Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies

Gérard Socié, Reginald A. Clift, Didier Blaise, Agnès Devergie, Olle Ringden, Paul J. Martin, Mats Remберger, H. Joachim Deeg, Tapani Ruutu, Mauricette Michallet, Keith M. Sullivan, and Sylvie Chevret

In the early 1990s, 4 randomized studies compared conditioning regimens before transplantation for leukemia with either cyclophosphamide (CY) and total-body irradiation (TBI), or busulfan (Bu) and CY. This study analyzed the long-term outcomes for 316 patients with chronic myeloid leukemia (CML) and 172 patients with acute myeloid leukemia (AML) who participated in these 4 trials, now with a mean follow-up of more than 7 years. Among patients with CML, no statistically significant difference in survival or disease-free survival emerged from testing the 2 regimens. The projected 10-year survival estimates were 65% and 63% with Bu-CY versus CY-TBI, respectively. Among patients with AML, the projected 10-year survival estimates were 51% and 63% (95% CI, 52%-74%) with Bu-CY versus CY-TBI, respectively. At last follow-up, most surviving patients had unimpaired health and had returned to work, regardless of the conditioning regimen. Late complications were analyzed after adjustment for patient age and for acute and chronic graft-versus-host disease (GVHD). CML patients who received CY-TBI had an increased risk of cataract formation, and patients treated with Bu-CY had an increased risk of irreversible alopecia. Chronic GVHD was the primary risk factor for late pulmonary disease and avascular osteonecrosis. Thus, Bu-CY and CY-TBI provided similar probabilities of cure for patients with CML. In patients with AML, a nonsignificant 10% lower survival rate was observed after Bu-CY. Late complications occurred equally after both conditioning regimens (except for increased risk of cataract after CY-TBI and of alopecia with Bu-CY). (Blood. 2001; 98:3569-3574)

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Introduction

Since the 1970s, allogeneic stem cell transplantation after high-dose cyclophosphamide (CY) and total-body irradiation (TBI) has been used successfully to treat myeloid leukemia. Bone marrow transplantation (BMT) may fail because of relapse, graft failure, or transplantation-related complications. Studies of a busulfan (Bu) and CY regimen in the early 1980s were motivated by a desire to reduce toxicity and improve the probability of long-term remission. Controversy concerning the optimal pretransplantation regimen for patients with myeloid malignancies still persists.

During the early 1990s, 4 randomized studies were carried out to address this controversy. For patients with acute myeloid leukemia (AML) in first remission, a French study compared these 2 regimens and found increased disease-free survival (DFS) and overall survival, and decreased relapse and transplantation-related mortality with CY-TBI. A second study from the Nordic group in patients with AML, chronic myelogenous leukemia (CML), or lymphoid malignancies, at different stages of the disease, also found better DFS and less toxicity with CY-TBI compared to Bu-CY, in patients with advanced diseases. In contrast, the Seattle group and a French multicenter trial found that outcome with the Bu-CY regimen was equivalent to CY-TBI with seemingly less early toxicity with Bu-CY for patients with CML. A meta-analysis of these 4 trials (and one other trial comparing Bu-CY with TBI-etoposide), examined 6 end points: survival, DFS, venoocclusive disease, acute and chronic graft-versus-host disease (GVHD), and interstitial pneumonitis. Trends suggested that survival and DFS were better with TBI-based regimens than with Bu-CY, but the differences were not statistically significant. In that study, a power analysis suggested that Bu-CY was not likely to have a clinically relevant survival advantage, but the analysis could not exclude the possibility that such an advantage might exist for the TBI-based regimen.

The 4 studies comparing CT-TBI with Bu-CY were reported with follow-up ranging from 24 to 42 months. In light of the above-mentioned uncertainties, we decided to examine and update the long-term follow-up of these randomized trials. Patients with acute lymphoblastic leukemia or lymphoma (n = 42) included in the Nordic trial were excluded and only patients with AML and CML were studied. Our aims were to: (1) compare long-term survival, relapse, return to work/school, and general health status according to the conditioning regimens; and (2) estimate incidence rates and risk factors of late complications. This study included 316 patients with CML and 172 patients with AML. The mean follow-up for surviving patients is now more than 7 years after BMT.

