In a randomized multicenter study the influence of hydroxyurea 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 receive hydroxyurea or busulfan. Of these, 90.7% were Philadelphia 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 = .008). The survival advantage for the hydroxyurea treated patients is recognized in all risk groups. Sixty four patients reached therapy resistance before blast crisis and were crossed over to the alternative drug. The 23 patients with primary hydroxyurea had a median 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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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 Hbihmann et al16 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 (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 were 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 0-7.83 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 (<100 × 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

Fig 1. Study outline.
was three times weekly due to the rapid action of hydroxyurea. Thrombocytopenia was documented in an initial documentation form. During the course dosage was increased. The dosage was reduced, if the WBC count (range 5 to 15 × 10^9/L). Control of the blood counts initially was three times weekly due to the rapid action of hydroxyurea. The WBC count dropped to below 20 × 10^9/L. 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 reduced following the formula: Score = exp. [0.0116 (age, 43.4) + 0.0345 (spleen size, 7.51) + 0.0188 ((platelets/700)^2 − 0.563) + 0.0887 (peripheral blasts, 2.10)]. All analyses were performed by the Biometric Center with the program package SAS.23

**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>
<th></th>
<th>BU (n = 216)</th>
<th>HU (n = 225)</th>
<th>Ph+ (n = 371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50.2</td>
<td>49.2</td>
<td>47.8</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>60.7</td>
<td>52</td>
<td>58.8</td>
</tr>
<tr>
<td>Fatigue, general ill feeling (%)</td>
<td>69</td>
<td>59</td>
<td>64</td>
</tr>
<tr>
<td>Symptoms due to organomegaly (%)</td>
<td>37</td>
<td>34.7</td>
<td>36</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>24</td>
<td>20.7</td>
<td>19</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>9.4</td>
<td>4.5</td>
<td>7</td>
</tr>
<tr>
<td>Karnofsky index (%)</td>
<td>87.1</td>
<td>88.7</td>
<td>88.2</td>
</tr>
<tr>
<td>Splenomegaly (%)</td>
<td>72.2</td>
<td>72.4</td>
<td>71.9</td>
</tr>
<tr>
<td>Hepatomegaly (%)</td>
<td>54.6</td>
<td>46.6</td>
<td>49.2</td>
</tr>
<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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(skin, lymphnodes) (%)</td>
<td>9</td>
<td>3.6</td>
<td>6</td>
</tr>
<tr>
<td>Ph-positive (%)*</td>
<td>91.5</td>
<td>89.9</td>
<td>100</td>
</tr>
<tr>
<td>Additional cytogenetic aberrations (%)</td>
<td>11</td>
<td>12.9</td>
<td>9.8</td>
</tr>
<tr>
<td>WBC × 10^9/L</td>
<td>161.9</td>
<td>156.6</td>
<td>169.1</td>
</tr>
<tr>
<td>Platelets × 10^9/L</td>
<td>454.3</td>
<td>488.4</td>
<td>493.9</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.2</td>
<td>11.9</td>
<td>12.1</td>
</tr>
<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>
</tr>
<tr>
<td>Circulating promyelocytes (%)</td>
<td>4.5</td>
<td>4.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Basophils (%)</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>1.1</td>
<td>0.9</td>
<td>1.0</td>
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<tr>
<td>ALP (index)*</td>
<td>15.2</td>
<td>16.0</td>
<td>15.5</td>
</tr>
<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></td>
<td></td>
<td></td>
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<tr>
<td>Low (%)</td>
<td>25.3</td>
<td>26.0</td>
<td>25.7</td>
</tr>
<tr>
<td>Intermediate (%)</td>
<td>41.6</td>
<td>36.0</td>
<td>38.2</td>
</tr>
<tr>
<td>High (%)</td>
<td>33.1</td>
<td>39.0</td>
<td>36.2</td>
</tr>
</tbody>
</table>

All features not specified as otherwise were recorded in 95% to 100% of patients.

* Features recorded in 93% (cytogenetics) and 80% (ALP) of patients.
† Features recorded in 74% of cases.
‡ Features recorded in 92.5% of Ph+ patients.
CML: PROLONGATION OF SURVIVAL BY HYDROXYUREA

Fig 3. Characteristics of Philadelphia-positive CML patients according to Sokal's prognostic subgrouping.

Fig 4. Survival of Philadelphia-positive CML patients according to treatment group.

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,$^{11-13}$ 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.$^6$ 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).
primary hydroxyurea (followed by busulfan) n = 23, median survival 5.6 years

primary busulfan (followed by hydroxyurea) n = 41, median survival 2.7 years

p = 0.02

Fig 7. Survival after crossover of therapy (checkpoint 1). (A) Survival from diagnosis; (B) survival from crossover.

progression of CML that the course of CML is determined by intrinsic factors rather than therapy.\textsuperscript{24,25} This has to be analyzed also in the context of the good survival data with interferon alpha (our unpublished observation).\textsuperscript{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 al\textsuperscript{29} 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).\textsuperscript{30}

In this context, the question has to be addressed why intensive combination chemotherapy did not show prolongation of survival as observed with hydroxyurea.\textsuperscript{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 vera\textsuperscript{33} 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...
untreated CML patients, or of CML patients treated with splenic irradiation, it cannot be excluded that its mutagenic effect has a negative impact on survival, which becomes visible, if busulfan is compared with hydroxyurea.

A third observation is the apparent gain of survival time by secondary busulfan after primary hydroxyurea therapy. Although the number of patients qualifying for an adequate trial with secondary busulfan is small (n = 19, 8.4% of hydroxyurea-treated patients), the survival advantage is significant and adds to the survival advantage of the hydroxyurea arm described in this report. Busulfan turned out to be inferior to hydroxyurea as first line treatment, but apparently plays a role after hydroxyurea resistance. One reason for the poor success of secondary hydroxyurea treatment after primary busulfan seems to be the high number of patients with cytopenias and/or bone marrow aplasia after busulfan therapy, which was not observed after primary hydroxyurea therapy. This agrees well with the known toxic pattern of busulfan. It appears that in the presence of busulfan-induced cytopenias hydroxyurea cannot add any survival advantage.

We cannot entirely exclude that our survival results are influenced by an earlier diagnosis than in previous eras. Our inclusion criteria for randomization and therapy, however, excluded patients who were very early in the course of disease. In addition, the percentage of our patients in the low-risk group is in contrast to Sokal's patients lower than the intermediate- and high-risk groups. This distribution argues against the possibility that our favorable survival results are due to a high number of low-risk patients or earlier diagnosis.

Since all parameters included in this report have been documented prospectively under the same mandatory modalities, the patient sample is well suited for the generation of a prognostic score (score 1) based on prospectively collected parameters as well as a detailed histomorphologic characterization of CML according to Ph status and clinical course, which is ongoing.

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, 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.

ACKNOWLEDGMENT

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APPENDIX


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