Drug Treatment is Superior to Allografting as First Line Therapy in Chronic Myeloid Leukemia


Short title: CML study III

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Keywords: Chronic myeloid leukemia, allogeneic stem cell transplantation, best available drug treatment, interferon α, imatinib, randomized comparison

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Abstract

Early allogeneic hematopoietic stem cell transplantation (HSCT) has been proposed as primary treatment modality for patients with chronic myeloid leukemia (CML). This concept has been challenged by transplantation mortality and improved drug therapy.

In a randomized study primary HSCT and best available drug treatment (IFN-based) were compared in newly diagnosed chronic phase CML patients. Assignment to treatment strategy was by genetic randomization according to availability of a matched related donor. Evaluation followed the intention-to-treat principle.

621 patients with chronic phase CML were stratified for eligibility for HSCT. 354 patients (62%, male; median age 40 (11-59) years) were eligible and randomized. 135 patients (38%) had a matched related donor of which 123 (91%) received a transplant within a median of 10 (2-106) months from diagnosis. 219 patients (62%) had no related donor and received best available drug treatment. With an observation time up to 11.2 (median 8.9) years survival was superior for patients with drug treatment (p=0.049), superiority being most pronounced in low risk patients (p=0.032).

The general recommendation of HSCT as first line treatment option in chronic phase CML can no longer be maintained. It should be replaced by a trial with modern drug treatment first.
Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has been recommended as first line treatment in chronic myeloid leukemia (CML) since it is considered to be the only treatment modality with curative potential (1;2). HSCT is most successful if it is done early within the first 2 years after diagnosis (3). Progress with drug treatment (4) and persisting transplantation mortality (5) have challenged the concept of first line transplantation. In view of the improved survival times after the introduction of interferon α (IFN) (6;7) and imatinib (8;9), the question came up of whether first line transplantation is still justified in all suitable patients with a donor, or whether drug treatment should precede transplantation as long as remission is maintained. No randomized study has yet compared outcome of treatment strategies of HSCT vs. drug treatment. In a simulation of such a study survival of IFN and hydroxyurea (HU)-treated patients of the German CML-study I (10) had been retrospectively compared with that of a matched cohort of transplanted patients registered with the IBMTR (11). Transplantation did not achieve a survival advantage in this historical analysis before year 6 after diagnosis in all patients and not at all in low risk patients during the observation period of up to eight years from diagnosis. Based on 5-year observation, survival with imatinib seems to be even better than that with IFN-based therapy (12). This has led to the expert recommendation of a trial with imatinib first before proceeding to HSCT (13).

In order to verify the data obtained from the retrospective study (11), a prospective randomized study was designed to compare treatment outcome in a cohort of patients predefined by eligibility for transplantation. Since randomization had to consider the availability of a donor, availability of a matched related donor was used as a random criterion (genetic randomization). The main goal of the study was to describe and compare survival times in patients treated with HSCT in early
chronic phase vs. best available drug treatment. Prognostic score at diagnosis and transplantation risk were taken into account (14;15). We here report the outcome 11 years after the start of the study.

Patients and Methods

Study protocol

All patients with Philadelphia chromosome (Ph) and/or BCR-ABL positive CML in chronic phase were examined for primary HSCT (age <55 years, no serious comorbidity, no other contraindications, informed consent). Patients eligible for HSCT were then genetically randomized according to availability of a matched related donor to primary HSCT or best available drug treatment. A matched related donor was defined as HLA identical sibling donor, or if a sibling donor was not available, another fully matched family donor.

Patients

Enrollment, allocation, follow-up and analysis of patients are depicted in the flow diagram in Fig. 1. In total, 682 patients fulfilling the inclusion criteria of, and consenting to the protocol were consecutively entered into the study by the participating centers between January 1995 and December 2001 and analyzed as of May 15, 2006. Survival documentation was complete except for one patient who was lost to follow up. Nineteen patients were excluded by the central data quality control. Fortytwo patients had Ph- and BCR-ABL negative CML and will be analyzed separately. 621 Ph- and/or BCR-ABL positive patients in chronic phase CML were therefore registered and stratified according to eligibility for primary HSCT. Median time from diagnosis to registration was 19 days. 356 of the 621 patients were eligible for transplantation and 354 were randomized to receive either allogeneic HSCT from a related donor (group 1, n=135) or best
available drug treatment (group 2, n=219). In two patients the donor status remained unknown. 354 eligible patients were thus used for analysis and comparison. 265 patients were not eligible for transplantation (group 3), due to age (n=213, median age 63 [47-90] years), comorbidity (n=19), other or unknown reasons (n=21) and no consent (n=12). They are included here to allow comparison with other studies e.g. concerning patients’ characteristics or survival.

