Allogeneic Bone Marrow Transplantation for Chronic Myeloid Leukemia in First Chronic Phase: A Randomized Trial of Busulfan-Cytoxan Versus Cytoxan-Total Body Irradiation as Preparative Regimen: A Report From The French Society of Bone Marrow Graft (SFGM)


From March 1988 to March 1991, 19 French bone marrow transplant (BMT) centers participated in a prospective randomized trial comparing two conditioning regimens for patients with chronic myeloid leukemia transplanted in first chronic phase with an HLA identical sibling donor. A total of 120 consecutive patients were randomized to receive either 120 mg/kg of cyclophosphamide followed by total body irradiation (CY-TBI; n = 55) or 16 mg/kg of busulfan followed by 120 mg/kg of CY (BU-CY; n = 65). Two different TBI regimens were used. Thirteen patients received a 10-Gy single-dose TBI (SDTBI), and 42 received a fractionated TBI (FTBI). Median time between diagnosis and BMT was 315 days. Overall 5-year actuarial survival was 62.9% (65.8% for CY-TBI and 38% for BU-CY; \( P = .44 \)). So far, with a median follow up of 42 months, 11 patients have relapsed; 9 relapses occurred after CY-TBI, mostly after FTBI (8 of 9) and 2 after BU-CY (\( P = .02 \)). The actuarial risk of relapse was 4.4% ± 6.7% after BU-CY, 11.1% ± 20.8% after SDTBI, and 31.3% ± 18.1% after FTBI (\( P = .039 \)). In addition, independently of the conditioning regimen, the increase of post-transplant immunosuppression in 16 patients with an anti-interleukin-2 receptor monoclonal antibody (MoAb) in addition to a short course of methotrexate and cyclosporine was shown to increase the actuarial risk of relapse (57% ± 30% with MoAb vs 9% ± 7.3% without MoAb; \( P = .001 \)). We conclude that BU is an acceptable alternative to TBI for patients with chronic myeloid leukemia in first chronic phase receiving BMT from HLA identical sibling donors. Both BU-CY and CY-TBI regimens gave similar transplant-related mortality, and the antileukemic efficiency of BU-CY regimen was either similar or even higher than that of CY-TBI.

A LLOGENEIC BONE MARROW transplantation (BMT) after preparation with high-dose cyclophosphamide (CY) and total body irradiation (TBI) is a highly efficient therapy for patients suffering from chronic myeloid leukemia (CML).1-3 In our experience,4 as in that of other groups, if BMT is performed during the first chronic phase, the relapse rate may not go beyond 10% provided that a non-T-cell-depleted graft is used. However, BMT may fail because of transplant-related death, for which total radiation dose was identified as one of the most significant risk factors.5 6 In addition, the use of TBI has also been associated with the development of a variety of long-term complications including secondary malignancies, cataracts, impaired growth, and endocrine dysfunction.7 8 Therefore, radiation-free conditioning regimens have been investigated. The association of busulfan (BU) and CY was reported to give a similar or even higher leukemic ablation than regimens including TBI.9-12 Nevertheless, overall results and long-term effects of BU-CY and CY-TBI regimens for patients with CML had not been prospectively evaluated so far. Therefore, as had other groups,13 we decided to randomly evaluate CY-TBI regimen versus BU-CY regimen. We report results of 120 consecutive patients who entered a national prospective trial initiated in 1988 by the French BMT Group (Société Française de Greffe de Moelle). This study compares the outcome of patients with CML in first chronic phase receiving allogeneic BMT prepared with CY (120 mg/kg) and either TBI or BU (16 mg/kg).

PATIENTS AND METHODS

Patients. To be entered in this trial, patients had to meet the following eligibility criteria: (1) diagnosis of Ph-positive CML; (2) being in first chronic phase, defined as normal or nearly normal blood counts, no significant symptoms, and no significant organomegaly; (3) having an HLA-identical, negative mixed lymphocyte culture sibling donor.

The protocol was reviewed by the ethical committee of University of Saint Louis-Lariboisière, and consent was obtained from all patients or legal guardians.

