky (NEG vs POS)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Performance status (ECOG 0-1 vs 2-3)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Dose intensity (&gt; 0.9 vs &lt; 0.9)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

OS: overall survival.

**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.

We wish to thank Lorena Munarini for computing assistance.

**Disclosures**

Conflict of interest: none.
Redundant publications: no substantial overlapping with previous papers.

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References