Upfront high-dose sequential therapy (HDS) versus VACOP-B with or without HDS in aggressive non-Hodgkin’s lymphoma: long-term results by the NHLCSG


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Background: There is not univocal concordance for using high-dose sequential therapy (HDS) as first-line treatment for aggressive non-Hodgkin’s lymphoma (NHL). We designed this study to evaluate the usefulness of HDS followed by high-dose therapy (HDT) with autologous stem cell transplantation as front-line treatment in different subsets of aggressive NHL.

Patients and methods: Among 223 patients aged 15–60 years with aggressive, advanced stage NHL, 106 patients were randomized to VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) for 12 weeks (plus HDS/HDT in case of persistent disease) (arm A), and 117 patients to VACOP-B for 8 weeks plus upfront HDS/HDT (arm B).

Results: According to the intention-to-treat analysis, the complete response rate was 75% for arm A and 72.6% for arm B. With a median follow-up of 62 months there was no difference in 7-year probability of survival (60% and 57.8%; \( P = 0.5 \)), disease-free survival (DFS) (62% and 71%; \( P = 0.2 \)) and progression-free survival (PFS) (44.9% and 40.9%; \( P = 0.7 \)) between the two arms. Subgroup analyses confirmed that the best results in terms of survival, DFS and PFS were achieved by patients with large B-cell NHL without bone marrow (BM) involvement, independently of the treatment arm. Results were poorer in other categories of patients and poorest in patients with BM involvement.

Conclusions: Aggressive NHL patients do not benefit from upfront HDS/HDT.

Key words: autologous stem cell transplantation, high-dose sequential therapy, high-grade NHL, VACOP-B

Introduction

Conventional chemotherapy for patients with aggressive non-Hodgkin’s lymphoma (NHL) results in a long-term probability of survival of ~50% [1–3], while it is disappointing for refractory or relapsed disease [4–6], with high-dose therapy (HDT) plus autologous stem cell transplantation (ASCT) being the standard salvage for patients with recurrent, chemosensitive disease [7, 8].

The role of HDT in patients with partially responsive disease still remains uncertain [9, 10].

Retrospective data [11–13] suggest that high–intermediate/high-risk NHL in first complete response (CR), as defined by the International Prognostic Index (IPI) [14], are a suitable target for HDT, but randomized studies could not demonstrate that HDT can improve outcome [15–17] and an early HDT in high-risk patients resulted to be inferior to chemotherapy [18].

In a previous randomized study high-dose sequential therapy (HDS) followed by HDT/ASCT achieved a superior event-free survival (EFS) compared with MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) in diffuse, large B-cell-type NHL [19].

Our group compared VACOP-B with VACOP-B plus autologous bone marrow transplantation (ABMT) [20] in patients with diffuse, aggressive NHL, as defined by the Working Formulation (WF) [21]; while the retrospective analysis suggested that
high-risk patients could have a significant advantage in terms of disease-free survival (DFS), the outcome in ABMT arm was not significantly better.

This study comparing VACOP-B ×12 weeks (plus HDS/HDT in case of failure) versus VACOP-B ×8 weeks followed by HDS/HDT was designed to evaluate the usefulness of ‘upfront HDS/HDT’ versus the flexible strategy ‘HDS when needed’.

 Patients and methods

Eligibility criteria

This study, including 18 participating centers from the NHLCSG, Italy, began in August 1995 and closed in March 2001. Inclusion criteria were: age 15–60 years, diffuse large cell-type NHL according to the WF (excluding lymphoblastic lymphoma and Burkitt’s lymphoma), stages II bulky (≥10 cm), III and IV (including patients with bone marrow (BM) involvement), according to the Ann Arbor system [22]; normal renal, pulmonary, cardiac and hepatic function, unless abnormal because of disease involvement; positive serology to HIV or hepatitis B or C virus, previous chemotherapy and written informed consent. The study protocol was approved by the ethics committee (institutional review board) of each center. All cases underwent central pathology review to confirm diagnosis.

Staging procedure

Extent of disease was assessed by physical examination, bilateral BM biopsies, and computed tomography (CT) scan of the chest, abdomen and pelvis. Magnetic resonance imaging and radionuclide scan were performed when necessary. The number and diameter of extranodal sites and tumor masses were determined. All patients underwent restaging at the end of treatment, every 3 months during the first year, every 6 months in the second year and then annually. All necessary tests were performed when clinically required.