Patients’ initial characteristics of all three groups are depicted in Table 1. There were no differences between the groups eligible for HSCT with or without donor with most variables available for all randomized patients including prognostic score at diagnosis determined according to Hasford et al. (14) which takes into account age, spleen size, platelet count, and percentages of blasts, basophils, and eosinophils in the peripheral blood. 14 patients were less than 20 years old, 5 in the transplant and 9 in the drug treatment group. There were significant differences between patients eligible for HSCT (groups 1 and 2) and those not (group 3). Differences mainly concerned age, symptoms due to organomegaly, WBC count and differential, hemoglobin, and prognostic score. Transplantation risk (EBMT-score) was determined according to Gratwohl et al. (15).

123 of 135 patients randomized to receive HSCT (91%) were transplanted (113 in chronic phase, ten patients had progressed to accelerated or blastic phase by the time of transplantation) and 12 patients (9%) were not (four because of death prior to transplantation [3 blast crises, 1 suicide] and eight due to secondary withdrawal of consent). Out of 219 patients (62% of 354) without a related donor 97 patients (44% of 219) received a matched unrelated donor (MUD) transplant during chronic phase (81 patients were considered to have an insufficient response to drug treatment, 12 patients on request, four patients due to unknown reasons) and 27 patients during accelerated or blastic phase. The comparison of risk profiles between MUD transplanted and non-
transplanted patients indicated that MUD transplanted patients had a better risk profile (low risk: n=62[64%], intermediate: n=30[31%], high: n=5[5%]) than not transplanted patients (low risk: n=67[55%], intermediate: n=42[34%], high: n=13[11%]), but this difference did not achieve statistical significance.

**Allogeneic HSCT/transplantation cohort**

Out of the 354 patients eligible for HSCT a total of 247 patients received a HSCT, 210 in chronic phase and 37 patients in accelerated and blastic phases. 11 of the 265 not eligible patients (3 older than 55 years) also received HSCT later on. In total 258 of 621 patients (42%) were transplanted. HSCT was performed at 29 accredited centers in Germany, Switzerland, Austria and Poland. The source of stem cells was peripheral blood in 56 patients (23%), marrow in all others. The median time from diagnosis to transplant from a related donor was ten months (range 2-106 months). The recommended treatment prior to HSCT was HU. IFN therapy had to be terminated not later than 90 days before HSCT (16). The 113 transplantations from related donors in first chronic phase were performed in: 1995 (n=4), 1996 (n=33), 1997 (n=29), 1998 (n=25), 1999 (n=9), 2000 (n=9), 2001 (n=3) and 2004 (n=1). The conditioning regimen basically consisted of busulfan 16 mg/kg p.o., 4 mg/kg daily for 4 days with or without cyclophosphamide 30 mg/kg daily for 4 days (n=110), cyclophosphamide plus total body irradiation (TBI) 12 Gy (n=135), or other drug combinations (n=2). GvHD prophylaxis and supportive therapy were conducted according to the standard practice of the individual center.

**Drug treatment**

At the time of recruitment to this study, the recommended primary drug treatment consisted of IFN in combination with HU (17). Therapy was started with HU (40 mg/kg and day). After
cytoreduction IFN was given at a dose of $5 \times 10^6$ IU/m$^2$ (in general $9 \times 10^6$ IU per day) s.c. IFN dosage was adjusted to maintain a WBC-count of $2-4 \times 10^9$/l. The platelet count was to be kept above $50 \times 10^9$/l. In most cases, the IFN dose required for maintenance was less than the initial IFN dose, on average $2-3 \times 10^6$ IU/day from years 3 to 4 on. HU was only continued if the desired white blood cell (WBC) count could not be maintained with IFN alone. Low-dose AraC was added in the case of IFN/HU failure.  

