Second generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia who have failed imatinib therapy

by Amr R. Ibrahim, Richard E. Clark, Tessa L. Holyoake, Jenny Byrne, Pat Shepherd, Jane F. Apperley, Dragana Milojkovic, Richard M. Szydlo, John M. Goldman, and David Marin

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Second generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukaemia who have failed imatinib therapy

Running title: 2G-TKI survival

Amr R. Ibrahim¹, Richard E. Clark², Tessa L. Holyoake³, Jenny Byrne⁴, Pat Shepherd⁵, Jane F. Apperley¹, Dragana Milojkovic¹, Richard Szydlo¹, John Goldman¹, and David Marin¹

¹Department of Haematology, Imperial College London, Hammersmith Hospital, UK;
²Department of Haematology, Royal Liverpool University Hospital, UK; ³Institute of Cancer Sciences, University of Glasgow, Glasgow; ⁴Nottingham University Hospitals Trust, and ⁵Department of Haematology, Western General Hospital, Edinburgh

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Correspondence
David Marin, Department of Haematology, Imperial College London, Du Cane Road, London W12 0NN, United Kingdom. Phone: international +44.20.83831627.
E-mail: d.marin@imperial.ac.uk
ABSTRACT

Background
It has not been clearly established whether second generation tyrosine kinase inhibitors actually improve the survival of chronic phase chronic myeloid leukaemia patients who fail imatinib and then receive nilotinib or dasatinib.

Design and Methods
To address this issue we compared the survival of 104 patients who failed imatinib as first line therapy and then were treated with second generation tyrosine kinase inhibitors with the outcome for 246 patients who had failed interferon-α therapy and did not receive tyrosine kinase inhibitor therapy.

Results
Patients treated with second generation tyrosine kinase inhibitors had longer overall survival than the interferon controls (adjusted Relative Risk= 0.28, p=0.0001). However this survival advantage was limited to the 64.4% of imatinib failure patients who achieved complete cytogenetic response with the subsequent tyrosine kinase inhibitor (adjusted Relative Risk =0.05, p=0.003), whereas the 35.6% of patients who failed to achieve complete cytogenetic response on the second or third inhibitor had similar overall survival to that of the controls (adjusted Relative Risk=0.76, p=0.65).

Conclusion
Patients who fail imatinib and receive sequential therapy with second generation tyrosine kinase inhibitors have an enormous advantage in survival over controls (palliative therapy); but this advantage is limited to the majority of the patients who achieve complete cytogenetic response.
INTRODUCTION
Imatinib is an extremely effective therapy for chronic myeloid leukaemia (CML) (1). Patients in chronic phase (CP) who achieve an optimal response may expect a normal life expectancy, (2) but not all patients achieve an adequate response or can tolerate imatinib. At 5 years approximately 40% of the patients have discontinued imatinib on account of an unsatisfactory response or toxicity (1). Patients who fail imatinib are often treated with second generation tyrosine kinase inhibitors (TKI) such as nilotinib or dasatinib. These drugs induce complete cytogenetic responses (CCyR) in approximately 50% of these patients, (3-7) but to date it is unclear whether the use of second generation TKI as second or third line therapy prolongs the survival of patients who have failed imatinib. This lack of evidence has allowed funding agencies in some countries to challenge the use of these drugs (8). In order to address this point we compared the survival of 283 patients who received imatinib as first line therapy (followed by second generation TKI in case of imatinib failure) in our institution with the outcome for 246 patients who had failed interferon-α therapy in the UK Medical Research Council’s (MRC) CML-III trial (9).

