Has the time for first-line treatment with second generation tyrosine kinase inhibitors in patients with chronic myelogenous leukemia already come? Systematic review and meta-analysis

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ABSTRACT

Second generation tyrosine kinase inhibitors have recently been introduced as first-line treatment for chronic phase chronic myelogenous leukemia. We aimed to evaluate the efficacy and safety of 2nd generation tyrosine kinase inhibitors *versus* imatinib as first-line treatment for these patients. We carried out a systematic review and meta-analysis of randomized controlled trials comparing 2nd generation tyrosine kinase inhibitors to imatinib as first-line treatment in chronic phase chronic myelogenous leukemia patients. Outcomes assessed were: complete cytogenetic response and major molecular response at 12, 18 and 24 months, all-cause mortality and progression to accelerated phase/blastic crisis at 12, 18 and 24 months, and chronic myelogenous leukemia related mortality and toxicity at last follow up. Relative risks were estimated and pooled using a fixed effect model. Our search yielded four trials including 2,120 patients. At 12 months, treatment with 2nd generation tyrosine kinase inhibitors significantly improved both complete cytogenetic response and major molecular response (relative risk 1.16, 95% CI: 1.09-1.23, and 1.68, 95% CI: 1.48-1.91, respectively). While major molecular response was improved at all time points, complete cytogenetic response improved at 18 months but not at 24 months. Importantly, rate of progression to accelerated phase/blastic crisis was significantly lower with the newer tyrosine kinase inhibitors throughout all time points. Second generation tyrosine kinase inhibitors improved chronic myelogenous leukemia related mortality without a statistically significant difference in all-cause mortality at 12, 18 and 24 months. We conclude that 2nd generation tyrosine kinase inhibitors can be added safely to the first-line treatment armamentarium of chronic phase chronic myelogenous leukemia patients. Although an advantage is suggested by surrogate parameters, longer follow up is necessary to see if this translates into superior overall survival.

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Introduction

Chronic myeloid leukemia (CML) is characterized by the presence of an aberrant gene, *BCR-ABL1*, which encodes for a constitutively activated tyrosine kinase.[1]

The prognosis of patients with newly diagnosed CML has been dramatically improved with the development of agents targeting the *BCR-ABL1* derived protein, i.e. tyrosine kinase inhibitors (TKIs).

The pivotal International Randomized Study of Interferon and STI571 (IRIS) established imatinib as first-line treatment in chronic phase (CP) CML.[2] It showed that 69% of patients given front-line imatinib treatment achieved complete cytogenetic response (CCyR) after 12 months of treatment, 57% of them also achieving a major molecular response (MMR). However, 7.9% progressed to accelerated phase (AP) or blastic crisis (BC).[2,3] At eight years, the event-free survival (EFS) (defined as time until the first occurrence of any of the following: death from any cause, progression to AP/BC, loss of a complete hematologic response or major cytogenetic response, or an increasing white cell count to over $20x10^9$/L) and projected overall survival (OS) were 81% and 85%, respectively.[4]

Despite the excellent results obtained in the IRIS trial, 40-45% of patients discontinue imatinib for various reasons. These include also unsatisfactory therapeutic outcomes in 16% of patients defined as failure to achieve response by a specific time point (i.e. complete hematologic response, CHR) at three months, or primary resistance, or the loss of initial response (e.g. loss of CCyR or secondary resistance).[5]

In addition, the results for high-risk CP-CML patients, based on prognostic scoring models[6,7] are less favorable, with estimated EFS of 67.3% compared to 90.8% for the low-risk patients.[8]

Second generation TKIs include nilotinib, dasatinib and bosutinib. Similar to imatinib, nilotinib binds an inactive conformation of *BCR–ABL1*, with a 30-50 fold increased binding affinity.[9] Dasatinib binds to a distinct, although overlapping,

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binding site within the ATP-binding pocket and is 325-fold more potent than imatinib.[10] Bosutinib binds to a conformation of ABL1 that is transitional between the active and inactive conformations and is approximately 25-fold more potent than imatinib *in vitro*.[11] Phase II clinical trials showed an advantage in 2nd generation TKIs when used as second-line treatment in patients with CP-CML.[12] These results in patients failing or intolerant to imatinib encouraged investigators to assess their role as first-line treatment in newly diagnosed CML patients. In prospective non-randomized phase II trials, these newer agents showed both earlier and higher rates of cytogenetic and molecular responses.[13,14]

These positive results led to the initiation of randomized controlled trials aiming to evaluate response rate and long-term outcomes of 2nd generation TKIs in comparison to imatinib as first-line treatment in patients with CP-CML.[15-19]

The aim of this systematic review and meta-analysis is to evaluate the efficacy and safety of 2nd generation TKIs as compared to imatinib for first-line treatment in CP-CML patients.