If no complete hematologic remission was achieved by months 3-9 or no cytogenetic response by months 12-18 treatment intensification with AraC ($2 \times 100$ mg/m$^2$/day over five days per month) and idarubicin 10 mg/m$^2$ i.v. on days 3 and 4; 8 mg/m$^2$ in patients >60 years (n=51, 10 in group 2) was offered in a randomized fashion. These data will be analyzed separately. In qualified hospitals high-dose chemotherapy with subsequent autologous SCT was offered as well to this patient group. With the availability of imatinib from 1999 on, imatinib was offered in the case of IFN-failure. 196 out of 621 patients received imatinib at some time, 15 in group 1 (11%), 62 in group 2 (43% of 122 non-transplanted and 9% of 97 MUD-transplanted patients) and 119 in group 3 (45%).  

Patients who did not achieve a cytogenetic remission on IFN (<35% Ph$^+$ metaphases) within 12-18 months had the option of a MUD transplant.  

**Statistics**  
The study had two main goals. Firstly, patients with consent and eligibility to HSCT were to be compared between transplantation with a transplant from a related donor and best available drug treatment and secondly, subject to having received conservative drug treatment and not achieving cytogenetic response within twelve months, patients were then randomized between HU/IFN and idarubicin/ara-C/plus IFN maintenance. Sample size was determined in alliance with the second
goal under the assumption to simultaneously enter also enough patients to be able to investigate the first goal with sufficient power.

As in the study by Archimbaud et al. (18) all patients eligible for HSCT and with a suitable related donor were scheduled to receive HSCT. The result of HLA-family typing was considered to be equivalent to genetic randomization between HSCT and best available drug treatment. All patients were analysed following the intention to treat principle. Thus “time-to-transplantation” bias could be avoided, i.e. patients assigned to receive a HSCT appropriately had to carry the risk of death while waiting for the day of transplantation. The statistical comparison between both groups benefited from all advantages of statistical randomization: comparable patient characteristics, best possible reduction of selection bias, and identical observation periods within both treatment arms.

Primary end point was survival time from diagnosis to cutpoint of survival curves. In the drug treatment group, survival times of patients who received a MUD transplant were censored at the day of transplantation, if patients were still in first chronic phase because the outcome could not be related to drug treatment anymore. Patients transplanted in accelerated or blastic phase were not censored, since drug treatment had failed before. Prior to the study, it was assumed that survival probabilities of transplanted patients would be less favorable in the beginning, but would be better than those of drug treated patients after an extended period of time. Hence, survival times to first cutpoint (and overall survival) were compared by Kaplan-Meier estimation and Wilcoxon-Gehan test (19) which is to be applied, if survival curves are non-proportional and cross, i.e. if they are rather logistic than exponential functions related (11). The significance level \( \alpha \) was chosen to be 0.05 two-sided. Patients’ characteristics at baseline were descriptively
compared using chi-square test, Student’s t-test, or Wilcoxon’s two-sample test, as appropriate. All analyses were performed with the program package SAS.

**Molecular analysis**

BCR-ABL transcript levels were determined by nested and quantitative reverse transcriptase polymerase chain reaction (RQ-PCR) following current international expert recommendations (20). Quantification of transcripts was achieved by measuring the BCR-ABL/ABL ratio according to the international scale (20). A major molecular response was defined by a BCR-ABL/ABL ratio of $\leq 0.1$, a complete molecular response by undetectable BCR-ABL transcripts using normal abl as an internal sensitivity control (20).

**Ethics**

The protocol followed the Declaration of Helsinki and was approved by the ethics committee of the Fakultät für Klinische Medizin Mannheim of the University of Heidelberg and by local ethics committees of participating centers. Written informed consent was obtained from all patients prior to entering the study.

**Results**

**Survival**

All patients: Median survival of all 621 patients was 7.5 years when patients were censored at the time of transplantation in first chronic phase and 8.1 years without censoring. The median observation time for living patients was 8.9 (4.2 - 11.2) years. Survival according to prognostic score at diagnosis is depicted in Fig. 2a. Five (10) year survival probabilities were 72% (49%) in low risk, 62% (36%) in intermediate risk and 49% (26%) in high risk patients, respectively. Five
year survival probabilities of the 354 patients eligible for transplantation were 81% (n=214) in low risk, 58% (n=116) in intermediate risk, and 56% (n=24) in high risk patients, respectively. Survival of all 247 transplanted patients according to EBMT-score is shown in Fig. 2b. Five year survival probabilities were 76% (n=97) for EBMT-scores 0, 1 and 2, 54% (n=125) for scores 3 and 4, and 26% (n=25) for scores 5, 6 and 7 (15). Survival of drug treated and transplanted patients is in line with published data (14;15).