Between March 1988 and March 1991, 120 patients were included in this trial and were randomized before transplant by 19 French centers. Randomization was performed per center. The median age of the population was 36 years old (range, 10 to 54 years old) with a sex ratio (M/F) of 77 to 43. Median interval between diagnosis

From the Bone Marrow Transplant Units of Hôpital Saint-Louis, Paris; Institut Paoli Calmettes, Marseille; Hôpital Purpan, Toulouse; Hôpital Edouard Herriot, Lyon; Hôpital Claude Huriez, Lille; Hôpital Henri Mondor, Créteil; Hôpital d'Enfants, Vandœuvre-les-Nancy; Centre Hospitalier Regional Universitaire, Angers; Hôpital Pontchaillou, Rennes; Hôpital J. Minjoz, Besançon; Hôpital Haute-pierre, Strasbourg; Hôpital Clemenceau, Caen; Hôpital Haut Lévêque, Bordeaux; Hôpital de Cimiez, Nice; Centre Hospitalier Universitaire, Nantes; Hôpital Necker, Paris; Hôpital Nord, Saint Etienne; Centre Henri Becquerel, Rouen; and Centre Hospitalier Universitaire, Grenoble, France.

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Address reprint requests to A. Devergie, MD, Service de Greffe de Moelle, Hôpital Saint Louis, 1, Avenue Claude Vellefaux, 75475 Paris CEDEX 10, France.

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and BMT was 315 days (range, 98 to 1,361 days). A total of 91 patients were transplanted within the first year of diagnosis, and 29 were transplanted later. Analysis was conducted after November 1993, giving a median follow-up of 42 months with a minimal follow-up of 32 months.

**Conditioning regimen.** All patients received 60 mg/kg CY intravenously on each of 2 consecutive days. For 65 patients (BU-CY group), this was preceded by the administration of BU. BU was administered orally at 1 mg/kg every 6 hours over 4 consecutive days for a total dose of 16 mg/kg, adjusted to the real body weight. For 55 patients (CY-TBI group), CY was followed by TBI. The irradiation protocol differed from one center to another, according to local facilities. Thirteen patients received a 10-Gy single-dose (SD) irradiation. The dose rate was 3 cGy per minute, and the lungs were shielded to a lung dose of 8 Gy. Forty-two patients received a fractionated (F) TBI to a median dose of 12 Gy (range, 11 to 12 Gy). Among these 42 patients, 30 received the same FTBI regimen (12 Gy in 6 fractions of 2 Gy twice daily over 3 days), with a median dose rate of 8 cGy per minute (range, 5 to 25 cGy) and a median lung dose of 10 Gy (range, 8 to 11 Gy). Fractionation schemes varied for 12 patients. One patient received hyperfractionated TBI (12 Gy in 24 fractions of 0.5 Gy over 3 days with a lung dose of 7 Gy); 7 patients received 12 Gy in 3 fractions of 4 Gy over 3 days, and 4 patients received 11 Gy in 5 fractions of 2.2 Gy over 5 days, with a lung dose of 8 Gy. Finally, all patients treated with either SDTBI or FTBI had a lung shielding to a median lung dose of 8.8 Gy (range, 7 to 11 Gy). Genodentical unmanipulated BM was infused 24 to 36 hours after the last day of conditioning regimen.

**Posttransplant immunosuppression.** All patients received short-course methotrexate (MTX) and cyclosporine (CSA) according to the Seattle group protocol. Intravenous CSA was substituted by an oral dose when tolerated, and the dose was adjusted according to CSA blood levels. In addition, 31 patients were included in a multicentric randomized trial of prophylaxis of graft-versus-host disease (GVHD), studying the efficacy of the adjunction of an anti--interleukin-2 receptor monoclonal antibody (anti-P55 MoAb) to the combination of MTX and CSA. This trial involved seven centers and included patients with acute or chronic leukemias in first remission or in first chronic phase. Therefore, 31 patients with CML in first chronic phase were included in both trials. A total of 16 patients were randomized to receive anti-P55 MoAb from day 1 to day 28, in addition to MTX and CSA, and 15 patients were entered in the control group (MTX and CSA). Among these 16 patients treated with prophylactic MoAb, 8 were conditioned with CY-TFBI and 8 with BU-CY.

**Relapse.** The monitoring strategy to evaluate the occurrence of relapse differed from one center to another. In our analysis, endpoint for relapse was persistent cytogenetic relapse, ie, the detection of Ph-positive metaphases in the BM after at least 2 months post-BMT, persisting in subsequent cytogenetic analysis.

**Statistical analysis.** Actuarial survival, relapse, and relapse-free survival curves were obtained using Kaplan-Meier product-limit estimates. Comparison of survival curves was based on the log-rank test. Endpoint for survival was the date the patient was last contacted before November 1993. The two variables significantly associated with a higher risk of relapse in univariate analysis, ie, the conditioning regimen and the prophylaxis of GVHD, were entered in a multivariate analysis using a Cox model. Our analyses were performed on an IBM personal computer (Paris, France) with BMDP statistical software.

