Dose-dense R-CHOP-14 supported by pegfilgrastim in patients with diffuse large B-cell lymphoma: a phase II study of feasibility and toxicity

Ecole Brusamolino
Chiara Rusconi
Luigi Montalbetti
Livio Gargantini
Lili Uziel
Grazia Pinotti
Sergio Fava
Guido Pagnucco
Cristiana Pascutto
Enrica Morra
Mario Lazzarino

Background and Objectives. The aim of this study was to evaluate the feasibility and toxicity of CHOP-14, with rituximab (R-CHOP-14), supported by pegfilgrastim, in untreated diffuse large B-cell lymphoma (DLBCL).

Design and Methods. This study included 50 patients with DLBCL with a median age of 55 years (range: 22-70). Sixty-two percent had an International Prognostic Index score >1, 40% had bulky disease and 52% had stage IV disease. CHOP was administered every 14 days, preceded on day 1 by rituximab (375 mg/m²) and followed on day 3 by pegfilgrastim (6 mg per cycle). Toxicity was calculated over 277 cycles administered; feasibility was calculated over 227, since the first cycle in each patient was not susceptible to delay or dose-reduction.

Results. Therapy was delivered on time in 92% of cycles, with the relative dose intensity being 95% for doxorubicin and cyclophosphamide. Grade 4 neutropenia developed in 19% of cycles and neutropenic fever in 4% of cycles (16% of patients), with a median duration of 3 days (range: 2-10). The program was completed in 40 of 50 patients (80%); reasons for withdrawal included progression in three patients, interstitial pneumonia in four, prolonged severe neutropenia in two and septic shock in one patient. Severe adverse events occurred on 12 occasions (4% of cycles), involving 11 patients (22% of total); the most frequent severe adverse event was interstitial pneumonia which occurred in seven patients (14% of total). In three cases, Pneumocystis carinii pneumonia was documented; no cotrimoxazole prophylaxis had been given and a correlation with hypogammaglobulinemia was observed. The complete remission rate was 74%; the 2-year event-free and overall survival rates were 72% and 68%, respectively.

Interpretations and Conclusions. A single dose of pegfilgrastim per cycle of R-CHOP allowed on-time delivery of this chemotherapy in DLBCL, with a low incidence of febrile neutropenia; the risk of P. carinii pneumonia makes cotrimoxazole prophylaxis essential in this setting.

Key words: dose-dense chemotherapy, diffuse large B-cell lymphoma, CHOP, rituximab, pegfilgrastim.

Haematologica 2006; 91:496-502
©2006 Ferrata Storti Foundation

CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) administered every 21 days has been the standard regimen for the treatment of advanced diffuse large B-cell lymphoma (DLBCL) for many years.12 The addition of rituximab to the conventional CHOP regimen, administered every 21 days, has conclusively demonstrated to lead to a significant improvement of the outcome in elderly patients with DLBCL1 and survival benefit is maintained over time, as recently shown by the 5-year update of the GELA study.4 In the French study, rituximab did not substantially add toxicity to the CHOP regimen, even though there was a trend to an increased occurrence of infections after the end of treatment in patients who received R-CHOP compared to those given CHOP.4 As far as dose-intensity is concerned, two studies by the German Study Group (DSHNHL) have recently demonstrated that standard-dose CHOP, administered every 14 days (CHOP-14), produces a longer overall survival than that produced by CHOP-21, both in patients between 18 and 60 years, with good prognosis (normal lactate dehydrogenase level)5 and those between 61 to 75 years of age.6 The need for granulocyte colony-stimulating factors (G-CSF) support to allow the CHOP-14 regimen to be administered on time at the planned dose had been underlined in a prior study by the Southwest Oncology Group.7 In the DSHNHL studies, patients treated with the 2-weekly regimen received filgrastim from day 4 to day 13, while filgrastim administration in the 3-weekly regimen was at the physician’s discretion. The toxicity of CHOP-14 and CHOP-21 was similar and, due to its favorable efficacy and toxicity profile, CHOP-14 was recommended as the new standard chemotherapy regimen for patients aged 60 or older.7 In these studies, rituximab was not added to CHOP and no information could be obtained on the CHOP-14 toxicity profile in the presence of this antibody. Moreover, only one full paper8 has appeared to date on the feasibility and toxicity of CHOP-14 with added rituximab. Recent studies have demonstrated that the
pegylated form of filgrastim (pegfilgrastim) stimulates granulocytopenia as efficiently as filgrastim and that a single fixed dose of 6 mg per cycle of pegfilgrastim is as safe and well tolerated as standard daily filgrastim administration in the management of chemotherapy-induced neutropenia in patients with breast cancer and lymphoma.\textsuperscript{9-11} We have recently devised a program of immuno-chemotherapy in DLBCL, combining rituximab and CHOP, every 14 days, to take advantage of both the higher dose intensity of CHOP-14 compared to CHOP-21 and the additive effect of rituximab. Furthermore, the clinical availability of pegfilgrastim prompted us to investigate the efficacy of this form of G-CSF in managing chemotherapy-induced neutropenia, when administered the day after chemotherapy, at the standard fixed dose of 6 mg per cycle. The primary end-point of this phase II study was to prospectively evaluate the feasibility and toxicity of R-CHOP-14 with the support of pegfilgrastim; the secondary end-point was an assessment of the antitumor efficacy of this program.

