Randomized Comparison of Busulfan and Hydroxyurea in Chronic
Myelogenous Leukemia: Prolongation of Survival by Hydroxyurea


In a randomized multicenter study the influence of hydrox-
yurea versus busulfan on the duration of the chronic phase
and on survival of chronic myelogenous leukemia (CML)
was determined. In addition cross resistance and adverse
reactions of the drugs were analyzed. From July 1983 to
January 1991, 441 CML patients were randomized to re-
ceive hydroxyurea or busulfan. Of these, 90.7% were Phil-
delphia positive; 25.7% were low, 38.2% intermediate,
and 36.2% high risk patients according to Sokal's score.
The median survival of the busulfan treated Philadelphia-
positive patients is 45.4 months and of the hydroxyurea
group 58.2 months (P = 0.008). The survival advantage
for the hydroxyurea treated patients is recognized in all risk
groups. Sixty four patients reached therapy resistance be-
fore blast crisis and were crossed over to the alternative
drug. The 23 patients with primary hydroxyurea had a me-
dian survival of 5.6 years, the 41 patients with primary
busulfan therapy a median survival of 2.7 years (P = .02).
Adverse reactions were less frequent with hydroxyurea
with no severe adverse effects (lung fibrosis, long lasting
bone marrow aplasia). The analysis of white blood cell
counts in the course of treatment showed lower counts in
the hydroxyurea patients. We conclude that hydroxyurea
is superior to busulfan in therapy of CML in chronic phase
and should be used as first line therapy. Busulfan may have
a role as secondary therapy after hydroxyurea resistance or
intolerance.

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DRUG THERAPY of chronic myelogenous leukemia
(CML) has basically been palliative until now, with
the drug of choice being busulfan for the past 40 years. Little
prolongation of life has been observed since the report by
Minot et al in 1924.1 Curative therapy can be offered only to
those 10% to 20% of CML patients of sufficiently young age,
who have an HLA compatible, related or unrelated, bone
marrow donor;2,3 Median survival of CML patients from
the time of diagnosis varied between 30 and 55 months,
depending less on the mode of therapy than on patient se-
lection and exclusion of high risk patients such as Philadelp-
phia-negative or preblastic ones.4

Busulfan, an alkylating agent active at the stem cell level,
is known to control CML-related signs and symptoms in
95% of patients for at least 3 months.5 All studies have
shown its efficacy and reliability since its introduction in
1953. Controlled comparison with a number of single
agents, radiotherapy, and with intensive combination ther-
apy has shown its superiority with regard to efficacy, adverse
reactions, and/or duration of disease control.6-10 The me-
dian (or mean) survival times of busulfan-treated CML pa-
ients range from 35 to 47 months.4

More recently, hydroxyurea, an inhibitor of the ribonucle-
otide reductase, became increasingly popular because of its
rapid action and low level of adverse effects.11 Some retro-
spective studies on small series of patients indicated a sur-
vival advantage of hydroxyurea-treated patients,12-15 which,
however, was never substantiated by a controlled study. As
early as 1972, Kennedy12 reported in a retrospective study
on 20 patients with unknown Philadelphia chromosome
status that hydroxyurea controlled all CML-related symp-
toms as well as busulfan. Hydroxyurea did not prevent pro-
gression to blast crisis, but the investigator felt that it could
prolong the duration of the chronic phase as compared with
busulfan. The median duration of response to hydroxyurea
was 41 months for 10 not pretreated patients and 8 months
for 10 pretreated and busulfan-resistant patients. Schwarz-
zenberg et al, in a study of 43 patients who were treated with
hydroxyurea, leukapheresis, and splenectomy, reported
that survival was similar to that after busulfan therapy.13
Schwarz and Canellos16 treated 35 patients, mostly resistant
to busulfan and/or in accelerated phase, with hydroxyurea
and had good results. Bolin et al17 reported the results of a
retrospective study on 30 busulfan- and 14 hydroxyurea-
treated patients. Expected median survival was 48 months
and >90 months for the busulfan and the hydroxyurea
groups, respectively. However, this difference was not signif-
ificant due to the small sample size.

In 1983, the German CML study group, therefore, de-
cided to compare in a randomized study the influence of
hydroxyurea versus busulfan on the duration of the chronic
phase and on survival of CML. Further goals of the study
were the examination of cross resistance of hydroxyurea
and busulfan and the determination of duration of efficacy
after cross over; the development of a prognostic score on
the basis of prospectively documented parameters of possi-
ble significance for the prognosis of CML; the comparison

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of the terminal phases of CML under the different treatment modalities; the determination of adverse drug reactions; and the comparison of the outcome of bone marrow transplantations after the different drug therapies. In the present report the results of the comparison of hydroxyurea with busulfan, and in particular, the prolongation of survival of CML patients treated with hydroxyurea will be reported.