**RESULTS**

Patients’ characteristics at time of transplant are summarized in Table 1. No significant statistical difference existed between the two groups for any parameter. GVHD prophylaxis was identical with the same number of patients receiving anti-P55 MoAb prophylaxis (CY-TBI, 8; BU-CY, 8).

Table 2 shows the outcome of the graft, including engraftment, toxicity of the two conditioning regimens, relapse, GVHD, overall and disease-free survival (DFS).

**Engraftment.** Engraftment was defined as a recovery of granulocytes to 0.5 × 10^9/L for 2 consecutive days. Four patients (CY-TBI, 2; BU-CY, 2) died prematurely before day 35 and were not evaluable for engraftment. Of the remaining 116 patients, all patients receiving CY-TBI (53 of 53) and 59 of the 63 patients in the BU-CY group had successful sustained engraftment. Four patients, all of them in the BU-CY group, either failed to engraft (n = 1) or rejected the graft (n = 3). There is no significant statistical difference between the two groups (P = .18).

**Toxicity of the conditioning regimen.** There was no difference between the two groups for early transplant-related complications. Veno-occlusive disease, defined as the association of serum bilirubin elevation and weight gain occurring during the first 28 days after BMT, was found in 9 of 120 patients (7.5%; BU-CY, 5; CY-TBI, 4) and was the cause of death in 8 and contributed to death in 7.

**GVHD.** Overall incidence of acute (A) GVHD grade II-IV among patients with sustained engraftment was 42%; there was no correlation with the conditioning regimen (respectively, 23 of 53 [43%] in the CY-TBI group and 24 of 59 [41%] in the BU-CY group). AGVHD was the primary cause of death in 5 patients and contributed to death in 7.

**Relapse.** So far, the relapse rate is low (11 of 120). Nevertheless, there was a significant statistical difference between the two conditioning regimens, because 9 relapses occurred after CY-TBI and 2 after BU-CY (P = .02). Only 1 relapse occurred after SDTBI and 8 after FTBI. Actuarial risk of relapse was 4.4% ± 6.7% after BU-CY, 11.1% ± 20.8% after SDTBI, and 31.3% ± 18.1% after FTBI (P = .039; see Fig 1). Prophylaxis of GVHD was also shown to be associated with relapse risk. Among 16 patients randomized to receive anti-P55 MoAb, 5 relapsed (actuarial risk, 57% ± 30%). On the contrary, relapse was observed in only 6 of 104 patients who did not receive MoAb (actuarial risk, 9% ± 7.3%; P = .001; see Fig 2). Multivariate analysis
confirmed these results (Table 3). Two factors were significantly correlated with an increased relapse risk, CY-TBI conditioning regimen (relative risk (RR) = 4.10; \( P = .04 \)) and the use of MoAb for GVHD prophylaxis (RR = 4.69; \( P = .006 \)).

Survival and DFS. Kaplan-Meier probability estimates for survival and DFS are presented in Figs 3 and 4, with no significant statistical advantage for patients receiving either CY-TBI or BU-CY. Overall survival was 62.9% (65.8% ± 12.5% after CY-TBI and 60.6% ± 11.7% after BU-CY; \( P = .5 \)), and overall DFS was 55% (51% ± 14% after CY-TBI and 59.1% ± 11.8% after BU-CY; \( P = .75 \)).

**DISCUSSION**

BU-CY regimen was initially described by Santos et al\(^{11} \) with 16 mg/kg of BU in combination with CY, 200 mg/kg (BU-CY 200). Because of the high incidence of treatment-related mortality initially reported with BU-CY 200, Tutschka et al\(^{12} \) lowered the CY dose to 60 mg/kg for 2 consecutive days (BU-CY 120). In nonrandomized studies, BU-CY 200 and BU-CY 120 regimens have both consistently permitted engraftment of BM from HLA genotypically identical siblings in patients with acute or chronic leukemias. Nevertheless, BMT from unrelated or mismatched donors or...