Design and Methods

Data sources

We searched PubMed (January 1966 to July 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) published in the Cochrane Library (June 2011), and the following conference proceedings for trials in hematology (2004 to 2011): Annual Meeting of the American Society of Hematology, European Group for Bone and Marrow Transplantation, Annual Meeting of the European Hematology Association (2006 to 2011), and the American Society of Clinical Oncology (2004 to 2011).

In addition, we searched databases of ongoing and unpublished trials: *http://www.controlled-trials.com*, *http://www.clinicaltrials.gov/ct* and *http://clinicaltrials.nci.nih.gov*. The search terms are described in the *Online Supplementary Appendix*.

For PubMed, we added the Cochrane highly sensitive search term for identification of clinical trials.[20] We scanned the references of all studies included and reviews identified for additional trials that did not come up in our search.

Inclusion criteria

We included all randomized controlled trials comparing 2nd and 3rd generation TKIs to imatinib as first-line treatment for newly diagnosed, previously untreated (except for treatment with hydroxyurea or anagrelide), CP-CML patients. The diagnosis of CML in the trials was based on cytogenetic and/or fluorescence *in situ* hybridization (FISH) and/or real-time polymerase chain reaction (RT-PCR) results. Patients were included irrespective of age or of risk based on prognostic score methods.[6,7]

We included trials regardless of publication status, date of publication or language. One author (RG) screened all references identified through our search strategy and references that could potentially fulfill inclusion criteria were drawn for further inspection. Two reviewers (RG, AG) independently inspected each of these abstracts and applied inclusion criteria. For articles that could possibly be relevant, or in the event of disagreement between the 2 reviewers, we obtained and independently inspected the full article.

Data extraction and risk of bias assessment

Two reviewers (RG, AG) independently extracted data from included trials. In the event of disagreement between them, a third reviewer (LV) extracted the data and agreement was reached by consensus. We contacted the authors of trials for missing data when necessary. The risk of bias of the included trials was independently evaluated by 2 reviewers (RG, AG). We individually assessed the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete reporting of outcome data, selective outcome reporting. Each domain was assessed separately and graded as low-risk for bias, unclear risk, or high-risk for bias according to the criteria specified in the Cochrane Handbook (version 5.1.0).[21]

Definition of outcomes

For the primary outcome, we chose both CCyR and MMR at 12 months. Secondary outcomes were CCyR at 18 and 24 months, MMR at 18 and 24 months, the rate of patients progressing to AP/BC at 12, 18 and 24 months, all-cause mortality at 12, 18 and 24 month, CML-related mortality at the end of follow up, and adverse events. Definitions of response criteria, i.e. CCyR and MMR, were based on the 2009 European Leukemia Network (ELN) recommendations.[12]

Data synthesis and analysis

For each trial, results were expressed as relative risks (RR) with 95% confidence intervals (CI) for dichotomous data.

We assessed heterogeneity using the I2 measure of inconsistency, which is more sensitive than the χ^2 test for detecting heterogeneity in a meta-analysis with a small number of trials. See further explanations on assessing heterogeneity in the *Online Supplementary Appendix*.

We conducted meta-analysis using a fixed-effect model that assumes a similar effect measure between studies and is appropriate when no significant clinical or statistical heterogeneity is present.[20,22] (Further details regarding this method are available in the *Online Supplementary Appendix*).

For CCyR and MMR, RR over 1 was in favor of the newer TKIs group. For progression to AP/BC, all-cause mortality, CML-related mortality and toxicity, and RR below 1 was in favor of the newer TKIs group.

