CLINICAL TRIALS AND OBSERVATIONS

Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: Results of the randomized CML-Study IV

Running Head: Negative impact of comorbidity on CML outcome

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*Equal contribution

**A complete list of the members of the German Chronic Myeloid Leukemia Study Group appears in the "Appendix."

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Key Points

- There is a strong negative association between comorbidities at diagnosis and overall survival
- There is no negative effect of comorbidities on remission rates and progression to advanced phases in CML

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Text 2462
Abstract

We studied the influence of comorbidities on remission rate and overall survival (OS) in patients with chronic myeloid leukemia (CML).

Participants of the CML-Study IV, a randomized five-arm trial designed to optimize imatinib therapy were analyzed for comorbidities at diagnosis using the Charlson Comorbidity Index (CCI).

511 indexed comorbidities were reported in 1519 CML patients. Age was an additional risk factor in 863 patients. Resulting CCI scores were: CCI 2: n=589, CCI 3 or 4: n=599, CCI 5 or 6: n=229, and CCI ≥ 7: n=102. No differences in cumulative incidences of accelerated phase, blast crisis, or remission rates were observed between patients in the different CCI groups. Higher CCI was significantly associated with lower OS probabilities. The 8-year OS probabilities were 93.6%, 89.4%, 77.6%, and 46.4%, for patients with CCI 2, 3-4, 5-6 and ≥ 7.

In multivariate analysis, CCI was the most powerful predictor of OS, which was still valid after removal of its age-related components.

Comorbidities have no impact on treatment success but do have a negative effect on OS indicating that survival of patients with CML is determined more by comorbidities than by CML itself. OS may therefore be inappropriate as outcome measure for specific CML treatments.

The study is registered at NIH, ClinicalTrials.gov: NCT00055874 (http://clinicaltrials.gov)
Introduction

Overall survival (OS) in patients with chronic myeloid leukemia (CML) under treatment with imatinib approaches 90% at 5 years and 88% at 8 years.\textsuperscript{1,2} Since the advent of second and third generation tyrosine kinase inhibitors (TKIs), faster and deeper remissions have been reported, including complete cytogenetic remission (CCyR), major molecular remission (MMR) and deep molecular response (MR\textsuperscript{4, MRR\textsuperscript{4,5}}).\textsuperscript{3-6} To date none of the clinical trials involving these new therapies have shown a convincing advantage in terms of OS, although the ENESTnd trial did demonstrate a favourable progression-free survival (PFS) in CML patients treated with nilotinib.\textsuperscript{7}

A number of different TKIs are now available, giving many treatment options for CML. After failure of one TKI a switch to a second or third line therapy is recommended\textsuperscript{8}. As a result, the influence of a certain TKI therapy on OS has become more difficult to assess.

Comorbidities are known to complicate longitudinal trials in diseases with expected long OS times e.g. in solid cancers such as breast cancer\textsuperscript{9} and in leukemia and related disorders\textsuperscript{10}. A tool to measure the influence of relevant comorbid diseases in terms of reduced life expectancies was introduced with the Charlson Comorbidity Index (CCI)\textsuperscript{11} which considers not only the presence but also the severity of the comorbid condition. The score is well established and validated.\textsuperscript{12} Comorbidities grouped according to the CCI have been shown to influence OS in patients with myelodysplastic syndrome or chronic lymphocytic leukemia (CLL).\textsuperscript{10,13,14}

The influence of comorbidities on outcome in CML patients has not been studied; comorbidities have only been taken into account when assessing the safety and suitability of different TKIs for CML patients.\textsuperscript{15-17}
We sought to identify the comorbidities in CML patients at diagnosis and to assess the influence of those comorbidities on OS and on remission rates. The Philadelphia chromosome and/or BCR-ABL-positive chronic-phase CML patients from the CML-Study IV\textsuperscript{1} were deemed to be specifically suited for this analysis because the trial was comprehensive with only few exclusion criteria with regard to comorbidities.
Patients and Methods:

Study design and goals: CML-Study IV is a five-arm randomized study comparing first-line imatinib 400 mg/d vs. imatinib 400 mg/d in combination with interferon-alpha (IFN) vs. imatinib 400 mg/d in combination with low-dose cytarabine (AraC) vs. imatinib 400 mg/d after IFN-failure vs. imatinib 800 mg/d. Recruitment was from July 2002 through March 2012. Only low- and intermediate-risk patients were assigned to primary IFN and, during a pilot-phase of 3 years, only high-risk patients were given imatinib 800 mg/d. In 2005, recruitment to imatinib+AraC and imatinib after IFN-failure was terminated and imatinib 800 mg/d was commenced as a full study arm. The first primary goal of CML-Study IV was to determine the impact of treatment on MMR status at 12 months. Other objectives were to assess remission rates and survival probabilities after transplantation. A further primary objective is a comparative survival analysis planned five years after completion of recruitment.

Exclusion criteria: Besides pre-treatment with IFN or chemotherapy other than hydroxyurea or anagrelide the exclusion criteria were defined as follows: i) second malignancy, if treatment was required and estimated life expectancy was shorter than the median survival of CML; ii) other serious illness; iii) pregnancy (including lactation period) or other conditions that could prevent compliance with the required protocol.

Treatment: Initial treatment in all study arms, except the arm imatinib after IFN-failure, was imatinib 400 mg once daily. If complete hematologic remission (CHR) was not reached after two months or if there was no partial cytogenetic remission after 6 months, a dose increase to 600 mg/d or 800 mg/d was recommended.

The full 800 mg/d dose was given after a 6-week run-in period with imatinib 400 mg/d to avoid excessive cytopenia. The dose could be reduced according to tolerability. Further details of the treatment protocol have been published elsewhere.
Definitions and endpoints: Definitions of CCyR and MMR followed the ELN recommendations.\textsuperscript{19,20} Risk assignment was done using the EUTOS-score criteria.\textsuperscript{21} The starting date for all time-to-event analyses was the date of diagnosis, except for time to adverse drug reactions where begin of imatinib treatment was the starting date. OS was defined as the time between diagnosis and death of any cause, whether the patient was on TKI treatment or not. All living patients were censored at the time of their last visit. When estimating the cumulative incidences of molecular or cytogenetic remissions, patients were censored when they received a 2nd-generation TKI or allogeneic stem cell transplantation. No patient was taken off the study, except at patient’s request (n=4).

Cytogenetic and molecular analyses: Cytogenetic analyses were performed as previously described.\textsuperscript{2} Follow-up analyses of CCyR included evaluation of at least 20 bone marrow metaphases. Molecular diagnostics for residual BCR-ABL transcripts followed the procedures and definitions of Hughes et al.\textsuperscript{22} and Cross et al.\textsuperscript{23} and were performed in standardized and accredited laboratories with defined conversion factors for equivalence of tests (Mannheim, Basel, Bern and MLL Munich).\textsuperscript{2,23}

Adverse events: Adverse events were reported at each follow-up visit according to the NCI common toxicity criteria (CTC) version 2.0. Severity grading was from grade 1 to 4. Evaluation focused on probably or definitely treatment-related events (adverse drug reactions or ADR) as determined by the investigators. For general safety analyses, patients were only counted if they had received imatinib as their first treatment and as long as they solely received imatinib. For comparisons, patients were only counted as long as they received the randomized treatment (as-treated-analysis).\textsuperscript{24}

Charlson Comorbidity index (CCI): The age-adjusted CCI is the most extensively studied comorbidity index\textsuperscript{11} and has been validated for long-term studies. Initially it was developed to predict the ten-year mortality for a patient who may have a range of comorbid conditions,
such as heart disease, acquired immunodeficiency syndrome, or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with the condition. Scores are summed to provide a total score to predict mortality. The index weights a) the severity of comorbidities (e.g. one point is allocated to myocardial infarction and diabetes, two points to non-active malignancies) and b) the age of patient (with one point for each decade above 40 years). The CCI at diagnosis was calculated for each randomized patient. Due to the presence of CML, the lowest possible score was two. For the purpose of analysis, patients were classified in CCI groups 2, 3-4, 5-6, and ≥7.