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Patients, materials, and methods

Patients

Patients with lymphoid malignancies (acute lymphoblastic leukemia and lymphomas) were excluded for 2 reasons. First, only the trial from the Nordic group included these diagnoses. Second, a retrospective study from the International Bone Marrow Transplant Registry (IBMTR) and the recent update from the randomized Nordic study strongly suggest that Bu-CY conditioning is inferior in patients with lymphoid malignancies.13

In the original trials 494 patients with myeloid malignancies were enrolled, and we were able to analyze the data for 488 patients (97.8% of the patients). The remaining 6 (2.2%) patients were enrolled in centers that declined to participate in this study. All patients received 120 mg/kg CY (60 mg/kg, on each of 2 consecutive days). For patients randomized in the Bu-CY regimen, 16 mg/kg Bu (1 mg/kg per dose orally every 6 hours over 4 consecutive days) was administered. TBI regimens varied in the different trials. In the Seattle study, all patients received 12 Gy TBI in a fractionated regimen. In the 2 French trials, most individuals (42 of 55 and 43 of 50 patients with CML and AML, respectively) were given TBI in a fractionated regimen for a mean total dose of 12 Gy. In the Nordic study, approximately two thirds of the TBI patients received fractionated irradiation.

The combination of cyclosporine and short-course methotrexate was used for prevention of GVHD disease in all 4 trials. In addition, 17 patients with CML and 16 patients with AML received an anti-interleukin-2 receptor (p55) antibody.

Details of the original trials have been previously published: 2 trials (Table 1). Three of the 4 trials enrolled only patients with early-stage diseases (ie, AML in first complete remission or CML in first chronic phase).

Sex distribution was almost identical in the 4 trials (ratio of men to women close to 60%). The cohort showed no difference in patient selection or interval from diagnosis to transplantation in CML patients, or time from first complete remission to transplantation in patients with AML. In these early AML trials, no cytogenetic data were available, but the distribution of AML subtypes according to the French-American-British (FAB) classification did not differ according to the conditioning regimens. Details concerning patients enrolled in this study are summarized in Table 2.

Methods

Updated survival and DFS as well as occurrence of late complications were obtained through a questionnaire sent to each French and Nordic center. Updates from the Fred Hutchinson Cancer Research Center (FHCRC) were obtained through the database of the long-term follow-up program, as previously reported. Specific requests included the occurrence, and date if any, of cataract, thyroid abnormalities, persistent alopecia (either partial or total), avasular osteonecrosis, pulmonary diseases (including obstructive bronchiolitis), secondary malignancies, return to work or school, and functional status at last follow-up (as assessed by the World Health Organization [WHO] score). Additional data included demographic and posttransplantation information (including data on acute and chronic GVHD).

We encountered no difficulty in the definition of relapse for patients with AML. On the other hand, we found considerable difficulty in defining relapse for patients with CML, where hematologic, cytogenetic, or molecular criteria could be used. Furthermore, transient cytogenetic relapse has also been described after transplantation for CML. Differences in the definition of CML relapse could not be reconciled in this multi-institutional retrospective study. We therefore decided to take into account hematologic or cytogenetic relapses in CML as a binary variable (yes/no) according to referring center reports.

Because the development of any late complication clearly depends on the frequency and methods used in searching such late complications, adjustments were made by stratifying by trial in the final models. Statistical analysis was performed separately in each diagnosis group (AML, CML). Times to occurrence of relapse, death, cataract, hypothyroidism or hyperthyroidism, persistent alopecia, avascular osteonecrosis, or late pulmonary diseases were estimated using the Kaplan-Meier method. Multivariable Cox models, stratified on the original trial, were fit to evaluate the influence of conditioning regimen, adjusted for patient-, disease-, and transplantation-related variables. For categorical variables, a dummy variable for each but one category was created, taking on the value of 1 for patients in that category and 0 otherwise. The proportionality of hazards was tested by using time-varying coefficients. Estimated hazard ratios (HRs) with a 95% confidence interval (95% CI) were computed.

Finally, we evaluated the influence of conditioning regimen, adjusted for patient-, disease-, and transplantation-related variables (including chronic GVHD), with hair loss using multivariable (logistic) regression models. Estimated odds ratios (ORs) with 95% CI were given. All P values were 2-sided, with values of .05 or less indicating statistical significance. No correction was made for multiple comparisons. Statistical analysis used the SAS (SAS, Cary, NC) and S-Plus Software.

