Outcome in Patients with Non-Hodgkin Lymphoma and With or Without Human Immunodeficiency Virus Infection

Michele Spina,1 Antonino Carbone,1 Emanuela Vaccaro,1 Annunziata Gloghini,2 Renato Talamini,3 Roberta Cinelli,1 Ferdinando Martellotta,1 and Umberto Tirelli1

Divisions of 1Medical Oncology A and 2Pathology and 3Epidemiology Unit, National Cancer Institute, Aviano (PN), Italy

We compared the clinical characteristics and outcomes of 100 patients with human immunodeficiency virus (HIV)–associated non-Hodgkin lymphoma (NHL; HIV-NHL) treated in the highly active antiretroviral therapy era with those of 82 HIV-negative patients with aggressive NHL. The 3-year overall survival (OS) was 37% among patients with HIV-NHL and 74% among HIV-negative patients with NHL (P < .0001). However, the response-adjusted OS was similar in the 2 groups (hazard ratio, 1.4 for HIV-infected patients vs. 1 for HIV-negative patients; P = .24). Therefore, the achievement of complete remission should be the main goal in the treatment of patients with HIV-NHL.

HIV infection is associated with a high incidence of aggressive, systemic non-Hodgkin lymphoma (NHL) presenting with widespread disease and extranodal involvement (e.g., gastrointestinal tract, bone marrow, liver, and CNS). Compared with high-grade NHL in HIV-negative patients, patients with HIV-associated NHL (HIV-NHL) had a lower complete remission rate, a higher relapse rate, and shorter overall survival (OS) [1, 2].

Since the introduction of HAART, the incidences of new AIDS-defining events and mortality among HIV-infected patients have decreased to less than one-tenth of the levels before the HAART era [3, 4]. Moreover, recent reports have shown a possible impact of HAART on the clinical presentation and outcome associated with a lower frequency of extranodal disease (i.e., in bone marrow and meninges), a higher complete remission rate, and longer disease-free survival (DFS) and OS, even if other reports failed to show any correlation between HAART and extranodal involvement [5–7].

**Patients and methods.** Our goal was to compare the clinical features at presentation to the hospital and outcomes for patients with high-grade HIV-NHL and for HIV-negative patients with NHL. We evaluated the clinical records of patients with lymphoma who received diagnoses and treatment at the National Cancer Institute (Aviano, Italy) from the same group of oncohematologists.

From January 1997 (when HAART was first used in our clinical practice) through April 2002, 329 cases of high-grade NHL (110 in HIV-positive patients and 219 in HIV-negative patients) were observed. Because age is the main prognostic factor of adverse events in patients with NHL, and because HIV-positive patients with NHL tend to be younger than HIV-negative patients with NHL, only patients <50 years of age (100 in the HIV-positive group and 82 in the HIV-negative group) were considered for enrollment in this study. The following variables were evaluated: demographic characteristics, histological findings, lymphoma stage (according to the Ann Arbor classification system [8]), presence of B symptoms (i.e., fever, night sweats, and weight loss), performance status (PS), body sites of extranodal involvement, international prognostic index (IPI) [9], chemotherapy regimens used, response and relapse rates, toxicity (according to World Health Organization criteria) [10], serum lactate dehydrogenase (LDH) level, and serum albumin level. The same criteria were used in staging and restaging evaluations performed in both groups.

OS was calculated as the interval between the date that chemotherapy was started and the date of death or the final time that the patient visited their oncohematologist. DFS was calculated for patients in complete remission as the interval between the date on which complete remission was first recorded and the date of relapse or the last known date on which the patient was disease free. OS and DFS were evaluated using the Kaplan-Meier method [11], and differences between subgroups were assessed by means of the log-rank test [12].

**Results.** The median age was 36 years (range, 16–50 years) in the HIV-positive group and 37 years (range, 17–50 years) in the HIV-negative group. More HIV-positive than HIV-negative patients were men (79% vs. 54%; P = .0003), according to the epidemiology of HIV infection in Italy. The PS was similar in both groups: in the HIV-positive group, 80% of patients had a PS of 0 or 1, compared with 81% of patients in...
the HIV-negative group. The distribution of NHL subtypes significantly differed in the 2 groups: diffuse, large B cell NHL was more common among HIV-positive patients than among HIV-negative patients (91% vs. 61%; \( P < .0001 \)), whereas Burkitt NHL was more often diagnosed in the HIV-positive group than in the HIV-negative group (25% vs. 6%; \( P < .0001 \)). Stage III and IV NHL were more frequently diagnosed in the HIV-positive group than in the HIV-negative group (77% vs. 58%; \( P = .006 \)). Similarly, extranodal involvement was more common among HIV-positive patients than among HIV-negative patients (81% vs. 69%, \( P = .04 \)), probably because the gastrointestinal tract was significantly more involved in the HIV-positive group than in the HIV-negative group (28% vs. 9%; \( P < .001 \)). In fact, the frequencies of involvement of other extranodal sites, such as bone marrow, CNS, liver, spleen, lung, or Waldeyer ring, were similar in both groups.

