Are hematopoietic colony-stimulating factors useful in association with chemotherapy in the treatment of HIV-related non-Hodgkin’s lymphomas?

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Key words: colony stimulating factors, HIV, non-Hodgkin's lymphoma, treatment

The treatment of patients with HIV/AIDS may be complicated by the myelotoxicity of antiretroviral, anti-infective and antineoplastic drugs that often are to be given concomitantly or subsequently when malignancies develop. Moreover, HIV-related bone marrow dysplasia, in particular granulocytopenia, often concomitantly present, could render such treatment, in particular antineoplastic chemotherapy, even more myelotoxic [1-3]. However, while hematopoietic colony-stimulating factors (CSF) i.e., granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) have been extensively investigated in cancer patients of the general population [4-6], they have been tested to a significantly lesser extent in the HIV setting [7, 8].

Ad hoc committees of the American Society of Clinical Oncology (ASCO) and the European School of Oncology (ESO) recently issued recommendations for the use of CSF in cancer patients receiving antineoplastic chemotherapy [9, 10]. Primary administration of CSF is recommended by the ASCO committee for patients who are expected to develop febrile neutropenia with an incidence equal to or more than 40% and in patients at higher risk for chemotherapy-induced infectious complications [9]. Moreover, the ESO committee justifies the use of CSF with the first chemotherapy cycle if life-threatening complications are anticipated or if a reduction in the scheduled dose might endanger long-term success [10]. Such recommendations are thought by the committees to be applicable also for patients with HIV-related non-Hodgkin’s lymphoma (HIV-NHL), although specific indications for such patients are not discussed in detail [9, 10]. We wish therefore to review the data published in full articles which have appeared in the literature regarding treatment of HIV-NHL with chemotherapy with or without CSF, and our experience as well, in order to verify whether ASCO and ESO recommendations fully apply also to patients with HIV-NHL who receive antineoplastic chemotherapy.

Review of the literature

The review of seven studies published in the literature regarding standard, or specifically devised combination chemotherapy regimens for patients with HIV-NHL, given without CSF support (Table 1) indicates that the rate of febrile neutropenia or sepsis was quite high [11-17] and grade 4 myelosuppression was observed in more than 40% of the patients as well, resulting in delays and reductions of cytotoxic drug dosage.

The reduction of the doses of first-line chemotherapy [18, 19] in another two studies and without CSF support did not substantially reduce the prevalence of febrile neutropenia episodes (Table 2). Most notably, a French-Italian Cooperative Study Group evaluated a low-dose chemotherapy regimen in 37 patients with HIV-NHL resulting in significant bone marrow toxicity with grade 4 leucopenia in almost 50% of the patients [18]. Similarly, Levine et al. reported that the use of low-dose chemotherapy was associated with a high rate (60%) of grade 4 leucopenia [19].

Since the CSF became available, only two studies investigating the use of CSF in combination with standard chemotherapy regimens for the treatment of HIV-NHL have been published in full articles in the literature. Kaplan and his co-workers at the San Francisco General Hospital used GM-CSF in association with the CHOP regimen and found that only when given from days 4 to 13 was the use of GM-CSF, associated with a higher mean nadir of absolute neutrophil count (ANC), shorter mean durations of neutropenia, fewer chemotherapy cycles complicated by neutropenia and fewer days of hospitalization for fever and neutropenia, all at statistically significant levels, when compared to patients who received the same dosage of CHOP chemotherapy without GM-CSF support. However, complete response rates and median survival times of the two groups of patients were superimposable. Patients in the former group, however, experienced an increase in p24 antigenaemia which was not observed in patients who
Table 1. Incidence of hematologic and infectious toxicities associated with standard or specifically devised chemotherapy regimens used in previously untreated patients with HIV-NHL.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of patients</th>
<th>Leukopenia (grade 4) (%)</th>
<th>Neutropenia (grade 4) (%)</th>
<th>Febrile neutropenia (%)</th>
<th>Infection* (grade ≥ 3) (%)</th>
<th>Infectious death (%)</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-BACOD</td>
<td>13</td>
<td>46</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>Novel regimen</td>
<td>9</td>
<td>44</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>MACOP-B and others</td>
<td>23</td>
<td>52</td>
<td>-</td>
<td>-</td>
<td>26</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Modified MACOP-B</td>
<td>30</td>
<td>76</td>
<td>-</td>
<td>53</td>
<td>17</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>ACVB</td>
<td>141</td>
<td>79</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Novel oral combination</td>
<td>18</td>
<td>50</td>
<td>-</td>
<td>43</td>
<td>-</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>MACOP-B</td>
<td>12</td>
<td>50</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>CDE</td>
<td>21</td>
<td>67</td>
<td>43</td>
<td>38</td>
<td>5</td>
<td>7</td>
<td>17</td>
</tr>
</tbody>
</table>