Table 1. Patient and disease characteristics in 4 randomized trials

<table>
<thead>
<tr>
<th>Disease</th>
<th>Stage</th>
<th>No. of patients (original report)</th>
<th>No. of patients with long-term follow-up (%)</th>
<th>Median age at transplant, y</th>
<th>Follow-up (original report, in mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blaise et al</td>
<td>AML</td>
<td>First CR</td>
<td>101</td>
<td>100</td>
<td>32</td>
</tr>
<tr>
<td>Cliff et al</td>
<td>CML</td>
<td>CP</td>
<td>147</td>
<td>96.5</td>
<td>37</td>
</tr>
<tr>
<td>Devergie et al</td>
<td>CML</td>
<td>CP</td>
<td>120</td>
<td>98.3</td>
<td></td>
</tr>
<tr>
<td>Ringden et al</td>
<td>CML/AML</td>
<td>CP/CR1</td>
<td>46/51</td>
<td>98.4</td>
<td>33</td>
</tr>
</tbody>
</table>

CR indicates complete remission; CP, chronic phase.

Results

In patients with CML, no statistically significant differences in survival or DFS were detected between the use of Bu-CY versus CY-TBI before transplantation (Figure 1). The projected 10-year survival estimates were 65% (95% CI, 57%-74%) and 63% (95% CI, 54%-73%) with Bu-CY and CY-TBI, respectively. The corresponding estimates of DFS were 52% (95% CI, 43%-61%) and 46% (95% CI, 36%-56%) with Bu-CY and CY-TBI, respectively.

In patients with AML, no statistically significant differences in survival or DFS were detected between the use of Bu-CY versus CY-TBI before transplantation (Figure 2). The projected 10-year survival estimates were 51% (95% CI, 41%-62%) and 63% (95% CI, 52%-74%) with Bu-CY and CY-TBI, respectively. The corresponding DFS estimates were 47% (95% CI, 36%-58%) and 57% (95% CI, 44%-70%) with Bu-CY versus CY-TBI, respectively. DFS rates were similar when the analysis was limited to patients with AML in first complete remission or CML patients in first chronic phase who did not receive the 33B3-1 antibody (data not shown).

The 5-year cumulative incidence of clinical extensive chronic GVHD reached 20% and 19% among patients with AML, and in...
37% and 39% among patients with CML, with Bu-CY versus CY-TBI, respectively.

The general health status was estimated through the WHO scale. Data concerning AML patients were available for only half the patients and were therefore not analyzed. In patients with CML, data on health status at last follow-up were available for more than 75% of the patients. More than 90% of these patients had normal health status or minimal impairment (WHO score 0 and 1), as assessed by their referring physician, without significant differences according to the conditioning regimen (P = .32; Table 3).

Data concerning return to work were not recorded in the FHCRC data set. In the European studies, between 72% and 88% of the patients returned to school or work at date of last contact, representing 72% of the patients receiving Bu-CY and CY-TBI, respectively. The risk of alopecia was decreased in the CY-TBI group (OR = 1.04; 95% CI, 0.1-0.8; P = .02), but differences were not statistically significant among patients with CML (P = .25). The protective effect of CY-TBI remained statistically significant in the AML group after adjustment for age and for acute and chronic GVHD (HR = 1.04; 95% CI, 1.001-1.01; P = .05).

In CML patients, chronic GVHD was associated with persistent alopecia (OR = 3.3; 95% CI, 1.1-9.6; P = .03). Secondary solid malignancies were reported in 5 patients (epidermoid carcinoma, n = 2; gastric carcinoma, n = 1; malignant melanoma, n = 1; and adenocarcinoma of unknown primary site, n = 1). Three cases occurred among patients who received CY-TBI, and 2 occurred among patients who received Bu-CY.

No statistically significant differences were detected in the causes of death among patients who survived more than 2 years without relapse (data not shown).

Discussion

Although the CY-TBI and Bu-CY regimens were introduced in the early 1980s as conditioning regimens before transplantation, it was only 10 years later that results of 4 randomized studies comparing both regimens were published.7-10 When reported, these studies had...
relatively short follow-up and even today, 20 years later, it was not clear if these 2 regimens could be used with similar efficacy in controlling leukemia and what was the spectrum of late complications that could be attributed to any of these regimens. This long-term follow-up examination of the 4 randomized studies provides more definitive answers in patients with CML but still cannot be definitive for patients with AML.

Our current results thus clearly confirm previous results published by Clift and coworkers and Devergie and colleagues and extends, in a larger group of patients, the updated Seattle results showing similar long-term survival and DFS rates with the use of Bu-CY compared to CY-TBI as the preparative regimen for patients with CML.