Karnofsky Performance Scale Index (KS) allows patients to be classified according to their functional impairment. The lower the KS, the worse is the survival for most serious illnesses. Patients were classified in groups according to their scores: group 1 50-80%, group 2 >80-<100%, group 3 100%.25

Statistical analysis: The chi-square test was used to assess the association between the KS groups and the CCI. OS probabilities were calculated using Kaplan-Meier curves. For the cumulative incidences of remission and progression to accelerated phase (AP) and blast crisis (BC), death without prior progression was considered as the competing risk.26 Cumulative incidence curves were compared using the Gray test.27 Cox models were estimated for the multivariate analysis. The prognostic significance of a candidate variable was assessed with the Wald test. When comparing BCR-ABL ratios above or below threshold at specific time points, the CHI-square test was used. The level of significance was set at 0.05. All calculations were performed with SAS software (SAS Institute, Cary, NC), besides the Gray test which was performed with R.

Ethics: The protocol followed the Declaration of Helsinki and was approved by the local ethics committees. Written informed consent was obtained from all patients before they entered the study.
Results:

Patients: Out of 1551 patients, 1519 patients were evaluable (see Fig 1). Median follow-up time was 67.5 months (data closing 24.05.2012), 612 (40.3%) patients had documented comorbidities, 384 (25.3%) with CCI relevant diseases. In these patients, 511 index comorbidities were reported. The most common CCI relevant comorbidities were diabetes mellitus (n=106), non-active cancer (n=102), chronic pulmonary disease (n=74), moderate to severe renal insufficiency (n=47), myocardial infarction (n=38), cerebrovascular disease (n=29), congestive heart failure (n=28), and peripheral vascular disease (n=28). Comorbidities not considered within the CCI were coronary heart disease/angina pectoris (n=68), arrhythmia (n=30), valvular disease (n=20), arterial hypertension (n=421), thrombosis/pulmonary embolism (n=32), thyroid dysfunction (n=98), acute pulmonary disease, gastrointestinal bleeding, inflammatory bowel disease, neurologic diseases except dementia and hemiplegia, hyperuricemia, benign tumor, anemia, inflammations like pancreatitis and acute infections, rheumatologic disease and coagulopathy.

In 863 patients, age lead to a higher CCI score, resulting in the following CCI groups: i) CCI 2: 589 patients, ii) CCI 3 or 4: 599 patients, iii) CCI 5 or 6: 229 patients, and iv) CCI \( \geq 7 \): 102 patients.

Patients’ characteristics according to CCI groups are shown in Table 1. Per definition age differed in the 4 groups. In concordance with previous reports the leukocyte count was highest in the younger patient group (CCI 2). The distribution of treatment arms was similar within each CCI group.

The distribution of patients to the CCI according to age groups is summarized in Table 2.

We found a positive correlation between the CCI and the KS (p<0.001).
Cytogenetic and molecular response according to the CCI:

No differences in remission rates were found between patients with CCI 2, 3-4, 5-6, or ≥ 7, neither for time to CCyR nor for time to MMR or to MR4.5. Median times to CCyR were 12.9, 12.6, 13.8, and 13.1 months, to MMR 17.6, 15.8, 15.7, and 19.6 months, and to MR4.5 4.5, 4.3, 5.0, and 7.0 years, respectively (Fig. 2A and B).

There was no statistically significant difference between the proportions of patients not achieving 10% BCR-ABL (IS) at 3 or 6 months according to the CCI groups.

Cumulative incidences for AP and BC, and OS:

No differences were observed between the CCI groups for the cumulative incidences of AP and BC (Fig 3).

For the total cohort causes of death were progression to AP or BC in 64 patients and not related to progression in 95 patients, The causes were different for the groups: In the group CCI 2, 16 patients died after progression to AP or BC and 13 patients without progression, in CCI 3, 29 and 23, in CCI 5-6, 10 and 33 and in CCI > 7, 9 and 33 patients, respectively.