Note: See cited publications for information regarding chemotherapy agents, doses and schedule.

Abbreviations: M-BACOD = cyclophosphamide, doxorubicin, vincristine, bleomycin, dexamethasone, and methotrexate; novel regimen = cytarabine, L-asparaginase, vincristine, methotrexate, cyclophosphamide, doxorubicin, etoposide, and prednisone; MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; others = cyclophosphamide, vincristine, prednisone, and doxorubicin; ACVB = doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisolone; novel oral combination = lomustine, etoposide, cyclophosphamide, and procarbazine; CDE = cyclophosphamide, doxorubicin, and etoposide.

Grade 4 leukopenia: WBC count < 1000 x 10^9/l.
Grade 4 neutropenia: ANC < 500 x 10^9/l.
Non-opportunistic infections only.
At least 6/13 patients.
At least 4/9 patients.

Table 2. Incidence of hematologic and infectious toxicities associated with low-dose chemotherapy regimens used in previously untreated patients with HIV-NHL.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of patients</th>
<th>Leukopenia (grade 4) (%)</th>
<th>Neutropenia (grade 4) (%)</th>
<th>Febrile neutropenia (%)</th>
<th>Infection* (grade ≥ 3) (%)</th>
<th>Infectious death (%)</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose CHVmp-P-VB</td>
<td>37</td>
<td>49</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Low-dose M-BACOD</td>
<td>42</td>
<td>60</td>
<td>21</td>
<td>57</td>
<td>12</td>
<td>5</td>
<td>19</td>
</tr>
</tbody>
</table>

Note: See cited publications for information regarding chemotherapy agents, doses, and schedule.

Abbreviations: CHVmp-P-VB = cyclophosphamide, doxorubicin, teniposide, prednisone, vincristine and bleomycin; M-BACOD = cyclophosphamide, doxorubicin, vincristine, bleomycin, dexamethasone, and methotrexate.

Grade 4 leukopenia: WBC count < 1000 x 10^9/l.
Grade 4 neutropenia: ANC < 500 x 10^9/l.
Non-opportunistic infections only.

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**Personal experience**

At the Centro di Riferimento Oncologico, Aviano, Italy, we have found that in 113 patients with HIV-NHL, the median white blood cell (WBC) count at NHL diagnosis was 3900 x 10^9/l (range 470 to 42800 and one-third of patients had less than 3000 x 10^9/l. Moreover, the median number of ANC was 2340 x 10^9/l (range 51 to 19094) and 40% of patients had less than 2000 x 10^9/l (Table 3). In 19 patients with bone marrow lymphomatous involvement, the median numbers of WBC and ANC were 2600 x 10^9/l and 1860 x 10^9/l, respectively, and the majority of our patients with HIV-NHL thus presented with leukopenia.

Apart from a brief experience in a compassionate study with GM-CSF and chemotherapy in 10 patients with various AIDS-related tumors [22], at our institution we have employed G-CSF systematically in all did not receive GM-CSF, suggesting a role for it in the stimulation of HIV replication. The clinical impact of this troublesome finding could not be determined, also because of the small number of patients [20].

In the only other study, Walsh et al. evaluated the association of GM-CSF with the m-BACOD regimen and showed that only 18% of cycles of chemotherapy were delayed for neutropenia, despite constitutional symptoms due to GM-CSF (fever, fatigue, rash, chills, and shortness of breath) observed in a substantial number of patients [21]. However, these side effects may be explained by the four-fold higher dosage (20 mcg/kg) than the current standard dose of GM-CSF (5 mcg/kg) employed in this study.
Table 3. White blood cell (WBC) counts and absolute neutrophil count (ANC) at HIV-NHL diagnosis in 113 patients observed at the Centro di Riferimento Oncologico, Aviano.