### Design and Methods

#### Patients

Patients eligible for the study had previously untreated DLBCL, according to the WHO classification,\textsuperscript{12} were aged between 18-70 years, had stage II-IV disease according to Ann Arbor criteria, and a performance status of 0-2 according to the Eastern Cooperative Oncology Group (ECOG) scale. Patients with all International Prognostic Index (IPI) scores\textsuperscript{13} were included. Bulky disease was defined by a mediastinal mass exceeding one third of the maximum intrathoracic diameter or by a nodal mass larger than 10 cm. Patients were also required to have normal renal, liver and cardiac function. Exclusion criteria included lymphoma other than DLBCL, the presence of cardiac or neurological diseases, central nervous system (CNS) involvement, seropositivity for hepatitis B virus and/or human immunodeficiency virus and the occurrence of a prior neoplasm. Staging procedures included clinical examination, thoracic and abdominal computerized tomography, blood count, bone marrow biopsy and echocardiography, with evaluation of left ventricular ejection fraction. All patients were re-evaluated after three cycles of chemotherapy and underwent a complete restaging at the end of the program and at intervals of three months for the first two years of follow-up. Thoracic and abdominal computerized tomography were programmed every six months for the first two years and then at the treating physician’s discretion. Positron-emission tomographic (PET) scanning was carried out in the presence of residual measurable disease at the end of immuno-chemotherapy to decide whether or not patients required adjuvant radiation therapy, and at the end of therapy to prove a complete remission. All patients gave written informed consent. The study complied with all provisions of the Declaration of Helsinki and was conducted in accordance with Good Clinical Practice rules. The characteristics of the 50 patients included in this phase II study are summarized in Table 1. The median age of the whole group was 55 years (range 22-70) and the male to female ratio was 0.92. Half of the patients were in stage IV (16% with bone marrow involvement) and 40% had bulky disease at presentation; the IPI score was 0-1 in 38%, 2-3 in 52% and > 3 in 10% of the patients.

#### Treatment

The immuno-chemotherapy program (R-CHOP-14) consisted of six cycles, administered every 14 days, of rituximab (375 mg/m$^2$) on day 1, followed on day 2 by CHOP at standard doses (cyclophosphamide 750 mg/m$^2$, doxorubicin 50 mg/m$^2$, vincristine 1.4 mg/m$^2$ up to a maximum dose of 2 mg, and prednisone 100 mg/day for 5 days), supported on day 3 by pegfilgrastim, in a single per cycle subcutaneous dose of 6 mg (Neulasta®, Amgen Inc. Thousand Oaks, CA, USA). Erythropoietin was administered, when appropriate, at the principal investigator’s discretion. Adjuvant radiotherapy at the dose of 30 Gy was delivered to 14 patients to sites of prior bulky disease at diagnosis (10 patients), or to sites of PET-positive residual disease after the immuno-chemotherapy (4 patients). No CNS prophylaxis was adopted. Toxicity of therapy was calculated over a total of 277 cycles, while feasibility was calculated over a total of 227 cycles, since the first cycles of therapy, which were not susceptible to delay or dose reduction because of toxicity, were not considered.