Significant differences were observed for OS (s. Fig 4A, p<0.001). Probabilities of OS at 8 years for patients with CCI 2, 3-4, 5-6, and ≥7 were 93.6%, (95%- Confidence Interval (CI): [91.0-95.8%]), 89.3% (95%-CI: [86.0-92.1%]), 77.6% (95%-CI: [70.4-84.0%]), and 46.4% (95%-CI: [31.5-61.7%]), respectively.

Taking into account the comorbidities only and separating age from the score led to four different CCI-C groups: CCI-C 2 (n=1135), CCI-C 3 (n=182), CCI-C 4 (n=142) and CCI-C ≥ 5 (n=60). The significant differences for OS were still observed between the groups with increasing CCI counts (see Fig 4B, p<0.001).
Adverse drug reactions:

No significant differences in the probabilities of adverse drug-related events between CCI groups could be detected, neither hematological nor non-hematological (Table 4).

Multivariate analysis:

In a multivariate analysis including CCI, KS, and EUTOS Score, the CCI was the most powerful predictive factor for OS (Wald test, p<0.001, Table 3). Sex, leukocytes, and hemoglobin level had no significant influence. Hazard ratios for KS >80-<100% and 50-80% (each vs. 100%) were 1.563 (95%-confidence interval, (CI) 1.080-2.262, p=0.018) and 1.724 (CI 1.071-2.778, p=0.025), respectively and for EUTOS high risk vs. low risk 1.793 (CI 1.140–2.821, p=0.012). Replacing EUTOS by Sokal score gave similar results. Hazard ratios for the CCI group 3-4, 5-6, ≥7 (each vs. 2), were 1.695 (CI 1.066-2.695, p=0.026), 3.231 (CI 1.942-5.376, p<0.001) and 6.495 (CI 3.817-11.111, p<0.001), respectively. When the CCI was separated into an age-related component and a comorbidity-related component, the comorbidity-related component was still an important predictive factor for OS (Wald test, p=0.002).


Discussion

The most important finding of this analysis is the strong negative association between comorbidities at diagnosis and overall survival. Imatinib-treated CML patients in this analysis die of their comorbidities rather than of CML. The data show that patients with multiple comorbidities derived significant benefit from treatment with imatinib as there is no negative effect of comorbidities on remission rates and progression to advanced phases, but comorbidities do have an impact on overall survival. In fact, comorbid patients’ chances of achieving MMR and CCyR were similar to their more healthy counterparts without comorbidities. Our findings are in line with results in other hematologic and oncologic diseases with long-term outcomes e.g. in CLL or breast cancer. In a recent analysis of CLL patients, comorbidities are an independent prognostic parameter for PFS and OS. In contrast to our CML population, in CLL patients the major cause of death remained the disease itself even in patients with more than two comorbidities\(^\text{10}\). When separating the CCI in an age-related and a comorbidity-related component, the effect was still relevant without the age component. It turned out that age is not as much of a factor in remission rates as has been believed previously. This is in line with reports on the development of the EUTOS score. This score was designed to predict CCyR at 18 months and age had no influence on either the univariate or multivariate analysis\(^\text{21}\). In contrast in a new evaluation of the EUTOS population taking long-term survival as an endpoint, age played an important role.\(^\text{29,30}\) Within the last decade, CML has changed from a disease that was almost always fatal to a chronic condition maintained by regular drug therapy. The registration studies for TKIs, had more stringent exclusion criteria than CML-Study IV from which our cohort was taken and which most probably represented a more untypical CML population.\(^\text{3,4}\)

There are few limitations of this analysis. Although the recruitment to CML study IV had less exclusion criteria than other trials, patients with limited survival expectancies due to
comorbidities should not be randomized. Besides, clinical trial patients are usually younger and fitter. Furthermore, we cannot completely exclude underreporting of comorbidities. Therefore, the distribution of the CCI here is probably not fully representative of the distribution of the CCI in CML patients in routine care.