Treatment

We randomized 223 patients to receive either: 12-week VACOP-B (arm A, 106 patients); or 8-week VACOP-B followed by HDS with high-dose cyclophosphamide (HD-CY, 7 g/m²) plus granulocyte colony-stimulating factor (G-CSF) and high-dose etoposide (HD-VP, 2 g/m²), plus HDT with BEAM (carmustine, etoposide, cytarabine, melphalan) [23] regimen and ASCT (arm B, 117 patients).

Arm A. Patients achieving CR or an unconfirmed CR (CRu) [24] underwent follow-up evaluation; for those not achieving CR [partial response (PR), no response (NR) or progressive disease (PD)], rescue treatment with HDS/HDT was planned. Patients in CR after VACOP-B who relapsed were to be treated with DHAP (dexamethasone, cisplatin, cytarabine) regimen for two courses and HDS/HDT.

Arm B. Patients were to proceed to HDS/HDT after 8-week VACOP-B. Patients relapsing after CR, or showing PD/NR during treatment, received DHAP as salvage treatment.

In both arms patients with bulky disease at diagnosis or residual masses after treatment received involved-field radiotherapy (IFRT) (3600–4000 cGy in 20 fractions). The trial design is reported in Figure 1.

VACOP-B [25]. HD-CY [19], HD-VP [19] and DHAP [5] were given according to original treatment schedules. Peripheral blood progenitor cells were collected after HD-CY plus G-CSF (5 μg/kg/day).

Patients were conditioned with BEAM [23] and PBPC were infused 24 h after the melphalan administration.

Supportive care during ASCT has been described elsewhere [20]. Platelet transfusions were given for platelet <10 × 10⁹/l and erythrocyte concentrates were administered when hemoglobin <8 g/dl; all patients received G-CSF 5 μg/kg/day subcutaneously until neutrophil recovery.

Patient characteristics and assessment of response

Pretreatment characteristics of patients are listed in Table 1. The two groups of patients were matched for the main characteristics. After the pathological review, five patients from arm B were ineligible: one due to serological positivity for hepatitis C and four because of histological error (one Burkitt’s lymphoma, two follicular mixed NHL, one Hodgkin’s lymphoma); however, they received the planned treatment according to the assigned arm by randomization and were included both in the response analysis and in the survival analysis, according to the intention-to-treat criteria.

CR was defined as a complete disappearance of disease for at least 4 weeks. Patients with persistent CT abnormalities but >75% regression of the initial tumor were said to be in CRu if all other parameters confirmed CR [24]. PR was defined as a 50–75% reduction of all measurable lesions and NR a <50% reduction in tumor mass. PD was defined as an increase of original masses or the appearance of new masses.

Conventional chemotherapy toxicity and HDS/HDT toxicity were evaluated according to World Health Organization (WHO) criteria.

Statistical methods

Randomization was carried out by telephone from the National Cancer Institute in Genoa, Italy. It was estimated that 223 patients, recruited over 5 years, would ensure a power of 80% (with an alpha error equal to 5%) to detect a 20% difference in 3 years survival rate in favor of the patients assigned to VACOP-B + HDS.

The primary end point was overall survival. Other main objectives were: response rates, DFS, progression-free survival (PFS) and toxicity; the two arms were compared according to the intention-to-treat basis. Patients were
considered progression free until one of the following events occurred: recurrence, a second malignancy or death from any cause. DFS only applied to patients who achieved a CR. Duration was calculated from the time of CR assessment to the date of relapse, or last follow-up evaluation that confirmed the patients to be free of lymphoma. Survival was defined as the time from randomization to death, independent of cause, or last follow-up evaluation. Curves were constructed using the method described by Kaplan and Meier [26] and compared using the log-rank test.

The relationship between parameters and outcome was examined by univariate and multivariate analysis according to the Cox hazards regression model. Test statistics for comparison of main objectives were regarded as significant if the two-sided $P$ value was <0.05.

Prognostic factors considered in the stepwise Cox analysis [27] were: sex, performance status (0 versus $\geq 1$), constitutional symptoms (A versus B), bulky disease (<10 versus $\geq 10$ cm), number of extranodal sites (0 versus $\geq 1$), lactate dehydrogenase (LDH) level (normal versus higher than normal), BM involvement at diagnosis (negative versus positive), Ann Arbor stage (II bulky versus III + IV) and spleen (no versus yes). WHO criteria were used for performance status.

Overall survival, PFS and DFS were also retrospectively analyzed according to the IPI score adjusted for age $\leq 60$ years. Patients were subdivided into four groups (low, low–intermediate, intermediate–high and high risk) according to the presence of 0, 1, 2 or 3 risk factors (performance status, LDH and Ann Arbor stage).