### Table 1. Characteristics of the patients treated with R-CHOP-14.

<table>
<thead>
<tr>
<th>Features</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>24/26</td>
<td></td>
</tr>
<tr>
<td>Median age (yrs)</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>range</td>
<td>18-39</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>40-60</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>&gt; 60</td>
<td>16</td>
</tr>
<tr>
<td>IPI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>IV</td>
<td>26</td>
<td>52</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Bone marrow involved</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Bulky disease</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>LDH &gt; 1xnormal</td>
<td>28</td>
<td>56</td>
</tr>
<tr>
<td>Beta-2 microglobulinemia &gt; 1xnormal</td>
<td>18/44</td>
<td>41</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>&gt; 1 extranodal site</td>
<td>12</td>
<td>24</td>
</tr>
</tbody>
</table>
Toxicity evaluation
A complete blood count was performed on days 1, 3, 6, 8, 10 and 13 of each cycle of therapy and the median absolute neutrophil count (ANC) values ×10^9/L were cumulatively plotted for a given day (all patients and all cycles considered) and according to the cycle of therapy. The limiting hematologic values for recycling were as follows: ANC < 1.5×10^9/L, and/or platelets < 100×10^9/L, and/or Hb < 10g/dl. No time limit to blood count recovery for the next cycle of chemotherapy was adopted. Relative dose intensity (RDI) for each drug of the CHOP combination was calculated according to Hryniuk.24 Hematologic and extra-hematologic toxicities were scored according to the WHO criteria.25 Severe adverse events were defined by the occurrence of a documented infection, and/or by organ or system toxicity requiring hospitalization. Pulmonary function was assessed at the end of therapy at the investigator's discretion, through pulmonary function tests including spirometric evaluation of forced vital capacity (FVC) and forced expiratory volume and measurement of single-breath carbon monoxide diffusing capacity (DLCO). The level of serum immunoglobulins and the numbers of CD4+ and CD8+ lymphocytes were monitored throughout the therapy.

Response evaluation and outcome measures
The procedures for the response evaluation were the same as those used for staging at diagnosis. PET scanning was not routinely used to assess the response, but in the case of residual measurable disease after immuno-chemotherapy, the response evaluation was aided by PET scans. Patients with PET-positive sites of residual disease were given adjuvant radiotherapy. The response to R-CHOP-14-p pegfilgrastim was evaluated on an intention-to-treat basis and classified, according to the proposed International Workshop criteria,26 as complete (CR), complete unproved (CRu), partial (PR) and no response or progressive disease (NR/PRO). Survival analysis was carried out on the whole series and stratified according to the IPI score. Outcome measures included event-free and overall survival. Events were defined as disease progression, or relapse or death of any cause without disease progression. Overall survival was calculated from the initiation of therapy to the date of last follow-up or death.

Statistical analysis
Numerical variables are summarized as the median and range; categorical variables are reported as counts and relative frequencies. Comparison of variables among treatment cycles was carried out using Friedman’s non-parametric ANOVA. Wilcoxon matched pairs test was applied to compare variables between pairs. The association between parameters at diagnosis and therapy delay, grade 4 neutropenia, fever, number of cycles completed, and RDI was assessed by means of the non-parametric Spearman rank order correlation. Overall and event-free survival rates were calculated according to the Kaplan-Meier method;27 differences in survival were evaluated with the log-rank test. All computations were carried out using STATISTICA for Windows 7.1® StatSoft, Inc. and Microsoft® Excel 2000. This study was designed by the HOST scientific committee; data were collected by the principal investigator at each participating Center and analyzed and interpreted by the biostatistician (CP) and by the writer of this article (EB).

Results
Feasibility
The overall number of cycles administered was 277. Feasibility was calculated over 227 cycles, having excluded the first cycle administered to each patient, which were not susceptible to delay or dose reduction. Of the 227 cycles considered, 208 (92%) were delivered on time, at the planned dose. The average RDI was 95% for doxorubicin and cyclophosphamide and 91% for vincristine. As illustrated in Table 2, therapy was delayed on 19 occasions; six cycles (2.6%) were postponed because of limiting neutropenia and 13 (5.8%) because of non-hematologic toxicity (grade 2 oral mucositis and non-neutropenic fever in four cases each, grade 2 diarrhea in two cases and severe fatigue in two cases); in a single case, cycle delay was due to a protocol violation. No significant differences were observed in the percentage of delays according to the course of therapy. Altogether, 40 of 50 patients (80%) completed the six-cycle program; the reasons for stopping the program were disease progression (three patients), or toxicity (interstitial pneumonia in four patients, prolonged severe neutropenia in two and septic shock in a single patient).