For primary outcomes, we conducted an intention to treat (ITT) analysis according to allocated treatment, and a per protocol analysis to evaluate sensitivity. In an ITT analysis, each randomized patient is accounted for and analyzed in the allocated group (whether the patient received the treatment or not) whereas per protocol analysis includes only patients who actually received the therapy and were followed with surveillance cytogenetic and molecular analysis. ITT analysis might mask differences between interventions. Therefore, we also conducted a per protocol analysis. We performed a subgroup analysis of patients at high risk according to acceptable prognostic score methods, namely the Sokal or the Hasford scores, as reported for each trial.[6,7] Both prognostic scores are described in more detail in the *Online Supplementary Appendix*. Data analysis was performed using Review Manager software (RevMan), version 5.1 for Windows (the Cochrane Collaboration, London, UK).

Results

The computerized search strategy identified 82 articles, 22 of which were considered relevant for this review since they potentially fulfilled the inclusion criteria according to their abstract form, and the full text of these articles was retrieved. Of these, 19 articles were excluded for various

reasons: 13 were non-randomized controlled trials, and 6 were randomized controlled trials that did not assess the relevant clinical question. Two trials reported as abstracts from conferences were also included[15,18] (Figure 1). Of the five publications considered relevant for the meta-analysis, two reported different outcomes of the same trial. Therefore, four trials conducted between the years 2006 and 2009 fulfilled inclusion criteria; these trials included 2,120 patients.[15-19] Imatinib at a daily dose of 400 mg was compared with dasatinib in two trials,[16,18] with nilotinib[17,19] and with bosutinib in one trial each.[15]

Table 1 describes the characteristics of the included trials and assessment of risk of bias of the included trials according to the Cochrane Handbook (version 5.1.0).21

Primary outcomes - CCyR and MMR at 12 months

CCyR rate at 12 months was higher in patients allocated to the 2nd generation TKIs arm as compared to patients allocated to the imatinib arm (RR 1.16, 95% CI: 1.09-1.23, I2=49%, 2,113 patients (Figure 2), meaning 16% more randomized patients taking 2nd generation TKIs achieved CCyR compared to those taking imatinib. Results were similar applying a per protocol analysis (RR 1.18, 95% CI: 1.11-1.25, I2=0%), thus supporting the validity of the two analyses.

Subgroup analysis of patients with high-risk CML also showed superiority of the newer TKIs regarding CCyR at 12 months (RR 1.33, 95% CI: 1.11-1.60, I2=0%, 333 patients), meaning 33% more patients taking 2nd generation TKIs achieved CCyR compared to those taking imatinib.

Similarly, there was a statistically significant advantage for the newer TKIs in terms of MMR at 12 months (RR 1.68, 95% CI: 1.48-1.91, I2=17%, 2,113 patients), meaning 68% more patients taking 2nd generation TKIs achieved CCyR compared to those taking imatinib (Figure 3).

Secondary outcomes

Compared to imatinib, treatment with 2nd generation TKIs significantly improved CCyR rates at 18 months but not at 24 months, with a RR of 1.09 (95% CI: 1.03-1.14, I2=53%, 1,867 patients) and 1.04 (95% CI 0.99 to 1.09, I2=77%, 1867 patients), respectively (Figure 2). Conversely, MMR was statistically superior in the 2nd generation TKIs arm both at 18 and 24 months, with a RR of 1.43 (95% CI: 1.29-1.58, I2=57%, 1,867 patients) and 1.40 (95% CI: 1.28-1.54, I2=64%, 1,867 patients), respectively (Figure 3). The rate of progression to AP/BC was significantly lower with the newer TKIs as compared to imatinib at 12, 18 and 24 months, resulting in a RR of 0.32 (95% CI: 0.17-0.59, I2=0%, 2,110 patients), 0.32 (95% CI: 0.17-0.58, I2=52%, 1,864 patients) and 0.34 (95% CI: 0.19-0.61, I2=0%, 1,864 patients), respectively (Figure 4). The number needed to treat (NNT) to prevent one case of progression to AP/BC at 24 months was 33 (95% CI: 20-100).

There was no statistically significant difference between the two allocated groups in all-cause mortality rates at 12, 18 and 24 months: RR 0.76 (95% CI: 0.42-1.37, I2=47%, 2,113 patients), RR 0.69 (95% CI: 0.40-1.19, I2=66%, 1,864 patients), RR 0.73 (95% CI: 0.46-1.17, I2=0%, 1,864 patients, 70 deaths), respectively (Figure 5). The rate of CML-related mortality at the end of follow up (ranging between 12 to 24 months) was statistically significantly lower with the use of the newer TKIs as compared to imatinib (RR 0.58, 95% CI: 0.34-0.98, I2=0%, 2,113 patients).