Since TKIs have reduced CML-related mortality so effectively, we also conclude that a sole unadjusted analysis of OS is no longer appropriate for assessing the efficacy of a new specific treatment for CML. An appropriate measurement seems to be progression-free survival, as this was at least in our cohort not influenced by comorbidities. There is a need for a consensus definition of surrogate endpoints in CML studies. We suggest that in future CML studies the analysis of OS should be stratified according to comorbidities – at least as part of an additional sensitivity analysis. For a valid comparative analysis and interpretation of OS between trials with CML patients, adjustment for comorbidity needs to be discussed.
Acknowledgements

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Thanks to the German Chronic Myeloid Leukemia Study Group for its participation in this study; a complete membership list appears in "Appendix."

Authorship

Contribution: S.S., M.-P.K. and M.C.M. had the primary responsibility for the publication.


Conflict-of-interest disclosure: S.S received honoraria from Pfizer, Novartis and Bristol Myers Squibb and received research funding by Bristol Myers Squibb and Novartis; R.H. received research funding by Bristol Myers Squibb and Novartis; S.W.K declares honoraria and research funding by Novartis; A.H. acted as a consultant for and received honoraria and research funding from Novartis, Bristol Myers Squibb, Pfizer and ARIAD, and received research funding by Novartis, Bristol Myers Squibb and Pfizer; M.C.M received honoraria
from ARIAD, Bristol Myers Squibb and Novartis and received research funding by Bristol Myers Squibb and Novartis. All other authors declare no competing financial interests.

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Appendix

Appendix: study group members
REFERENCES


Table 1

Characteristics of patients in the groups defined according to Charlson Comorbidity Index (CCI, n= 1519)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CCI 2 (n = 589)</th>
<th>CCI 3-4 (n=599)</th>
<th>CCI 5-6 (n=229)</th>
<th>CCI ≥ 7 (n=102)</th>
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<tbody>
<tr>
<td>Age, years</td>
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<td></td>
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<tr>
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<td>57</td>
<td>68</td>
<td>72</td>
</tr>
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<td>53-88</td>
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<td>Sex</td>
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<td>Female</td>
<td>206</td>
<td>258</td>
<td>96</td>
<td>42</td>
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<td>Hemoglobin, g/dL</td>
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<td>12.6</td>
<td>12.7</td>
<td>12.3</td>
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<tr>
<td>Range</td>
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<tr>
<td>Median</td>
<td>111</td>
<td>67</td>
<td>46</td>
<td>57</td>
</tr>
<tr>
<td>Range</td>
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<td>2.6-630</td>
<td>2.8-582</td>
<td>6.3-355</td>
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<tr>
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<tr>
<td>Range</td>
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<td>70-2337</td>
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<td>EUTOS Score</td>
<td></td>
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<tr>
<td>Low</td>
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<td>94</td>
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<tr>
<td>High</td>
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<td>Median time from</td>
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<td>66</td>
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<td>IM 400+IFN</td>
<td>163</td>
<td>28</td>
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<td>IM 400 + AraC</td>
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<td>10</td>
<td>76</td>
<td>13</td>
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<tr>
<td>IM 400 after IFN</td>
<td>49</td>
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<td>8</td>
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<tr>
<td>IM 800</td>
<td>173</td>
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<td>158</td>
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</table>

n; number of patients; WBC, white blood cells; IM400, imatinib 400 mg/d; IM800, imatinib 800 mg/d; IFN; Interferon alpha
Table 2

Assignment of patients to the CCI according to age.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>CCI 2</th>
<th>CCI 3-4</th>
<th>CCI 5-6</th>
<th>CCI ≥ 7</th>
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<td>≥ 80</td>
<td>18</td>
<td>4</td>
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Table 3