Hematologic toxicity
The incidences of severe neutropenia (WHO grade 3 or 4) and febrile episodes were calculated over 277 cycles. Grade 3 and grade 4 neutropenia occurred in 54% and 19% of the total courses of therapy, respectively; patients younger than 60 showed a significantly (p=0.01) lower incidence of grade 4 neutropenia (16%) compared to the older patients (26%). The median duration of grade 4 neutropenia was 1 day (range: 1-6). Overall, 48% of patients experienced at least one episode of grade 3 or grade 4 neutropenia; this rate was significantly higher (65%) in patients over 60 years old. No difference was found in the incidence of severe neu-
tropenia according to the course of therapy. Figure 1 illustrates the median ANC values, with the range and percentiles, at given days, according to the cycle. In all cycles, the highest median ANC value was observed on day 6, while the nadir ANC was invariably observed on day 10; no significant differences were found in the median nadir ANC values according to the cycle. All cycles considered, the mean ANC value was $34\pm21.9\times10^9/L$ on day 6 and $2.7\pm2.3\times10^9/L$ on day 10.

Neutropenic fever developed on 11 occasions (4% of cycles) in eight patients (16% of total), who accounted for one third of those experiencing severe neutropenia; the median duration of neutropenic fever was 5 days (range: 2-10). Febrile episodes with ANC values above the median duration of neutropenic fever was 3 days for one third of those experiencing severe neutropenia; cycles) in eight patients (16% of total), who accounted for one third of those experiencing severe neutropenia; the median duration of neutropenic fever was 5 days (range: 2-10). Febrile episodes with ANC values above the median were observed on 17 occasions (6% of cycles) in 14 patients (28% of total), and lasted a median of 3 days (range: 1-12). Grade 3 and grade 4 thrombocytopenia occurred in 4% and 3% of cycles, respectively, involving six patients (12% of total). Severe anemia (grade 3 and 4) requiring transfusion therapy developed in 8% of cycles, involving 10 patients (20% of total); erythropoietin was administered to two patients (darbepoetin-$\alpha$ 150 $\mu$/g/week). An inverse correlation was found between the number of cycles administered and the age at diagnosis ($p=0.011$); therapy delay and RDI inversely correlated with bone marrow involvement ($p=0.046$).

No significant correlation was found between bone marrow involvement and the occurrence of grade 4 neutropenia and/or fever episodes.

**Severe adverse events**

Severe adverse events were registered in 12 out of the 277 cycles (4% of all cycles). Eleven patients were involved (22% of total); six of them experienced a severe adverse event while on therapy and five after the end of the program. The severe adverse events consisted of interstitial pneumonia in seven patients (14% of total), septic shock and bacterial pneumonia in two cases each, and gastro-intestinal hemorrhage in a single case. All cases of interstitial pneumonia developed within 120 days from the start of therapy and the diagnosis was made through high-resolution chest computed tomography scans, while standard chest X-ray was apparently normal in five of the seven patients. No patient was neutropenic at the onset of pulmonary symptoms and the median ANC was $5.7\times10^9/L$ (range: 3.0-11.1). Clinical conditions allowed bronchoalveolar lavage in five patients; *Pneumocystis carinii* pneumonia (PCP) was microbiologically documented in three patients, while hemorrhagic bronchiolitis and lymphocytic diffuse pneumonia were diagnosed in one case each. Patients who developed PCP had not been given cotrimoxazole prophylaxis, had low serum gammaglobulin levels (390, 790, and 200 mg/dL) and a number of circulating CD4$^+$ lymphocytes lower than 400/$\mu$L (168, 359 and 190/$\mu$L). Altogether, the occurrence of a severe adverse event prompted the discontinuation of therapy in four patients; the outcome after these events was favorable in all but one patient who had visceral perforation after the first cycle of therapy and eventually developed fatal septic shock.

**Serum immunoglobulins and peripheral blood lymphocytes**

The median level of serum immunoglobulins at diagnosis was 1660 mg/L (range: 500-3000 mg/L), while at the end of the program, the median value was 325 mg/dL (range 250-1370 mg/dL); this decrease in median serum immunoglobulin levels is highly significant by the Wilcoxon matched pairs test, ($p=0.00008$). We do not yet have conclusive data on the time to recovery of the immunoglobulin serum levels after the end of therapy.