DESIGN & METHODS
TKI patients
Between June 2000 and September 2009 283 consecutive adult patients with BCR-ABL-positive CML in CP received imatinib 400 mg daily as first line therapy as described elsewhere (1). The study protocol was reviewed and approved by the local IRB committee and patients gave written informed consent to participate. The median follow up was 67.9 months (range 14-122). Of the 283 patients, 104 patients required second line therapy with dasatinib (n=67) or nilotinib (n=37) at some point after having failed (3) imatinib therapy. Dasatinib and nilotinib were administered as described elsewhere (3). Twenty-one patients who failed dasatinib or nilotinib second line were treated with the alternative TKI as previously described (10). Complete, partial (PCyR) and major (MCyR) cytogenetic responses were defined using standard criteria (1).
Control patients
Between September 1986 and April 1994, 587 patients with CML in CP were randomly allocated to receive either interferon-α or chemotherapy (busulfan or hydroxyurea) as maintenance therapy after initial induction treatment with chemotherapy as part of the UK Medical Research Council’s CML-III trial (9). 293 patients were allocated to the interferon-α arm, of whom 246 failed to respond to interferon-α at some stage as described elsewhere (11). Thus data on these 246 patients were eventually used for this study. After satisfying criteria for interferon-α failure 122 (49.6%) patients remained on interferon-α-containing regimens until disease progression, whereas 124 (50.4%) abandoned interferon-α therapy at some stage after failure; of these 117 (94.3%) were treated with hydroxyurea and 7 (5.7%) with busulfan. The median follow up was 50.4 months (range 2-202).

Statistical Methods
The probability of overall survival (OS) from the time point of diagnosis was calculated using the Kaplan-Meier method. Patients were censored at the time of allogeneic stem cell transplant (28 and 63 patients for the TKI and the control group respectively). Univariate analyses to identify prognostic factors for OS were carried out using the log-rank test. A Cox regression model of time to death was used to compare the outcome of the TKI and control group. In addition to the treatment group the model was adjusted for the independently significant variables shown in Table-1 (age at diagnosis and Sokal risk group). The influence of cytogenetic response on OS was studied in a time-dependent Cox model (also adjusted as described above).

RESULTS
Improved survival on TKI therapy is limited only to those patients who achieve CCyR on first or subsequent line of therapy
Table-1 shows the seven year probabilities of OS according to the characteristics of the patients. Unsurprisingly the 283 patients who received imatinib as first line therapy had an OS dramatically superior to that of the 246 interferon-α treated controls, (adjusted Relative Risk (aRR) =0.11, (p<0.0001).
Equally, the 179 (63.2%) patients who achieved and sustained CCyR on imatinib first line had an even greater advantage in OS over the interferon controls (aRR=0.02, 95CI= 0.002-0.126, p<0.0001).

The remaining 104 (36.8%) patients were deemed at some point to have failed imatinib (73 had primary cytogenetic resistance, 8 lost their CCyR and 23 were imatinib intolerant). These patients had an OS longer than the interferon failure control patients (aRR=0.28, 95CI=0.145-0.531, p=0.0001; Figure 1). Sixty-seven (64.4%) of the 104 patients who had failed imatinib achieved CCyR on second (n=49) or third (n=14) line therapy with another TKI. These patients also had an OS longer than the interferon controls (aRR=0.05, 95CI=0.007-0.36, p=0.003) and similar to the OS of imatinib responders; in contrast the 37 patients who failed to achieve CCyR on second or third line TKI therapy had an OS similar to that of the control patients (aRR=0.76, p=0.65); thus the survival benefit conferred by TKI therapy is limited to the majority of patients who achieve a sustained CCyR either on imatinib or on subsequent TKI therapy, while the patients who failed imatinib and then failed to achieve a CCyR with subsequent TKI(s) had a prognosis similar to the interferon-failure controls.

**PCyR does not confer survival advantage**

Fourteen (5.5%) of the 256 patients who achieved PCyR (≤35% Ph-positivity) on TKI therapy (either on first second or third line) failed to achieve CCyR (i.e. the response did not improve to CCyR). These 14 patients had significantly worse OS that the 242 patients who eventually achieved CCyR (aRR=6.64, 95CI=1.74-25.4, p=0.006), and an OS similar to that of the interferon failure controls (aRR=0.6, p=0.4), indicating that PCyR *per se* may not be an adequate therapeutic target.