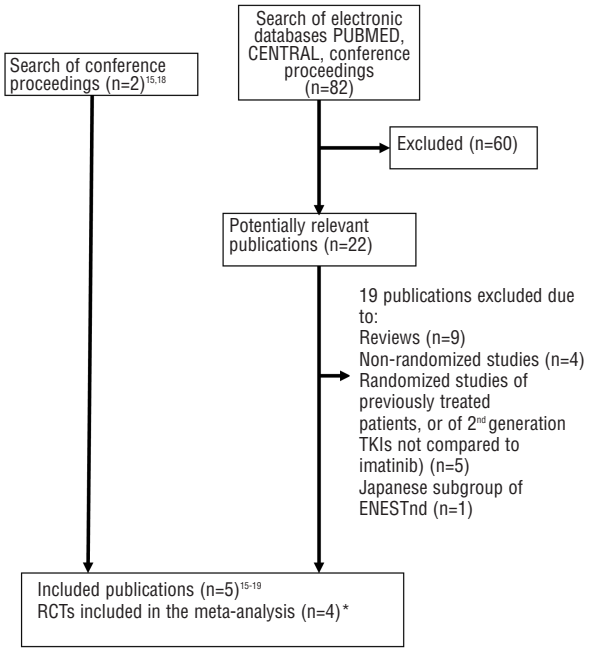

Figure 1. Trial flow according to PRISMA (Quality of Reporting Meta-Analysis): inclusion and exclusion criteria.

Assuming 2% CML-related mortality rate in the control arm (imatinib), we calculated a NNT of 100 (95% CI: 33-1,000), meaning 100 patients need to be treated in order to prevent one CML-related death.

Safety analysis

We could not perform a meta-analysis comparing adverse events between imatinib and the 2nd generation TKIs as there was clinical heterogeneity stemming from the fact that three different 2nd generation TKIs with different adverse event profiles were compared to imatinib. In three trials, there was no difference between the two arms in the number of adverse events requiring discontinuation of the TKIs,[16,18,19] while in one trial, assessing bosutinib, there were significantly more adverse events requiring discontinuation in the 2nd generation TKIs arm compared to imatinib, with a RR of 3.66 (95% CI: 2.03-6.59).[15] Notable non-hematologic adverse events reported included elevated liver function tests, bilirubin, lipase and glucose levels for nilotinib, pleural effusions for dasatinib, and diarrhea, vomiting and elevated liver function tests for bosutinib. As far as hematologic adverse events are concerned, two trials showed a higher rate of grade 3-4 neutropenia in the imatinib arm compared to the newer TKIs arm[15,19] while the other two trials (both comparing dasatinib to imatinib) showed no difference between the two arms.[16,18] The opposite trend was demonstrated with regard to grade 3-4 thrombocytopenia, with the two dasatinib trials demonstrating a higher rate of thrombocytopenia with the use of the newer TKIs,[16,18] and no difference in the other two trials.[15,19] There was no difference in the number of patients with grade 3-4 anemia between any of the trials.

Table 1. Characteristics of included trials.

	N. of high-risk patients*	Median age in years (range)	N. of patients randomized	Daily dose of TKI	Type of TKI	Risk of bias assessment: Allocation concealment (selection bias)	Sequence generation (selection bias)	Selective outcome reporting (reporting bias)	Incomplete outcome data (attrition bias)	Blinding of participants and personnel (performance bias) and blinding of outcome assessors (detection bias)	Allocation concealment (selection bias)	Sequence generation (selection bias)
Saglio *et al.*[17,19]	78 (27.6)	47 (18-85)	563	300/400 mg	nilotinib	Low risk (central randomization)	Low risk (using computer random number)	Low risk	Low risk	Unclear risk	Low risk (central randomization)	Low risk (using random number)
	78 (27.6)	46 (18-80)	283	400 mg	imatinib							
Kantarjian *et al.*[16]	49 (18.8)	46 (18-84)	260	100 mg	dasatinib	Low risk (central randomization)	Unclear risk	Low risk	Low risk	Unclear risk	Low risk (central randomization)	Unclear risk
	50 (19.2)	49 (18-78)	259	400 mg	imatinib							
Radich *et al.*[18]	39 (31)	48 (19-91)	126	100 mg	dasatinib	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
	33 (26)	51 (20-89)	127	400 mg	imatinib							
Gambacorti-Passerini *et al.*[15]												
	45 (18)	48 (19-91)	250	500 mg	bosutinib	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
	45 (18)	47 (18-89)	252	400 mg	imatinib							