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**Table 2. Outcome**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>CV TBI (n = 55)</th>
<th>BU CY (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engraftment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>Permanent take</td>
<td>53</td>
<td>59</td>
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<tr>
<td>Rejection (( P = .18 ))</td>
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<tr>
<td>VOD</td>
<td>4</td>
<td>5</td>
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<tr>
<td>AGVH grade II IV</td>
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<td>24</td>
</tr>
<tr>
<td>Int Pneum</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Hemorragic Cystitis</td>
<td>5</td>
<td>7</td>
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<tr>
<td>Cause of death</td>
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<td></td>
</tr>
<tr>
<td>AGVH</td>
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<td>3</td>
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<tr>
<td>Int Pneum</td>
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<td>2</td>
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<tr>
<td>AGVH + Int Pneum</td>
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<td>5</td>
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<tr>
<td>CGVH</td>
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<td>2</td>
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<tr>
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<td>4</td>
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<tr>
<td>VOD</td>
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<td>3</td>
</tr>
<tr>
<td>Rejection</td>
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<td>3</td>
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<tr>
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<td>0</td>
</tr>
<tr>
<td>Relapse</td>
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<td>1</td>
</tr>
<tr>
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<td>2</td>
</tr>
<tr>
<td>Total</td>
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<td>25</td>
</tr>
<tr>
<td>Relapse (( P = .02 ))</td>
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<td>2</td>
</tr>
<tr>
<td>Transplant-related mortality (( P = .44 ))</td>
<td>29%</td>
<td>38%</td>
</tr>
<tr>
<td>Survival (( P = .5 ))</td>
<td>65.8%</td>
<td>60.6%</td>
</tr>
<tr>
<td>DFS (( P = .75 ))</td>
<td>51%</td>
<td>59%</td>
</tr>
</tbody>
</table>

**Table 3. Risk of Relapse: Multivariate Analysis (COX Model)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% Confidence Interval for RR</th>
<th>Coefficient</th>
<th>( P ) Value</th>
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<tr>
<td>Conditioning regimen</td>
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<td>BU-CY</td>
<td>1.00</td>
<td>1.41</td>
<td>.04</td>
<td></td>
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<tr>
<td>CY-TBI</td>
<td>4.10</td>
<td>1.00-20.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GVHD prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No MoAb</td>
<td>1.00</td>
<td>1.54</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>MoAb</td>
<td>4.69</td>
<td>1.37-15.79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig 1.** Comparison of Kaplan-Meier probabilities of relapse for patients having received BU-CY (\( \cdots \); \( n = 65; 4.4\% \pm 6.7\% \), SDTBI (\( \cdots \); \( n = 13; 11.1\% \pm 20.8\% \)), and FTBI (\( \cdots \); \( n = 42; 91.3\% \pm 18.1\% \)) \( P = .039 \).

**Fig 2.** Comparison of Kaplan-Meier probabilities of relapse for patients having received GVHD prophylaxis with MTX+CSA (\( \cdots \); \( n = 104; 9\% \pm 7.3\% \)) or with MTX+CSA+MoAb (\( \cdots \); \( n = 16; 57.6\% \pm 39\% \)) \( P = .001 \).
with in vitro T-cell depletion of the BM after preparation with BU-CY 120 appears to be associated with a higher incidence of engraftment failure than that after preparation with CY-TBI.\(^{14-17}\) Furthermore, Blaise et al\(^{18}\) have shown in a randomized trial in patients with acute myeloid leukemia (AML) in first remission, receiving allogeneic BMT after a preparation with CY-TBI or BU-CY 120, that a higher relapse rate and a decreased survival were associated with BU-CY 120 regimen. Thus, it is not clear whether the immunosuppressive and antileukemic capacity of BU-CY 120 is as great as that of standard CY-TBI regimens.

Our multicentric trial was designed to compare prospectively the chemotherapeutic preparation consisting of BU 16 mg/kg and CY 120 mg/kg (BU-CY 120) versus the "standard" conditioning regimen with CY 120 mg/kg and TBI (CY-TBI) in patients with CML in first chronic phase. Moreover, there were two additional variants of the conditioning regimen. One is the use of two different TBI regimens, i.e., SDTBI versus FTBI, and the other is the use of MoAb for GVHD prophylaxis in a subpopulation of patients. Both of these variations were shown to be important for the outcome on influencing the relapse rate.

In our study, overall results in survival and DFS for the 2 groups of patients, treated with either BU-CY 120 or CY-TBI, are not significantly different. This finding matches the recently published results of a unicentric randomized trial conducted by Clift et al\(^{19}\) comparing BU-CY 120 with CY-TBI in patients with CML in first chronic phase that showed no significant statistical differences between the treatment arms regarding survival or nonrelapse mortality. Nevertheless, in our trial, we observed two differences between the two groups of patients, (1) an unexpected occurrence of graft failure after BU-CY and (2) an increased risk of relapse after CY-TBI, especially FTBI.