**DISCUSSION**

The results of observational studies based on historical comparisons, such as the present study, have been regarded by some as intrinsically less reliable than results of randomized prospective studies. There is evidence however that the results obtained in well designed observational studies do not differ from those of randomized trials (12, 13) and there are circumstances when randomized prospective studies would be impossible to design or indeed unethical (11).
Moreover bias is not inevitable in observational studies if the prognostic factors used in the adjustment strongly predict the outcome (14, 15), and if physicians are prevented from selecting a preferred therapy, even inadvertently, for the patients with the poorest prognosis (12).

Our study appears to satisfy these three conditions: firstly, it is unlikely that a randomized trial involving the patients we have studied will ever be possible; secondly, the model was adjusted for strongly predictive factors; and thirdly, the clinicians had no opportunity to influence the treatment allocation. In other words, the MRC CML-III patients could only continue interferon or switch to palliative treatment since TKI were not available at the time and all later patients in our catchment area were treated with imatinib.

We used an adjusted Cox model to study a population of patients with CML in CP who received imatinib as first line therapy, and compared their outcome with that of a patient population treated originally with interferon-α and who eventually failed therapy but then continued treatment with interferon-α, hydroxyurea or occasionally busulfan. As this control population represents the outcome of CML patients treated with palliative therapy, it is not surprising that imatinib responders have a dramatically better outcome. Patients who fail imatinib and receive sequential therapy with TKI also have an enormous advantage in survival over these controls (aRR=0.28, p=0.0001, Figure-1), but we found that this survival advantage was limited only to those patients who achieved CCyR after imatinib failure, while the other patients had a prognosis identical to the controls. In other words patients who fail to achieve CCyR did not fare better than if they had been given palliative therapy. Therefore it is of paramount importance to ensure that patients who fail imatinib are treated subsequently with at least one other TKI and if necessary preferably with two TKIs.

**AUTHORSHIP AND DISCLOSURES:**
The authors do not have relevant conflicts of interest to disclose.
Amr R Ibrahim: collected patient data, performed statistical analysis and wrote the manuscript.
Richard Clark: provided patient care and commented on the manuscript.
Tessa L Holyoake: provided patient care and commented on the manuscript.
Jenny Byrne: provided patient care and commented on the manuscript.
Pat Shepherd: provided patient care and commented on the manuscript.
Jane F Apperley: provided patient care and commented on the manuscript.
Dragana Milojkovic: provided patient care and commented on the manuscript.
Richard Szydlo: reviewed the statistical analysis and commented on the manuscript.
John M Goldman: wrote the manuscript.
David Marin: designed the study, performed the statistical analysis, provided patient care and wrote the manuscript.

References


Table 1. Seven year probability of OS according to the patients’ characteristics.

<table>
<thead>
<tr>
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<th>Seven Year Probability of OS</th>
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<tr>
<td></td>
<td>Total population</td>
<td>Controls</td>
<td>imatinib first line</td>
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<td>p&lt;0.0001</td>
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* CE stands for additional cytogenetic abnormalities other than the Ph chromosome. Data was missing in 75 patients.

** Sokal risk group and the age at diagnosis were the only independent predictors for OS in the global population as well as in the separate cohorts of patients.
Figure 1. Adjusted probabilities of survival for imatinib failure patients and controls (panel A) and unadjusted probabilities of overall survival in the different patient groups (panel B).

Panel A shows the adjusted probabilities of OS for the 104 patients who failed imatinib and the 246 interferon failure controls (adjusted RR (aRR) = 0.28, 95CI=0.145-0.531, p=0.0001). The unadjusted probabilities of 7-year survival for both groups were 73.4 and 34.4% respectively.

Panel B shows the unadjusted 7-year probability of OS for the 246 interferon controls (34.4%), the 179 patients who achieved and sustained CCyR on imatinib (96.6%), the 67 patients who achieved CCyR on second line TKI therapy (100%) and the 37 patients who failed to achieve a satisfactory response on TKI therapy (30.2%). We also show the adjusted RR for OS with respect the interferon controls, see text.
Interferon controls, aRR=1

TKI non responders aRR= 0.76, p=0.65

Imatinib responders, aRR= 0.18, p<0.0001

2G-TKI responders, aRR=0.05, p=0.003

Time from diagnosis (years)

Probability of OS