**In two trials the risk groups were classified by Hasford prognostic model[16,18] and in two trials by Sokal prognostic score.[15,17,19]*

Discussion

Our systematic review and meta-analysis showed a significant advantage from 2nd generation TKIs, as compared to imatinib, in terms of CCyR and MMR at 12 and 18 months for first-line treatment of CP-CML patients. This benefit was maintained at 24 months for MMR, but not for CCyR. There was a statistically significant difference regarding progression to AP/BC at all time points in favor of the newer TKIs. However, no significant difference was found in all-cause mortality between imatinib and the newer TKIs, although CML-related mortality at the end of follow up was lower with the newer agents.

The up-dated 2009 ELN recommendations endorse the use of imatinib for first-line treatment in patients with CP-CML and the newer TKIs, dasatinib and nilotinib, are recommended only for second-line treatment in case of intolerance, suboptimal response or imatinib failure.[12] Recently, both drugs have been approved by the FDA for first-line treatment; these recommendations are under review and the updated guidelines are due soon.

We chose both CCyR and MMR at 12 months as primary outcomes since there is still a debate about which of them is the best surrogate for survival.[23-28] A 5-year analysis of the IRIS trial showed that patients who achieved CCyR and MMR at an earlier stage had a more favorable clinical outcome, mainly in terms of progression-free survival.[29] Also, according to the IRIS trial, none of the patients who achieved both CCyR and MMR at 12 months progressed to AP/BC.[3] Jabbour *et al.* have recently shown that achieving CCyR at three months in patients treated with 2nd generation TKIs is a surrogate marker for long-term outcome regardless of the achievement of MMR.[25] While Marin *et al.* have argued that reaching MMR at three months is the most important prognostic factor for event-free and overall survival.[27] Therefore, one can argue that early achievement of CCyR and/or MMR are harbingers for long-term outcome.[30] Nevertheless, the strength of the association between these surrogate markers and overall survival is variable and not unequivocal.[31] In our systematic review, the superiority of the newer TKIs was demonstrated in terms of both CCyR and MMR. Even so, advantage in CCyR was not maintained at 24 months. This might be attributed to the single trial comparing bosutinib to imatinib, probably due to a high drop-out rate in the bosutinib arm.[15] Alternatively, there might really be no difference at 24 months and a longer follow up is warranted to clarify this.

Although individual studies have shown higher rates of complete molecular response (CMR) with 2nd generation TKIs compared to imatinib, we did not have enough data to compare the depth of response between the two investigated groups. CMR could serve as a forerunner for *cure* and as a parameter allowing for TKI cessation. Interestingly, one study that applied a highly sensitive patient-specific nested quantitative PCR analyzing genomic DNA, provided evidence that even patients who maintained a CMR may harbor residual leukemia after stopping imatinib. Taken together, it is suggested that CMR and/or methods using genomic DNA analysis to monitor residual disease might serve in the future as a surrogate for clinical end points such as overall survival.[32]

The present meta-analysis showed a statistically significant advantage in terms of CCyR in favor of the newer TKIs also in patients with high-risk CML. Since, according to the IRIS trial, the risk of progression to AP/BC at five years is higher in this risk group than in the low-risk group (17% *versus* 3%, respectively), this finding might have practical implications for these patients.[29]

One interesting result is the fact that progression to

advanced stages (AP and BC) was halted by the newer TKIs with a NNT of 33. This is very significant in view of the dismal prognosis of patients proceeding to these stages, even in the era of TKIs.[33] Furthermore, analysis of CML-related mortality at the end of follow up (ranging between 12 and 24 months) showed a lower mortality in patients given the newer TKIs, with a NNT of 100.