**PATIENTS AND METHODS**

*Study design.* The study outline is shown in Fig 1 (see Hehlmann et al 44 for comparison). After development of resistance to the randomized drug, therapy was crossed over to the other drug. Checkpoints were 1) the end of the chronic phase, defined as resistance to doubling of the initial dose of the randomized drug with cross over of drugs (hydroxyurea for busulfan resistant patients, busulfan for hydroxyurea resistant patients); 2) resistance to the alternative therapy; 3) diagnosis of blast crisis; and 4) death. Blast crisis was diagnosed, if blasts and promyelocytes were more than 30% of peripheral white blood cells (WBCs), or more than 50% of nucleated cells in the bone marrow. Patients with bone marrow transplantations were censored as lost to follow up at the time of transplantation.

*Patients.* All newly diagnosed patients with CML in chronic phase were randomized to receive either busulfan or hydroxyurea when they fulfilled at least one of the following six criteria: general ill feeling and fatigue, weight loss of more than 10% in 6 months, unexplained fever of more than 38.5°C on 5 consecutive days, organomegaly related symptoms, leukocytosis of more than 50×10⁹/L, thrombocytosis of more than 1×10¹²/L.

Exclusion criteria were no chronic phase diagnosis (n = 5), no treatment required (n = 10), pretreatment with cytostatics, interferon alpha or splenic irradiation (n = 6), lack of informed consent (n = 38), second neoplasia (n = 10), and other reasons that made a therapy according to protocol a priori unlikely (n = 11).

From July 1983 to January 1991, 458 patients were randomized by 60 centers in Germany and Switzerland, 226 to receive busulfan and 232 hydroxyurea (see flow diagram in Fig 2). A third arm with interferon alpha was opened later and is not yet evaluable. Eleven CML patients had exclusion criteria recognized after randomization: not in chronic phase (accelerated or blastic phase, 9 patients), decision of patient (1 patient), and other reasons (1 patient).

One hundred seven patients were censored (52 in the hydroxyurea arm, 55 in the busulfan arm) when the following events happened: bone marrow transplantation (44 patients), diagnosis of second neoplasia, withdrawal of consent, or noncompliance (63 patients). One hundred ninety two patients died—131 in blast crisis, 34 of CML independent causes. Other causes of death (20 patients) were infection, hemorrhage, marasmus, bone marrow aplasia, and bone marrow fibrosis. In seven patients the cause of death was unknown. One hundred forty two patients are in-study and alive (88 in the hydroxyurea arm, 54 in the busulfan arm).

The present report is based on the 441 documented and randomized CML patients on an intention-to-treat basis. The median observation time of all 441 patients is 2.03 years (range 0.73 years).

*Diagnostic investigations.* Pretherapeutic diagnostic evaluation consisted of history, physical examination, complete blood count including reticulocytes, alkaline leukocyte phosphatase (ALP), and lactate dehydrogenase (LDH), chromosome analysis, and bone marrow cytology and histology. Review panels controlled quality of bone marrow histology and chromosome analyses.

Follow up investigations were performed and documented every 6 months, at 12 months, and at disease progression (checkpoints 1, 2, and 3). Investigations at 6 month intervals included inquiry for symptoms (fever, fatigue, drug side effects), physical examination (spleen size, extramedullary manifestations, adverse drug reactions, weight), complete blood count including reticulocytes, and LDH. Investigations at 12 month intervals included chromosome analysis and bone marrow cytology and histology. In addition, the annual dosages of the respective drugs were determined.

*Therapy.* Busulfan was administered in a dosage of 0.1 mg/kg/d. The dosage was reduced when thrombocytopenia (≤ 10⁹ platelets/L) was present. The initial dosage was continued until the WBC count was reduced by 50%, and then it was reduced by 50%. WBC counts were controlled weekly. The dosage was further reduced by 50% with each further reduction of WBC counts by 50%. Therapy was discontinued, when the WBC count dropped below 20×10⁹/L. Therapy was renewed at a WBC count of more than 50×10⁹/L. If there was no sufficient therapeutic response or disease progression the dosage was increased up to twice the initial dose. In

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**Fig 1.** Study outline.
the presence of rapidly rising WBC counts (cell doubling in less than 2 months) low dose continuous busulfan therapy was acceptable.