Previously published results did not show an increase in graft failure after BU-CY regimen, as long as an unmanipulated HLA identical related BM was used. In a multi-institutional study, primary failure of engraftment occurred in only 3 of 281 patients with AML (n = 127),\(^{20}\) acute lymphoblastic leukemia (n = 39),\(^{21}\) or CML (n = 115).\(^{22}\) Among the 142 patients described by Clift et al,\(^{19}\) all patients achieved sustained engraftment, and late rejection did not occur. On the contrary, preliminary analysis of our randomized trial\(^{23}\) showed a borderline difference in transplant rejection rate between the two groups. Rejection is an extremely rare event for patients grafted for acute or chronic leukemias and conditioned with a TBI regimen. Nevertheless, graft failure can be observed after a T-cell–depleted BMT and is associated with an increased risk of relapse.\(^{24}\) Thus, the occurrence of 4 rejections in the BU-CY group led us to fear for an increased risk of late relapses. As a matter of fact, it was not the case.

On the contrary, with a median follow up of 42 months, there was a higher risk of relapse after TBI. This difference was observed only in patients who had received a fractionated irradiation and not for patients conditioned with an SDTBI. Finally, the antileukemic efficacy of BU-CY 120 regimen was at least as good as conventional CY-TBI regimen (SDTBI) and was better than CY-FTBI regimen. The impact of fractionation of TBI on the relapse rate for patients transplanted for CML in first chronic phase is discussed, and discordant results have been reported. In a review of the literature concerning TBI fractionation,\(^{25}\) including both acute and chronic leukemias, the same relapse rate was found for SDTBI (15.8%) and for FTBI (15.7%) used as conditioning regimen before non–T-cell–depleted BMT. A report from the International Bone Marrow Transplant Registry did not show TBI fractionation to be a significant parameter for relapse after BMT for CML in chronic phase.\(^{2}\) On the contrary, in a previous retrospective study from the French Registry on 180 patients with CML who received an unmanipulated BM graft after a CY-TBI regimen, we reported a significant increase of relapse risk after FTBI compared with SDTBI.\(^{26}\) Thus, it is suggested that the fractionation’s sparing effect for extramedullary organs, especially when associated to systematic lung shielding, could be offset by a less effective leukemic cell kill, in any case for first chronic phase CML. Nevertheless, the statistical power of our study is

![Figure 3](https://example.com/fig3.png)

**Fig 3.** Comparison of Kaplan-Meier probabilities of survival in BU-CY group (---; n = 65; 60.6% ± 11.7%) and CY-TBI group (---; n = 55; 65.6% ± 12.5%) \(P = .56\).

![Figure 4](https://example.com/fig4.png)

**Fig 4.** Comparison of Kaplan-Meier probabilities of DFS in BU-CY group (---; n = 65; 59.1% ± 11.8%) and TBI group (---; n = 55; 51% ± 14%) \(P = .72\).
limited because of the low number of relapse events. Although the RR of relapse for patients receiving CY-TBI is 4.1 against the standard of patients receiving BU-CY, because the lower limit of the standard deviation includes 1.00, the relationship is, therefore, probably weak.

In our present study, another variable was shown to be correlated with relapse incidence, ie, prophylaxis of acute GVHD with anti-P35 MoAb. Multivariate analysis showed that prophylaxis of GVHD was an independent significant risk factor for relapse. Thus, as it has been established for T-cell depletion, it is suggested that an increase of post-transplant immunosuppression could be followed by an increased risk of relapse for patients with CML.

In this trial, the early transplant toxicity and the transplant-related mortality were comparable when using either CY-TBI or BU-CY. This finding is comparable with the results of another randomized trial comparing BU-CY with CY-TBI, conducted by the Nordic Bone Marrow Transplantation Group, in which relapse-free survival and transplant-related mortality were similar in the two groups for patients with early disease. In the Seattle trial, the BU-CY regimen was tolerated even better than the CY-TBI regimen.

To conclude, BU-CY 120 compared with CY-TBI appears to be possibly associated with a higher incidence of graft rejection, indicating that the immunosuppressive capacity of this regimen could be insufficient; nevertheless, the difference is not significantly different. In this study, in contrast with results previously published on AML patients, leukemic cell kill of BU-CY 120 regimen appears to be sufficient, maybe because the probability of relapse in first chronic phase CML is much lower than in AML. Finally, overall results show that BU-CY 120 can be favourably compared with classical CY-TBI regimen.

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A Devergie, D Blaise, M Attal, JD Tigaud, JP Jouet, JP Vernant, P Bordigoni, N Ifrah, C Dauriac and JY Cahn

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