Randomized patients: Fig. 3 shows the survival of the 354 randomized patients by presence or absence of a matched related donor. Survival was better for drug treated patients (no related donor) both for the time until the curves converge (cutpoint) at year 8 (p=0.041) and for the entire observation period up to year 11 (p=0.049) and most marked at three years after diagnosis. At 8 years after diagnosis survival curves are no longer distinct. Survival differences were most pronounced in patients with low risk features at diagnosis (Fig. 4a) both for the time to the cutpoint at year 8 (p=0.027) and for the entire observation period of 11 years (p=0.032), with the same pattern of convergence. No survival difference was observed between intermediate or high risk patients with or without a related donor (Fig. 4b). Intermediate and high risk patients were combined, since their survival curves were similar in this study. The survival probabilities after 2, 5, 8 and 10 years of groups 1-3 and of all patients, overall and according to risk profile at diagnosis are shown in Table 2.

At the time of evaluation 74 of the 135 patients (55%) with related donor and 128 of the 219 patients (60%) without related donor (including 67 recipients of MUD transplants in chronic phase) were still alive. These patients were analyzed for their state of health (signs and symptoms of CML relapse such as fatigue, spleen related symptoms, weight loss, fever, anemia,
thrombocytopenia and leukopenia, or adverse drug effects). No differences were found between the two groups.

**Causes of death**

The causes of death are listed and assigned to groups 1-3 in Table 3. Blast crisis, as expected, was with 42.5% the most frequent cause of death particularly in groups 2a (no related donor available, no MUD-transplant) and 3 (not eligible for HSCT). This was followed by transplant related mortality (26.1%) in groups 1 (related donor available) and 2b (no related donor available, MUD transplant in second line) and by other CML related causes (12.6%). It is noteworthy that with the long survival times observed in this study 17.6% of all causes of death were not directly CML-related.

**Current drug treatment**

At the time of evaluation 20 of 54 living patients (37%) in group 2 (no related donor available, no MUD transplant) still received IFN or HU, but 31 patients (57%) had been changed to imatinib and other BCR-ABL tyrosine kinase inhibitors afterwards (nilotinib, n=1; dasatinib, n=2)(21;22), mostly after IFN-failure. When patients were censored at the start of imatinib treatment, survival curves did not change indicating that these patients represented a group with more advanced disease and limited response to imatinib.

**Cytogenetic and molecular responses**

Differences between the transplant and drug treatment groups were found regarding cytogenetic and molecular remissions. All patients surviving at least 5 years and evaluable (group 1: n=113; group 2, no MUD: n=92) were analyzed for cytogenetic and molecular responses (Table 4).
Significantly higher proportions of complete cytogenetic remissions (91% vs 48%, \( p=0.002 \)) and of major molecular responses (81% vs 45%, \( p=0.0001 \)) were found in group 1 indicating higher levels of residual disease in group 2 receiving drug treatment.

**Discussion**

This is the first trial that quantifies survival after drug treatment and transplantation in CML by randomized controlled comparison. 91% of the patients randomized for transplantation were indeed transplanted demonstrating protocol feasibility and compliance. Four patients (3%) died prior to planned HSCT. Main reason for the high compliance rate was the acceptance of the curative potential of transplantation by most patients. It was ascertained that censoring of MUD patients would not introduce a bias against the HSCT group. MUD patients had even slightly better prognostic scores than the rest of the patients without a related donor. In total, transplantation was available to 42% of all patients. Results of transplantation outcome in this study were in line with data of concurrent transplants in the literature (15).

The superiority of drug treatment in all, and particularly in low-risk patients during the first eight years after diagnosis is evident and significant. Although IFN was used as primary treatment in this study, the results are valid and relevant also in the imatinib era, since survival with primary imatinib treatment is even better. There is no evidence that the situation is different in very young patients (<20 years old). There is no hint so far that the years lost early due to transplant related mortality will be compensated in the course of the transplant group later on. Long-term observations of transplanted CML-patients (5) demonstrate that survival curves continuously decline at a rate of 1% per year due to late transplant related mortality or relapse.
Transplantation procedures have improved since the start of this study (23;24). In this study patients transplanted between 1995 and 1998 had no significantly different survival from patients transplanted between 1999 and 2004 (5-year survival 64% and 68%, respectively). In a comparison of transplantation results 1995-1998 vs. 1999-2002 by the EBMT, 5-year survival increased by 6% (from 57% to 63%) (5). Such an increase in transplant survival would not alter the conclusion of this study.