Hydroxyurea was administered at an initial dosage of 40 mg/kg/d. The initial dosage was reduced in the presence of thrombocytopenia (<100 × 10^9 platelets/L). Control of the blood counts initially was three times weekly due to the rapid action of hydroxyurea. When the WBC count dropped to below 20 × 10^9/L, the hydroxyurea dosage was reduced to 20 mg/kg/d. This dosage was then adapted individually. If WBC counts rose above 20 × 10^9/L, the dosage was increased. The dosage was reduced, if the WBC count dropped below 10 × 10^9/L, and was interrupted, if the WBC count was below 5 × 10^9/L. Therapeutic goal was a normal WBC count (range 5 to 15 × 10^9/L).

Documentation. At diagnosis and randomization all data were documented in an initial documentation form. During the course of the study documentation forms were completed every 6 months. Whenever a checkpoint was reached (see study outline) a separate checkpoint form was filed. After a patient had died or was lost to follow up (including bone marrow transplantation), a final documentation form was filed. Adverse events were documented according to WHO grading.

Biositistics. Sample size estimation was done according to George and Desu. Assuming α = 0.05 (two-sided) and β = 0.20, 388 patients (194 per group) were necessary to detect a relative risk of at least 1.42 in the median survival time in favor of hydroxyurea. The randomization lists were computed according to Efron's stratified for participating hospitals. After getting informed consent suitable patients were randomized centrally by phone by the Biometric Center for Therapeutic Studies.

Five interim analyses were performed as planned in the trial protocol. The probability for type I error α was adjusted following O'Brien and Fleming, safeguarding an overall error probability < 0.05. The required α for the final analysis was 0.04009. The analyses followed the intention-to-treat strategy. Survival was analyzed with the Kaplan-Meier estimator and logrank test. Analyses for prognostic factors were performed with Cox proportional hazards regression model. The calculation of risk groups was performed with the equation:

\[ \text{Score} = \exp \left[ 0.0116 \times \text{age} + 43.4 + 0.0345 \times \text{spleen size} + 7.51 + 0.0188 \times \left( \frac{\text{platelets}}{10^5} \right) - 0.563 + 0.0887 \right] \]

All analyses were performed by the Biometric Center with the program package SAS.

**Ethics.** The protocol followed the declaration of Helsinki and was approved by the ethics committees of the Universities of Munich and Ulm. Informed consent was obtained from all patients.

### RESULTS

**Initial patients' characteristics.** The initial characteristics of the 441 randomized and documented CML patients are shown in Table 1 according to treatment group and Philadelphia (Ph) status. The Ph status was known for 409 patients of which 371 (90.7%) were Ph positive (187 in the hydroxyurea, 184 in the busulfan arm). All patients are shown including the nine patients who were not in chronic