Several other options have been studied for first-line treatment in CML. In a recent meta-analysis published by our group, we showed improved cytogenetic and molecular outcomes with higher doses of imatinib. Unlike the present meta-analysis, decreased CML-related mortality or lower incidence of progression to advanced stages could not be shown.[34] Alternatively, a combination of imatinib with another drug can be used. The combination of imatinib and interferon as first-line treatment in CML has been explored in two randomized trials: the French SPIRIT study and the CML study IV, as well as in a phase II study by the Nordic CML Study Group.[35-37] In general, the combination of standard dose imatinib with interferon was associated with better cytogenetic and molecular responses but with higher toxicity, with no advantage in terms of overall survival. Recently, a phase I trial of nilotinib in combination with low-dose interferon has been initiated

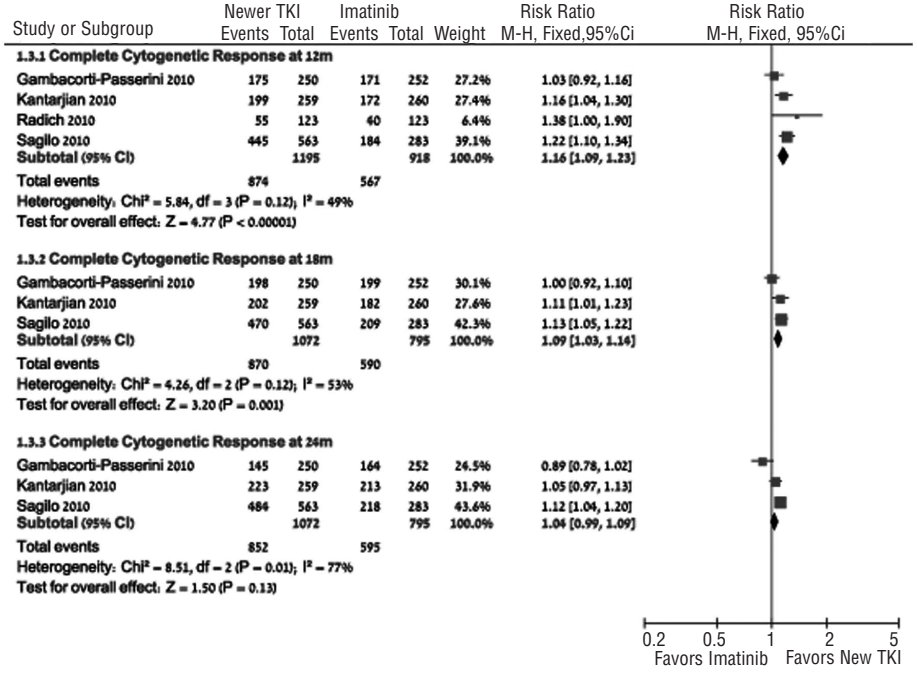

Figure 2. Imatinib *versus* 2nd generation TKIs: rate of patients who achieved complete cytogenetic response at 12, 18 and 24 months. Black squares represent the point estimate, their sizes represent their weight in the pooled analysis, and the horizontal bars represent the 95% CI. The black diamond at the bottom represents the pooled point estimate. CI: confidence interval; RR: relative risk; TKIs: tyrosine kinase inhibitors; m: months.