The study shows that both approaches, drug therapy and HSCT are potent treatment forms for patients with CML, with a high potential for good long term outcome and specific advantages and disadvantages. It remains open, whether the higher rate of major cytogenetic and molecular responses after HSCT will translate into a survival advantage some time in the future. Some form of immunotherapy(25), might be necessary for durable control of leukemic stem cells after drug treatment. Improvements can occur in either arm. Reassessment after 20 years would therefore be of interest. In the meantime, transplant related mortality and morbidity and early years of life lost due to transplants justify a change in policy.

This prospective randomized comparison of primary HSCT versus best available drug treatment provides clear results. On the basis of up to 11 years of follow-up the general recommendation of HSCT for all patients as first line treatment in chronic phase CML can no longer be maintained. It should be replaced by a trial with modern drug treatment first. Exceptions may be patients’ preference, very low transplantation risk and economic reasons. HSCT is regarded as an important salvage therapy in patients without optimal response to drug therapy or in early relapse.
Conflict of interests statement: There are no conflicts of interests for any of the authors and study participants.

Authors’ contribution: All authors made a major contribution to this paper as follows, and have approved the submitted manuscript: RH wrote the paper and initiated the project. MP performed the final analyses and was supported by JH. All authors performed the trial, contributed the data, and commented on the manuscript. AG performed data checking and checking of preliminary analyses. AH, UB, AR, TL, OM collected the data and corresponded with the contributors.

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Reference List


Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: Eligibility for HSCT and related donor available (n=135) Median(range) or proportion (%)</th>
<th>Group 2: Eligibility for HSCT and no related donor available (n=219) Median(range) or proportion (%)</th>
<th>Group 3: No eligibility for HSCT (n=621*) Median(range) or proportion (%)</th>
<th>Total</th>
<th>Group 1 vs. group 2</th>
<th>Groups1 and 2* vs. group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>39 (11-59)</td>
<td>40 (14-58)</td>
<td>61 (25-90)</td>
<td>49 (11-90)</td>
<td>0.8004</td>
<td>&lt;0.0001</td>
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<tr>
<td>&lt; 20</td>
<td>3.7</td>
<td>4.1</td>
<td>0</td>
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<td>20-40</td>
<td>49.6</td>
<td>48.0</td>
<td>1.1</td>
<td>28.2</td>
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<td>&gt;40</td>
<td>46.7</td>
<td>48.0</td>
<td>98.9</td>
<td>69.6</td>
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<td>Prognostic score</td>
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<td></td>
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<td>0.3707</td>
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<tr>
<td>Low</td>
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<td>58.9</td>
<td>17.8</td>
<td>42.3</td>
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<tr>
<td>Intermediate</td>
<td>32.6</td>
<td>32.9</td>
<td>64.0</td>
<td>46.1</td>
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<tr>
<td>High</td>
<td>4.4</td>
<td>8.2</td>
<td>18.2</td>
<td>11.6</td>
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<td></td>
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<tr>
<td>Sex (% male)</td>
<td>60.7</td>
<td>62.1</td>
<td>56.6</td>
<td>59.6</td>
<td>0.7984</td>
<td>0.1921</td>
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<tr>
<td>Fatigue</td>
<td>44.4</td>
<td>47.5</td>
<td>51.5</td>
<td>48.6</td>
<td>0.5769</td>
<td>0.2031</td>
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<td>Symptoms due to organomegaly</td>
<td>23.7</td>
<td>24.7</td>
<td>15.2</td>
<td>20.3</td>
<td>0.8389</td>
<td>0.0059</td>
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<tr>
<td>Weight loss of more than 10%</td>
<td>14.1</td>
<td>13.3</td>
<td>18.9</td>
<td>15.8</td>
<td>0.8372</td>
<td>0.0678</td>
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<tr>
<td>Fever</td>
<td>6.7</td>
<td>6.4</td>
<td>3.8</td>
<td>5.3</td>
<td>0.9279</td>
<td>0.1405</td>
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<tr>
<td>Extramedullary manifestation</td>
<td>0.7</td>
<td>2.7</td>
<td>2.7</td>
<td>2.3</td>
<td>0.2589</td>
<td>0.5701</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.7 (6.8-16.5)</td>
<td>11.8 (7.2-16.0)</td>
<td>12.1 (5.1-18.8)</td>
<td>12.0 (5.1-18.8)</td>
<td>0.9889</td>
<td>0.0182</td>
</tr>
<tr>
<td>WBC count, x10^9/L</td>
<td>116 (4-560)</td>
<td>122 (1-560)</td>
<td>82 (4-650)</td>
<td>101 (1-650)</td>
<td>0.8735</td>
<td>&lt;0.0001</td>
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<td>PB eosinophils, %</td>
<td>2 (0-15)</td>
<td>2 (0-15)</td>
<td>2 (0-51)</td>
<td>2 (0-51)</td>
<td>0.2195</td>
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<td>PB basophils, %</td>
<td>3 (0-23)</td>
<td>3 (0-22)</td>
<td>3 (0-40)</td>
<td>3 (0-40)</td>
<td>0.1884</td>
<td>0.9597</td>
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<tr>
<td>PB blasts, %</td>
<td>1 (0-15)</td>
<td>1 (0-25)</td>
<td>1 (0-33)</td>
<td>1 (0-33)</td>
<td>0.7275</td>
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<td>BM blasts, %</td>
<td>3 (0-25)</td>
<td>2 (0-17)</td>
<td>2 (0-25)</td>
<td>3 (0-25)</td>
<td>0.3581</td>
<td>0.8913</td>
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<td>Platelet count, x10^9/L</td>
<td>409 (63-1880)</td>
<td>373 (90-2343)</td>
<td>371 (49-2694)</td>
<td>381 (49-2694)</td>
<td>0.8584</td>
<td>0.6325</td>
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</table>