Peripheral blood CD4$^+$ and CD8$^+$ lymphocyte counts were determined in a subgroup of ten patients. The median value of circulating CD4$^+$ lymphocytes was 596/$\mu$L (range: 205-1783) before treatment and 371/$\mu$L (range: 138-942) at the end of therapy; the median value of circulating CD8$^+$ lymphocyte was 399/$\mu$L (range: 153-1480) before treatment and 491/$\mu$L (range: 94-1275) at the end of therapy.
Response to therapy and survival

On an intention-to-treat basis, 37 of 50 patients (74%) achieved a complete or an unproved complete response. Altogether, adjuvant radiotherapy was administered to 14 patients, nine of whom were in complete or unproved complete remission after R-CHOP-14 and were irradiated at the site of prior bulky disease while five patients were given radiotherapy to PET-positive residual disease. Four of these five patients entered a complete remission. Five (10%) patients obtained a partial remission, seven (14%) proved to be resistant and one died after the first cycle of therapy of a severe complication (visceral perforation with peritonitis).

At the time of this analysis, the median follow-up for the entire group is 20 months. Three patients have relapsed so far (8% of those who achieved remission); the sites of relapse involved the CNS in two cases and bone in one case. No toxic or fatal events occurred among patients in continuous complete remission. Thirteen events were registered: three relapses, seven cases of progressive disease and three deaths not related to tumor progression; the 2-year actuarial event-free survival is 72% (Figure 2A). Altogether, 13 patients have died so far; the causes of death were relapse (ten patients), disease progression with disease-related complications (two patients), and acute toxicity after the first cycle of R-CHOP-14 therapy (gastrointestinal perforation) in one patient. The 2-year actuarial overall survival is 68% (Figure 2B). A survival analysis, stratified according to IPI score, showed significantly better event-free survival (92% vs 51%; \( p = 0.0013 \)) and overall survival (87% versus 49%; \( p = 0.0004 \)) for patients with IPI 0-1 compared to those with more than one IPI risk factor (Figures 3A and 3B).

Discussion

This is the first full paper reporting on pegfilgrastim support of dose-dense R-CHOP-14 in DLBCL. The results of this phase II study demonstrate that a single pegfilgrastim dose of 6 mg per cycle successfully supported dose-dense R-CHOP-14 in DLBCL, allowing on-time delivery of therapy in 92% of cycles, with an optimal average dose intensity. These results are in accordance with the figures of adherence to the DSHNHL trials in patients treated with CHOP-14, without rituximab, and supported with filgrastim, in which only 9% and 11% of all young and elderly patients, respectively, received less than 90% of the planned dose. In our experience, delays due to severe neutropenia occurred in a minimal percentage of cycles (3%) and concerned a
low fraction of patients. This observation indicates that, as far as neutropenia is concerned, the addition of rituximab does not modify the toxicity profile of dose-dense CHOP-14. In our experience, only 4% of cycles resulted in neutropenic fever; this figure is identical to the 3.7% of the MSKCC study and very substantially lower than the 60% reported in a dose-finding study of high-dose CHOP in the pre-filgrastim era. Altogether, 20% of patients did not complete the therapy; apart from the three patients who were withdrawn because of progression during therapy, one patient died early, two stopped the program because of prolonged severe neutropenia and four (8%) because of the occurrence of an interstitial pneumonia, which correlated with a low level of gammaglobulins and a borderline number of circulating CD4 lymphocytes. In our experience, the most worrisome adverse event was Pneumocystis carinii pneumonia (PCP) which occurred in 6% of patients, in the absence of routine cotrimoxazole prophylaxis; this is at variance with other reports on R-CHOP-14 supported by pegfilgrastim in DLBCL (so far published only in abstract form), in which no unexpected toxicities were documented. In the MSKCC experience with R-CHOP-14 supported by filgrastim, the infectious risk after R-CHOP-14 could effectively be managed by the routine use of anti-PCP prophylaxis and by anti-fungal and anti-herpes therapy. Since half of our cases of interstitial pneumonia were due to Pneumocystis carinii, we strongly recommend anti-PCP prophylaxis in this setting.