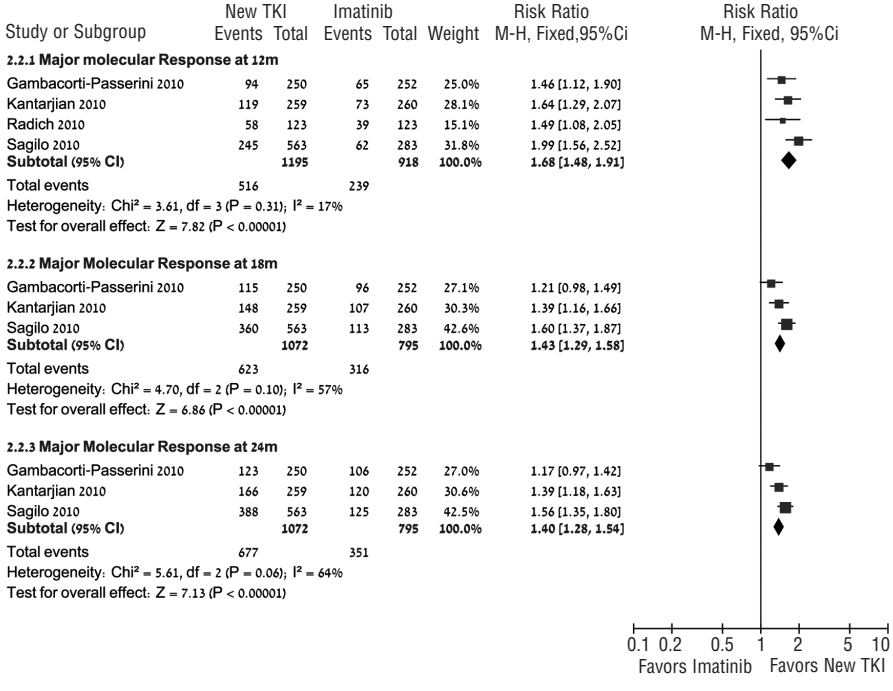

Figure 3. Imatinib *versus* 2nd generation TKIs: rate of patients who achieved major molecular response at 12, 18 and 24 months. Black squares represent the point estimate, their sizes represent their weight in the pooled analysis, and the horizontal bars represent the 95% CI. The black diamond at the bottom represents the pooled point estimate. CI: confidence interval; RR: relative risk; TKIs: tyrosine kinase inhibitors; m: months.

by the German CML Study V to determine the optimal interferon dose for this combination.

Another approach, examined by the Australian group in their Therapeutic Intensification in De Novo Leukemia (TIDEL) I and TIDEL II trials, is based on selective intensification. Patients not responding to an initial imatinib dose of 600 mg daily were switched to higher doses of imatinib in the TIDEL I trial[38] or either directly to nilotinib or to higher imatinib doses, and then if molecular targets were not reached, to nilotinib in the TIDEL II study.[39] Results from these trials showed that the TIDEL-II strategy using nilotinib has achieved a higher rate of MMR at 12 months compared to the strategy of imatinib intensification used in the TIDEL-I study.

Our meta-analysis has several limitations. The first is the small number of trials included and the limited sample size that did not allow differences in overall survival to be assessed (the most important outcome). Moderate heterogeneity was detected so heterogeneity stemmed from different magnitudes of the same effect and not from different directions of effects. Another limitation is the short-term follow up of the trials included. This might explain

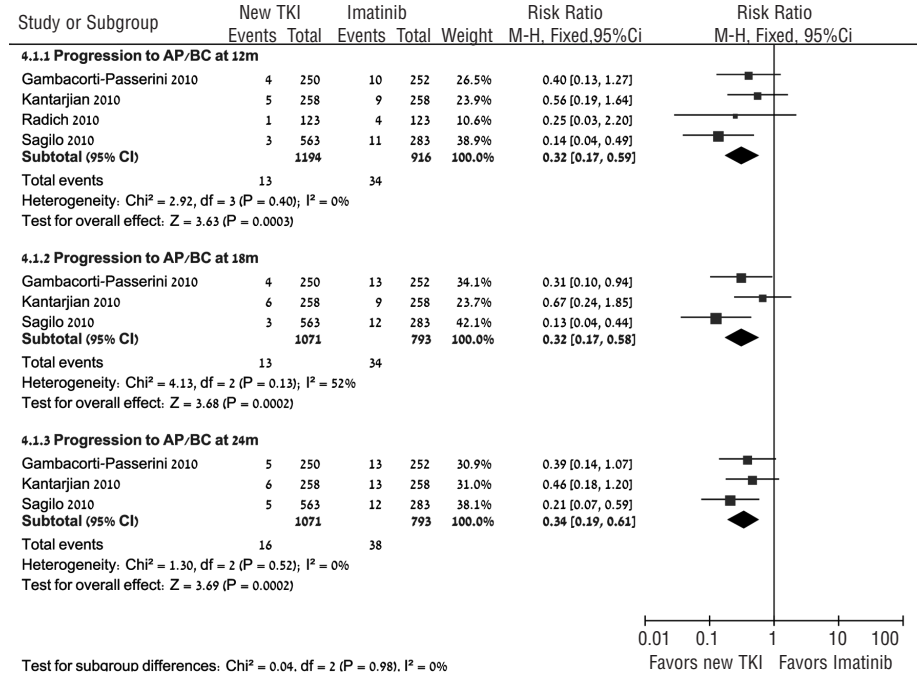

Figure 4. Imatinib *versus* 2nd generation TKIs: rate of patients who progressed to accelerated phase or blastic crisis at 12, 18 and 24 months. Black squares represent the point estimate, their sizes represent their weight in the pooled analysis, and the horizontal bars represent the 95% CI. The black diamond at the bottom represents the pooled point estimate. CI: confidence interval; RR: relative risk; TKIs: tyrosine kinase inhibitors; TKIs: tyrosine kinase inhibitors.