The distribution of age-adjusted IPIs [12] significantly differed in the 2 groups. In fact, an IPI of 0 or 1 was reported in 36% of HIV-positive patients, compared with 52% of HIV-negative patients, whereas an IPI of \( \geq 2 \) was observed in the remaining 64% of HIV-positive patients and 48% of HIV-negative patients (\( P = .04 \)). The LDH level was abnormal in 71% of patients in the HIV-positive group, compared with 58% of patients in the HIV-negative group (\( P = .07 \)); similarly, a serum albumin level that was less than the normal value was observed significantly more frequently in HIV-positive patients than in HIV-negative patients (61% vs. 28%; \( P < .001 \)). All HIV-positive patients received HAART: 55 had received HAART before the diagnosis of NHL and continued HAART during chemotherapy, whereas 35 started HAART concomitantly with chemotherapy, and only 10 started HAART at the end of chemotherapy.

All patients were enrolled in prospective studies performed at the time of diagnosis at our institution, and they received comparable doxorubicin-based chemotherapy (i.e., cyclophosphamide-doxorubicin-vincristine-prednisone [CHOP] or CHOP-like regimens). Only 3 (4%) of 82 HIV-negative patients underwent autologous bone marrow transplantation as part of their first-line treatment. The complete remission rate was significantly lower in the HIV-positive group than in the HIV-negative group (51% vs. 74%; \( P = .007 \)), whereas the relapse rate was similar in the 2 groups (26% of HIV-positive vs. 24% of HIV-negative patients; \( P = .75 \)). Fifty-seven (57%) of 100 HIV-positive patients had died at the time of writing, compared with 18 (22%) of 82 HIV-negative patients (\( P < .0001 \)). The 3-year OS significantly differed in the 2 groups (37% for HIV-positive patients vs. 74% for HIV-negative patients; \( P < .0001 \)), even though the response-adjusted OS was similar in the 2 groups (hazard ratio, 1.4 for HIV-positive patients vs. 1 for HIV-negative patients; \( P = .24 \)). Our data are summarized in Table 1.

### Discussion

Our data show that the overall prognosis for patients with HIV-NHL is worse than that for HIV-negative patients, mainly because of underlying HIV infection. However, when complete remission is achieved, the relapse rate and response-adjusted OS are very similar to those of HIV-negative patients.

In conclusion, in the HAART era, we have shown for the first time to our knowledge that patients with HIV-NHL who achieve complete remission while receiving doxorubicin-based regimens and HAART have the same outcome as HIV-negative patients with high-grade NHL. Therefore, the achievement of complete remission using the combination of doxorubicin-based regimens and HAART should be the main goal in the treatment of patients with HIV-NHL.

### Acknowledgments

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### References


4. Palella FJ, Delaney KM, Moorman AC. Declining morbidity and mor-

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**Table 1.** Clinical characteristics of and outcomes for HIV-positive and HIV-negative patients with non-Hodgkin lymphoma (NHL).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-positive patients</th>
<th>HIV-negative patients</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B cells</td>
<td>61</td>
<td>91</td>
<td>...</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>25</td>
<td>6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Stage III or IV NHL</td>
<td>77</td>
<td>58</td>
<td>.006</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td>81</td>
<td>69</td>
<td>.04</td>
</tr>
<tr>
<td>Gastrointestinal tract involvement</td>
<td>28</td>
<td>9</td>
<td>.0009</td>
</tr>
<tr>
<td>Serum LDH level greater than normal</td>
<td>71</td>
<td>58</td>
<td>.07</td>
</tr>
</tbody>
</table>

**Outcome**

- Achieved complete remission: 51/74, \( P = .007 \)
- Relapsed: 26/24, \( P = .75 \)
- OS 3 years after presentation: 37/74, \( P < .0001 \)
- Response-adjusted OS, hazard ratio: 1.40/1.24, \( P = .24 \)

**NOTE.** Data are percentage of patients, unless otherwise indicated. LDH, lactate dehydrogenase; OS, overall survival.