The $\chi^2$-test or Fisher's exact test were used to compare groups for toxicity or response rate.

## Results

### Response to treatment and toxicity

Between August 1995 and March 2001, 106 patients were randomized to arm A and 117 to arm B.

#### Arm A

After 12-week VACOP-B ± IFRT, 65 (61.3%) patients achieved CR/CRu (four patients achieved CR after IFRT), 31 (29.3%) patients achieved PR and 10 patients were NR or PD. Forty-one patients with persistent disease were eligible for HDS/HDT, but 12 (29%) did not receive or complete this therapy owing to progressive disease (10 patients) or cardiac toxicity (two patients). Twenty-nine patients completed HDS/HDT and 15 (51.7%) of them achieved CR (two achieved CR after IFRT).

**Table 1. Patient characteristics according to treatment**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Arm A*</th>
<th>Arm B**</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>42 56.6</td>
<td>46 51/117 43.6</td>
</tr>
<tr>
<td>Range</td>
<td>15–60</td>
<td>18–59</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 60/106 56.6</td>
<td>Female 46/106 43.4</td>
</tr>
<tr>
<td>Performance status</td>
<td>0 51/106 48.2</td>
<td>1 40/106 37.7</td>
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<tr>
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<td>Diffuse large-cell 69/106 65.0</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Other</td>
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<td>Stage</td>
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<td>III 23/106 21.7</td>
</tr>
<tr>
<td></td>
<td>IV 63/106 59.4</td>
<td>Symptons</td>
</tr>
<tr>
<td></td>
<td>B 51/106 48.1</td>
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<td></td>
<td></td>
<td>1 29/106 27.4</td>
</tr>
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<td></td>
<td></td>
<td>=$/&gt;2 23/106 21.7</td>
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<td></td>
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<td>Bone Marrow Involvement</td>
<td>No 86/106 81.1</td>
<td>Yes 20/106 18.9</td>
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<tr>
<td>Bulky disease</td>
<td>No 67/106 63.2</td>
<td>Yes 39/106 36.8</td>
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<tr>
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</tr>
<tr>
<td></td>
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<tr>
<td>International Index</td>
<td>Good risk 34/106 32.1</td>
<td>Poor risk 72/106 67.9</td>
</tr>
</tbody>
</table>

Abbreviations: *Arm A, VACOP-B; **VACOP-B plus HDS/HDT; NA, not available; ***predominantly large cell.
platelets $>20 \times 10^9/l$ was 10 days (range 9–18). Infection occurred in $\sim 20\%$ of patients and only one patient developed grade 3 infection.

Overall, 38 (36%) patients died: 35 of early or late progression and one (1%) of cardiac failure; two (2%) other patients died of a second neoplasia while in CR after VACOP-B. Currently, 68 out of 106 patients are still alive.

**Arm B.** Following 8-week VACOP-B, 79 (68%) patients completed HDS/ASCT.

Seventeen patients (15%) did not receive HDS/ASCT: 10 patients refused while in clinical and instrumental CR after VACOP-B; five were ineligible, one was lost to follow-up and there was one protocol violation.

Median delivery time of HDS/ASCT was 87 days (range 78–155). Patients received a median of 15.2 $\times 10^6$ CD34+ cells per kilogram of body weight (range 3.5–66.4) collected with a median of two (range one to five) aphereses.

Seven patients did not complete HDS/ASCT procedure because of toxicity: renal toxicity in three; interstitial pneumonia in two; neuropathy in one patient; and perforated stomach ulcer in one patient. Fourteen PD patients did not complete HDS/HDT because of progressive disease and death.

At the end of procedure, 85 (72.6%) patients achieved CR/CRu (four patients achieved CR after IFRT) and 15 (12.8%) patients PR; 17 (14.6%) patients had PD.

During VACOP-B, grade 3–4 WHO granulocytopenia was observed in 24% of patients: anemia in 3%, mucositis in 2%, infection in 3.6%, renal toxicity in 2% and peripheral neurotoxicity in 2%. After HD-CY, grade 3–4 granulocytopenia occurred in 82% of patients. Five (6%) patients suffered grade 3–4 infection. One patient died of interstitial CMV-related pneumonia. Following HD-VP, 38% of patients showed grade 3–4 granulocytopenia and two patients grade 3 pulmonary infection. One patient died of renal toxicity. All patients engrafted; median time to granulocyte count $>0.5 \times 10^9/l$ was 10 days (range 8–26); median time to platelets $>20 \times 10^9/l$ was 11 days (range 7–33). Infection occurred in $\sim 30\%$ of patients. One patient developed a grade 3 cardiac toxicity and one grade 3 liver toxicity.