<table>
<thead>
<tr>
<th>WBC count</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number (10^9/l) (range)</td>
<td>3900 (470–42800)</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>2 (2)</td>
</tr>
<tr>
<td>1001–2000</td>
<td>13 (12)</td>
</tr>
<tr>
<td>2001–3000</td>
<td>21 (19)</td>
</tr>
<tr>
<td>3001–4000</td>
<td>24 (21)</td>
</tr>
<tr>
<td>&gt;4000</td>
<td>53 (47)</td>
</tr>
<tr>
<td>ANC count</td>
<td>2340 (51–19094)</td>
</tr>
<tr>
<td>Median number (10^9/l) (range)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>&lt;500</td>
<td>7 (6)</td>
</tr>
<tr>
<td>501–1000</td>
<td>34 (30)</td>
</tr>
<tr>
<td>1001–2000</td>
<td>30 (27)</td>
</tr>
<tr>
<td>&gt;3000</td>
<td>38 (34)</td>
</tr>
</tbody>
</table>

Consecutive patients with HIV-NHL undergoing chemotherapy since G-CSF became available in the clinics, in July 1991. We have therefore retrospectively compared the outcome of the first 18 patients consecutively treated with standard chemotherapy regimens (LNH 84 or CHVmp vincristine-Bleo) and G-CSF with 19 patients treated with the same chemotherapy regimens before July 1991 [23]; the only reason for using or not using G-CSF was its availability. The study groups were well balanced for age, sex, performance status, p24 antigenemia, prior zidovudine therapy, stage and histology of NHL and bone marrow involvement. CD4/mm^3 count was lower in patients treated with G-CSF, although not to a significant extent, than in the other group (148 versus 231). G-CSF (5 mcg/kg/day) was given subcutaneously 24 hours after chemotherapy for 13 days in all cycles. G-CSF significantly reduced the duration of nadir WBC to a mean of 8.4 days compared with 10.8 days in the control group (P = 0.006). Among patients with a CD4 count ≥ 200/mm^3, the nadir WBC was significantly higher in the G-CSF than in the control group (mean 1293 ± 143 versus 410 ± 285) (P = 0.009). Taking into consideration all patients with any CD4 count, this difference was lower, but at a borderline statistical significance (P = 0.09). The event rates for febrile neutropenia were comparable between the two groups. Although we observed the same number of culture-confirmed infections in the two groups of patients, the infections observed in the group treated without G-CSF, almost all broncopulmonary infiltrates, were more severe (WHO) than in the group treated with G-CSF, requiring more days of hospitalization with antibiotic therapy until radiological resolution. In fact, in most of these patients, because of their socio-economic conditions (ex-intravenous drug users), treatment could not have been continued in an outpatient setting or at home in a reliable way. Moreover, the overall number of opportunistic infections (C-1 according to the Centers for Disease Control classification for HIV infection) was higher in the group which did not receive G-CSF and this increased the number of days of hospitalization. The mean number of chemotherapy cycles and the proportion of patients who received full doses of chemotherapy were not significantly different in the two groups. However, the mean duration of delays between cycles was reduced from 9 days in the control to 4 days in the G-CSF-treated patients (P = 0.01). The episodes of WHO grades 3 and 4 mucositis were more common, although not at a significant level, in the group treated without G-CSF (47% versus 22% i.e., 9/19 versus 4/18 patients), requiring in the latter group a more frequent use of total parenteral nutrition and subsequently a prolonged stay in the hospital. A transitory slight weight increase in 2 patients due to fluid retention, that did not preclude the further administration of G-CSF, was the only adverse event related to G-CSF. In no patients with negative p24 antigenemia did we observe a seroconversion at the end of therapy with G-CSF, while all patients with detectable p24 antigenemia were still positive at the end of treatment. The complete response rates were superimposable, being 69% (median duration 8 months, range 2–36) in the group treated with G-CSF and 67% (median duration 10 months, range 3–65) in the control group. Although survival was not the major endpoint for evaluating G-CSF efficacy in this study, we observed median durations of survival of 4 months and 10 months (P = 0.04) in the groups treated with and without G-CSF, respectively. The difference, however, could be explained by the lower median CD4 count in the G-CSF-treated patients than in the control group.