**Table 1. CML: Initial Patients' Characteristics**

<table>
<thead>
<tr>
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<th>BU</th>
<th>HU</th>
<th>Ph+</th>
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<tr>
<td>Age (yr)</td>
<td>50.2</td>
<td>49.2</td>
<td>47.8</td>
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<tr>
<td>Sex (% male)</td>
<td>60.7</td>
<td>52.0</td>
<td>58.8</td>
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<tr>
<td>Fatigue, general ill feeling (%)</td>
<td>69</td>
<td>59</td>
<td>64</td>
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<td>Symptoms due to organomegaly (%)</td>
<td>37</td>
<td>34.7</td>
<td>36</td>
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<tr>
<td>Weight loss (%)</td>
<td>24</td>
<td>20.7</td>
<td>19</td>
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<tr>
<td>Fever (%)</td>
<td>9.4</td>
<td>4.6</td>
<td>7</td>
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<tr>
<td>Karnofsky index (%)</td>
<td>87.1</td>
<td>88.7</td>
<td>88.2</td>
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<td>Splenomegaly (%)</td>
<td>72.2</td>
<td>72.4</td>
<td>71.9</td>
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<td>Hepatomegaly (%)</td>
<td>54.6</td>
<td>46.6</td>
<td>49.2</td>
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<tr>
<td>Spleen size in cm below costal margin</td>
<td>6.4</td>
<td>6.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Liver size in cm in MCL</td>
<td>12.9</td>
<td>12.6</td>
<td>12.6</td>
</tr>
<tr>
<td>Extramedullary manifestations (skin, lymphnodes) (%)</td>
<td>9</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Ph-positive (%)</td>
<td>91.5</td>
<td>89.9</td>
<td>100</td>
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<tr>
<td>Additional cytogenetic aberrations (%)</td>
<td>11</td>
<td>12.9</td>
<td>9.8</td>
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<td>WBC × 10^9/L</td>
<td>161.9</td>
<td>156.6</td>
<td>169.1</td>
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<tr>
<td>Platelets × 10^12/L</td>
<td>454.3</td>
<td>488.4</td>
<td>493.9</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.2</td>
<td>11.9</td>
<td>12.1</td>
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<tr>
<td>LDH (U/L)</td>
<td>725</td>
<td>720</td>
<td>749</td>
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<tr>
<td>Circulating blasts (%)</td>
<td>2.9</td>
<td>3.4</td>
<td>3.1</td>
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<tr>
<td>Circulating promyelocytes (%)</td>
<td>4.5</td>
<td>4.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Basophilia (%)</td>
<td>4.5</td>
<td>4.5</td>
<td>4.9</td>
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<tr>
<td>Reticulocytes (%)</td>
<td>23.0</td>
<td>23.7</td>
<td>23.3</td>
</tr>
<tr>
<td>Erythroblasts (per 100 WBC)</td>
<td>1</td>
<td>0.9</td>
<td>1.0</td>
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<tr>
<td>BM blasts (%)†</td>
<td>4.1</td>
<td>4.4</td>
<td>3.9</td>
</tr>
<tr>
<td>BM promyelocytes (%)†</td>
<td>10.1</td>
<td>10.7</td>
<td>10.1</td>
</tr>
<tr>
<td>Grouping into risk groups (Ph+ only)‡</td>
<td>25.3</td>
<td>26.0</td>
<td>25.7</td>
</tr>
<tr>
<td>Low (%)</td>
<td>41.6</td>
<td>35.0</td>
<td>38.2</td>
</tr>
<tr>
<td>Intermediate (%)</td>
<td>33.1</td>
<td>39.0</td>
<td>36.2</td>
</tr>
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* Features not specified as otherwise were recorded in 95% to 100% of patients.
† Features recorded in 93% (cytogenetica) and 80% (ALP) of patients.
‡ Features recorded in 74% of cases.
phase at randomization. The patients' characteristics are distributed evenly in the two randomization groups. Figure 3 shows the characteristics of the Ph-positive patients according to Sokal's prognostic subgrouping. The proportion of low risk patients is 25.7%. The distribution of busulfan and hydroxyurea treated patients is similar in all three risk groups (Table 1). There are somewhat more hydroxyurea patients in the high risk group (39% vs 33%).

Survival. The median survival of all CML patients is 43.6 months in the busulfan group and 56.2 months in the hydroxyurea group ($P = .01$); that of the Ph-positive patients in the busulfan group is 45.4 months and in the hydroxyurea group 58.2 months ($P = .008$, Fig 4).

Duration of the chronic phase. Figure 5 shows the duration of the chronic phase defined by resistance to the randomized therapy or diagnosis of blast crisis (checkpoint 1, 2, or 3). The median duration from diagnosis to checkpoint 1, 2, or 3 is 37 months for the busulfan and 47 months for the hydroxyurea group ($P = .04$).

Analysis according to risk factors. The survival advantage in the hydroxyurea arm is recognized in all Sokal prognostic subgroups (Fig 6). In spite of the smaller numbers in the subgroups, the survival difference in the intermediate risk group is significant at $P = .01$.

Checkpoint 1 and crossover of therapy. Sixty four patients reached checkpoint 1 first, 41 in the busulfan and 23 in the hydroxyurea group, and were crossed over to the other therapy. The mean duration of therapy before crossover was 21.1 months in the busulfan and 22.3 months in the hydroxyurea group. The mean duration of secondary...
busulfan therapy was 20 months, that of secondary hydroxyurea therapy 11.7 months. Eleven patients progressed to blast crisis within 1 month after crossover (four in the group with primary hydroxyurea therapy, seven in the group with primary busulfan therapy). Because of secondary resistance before blast crisis (checkpoint 2) interferon alpha was added in seven cases (four busulfan patients, three hydroxyurea patients), other chemotherapy (arabinosylcytosin, mitomycin, thioguanin) in 10 patients (five in each therapy group).

It is evident from Fig 7 that secondary busulfan after hydroxyurea resistance has an additional impact on survival. There is a survival advantage for primary hydroxyurea and secondary busulfan in all subgroups of Table 2. Most notably, patients with cytopenia and/or bone marrow aplasia, who carry a poor prognosis, are only found in the primary busulfan group. But even without the 16 cytopenic patients, the survival difference between the treatment groups after crossover is significant ($P < .01$).

Once blast crisis has developed no survival difference is observed between the treatment groups (data not shown).