Overall, 45 patients died: five (4%) of treatment-related toxicity; among these one died of interstitial pneumonia after HD-CY, one of kidney failure after HD-VP, three while in CR after HDT/ASCT (acute hepatitis C and B virus and acute encephalitis). Two patients developed a second tumor while in CR after ASCT: one died of acute myeloid leukemia and one was operated on for colon cancer. Currently, 72 of 117 patients are still alive.

According to intention-to-treat basis, the CR rate was similar in the two arms: arm A, 75.5%; arm B, 72.6% ($P = 0.06$).

**Relapse**

**Arm A.** Twenty-eight (35%) of 80 patients in CR relapsed in a median time of 6 months (range 1–55). Twelve of them (43%) achieved a second CR: six after DHAP plus HDS/HDT and six after DHAP or different second-line therapy. Ten of them are now alive and well. Among the remaining 16 patients, 14 died of PD, one was lost to follow-up and the last one is alive and well following allogeneic transplantation.

**Arm B.** Twenty-two (26%) out of 85 patients in CR relapsed in a median time of 9 months (range 1–35); six achieved a second CR, three are alive on therapy and 13 died of PD.

**Survival**

With a median follow-up of 62 months (range 2–98), the estimated 7-year overall survival of 223 patients was 58.8% [standard error (SE) 3.8%]. On the intention-to-treat basis, no statistically significant difference in 7-year survival was observed between arm A and arm B, with rates of 60% (SE 5.4%) and 57.8% (SE 5.2%), respectively ($P = 0.5$) (Figure 2).

Univariate analysis showed the adverse factors were performance status $\geq 1$ ($P = 0.007$), stage III–IV ($P = 0.0025$), B symptoms ($P = 0.02$), $\geq 1$ extranodal localization ($P = 0.02$), BM involvement ($P = 0.0009$) and LDH elevation ($P = 0.005$). Multivariate analysis showed that BM involvement ($P = 0.01$) and LDH elevation ($P = 0.01$) remained significant.

Of the 165 patients who achieved CR, 66.6% (SE 3.9%) were estimated to be alive and disease-free at 7 years. The 7-year probability of DFS was 62% (SE 5.8%) in arm A and 71% (SE 5.3%) in arm B ($P = 0.2$) (Figure 2). Univariate analysis selected stage III–IV ($P = 0.003$), BM involvement ($P = 0.02$), T-cell phenotype ($P = 0.004$) and histology (G + H versus others; $P = 0.05$) as adverse factors. G + H histology refers to the Working Formulation (WF) classification: type G is diffuse large cell lymphoma; H is immunoblastic large cell lymphoma. Multivariate analysis showed BM as the poorest negative factor although without statistical significance ($P = 0.07$).

The overall 7-year PFS probability was 43.6% (SE 4.3%), it was 44.9% (SE 5.1%) for arm A and 40.9% (SE 7.7%) for arm B ($P = 0.7$), respectively (Figure 2). Univariate analysis selected as negative factors performance status $\geq 1$ ($P = 0.03$), stage III–IV ($P = 0.0004$), $\geq 1$ extranodal localization ($P = 0.01$), BM involvement ($P = 0.001$) and B symptoms ($P = 0.006$). In multivariate analysis, stage III–IV ($P = 0.02$) and BM involvement ($P = 0.015$) remained significant.

**Subgroup analysis**

**BM involvement.** According to univariate and multivariate analysis, BM involvement was the most important independent factor predicting a poor outcome. Comparison of patients with or without BM involvement showed a statistically poorer survival ($P = 0.0009$), DFS ($P = 0.02$) and PFS ($P = 0.001$) for patients with BM involvement (Figure 3). There was no difference in overall survival, DFS and PFS regardless of the randomized treatment received in the two patient groups.

**Large B-cell NHL.** Overall 120 patients with large B-cell lymphoma (groups G and H/WF) without BM involvement were analyzed. This subgroup showed a better outcome.

Again no statistical difference was found between the two arms, but these patients showed a statistically better overall survival ($P = 0.02$), DFS ($P = 0.002$) and PFS ($P = 0.01$) over
the remaining 103 patients (other histology, T-cell phenotype, BM involvement) (Figure 4).