In patients with AML, prior results have been less clear. In the French study, Blaise and associates previously reported a statistically significant disadvantage in both the DFS and survival rates in the Bu-CY arm (a finding recently confirmed in an update of this French study). A similar difference in the DFS rates among patients with AML has been found with a recent retrospective analysis of the IBMTR. In the Nordic study, the initial reports did not provide a separate analysis for patients with AML. In the updated results of this later study, Ringden and coworkers did not find a statistically significant difference in DFS between Bu-CY and CY-TBI regimens among patients with AML. Furthermore, Bu plasma levels were not measured as a risk factor that strongly influences the risk of relapse after transplantation. These factors limit the interpretation of our results. The answer to this question could come from another trial with stratification on cytogenetic risk groups and with individually adjusted Bu levels, but it is very unlikely that such a trial will be done.

In the European studies, 72% to 88% of the patients went back to school or work without significant differences according to the conditioning regimen or the initial diagnosis.

Only the Nordic study has previously evaluated the incidence of late complications among patients who received Bu-CY as compared to those who received CY-TBI. These authors found that Bu-CY was associated with an increased risk of chronic GVHD, obstructive lung disease, and alopecia. In our analysis, the pretransplantation conditioning regimen did not influence the incidence of chronic GVHD. We found that late obstructive lung disease was associated with chronic GVHD but not with the use of Bu-CY as described in the Nordic study. The reason for the association between chronic GVHD and obstructive lung disease among patients with CML but not among patients with AML remains unclear. Only 9 patients with AML developed late pulmonary diseases, thus preventing any meaningful statistical analysis. Some patients with CML may have received Bu, an agent known to induce pulmonary fibrosis, before the transplantation, but data concerning the type and duration of pretransplantation treatment were not available for our study. We found an increased risk of alopecia in AML patients who received Bu-CY, similar to results of the Nordic study. Chronic GVHD was associated with alopecia in CML patients. Hair follicles are targets of GVHD, and alopecia has been associated with the sclerodermatous form of chronic GVHD. Although alopecia is not life-threatening, this complication does affect quality of life. In 7 patients who all received Bu-CY, alopecia was total and permanent. Cataract formation has long been described as a late complication of TBI. The 47% incidence rate of cataract after the use of TBI in our study fits with the incidence rate reported by Tichelli et al and that published by the FHCRC group.

### Table 3. Health, functional status, and return to work/school in the 4 randomized trials

<table>
<thead>
<tr>
<th>End point</th>
<th>AML Bu-CY/CY-TBI</th>
<th>CML Bu-CY/CY-TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO score: number of patients alive at last follow-up: N (%)</td>
<td>48 (52)/51 (64)</td>
<td>114 (68)/103 (69)</td>
</tr>
<tr>
<td>WHO score: 0-1 number available (%)</td>
<td>—</td>
<td>83.87 (95.4)/68.72 (94.4)</td>
</tr>
<tr>
<td>Work: number available (not available for the FHCRC)</td>
<td>33/34</td>
<td>43/44</td>
</tr>
<tr>
<td>Return to work/school: Yes/No (%)</td>
<td>29.33 (88)/34/40 (85)</td>
<td>31.43 (72)/36/44 (81)</td>
</tr>
</tbody>
</table>