In the present economic climate, evaluation of the cost-effective balance of new medical technology is becoming increasingly important. The cost of CSF is high, but theoretically CSF could reduce the cost of the overall treatment by substantially decreasing the antibiotic therapy required for treatment of infectious complications related to bone marrow toxicity, and the days of hospitalization required for the bone marrow toxicity as well [24]. Therefore, in our study, we made a cost-effect evaluation [23]. Costs were expressed in U.S. dollars. The mean cost of one day of hospitalization per haematologic toxicity at our Division was estimated to be about 450 U.S. dollars, which is, however, probably underestimated. For cost evaluation the following items were considered: 1) daily cost of hospital stay (263 U.S. dollars); 2) antibiotic prophylaxis against Pneumocystis carinii pneumonia and antifungal prophylactic therapy (daily cost/patient: 22 U.S. dollars); 3) antibiotic therapy administered during hematologic toxicity (parenteral cefalosporin plus aminoglicoside therapy, mean daily cost/patient: 67 U.S. dollars); 4) supportive therapy including diagnostic procedures (mean daily cost/patient/toxic episode: 90 U.S. dollars); 5) recombinant G-CSF (the current cost of a 300 mcg vial in Italy is 100 U.S. dollars). Therapy and hospital cost did not change over the time period of the study.

At our Center the policy at that time was that
patients with HIV-NHL were hospitalized both for the administration of cycles of chemotherapy, when chemotherapy-related toxicity and HIV-related infections were observed. This approach was based on the high risk of severe complications associated with intensive chemotherapy in such patients with unfavourable NHL and severe immunodeficiency, and to the peculiar features of our HIV-positive population, i.e., the usual distant geographical area of residence, and logistic problems connected with the lifestyle of these patients who are often drug users or ex-drug users. While the number of hospitalizations was similar in the two groups, there was a statistically significant decrease in the mean duration of hospitalization for toxicity per patient treated with G-CSF compared to that of the control group (6.4 ± 9.1 days versus 18 ± 13.2 days \( P = 0.003 \)). Taking into consideration the cost of G-CSF and the cost of hospitalization, the mean cost per cycle was $3232 (± 2283) U.S. dollars in patients treated with chemotherapy without G-CSF versus $2282 (± 1345) U.S. dollars in patients treated with G-CSF. This difference was, however, not statistically significant. Therefore, in contrast to what might have been expected, the cost of chemotherapy plus G-CSF versus chemotherapy alone did not increase, but actually decreased. Because this is not a randomized study but rather a retrospective evaluation of patients treated during two different periods of time, although consecutive, it is possible that in the first time period, when patients were treated without G-CSF, the sparse experience in the management of patients with HIV-related lymphoma, a very recently described pathology, could have played a role in increasing the number of days of hospitalization. On the other hand, in the second period of time, when patients were treated with G-CSF, the experience accumulated over the years in the management of these patients could have made possible their earlier hospital discharge.

Conclusions and recommendations

The review of the literature, and the overall experience of the Centro di Riferimento Oncologico of Aviano including a cost-effect study, strongly support the primary use of CSF in patients with HIV-NHL treated with chemotherapy, in order to reduce the myelosuppression and its associated morbidity, although the response rate and survival are not influenced. Moreover, CSF may improve patients' quality of life by decreasing the frequency of hospital admissions and the number of days spent in the hospital for episodes of fever with neutropenia. Although the tolerability profiles of G-CSF and GM-CSF are now quite superimposable in the population at large due to the fact that the dose of GM-CSF has been lowered, in the HIV setting the risk of an increased retroviral replication with GM-CSF should be considered [20] and GM-CSF should be employed only with a concomitant antiretroviral treatment. We therefore advise the use of G-CSF in the HIV setting. Further evaluation of the effect of G-CSF administration on response rate and survival in the HIV setting, as well as the importance of chemotherapy dose intensity, are currently been evaluated within the European Intergroup Study HIV-NHL in a large number of patients.

Acknowledgment

Supported by grants of ISS '95 and AIRC '95.

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Received 11 October 1995; accepted 23 January 1996.

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