IPI groups. In both arms patients without negative factors were pooled with those with one negative factor (low-risk patients), and patients with two negative factors with those with three negative factors (high-risk patients). Low-risk patients showed better 7-year overall survival (82.6% versus 48.7%; \( P = 0.0000 \)) and better PFS (56.6% versus 38.5%; \( P = 0.0002 \)), while DFS was similar (68.1% versus 65.5%, \( P = 0.6 \)).

Again no statistical difference between the two arms was observed, in terms of overall survival, DFS and PFS, both in low- and high-risk patients (Figure 5).

Discussion

This study in aggressive NHL comparing standard VACOP-B plus HDS/HDT ‘when needed’ versus short VACOP-B plus HDS/HDT ‘upfront’ shows that there is no difference between these two strategies in terms of outcome and CR.

Treatment related-death of 1% in arm A and of 4% in arm B were lower than that reported by us in the same categories

Figure 2. Estimated 7-year (A) overall survival, (B) disease-free survival (DFS) and (C) progression-free survival (PFS) according to treatment arm. Arm A, VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin); arm B, VACOP-B + high-dose sequential therapy/high-dose therapy.

Figure 3. Estimated 7-year (A) overall survival, (B) disease-free survival (DFS) and (C) progression-free survival (PFS) for patients with negative bone marrow (BM) (A) versus patients with positive BM (B).
of patients with HDT [20] and by others with HDS/HDT [19] approaches. The incidence of second tumor was similar in the two arms.

Seventeen patients (15%) from arm B patients did not undergo HDS/HDT, in most cases they refused to undergo the transplant procedure after achieving the CR and the majority of these patients are alive and well and should not detract from the statistical analysis as a negative bias. Twelve patients (29%) from arm A and 21 (18%) from arm B, eligible for HDS/HDT, were not able to complete procedure because of PD or treatment-related toxicity.

According to the intention-to-treat analysis, the overall 7-year survival in all patients of patients was 58.8% with a DFS 66.6% and a PFS of 43.6%. These results appeared inferior to those reported by the Milan Group using the HDS/HDT strategy [19] in 1997 and by ourselves using of HDT [20] in 1998. The Milan group study included only patients with B large-cell NHL (groups G and H/WF) without BM involvement and our study included all categories of aggressive NHL, including patients with BM involvement, and univariate and multivariate analysis.

Figure 4. Estimated 7-year (A) overall survival, (B) disease-free survival (DFS) and (C) progression-free survival (PFS) for patients with large B-cell non-Hodgkin’s lymphoma (G + H/WF) without bone marrow involvement (A) versus all others (B).

Figure 5. Estimated 7-year (A) overall survival, (B) disease-free survival (DFS) and (C) progression-free survival (PFS) for high-risk patients according to treatment arm. Arm A, VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin); arm B, VACOP-B + high-dose sequential therapy/high-dose therapy.
showed BM involvement as the most important independent factor predicting a poor outcome.

Patients without BM involvement showed a significantly better outcome and their outcome fit well with our historical data, suggesting that 12 weeks VACOP-B plus HDT is comparable to 8 weeks VACOP-B plus HDS/HDT in similar categories of patients. The subgroup of patients with large B cell NHL, without BM involvement, showed a better outcome, but the best outcome (regardless of the arm of randomization) was observed in patients with large B-cell NHL without BM involvement.

As expected, the IPI subgroup outcome analysis showed a large statistical advantage for low-risk patients, but no advantage was found for one of the two arms either in low- or high-risk patients (Figure 5); high-risk patients showed an outcome comparable to that reported in the past with HDT [15–18].

A recent randomized study suggests the superiority of HDT versus CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in terms of EFS, but not survival; nevertheless the retrospective analysis showed a statistical advantage both in survival and EFS in high–intermediate IPI risk patients [28], like other retrospective data [11–13, 20], but again not with the results of the prospective trials [15–18].

In conclusion, this trial, like other randomized studies, was unable to demonstrate the usefulness of HDS/HDT as front-line treatment for aggressive NHL, without evidence of benefit for given categories of patients with different prognostic score. As different strategies (HDS/HDT in all cases or only when needed) can give similar results in different subsets of patients, we think that in patients under 60 years old, HDS/HDT should be used in case of persistent disease after front-line therapy. The current availability of rituximab for treating patients with CD20+ diffuse large B-cell lymphoma and the superiority of the association CHOP–rituximab versus CHOP alone in older patients [29], suggest that it would be of interest to evaluate the opportunity of supplementing the HDS/HDT strategy with rituximab in younger patients; indeed the very promising results claimed also in young patients [30] suggest the possibility of comparing the two strategies (CHOP-like plus rituximab versus HDS/HDT plus rituximab).

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References