Results of the multivariate analysis; leukocytes, hemoglobin and sex without influence.
The Hazard ratio including the confidence intervals of tested category vs. the reference
category for the different variables are listed.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tested Category</th>
<th>Reference category</th>
<th>Hazard Ratio</th>
<th>Confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charson C. Index</td>
<td>3-4</td>
<td>2</td>
<td>1.695</td>
<td>1.066 – 2.695</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>5-6</td>
<td></td>
<td>3.231</td>
<td>1.942 – 5.376</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>≥7</td>
<td></td>
<td>6.495</td>
<td>3.817 – 11.111</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Karnofsky Score</td>
<td>&gt;80 – &lt;100%</td>
<td>100%</td>
<td>1.563</td>
<td>1.080 – 2.262</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>50 – 80%</td>
<td></td>
<td>1.724</td>
<td>1.071 – 2.778</td>
<td>0.025</td>
</tr>
<tr>
<td>EUTOS Score</td>
<td>high</td>
<td>low</td>
<td>1.793</td>
<td>1.140 – 2.821</td>
<td>0.012</td>
</tr>
</tbody>
</table>
Cumulative incidence of adverse drug related events (ADR) according to CCI; (A) any ADR grade 1-4; (B) non-hematological ADR grade 1-4. No significant differences were found.

<table>
<thead>
<tr>
<th>(A) Any non-hematological ADR</th>
<th>3-year cumulative incidence (95% CI)</th>
<th>5-year cumulative incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCI</td>
<td>3-year cumulative incidence (95% CI)</td>
<td>5-year cumulative incidence (95% CI)</td>
</tr>
<tr>
<td>2</td>
<td>59.9 (54.4-65.2)</td>
<td>63.7 (57.9-69.3)</td>
</tr>
<tr>
<td>3-4</td>
<td>62.8 (57.5-67.8)</td>
<td>69.4 (63.8-74.7)</td>
</tr>
<tr>
<td>5-6</td>
<td>52.4 (43.9-60.8)</td>
<td>58.7 (49.2-67.9)</td>
</tr>
<tr>
<td>7+</td>
<td>71.9 (58.5-83.6)</td>
<td>86.4 (69.8-96.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) Any ADR</th>
<th>3-year cumulative incidence (95% CI)</th>
<th>5-year cumulative incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCI</td>
<td>3-year cumulative incidence (95% CI)</td>
<td>5-year cumulative incidence (95% CI)</td>
</tr>
<tr>
<td>2</td>
<td>63.1 (57.8-68.2)</td>
<td>66.6 (61.0-71.9)</td>
</tr>
<tr>
<td>3-4</td>
<td>65.3 (60.2-70.2)</td>
<td>72.7 (67.2-77.9)</td>
</tr>
<tr>
<td>5-6</td>
<td>55.2 (46.9-63.4)</td>
<td>60.2 (51.0-69.0)</td>
</tr>
<tr>
<td>7+</td>
<td>71.9 (58.5-83.6)</td>
<td>86.4 (69.8-96.9)</td>
</tr>
</tbody>
</table>
Legends to figures:

Fig 1 Flow chart of patient disposition

Fig 2: Cumulative incidence of response according to Charlson Comorbidity Index (CCI) (A) of complete cytogenetic remission (CCyR); (B) of major molecular remission (MMR)

Fig 3: Cumulative incidence of accelerated phase (AP) and blast crisis (BC) according to CCI

Fig 4: Overall survival (OS) according to CCI (A) considering age; (B) without considering age
Figure 3

Cumulative incidence of AP/BC:

- CCI 7+, n=103, 8-year CI: 10%
- CCI 5–6, n=231, 8-year CI: 5%
- CCI 3–4, n=598, 8-year CI: 8%
- CCI 2, n=587, 8-year CI: 7%

Years after diagnosis
4A

Survival probability

CCI 7+, n=102, 8-year survival: 46%
CCI 5–6, n=229, 8-year survival: 78%
CCI 3–4, n=599, 8-year survival: 89%
CCI 2, n=589, 8-year survival: 94%

years after diagnosis

4B

Survival probability

CCI–C 5+, n=60, 8-year survival: 48%
CCI–C 4, n=142, 8-year survival: 75%
CCI–C 3, n=182, 8-year survival: 82%
CCI–C 2, n=1135, 8-year survival: 91%

years after diagnosis
Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: Results of the randomized CML-Study IV

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