### Table 4. Estimation of conditioning effect in each diagnostic group on each end point

<table>
<thead>
<tr>
<th>End point</th>
<th>AML (n = 172) (95% CI; P)</th>
<th>CML (n = 316) (95% CI; P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>BUCY vs CY-TBI 1.05 (0.32-3.44; .94) 2.67 (1.56-4.57; .0003)</td>
<td>BUCY vs CY-TBI 0.30 (0.12-0.80; .0035)</td>
</tr>
<tr>
<td>Multivariable model</td>
<td>Acute GVHD 1.05 (0.30-3.69; .94) 1.37 (0.76-2.48; .30)</td>
<td>Acute GVHD 0.79 (0.21-3.03; .73) 1.33 (0.44-4.01; .61)</td>
</tr>
<tr>
<td>Chronic GVHD 0.27 (0.03-2.39; .24) 2.99 (1.64-5.45; .0203)</td>
<td>Chronic GVHD 1.60 (0.30-8.48; .51) 2.62 (1.31-5.27; .0067)</td>
<td></td>
</tr>
<tr>
<td>Age 1.02 (0.96-1.08; .51) 0.998 (0.975-1.023; .89)</td>
<td>Age 1.02 (0.94-1.05; .34) 0.988 (0.95-1.01; .45)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>9 events 66 events</td>
<td>9 events 66 events</td>
</tr>
<tr>
<td>Multivariable model</td>
<td>BUCY vs CY-TBI 0.75 (0.20-2.80; .26) 0.80 (0.44-1.48; .48)</td>
<td>BUCY vs CY-TBI 0.75 (0.20-2.80; .26) 0.80 (0.44-1.48; .48)</td>
</tr>
<tr>
<td>Acute GVHD 1.04 (0.30-3.64; .95) 2.52 (0.86-7.43; .004)</td>
<td>Acute GVHD 0.79 (0.21-3.03; .73) 1.33 (0.44-4.01; .61)</td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD 3.18 (0.60-16.9; 17) 7.01 (1.85-26.5; .0041)</td>
<td>Chronic GVHD 1.60 (0.30-8.48; .51) 2.62 (1.31-5.27; .0067)</td>
<td></td>
</tr>
<tr>
<td>Age 0.972 (0.917-1.030; .34) 0.929 (0.880-0.972; .0021)</td>
<td>Age 0.972 (0.917-1.030; .34) 0.929 (0.880-0.972; .0021)</td>
<td></td>
</tr>
<tr>
<td>Avascular osteonecrosis</td>
<td>10 events 19 events</td>
<td>10 events 19 events</td>
</tr>
<tr>
<td>Multivariable model</td>
<td>BUCY vs CY-TBI 1.04 (0.30-3.64; .95) 2.52 (0.86-7.43; .004)</td>
<td>BUCY vs CY-TBI 0.79 (0.21-3.03; .73) 1.33 (0.44-4.01; .61)</td>
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<td></td>
</tr>
<tr>
<td>Hair loss</td>
<td>58 events 66 events</td>
<td>58 events 66 events</td>
</tr>
<tr>
<td>Multivariable model</td>
<td>BUCY vs CY-TBI 0.30 (0.12-0.80; .26) 0.61 (0.26-1.43; .25)</td>
<td>BUCY vs CY-TBI 0.30 (0.12-0.80; .26) 0.61 (0.26-1.43; .25)</td>
</tr>
<tr>
<td>Acute GVHD 2.74 (0.50-15.0; 25) 3.26 (1.11-9.59; .023)</td>
<td>Acute GVHD 2.74 (0.50-15.0; 25) 3.26 (1.11-9.59; .023)</td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD 1.04 (1.001-1.094; .046) 1.027 (0.972-1.077; .37)</td>
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</tr>
</tbody>
</table>

Results show estimation of conditioning effect in each diagnostic group on each end point either unadjusted or adjusted on baseline covariates, stratified on trial, using Cox models with estimated HR (for cataracts, pulmonary complications, and avascular osteonecrosis) or logistic models with estimated OR (for hair loss). Significant P values are in bold.
We found very few cases of late cancers, but the median follow-up was only 7 years. Because cancer incidence rates do not begin to increase until more than 6 years BMT, it is probably too soon to draw any conclusions about the risk of cancer after Bu-CY as compared with CY-TBI. It is already clear, however, that late cancers can occur after Bu-CY conditioning. For this reason, these patients should have close monitoring for second cancers after the transplantation. How can these findings be relevant to new paradigms for allogeneic transplantation conditioning regimens (nonmyeloablative conditioning) and in the era of STI571 (the bcr-abl inhibitor) ? Both use of nonmyeloablative conditioning regimens and of STI571 have led to highly encouraging results in phase I and II trials. This would probably lead to an extended role of allogeneic transplantation for older patients after nonmyeloablative conditioning regimens, and to reduced (or delayed) indication of transplantation in patients with CML. However, both of these new treatment modalities have only been recently introduced and follow-up is clearly lacking, as yet. Long-term results, as those presented in this study, are therefore important as a referent treatment modality before results of phase III trials (comparing nonmyeloablative conditioning regimen versus standard Bu-CY or CY-TBI, or STI571 versus transplantation) will become available. On the other hand, these new therapeutic modalities may prove to be useful for the treatment of leukemia relapse, STI571 may be used as an alternative to donor lymphocyte infusion in patients with CML who relapse after transplantation. Nonmyeloablative conditioning followed by peripheral blood stem cell transplantation would probably reduced transplantation-related mortality in patients with AML who relapse after a first transplantation in which a conventional therapy has been used.

In conclusion, Bu-CY and CY-TBI lead to similar long-term outcomes in patients with myeloid malignancies (although TBI provides slightly better long-term survival in patients with AML). Long-term complications, general health status, and return to work were mostly influenced by chronic GVHD and rarely by the conditioning regimens.

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References


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