**Cytogenetic response rates.** Four patients in the hydroxyurea arm and two patients in the busulfan arm showed cytogenetic responses (reduction of Ph-positive cells by 10% to 100%) during the course of therapy corresponding to 3% and 2% of the evaluable patients. One complete cytogenetic remission was observed in a hydroxyurea treated case. Some of the responses may be due to additional therapy added to the monotherapy later on when secondary resistance was observed (checkpoint 2) (the one case with a complete cytogenetic remission also had polychemotherapy, another case also had interferon alpha).

**Adverse effects.** Data were available from 209 patients treated with hydroxyurea and from 204 patients treated with busulfan. The frequency of adverse effects is lower with hydroxyurea than with busulfan (15.8 vs 24.2 symptoms per 100 patient years). Most importantly, serious adverse effects such as long lasting bone marrow aplasia or lung fibrosis were virtually not observed in the hydroxyurea arm (one transient event under hydroxyurea vs 13 events in the busulfan arm). This low toxicity may have facilitated a possibly more intensive treatment with hydroxyurea.

**Correlation of survival with WBC counts.** Since one reason for the difference of survival might be a difference in disease control, we analyzed the WBC counts in both groups during the first 24 months of treatment. After 18 and 24 months 43% and 34% of the hydroxyurea-treated, but only 11% and 16% of the busulfan-treated patients had normal WBC counts, respectively. In the hydroxyurea group patients with normal WBC counts had a survival advantage compared with those with elevated counts ($P < .06$).

**DISCUSSION**

The most important observation in this study is the significantly better median survival of the patients treated with hydroxyurea as compared with those treated with busulfan. This result confirms some reports of a possible survival advantage by hydroxyurea in small, uncontrolled trials, but the magnitude of the survival advantage came as a surprise. The result raises several biologic as well as therapeutic questions.

First, the question has to be addressed whether hydroxyurea prolongs the survival of CML patients or whether busulfan therapy was suboptimal. The median survival time of 45.4 months with busulfan compares well with an earlier controlled study that finds a median survival of busulfan-treated CML patients of 44 months. In addition, it has to be excluded that the survival difference is due to an unequal distribution of prognostic factors. In Table 1 we show that the relevant prognostic parameters as well as the distribution of risk groups did not favor the hydroxyurea group. There were more hydroxyurea patients in the high risk group (39% vs 33%), although this was not significant. We therefore conclude that the survival difference is the result of the different therapies.

Second, the apparent prolongation of survival of the hydroxyurea group is contrary to some earlier notions on pro-
Fig 6. Survival curves of the treatment groups according to risk group (Sokal's prognostic score: [A] low risk; [B] intermediate risk; [C] high risk).
gression of CML that the course of CML is determined by intrinsic factors rather than therapy.24,25 This has to be analyzed also in the context of the good survival data with interferon alpha (our unpublished observation).26-28 One interpretation would be that a decrease of tumor mass and/or a slowing of granulocyte proliferation rate decreases the progression rate to blast crisis. The hypothesis would be that the number of clonal cells in the mitotic pool correlates with likelihood of blast transformation implying that the less tumor burden and proliferation are present the less likely blast transformation might occur. This hypothesis is supported by the observation of Kolitz et al29 that intensive hydroxyurea therapy induces cytogenetic responses in nine of 14 patients of 25% to 100% and that the level of bone marrow hypocellularity correlates with cytogenetic response. If this hypothesis is true, the more efficient reduction of WBC counts, which probably reflect tumor cell mass, by hydroxyurea might in part account for the survival advantage.

Therefore, if there is a correlation between tumor mass and probability of blast transformation, a more efficient reduction of WBC counts by the combination of suitable antiproliferative drugs might result in a further prolongation of survival in CML (eg, hydroxyurea and interferon alpha as in our ongoing randomized CML study II or combinations with arabinosylcytosine).30

In this context, the question has to be addressed why intensive combination chemotherapy did not show prolongation of survival as observed with hydroxyurea.8-10,31,32 The goal of these studies, however, primarily was cure of CML by the intensive approach and not continuous control of myeloproliferation over extended periods of time as in our study.

Finally, the high mutagenic potential of busulfan with subsequent promotion of acute leukemia as observed in polycythemia vera33 has to be considered. Although the median survival time of the busulfan-treated patients of more than 45 months is longer than that of historic controls of
therapy of CML in chronic phase and should be used as first line therapy. Busulfan may, however, have a role as second line treatment after hydroxyurea resistance or intolerance. The importance of the reduction of WBC in the chronic phase for prolongation of survival in CML, irrespective of the cytostatic drug used, will be analyzed further within ongoing randomized studies.

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APPENDIX


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Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: prolongation of survival by hydroxyurea. The German CML Study Group

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