* Including two patients eligible for HSCT but with missing data on availability of related donor. These patients are not part of groups 1, 2, and 3.
& The two eligible patients with missing data on availability of related donor are added to groups 1 and 2 for comparison with group 3.
PB=peripheral blood, BM=bone marrow
Table 2: Survival probabilities

<table>
<thead>
<tr>
<th></th>
<th>At diagnosis</th>
<th>After 2 years</th>
<th>After 5 years</th>
<th>After 8 years</th>
<th>After 10 years</th>
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<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>% [95% C.I.]*</td>
<td>n</td>
<td>% [95%-C.I.]</td>
</tr>
<tr>
<td><strong>Group1: Patients eligible for HSCT and related donor available</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>135</td>
<td>103</td>
<td>76[68; 83]</td>
<td>84</td>
<td>62[53; 70]</td>
</tr>
<tr>
<td>Low risk</td>
<td>85</td>
<td>66</td>
<td>78[67; 85]</td>
<td>58</td>
<td>68[57; 77]</td>
</tr>
<tr>
<td>“Non-low” risk</td>
<td>50</td>
<td>37</td>
<td>74[59; 84]</td>
<td>26</td>
<td>52[37; 65]</td>
</tr>
<tr>
<td><strong>Group2: Patients eligible for HSCT and no related donor available</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>219</td>
<td>130**</td>
<td>89[84; 93]</td>
<td>81</td>
<td>73[64; 79]</td>
</tr>
<tr>
<td>Low risk</td>
<td>129</td>
<td>81</td>
<td>93[87; 97]</td>
<td>54</td>
<td>85[75; 91]</td>
</tr>
<tr>
<td>“Non-low” risk</td>
<td>90</td>
<td>49</td>
<td>84[74; 90]</td>
<td>27</td>
<td>56[42; 68]</td>
</tr>
<tr>
<td><strong>Group3: Patients not eligible for HSCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>265†</td>
<td>241</td>
<td>91[87; 94]</td>
<td>152</td>
<td>60[54; 66]</td>
</tr>
<tr>
<td>Low risk</td>
<td>47</td>
<td>42</td>
<td>91[79; 97]</td>
<td>24</td>
<td>58[42; 71]</td>
</tr>
<tr>
<td>“Non-low” risk</td>
<td>217</td>
<td>198</td>
<td>91[87; 94]</td>
<td>128</td>
<td>61[54; 67]</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>621‡</td>
<td>476</td>
<td>87[84; 90]</td>
<td>317</td>
<td>64[59; 67]</td>
</tr>
<tr>
<td>Low risk</td>
<td>262</td>
<td>190</td>
<td>87[82; 91]</td>
<td>136</td>
<td>72[66; 78]</td>
</tr>
<tr>
<td>“Non-low” risk</td>
<td>358</td>
<td>285</td>
<td>87[83; 90]</td>
<td>181</td>
<td>58[53; 63]</td>
</tr>
</tbody>
</table>

*95% C.I.: 95% confidence interval.