The issue of interstitial pneumonia in patients receiving rituximab for the treatment of B-cell lymphoma, alone or in combination with chemotherapy, has already been raised. Apart from an infectious etiology (which is the case for PCP in immunosuppressed patients), different mechanisms may be involved in the development of interstitial pneumonia in patients receiving rituximab, which is known to produce complement activation, B lymphocyte cytolysis and tumor necrosis factor release. Although prior exposure to rituximab cannot be ruled out as a possible contributing factor to the development of interstitial pneumonia, the rate of all cases of possible rituximab-induced lung complications is currently less than 0.3 percent, with more than 300,000 patients worldwide having been exposed to rituximab. Prednisone administered for 5 days every two, instead of three weeks, may have had a role in raising the risk of PCP.

On an intention-to-treat basis, the complete remission rate in this cohort of patients was 74%; this figure is comparable to the 75% in the R-CHOP-21 arm of the GELA study, to the 76% in the CHOP-14 arm of the DSHNHL study in the elderly and to the 82% of the MSKCC study. Because the present study was intended to analyze the supportive capacity of pegfilgrastim in a dose-dense setting, patients belonging to all IPI categories (20% had no IPI risk factors) were included and the age limit was extended to 70 years (32% were older than 60). A longer follow-up is needed for conclusive data on survival after R-CHOP-14-pegfilgrastim in DLBCL. A stratified analysis has confirmed that the presence of more than one IPI risk factor has a significant negative impact on both event-free and overall survival.

In conclusion, the results of this study indicate that a single dose of pegfilgrastim per chemotherapy cycle successfully supported a dose-dense R-CHOP-14 regimen in DLBCL, allowing on-time delivery of therapy in 92% of cycles and preventing severe neutropenia, with its attendant septic complications. Patient withdrawal from the program was mostly due to non-hematologic toxicity. The unexpectedly high incidence of interstitial pneumonia makes anti-PCP prophylaxis mandatory in this clinical setting.

Appendix

The following persons and Institutions of the HOST (Hematology/Oncology Studies and Trials) Cooperative Group, Italy, participated in this study:

Division of Hematology, IRCGS Policlinico San Matteo, Pavia: Ercole Brusamolino, Chiara Rusconi, Maurizio Bonfichi, Laura Vaneli, Cristiana Pascutto, Mario Lazzerino; Division of Oncology, Ospedale di Circolo, Busto Arsizio: Luigi Montalbetti, Maria La Targia; Division of Hematology, Ospedale Niguarda “Ca’ Granda”, Milano: Livio Gargantini, Michela Draisci, Enrica Morra; Division of Oncology, Ospedale San Paolo, Milano: Lilij Uziel, Danis Ferrari; Division of Oncology, Ospedale di Circolo “Fondazione Macchi”, Varese: Graziella Pinotti, Ilaria Vallini; Division of Oncology, Ospedale di Legnano: Sergio Fava, Sergio Pauli, Emanuela Grimi; Division of Hematology, Azienda Ospedaliera Careggi, Firenze: Luigi Rigacci, Alberto Basi; Division of Hematology, Ospedale Civico, Palermo: Guido Pagnucco, Laura Tomasselli; Division of Oncology, Ospedale Valduce, Como: Guido Frigerio, Franco Alberti; Division of Oncology, Ospedale di Sondrio: Mario Fiuanì; Division of Oncology, Ospedale di Saronno: Luciano Banfi; Division of Hematology, Ospedale San Bortolo, Vicenza: Francesco Rodighiero, Maurizio Frezzato; Division of Oncology, Ospedale di Lecco: Giovanni Ucci, Michela Anghileri; Division of Oncology, Ospedale di Magenta: Alberto De Paoli; Division of Oncology, Ospedale di Vigevano: Giuseppe Attardo Parrinello.

EB: author taking primary responsibility for the paper; EB: created the Tables; EB, CP: created the Figures. EB: conception and design of the study, data analysis and interpretation; CR: data collection and interpretation; LM, LG, LU, GP, SF, LR, GP: provision of study patients; CP: data analysis and interpretation, statistical evaluation; EM: conception and design of the study, data analysis and interpretation; ML: conception and design of the study, data analysis and interpretation, final approval of the manuscript. The authors declare that they have no potential conflict of interest. Manuscript received November 13, 2005. Accepted January 30, 2006.
References