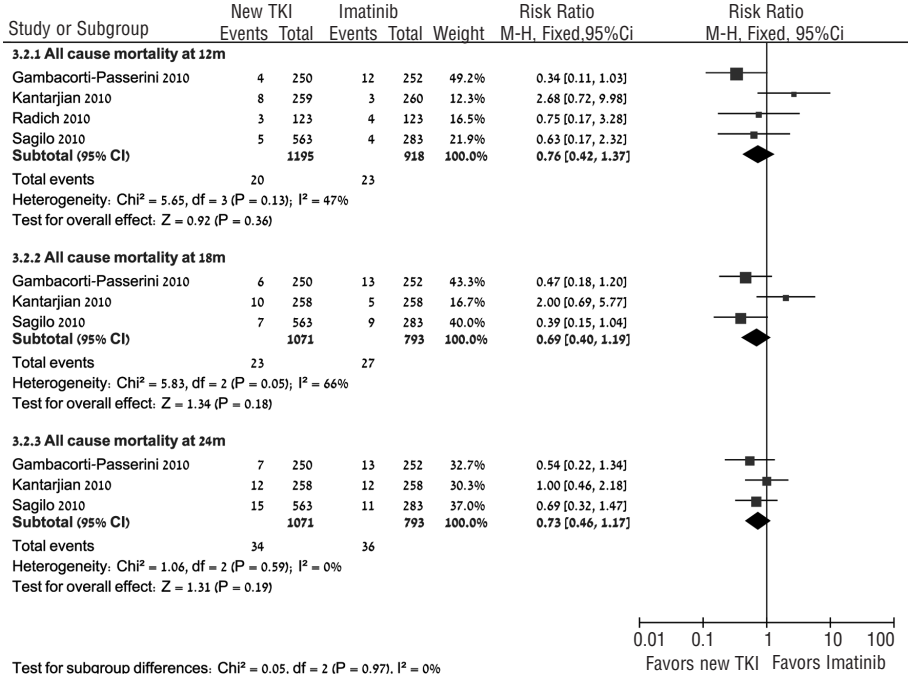

Figure 5. Imatinib *versus* 2nd generation TKIs: all cause mortality at 12, 18 and 24 months. Black squares represent the point estimate, their sizes represent their weight in the pooled analysis, and the horizontal bars represent the 95% CI. The black diamond at the bottom represents the pooled point estimate. CI: confidence interval; RR: relative risk; TKIs: tyrosine kinase inhibitors.

why no difference in survival was observed between the two arms, especially in view of the longevity of CML in the imatinib era.[8] Finally, lack of data meant that we could not compare the rates of *BCR-ABL1* mutations in the two arms. This important outcome might influence long-term clinical parameters. The only trial that reported the rates of BCR-ABL1 mutations was the ENESTnd trial which showed that there were more *BCR-ABL1* mutations in the imatinib arm compared to the nilotinib arm, with no difference in the number of T315I mutations between the treatment groups.[17,40] Interestingly, 65% of patients with mutations emerging on imatinib, had nilotinib-sensitive, imatinib-resistant mutations, while nilotinib was effective in preventing the emergence of clones with nilotinib-sensitive mutations, i.e. all mutations except for E255 K/V, E359 C/V, Y235H.

Longer follow up is needed to ascertain whether these results can be translated into greater longevity, and to identify which subgroup of patients might benefit most from their use upfront. Furthermore, prolonged follow up might resolve some of the safety issues concerning 2nd generation TKIs, including late adverse effects. Finally, differences between imatinib and the 2nd generation TKIs in terms of stable and lasting complete molecular remissions with sustained undetectable disease might become more distinct over time, thus allowing for a higher proportion of patients to stop treatment.

In conclusion, 2nd generation TKIs can be safely added to the first-line treatment armamentarium of CP-CML patients. Despite the fact that several surrogate parameters have suggested an advantage, the finding most pertinent to clinical practice and patient management is the significant reduction in progression to AP/BC and the decrease in CML-related mortality. Nevertheless, there are not sufficient data for us to replace imatinib with these agents across the board as front-line treatment in CML. Future trials should: i) compare the newer TKIs with high-dose imatinib as front-line treatment in newly diagnosed CP-CML patients; ii) examine the option of discontinuing TKIs after the achievement of complete molecular response; and iii) evaluate novel therapeutic strategies, such as combination or consecutive use of different TKIs, as well as combinations with agents which influence the quiescent stem cell compartment.[41]

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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