#For one patient, the prognostic score was not available.

‡Additional to groups 1, 2, and 3, two patients eligible for HSCT were added for whom information on donor availability was missing.

#Between diagnosis and two years, reduction in patient number was mainly due to MUD transplants in first chronic phase.
Table 3: Causes of death

<table>
<thead>
<tr>
<th>Reported main cause</th>
<th>All patients (n=621, 318 died)</th>
<th>Eligible for HSCT (n=356, 154 died)*</th>
<th>Group 1: with related donor (n=135, 61 died)</th>
<th>Group 2a: without related donor, no transplant in chronic phase (n=122, 61 died)</th>
<th>Group 2b: without related donor, but MUD transplant in chronic phase (n=97, 30 died)</th>
<th>Group 3: not eligible for HSCT (n=265, 164 died)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blast crisis</td>
<td>135</td>
<td>50*</td>
<td>12</td>
<td>35</td>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>(42.5%)</td>
<td>(32.5%)</td>
<td>(19.7%)</td>
<td>(57.4%)</td>
<td>(6.7%)</td>
<td>(51.8%)</td>
</tr>
<tr>
<td>Transplant – related **</td>
<td>83</td>
<td>78</td>
<td>78</td>
<td>83</td>
<td>78</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>(26.1%)</td>
<td>(50.7%)</td>
<td>(50.7%)</td>
<td>(26.1%)</td>
<td>(50.7%)</td>
<td>(50.7%)</td>
</tr>
<tr>
<td>CML related other than blast crisis</td>
<td>40</td>
<td>10*</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>(12.6%)</td>
<td>(6.5%)</td>
<td>(6.6%)</td>
<td>(6.6%)</td>
<td>(6.6%)</td>
<td>(6.6%)</td>
</tr>
<tr>
<td>Not directly CML related***</td>
<td>56</td>
<td>16</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>(17.6%)</td>
<td>(10.4%)</td>
<td>(9.8%)</td>
<td>(11.5%)</td>
<td>(10.0%)</td>
<td>(24.4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(1.3%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(2.4%)</td>
</tr>
</tbody>
</table>

* For two patients, availability of a related donor remained unknown. Thus, the patients could not be classified into groups 1, 2a, or 2b.

** Transplanted in accelerated or blastic phase: group 1 (n=4), group 2a (n=15), group 2b (n=0), group 3 (n=1), all patients (n=20).

*** Not directly CML related causes of death were: organ failure (heart, kidney, liver, lung) (n=20), thromboembolism (n=9), other neoplasia (n=9), infection (n=8), suicide (n=4), other (accident, hemorrhage (2), aortic aneurysm, seizures, Creutzfeld-Jakob) (n=6).
Table 4: Current cytogenetic and molecular responses of patients of groups 1 (eligible for HSCT, donor available, n=113) and 2 (no related donor available, no MUD transplant in any phase, n=92) surviving at least 5 years.

<table>
<thead>
<tr>
<th></th>
<th>Group 1: Eligible for HSCT, related donor available (n=113)</th>
<th>Group 2: Eligible for HSCT, no related donor available, no MUD transplant (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow up (range), years</td>
<td>6.6 (4.1 – 10.8)</td>
<td>8.1 (4.6 – 10.0)</td>
</tr>
<tr>
<td>Evaluable for cytogenetic response</td>
<td>55 (49%)</td>
<td>52 (57%)</td>
</tr>
<tr>
<td>Median proportion of Ph+ metaphases</td>
<td>0 %</td>
<td>8 %</td>
</tr>
<tr>
<td>Complete cytogenetic response (Ph+ = 0%)</td>
<td>50 (91%)</td>
<td>25 (48%)</td>
</tr>
<tr>
<td>Major cytogenetic response (Ph+ &lt;35%)</td>
<td>50 (91%)</td>
<td>32 (61%)</td>
</tr>
<tr>
<td>Evaluable for molecular response</td>
<td>58 (51%)</td>
<td>40 (43%)</td>
</tr>
<tr>
<td>Median ratio BCR-ABL/ABL (%)</td>
<td>0</td>
<td>0.19</td>
</tr>
<tr>
<td>Undetectable BCR-ABL</td>
<td>42 (72%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Major molecular response (Ratio BCR-ABL/ABL &lt;0.1%)</td>
<td>47 (81%)</td>
<td>18 (45%)</td>
</tr>
</tbody>
</table>
Excluded (n=61);
Ph- and BCR-ABL negative CML (n=42),
not meeting inclusion criteria (n=19)

Assessed for eligibility to study (n=682)
Informed consent obtained

Stratification: Eligible for HSCT? (n=621)

Eligible for HSCT (n=356)

Genetic randomisation:
Related donor available? (n=354), unknown (n=2)

Yes

Allocated to HSCT with related donor (n=135), group 1
Allo-HSCT (n=123);
- in chronic phase (n=113)
- in accelerated or blastic phase (n=10)
- suicide before planned HSCT (n=12)
- blast crisis before planned HSCT (n=3)
- withdrawal of consent to HSCT (n=8)

No

Not eligible for HSCT (n=265), group 3

No eligible for HSCT

Best available drug treatment (n=219), group 2

Matched unrelated donor (MUD) available?

Yes

HSCT with MUD in chronic phase (n=97), group 2b

No HSCT with MUD in chronic phase (n=122), group 2a

HSCT with MUD in advanced phase due to failure of best available drug treatment, n= 27
No HSCT/best available drug treatment, n=95
Fig. 2a

Low risk (n=262, 60 died, m.s.: 9.6 years)

Intermediate risk (n=286, 133 died, m.s.: 6.9 years)

High risk (n=72, 43 died, m.s.: 5.0 years)

p=0.001
Fig. 2b

- Scores 0,1,2 (n=97, 28 died, 5-year surv. prob.: 0.76)
- Scores 3,4 (n=125, 59 died, 5-year surv. prob.: 0.54)
- Scores 5,6,7 (n=25, 18 died, 5-year surv. prob.: 0.26)

Probability of survival vs. Years after SCT

p < 0.001
Fig. 3

Probability of survival vs. Years after diagnosis for two groups:
- Dotted line: No Related donor available (n=219, 61 died, m.s.: 10.1 years)
- Solid line: Related donor available (n=135, 61 died, m.s.: not observed)

p = 0.049
Fig. 4b

- No Related donor available (n=90, 36 died, m.s.: 5.9 years)
- Related donor available (n=50, 28 died, m.s.: 6.1 years)

Years after diagnosis

Probability of survival
Legends to figures

Fig. 1: Flow diagram of enrollment, allocation, follow-up and analysis of patients.

Fig. 2: a) Survival of 620 registered Ph or BCR-ABL positive patients with CML in chronic phase categorized by risk profile at diagnosis (14). For one patient the prognostic score was not available. The survival times of patients who received an allogeneic transplant in first chronic phase were censored at the day of transplantation. The 620 patients were later stratified according to eligibility to receiving a transplant from a related donor. The survival differences between the three curves were significant (Log-rank test: p = 0.001). m.s.=median survival. The error bars signify 95% confidence intervals (19).

b) Survival of 247 patients who actually received an allogeneic transplant stratified for transplantation risk according to the EBMT-score (15). The survival differences between the three curves were significant (Log-rank test: p < 0.001).

Fig. 3: Survival of all 354 Ph- or BCR-ABL positive CML-patients that were eligible for transplantation and genetically randomized according to availability of a related donor. The survival times of patients who received an unrelated transplant in first chronic phase were censored at the day of transplantation. The survival differences were significant for the entire period and for the time until the curves converge (first cutpoint, year 8) (Wilcoxon-Gehan test: p = 0.049 and 0.041, respectively). For patients at risk see Table 2. m.s.=median survival. The error bars signify 95% confidence intervals (19).

Fig. 4: Survival of the 354 patients eligible for transplantation and genetically randomized according to risk profile a) low-risk and b) non-low-risk patients. The survival times of patients who received an unrelated transplant in first chronic phase were censored at the day of transplantation. The survival differences in the low-risk group were significant
for the entire period and for the time until the curves converge (first cutpoint at year 8) (Wilcoxon-Gehan test: p=0.032 and 0.027, respectively). For patients at risk see Table 2. m.s.=median survival. The error bars indicate 95% confidence intervals (19).
Drug treatment is superior to allografting as first line therapy in chronic myeloid leukemia

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