Comparative Effectiveness of Newer Tyrosine Kinase Inhibitors Versus Imatinib in the First-Line Treatment of Chronic-Phase Chronic Myeloid Leukemia Across Risk Groups: A Systematic Review and Meta-Analysis of Eight Randomized Trials

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Abstract

The goal of the present study was to compare the outcomes of new generation tyrosine kinase inhibitors (NG-TKIs) versus imatinib in patients with newly diagnosed chronic phase chronic myeloid leukemia and to assess the effect of the risk scores on the treatment response. NG-TKIs resulted in a greater major molecular response, and the degree of benefit from NG-TKIs on the complete cytogenetic response and major molecular response was equivalent across the risk groups.

Background: BCR-ABL1 tyrosine kinase inhibitors (TKIs) have significantly improved the survival outcomes for patients with chronic myeloid leukemia (CML). In addition to imatinib, 3 newer generation TKIs (NG-TKIs) have been approved as first-line treatment of chronic phase (CP)-CML. These have been preferably used in patients with CP-CML with a high Sokal or Hasford risk score. We performed a systematic review and meta-analysis to compare the outcomes with NG-TKIs as a category versus imatinib in patients with newly diagnosed CP-CML and to indirectly compare the efficacy of NG-TKIs among each other. Furthermore, we assessed the effect of the risk scores on the complete cytogenetic response (CCyR) and major molecular response (MMR). **Materials and Methods:** The eligible studies were limited to randomized controlled trials comparing the efficacy of first-line treatment using NG-TKIs versus imatinib in adult patients (aged $\geq$ 18 years) with CP-CML. **Results:** The differences in the CCyR, progression-free survival, and overall survival between the NG-TKIs and imatinib were not statistically significant. NG-TKI-treated patients showed a significantly greater likelihood of MMR (relative risk [RR], 0.76; 95% confidence interval, 0.63-0.91; $P = .003$) and lower likelihood of progression to an accelerated phase/blast crisis (RR, 0.37; 95% confidence interval, 0.20-0.67; $P = .001$) than did imatinib-treated patients. Nilotinib, dasatinib, and radotinib showed significantly greater CCyR rates compared with bosutinib and ponatinib. All risk groups showed statistically equivalent benefits from NG-TKIs for the CCyR and MMR. **Conclusion:** In first-line treatment, the NG-TKIs as a category showed greater effectiveness in MMR and prevention of accelerated phase/blast crisis progression. Risk stratification was not found to affect the RR of CCyR and MMR.

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Introduction

The BCR-ABL1 oncoprotein plays an essential role in chronic myeloid leukemia (CML) leukemogenesis.[1] Imatinib, which targets the ABL1 kinase domain, significantly improved the survival outcomes for patients with chronic phase (CP)-CML,[2,3] and subsequent newer generation tyrosine kinase inhibitors (NG-TKIs; nilotinib, dasatinib, bosutinib, ponatinib, and radotinib) demonstrated greater potency in newly developed and imatinib-resistant CML.[4-9] Among these, 3 NG-TKIs have been approved as first-line therapy for patients with CP-CML based on recent randomized trials that showed better cytogenetic and molecular responses compared with imatinib (nilotinib and dasatinib has been approved by the U.S. Food and Drug Administration [FDA], and radotinib by the Korea FDA).[10-12] The prognostic effect of a complete cytogenetic response (CCyR) and major molecular response (MMR) on survival outcomes in patients with CP-CML has been well studied in previous trials.[13-15] However, the variability in the CCyR and MMR to NG-TKIs seems to be significant, and no NG-TKI has demonstrated a clear survival advantage compared with imatinib.[10-12,16-20] Nilotinib or dasatinib has been preferably selected as the first-line agent for patients with CP-CML with high risk scores in the expectation of a deeper molecular response to minimize the risk of disease progression.[21,22] However, a paucity of data is available to support that the degree of benefit from first-line approved NG-TKIs compared imatinib in high-risk patients is greater than that in those with intermediate- or low-risk scores.

Therefore, we performed a systematic review and meta-analysis to compare the efficacy of NG-TKIs as a category versus imatinib in patients with CP-CML as first-line treatment and to indirectly compare the efficacy of NG-TKIs because no head-to-head or comprehensive multiagent comparison has been performed. Furthermore, we assessed the prognostic effect of risk stratification on the cytogenetic and molecular response outcomes. The primary outcomes of the present study included the CCyR and MMR rates at 12 months of TKI treatment. The secondary outcomes included progression to acute phase (AP)/blast crisis (BC), ABL1 kinase domain (KD) mutation, progression-free survival (PFS), and overall survival (OS) at 12 months.

Materials and Methods

Study Selection

The following criteria were used to select the eligible randomized controlled trials: (1) assessment of the efficacy of any NG-TKIs versus imatinib; (2) inclusion of adult patients aged $\geq$ 18 years with newly diagnosed CP-CML according to the European LeukemiaNet criteria[23] and naive to any TKI; (3) CCyR and/or MMR outcomes reported at 12 months of TKI treatment; and (4) published as peer-reviewed reports or abstracts.

Data Sources

The main key words for the literature search included CML, TKI, imatinib (Gleevec/Glivec or STI-571), nilotinib (Tasigna or AMN107), dasatinib (Sprycel or BMS-354825), bosutinib (Bosulif or SKI-606), ponatinib (Iclusig or AP24534), radotinib (Supect or IY5511), and randomized trial. Relevant studies were identified by searching PubMed, EMBASE, and the Cochrane Database of Systemic Reviews up to January 2016. A bibliography of the identified studies and additional reports from the references were further reviewed manually to identify any relevant studies.

Data Extraction and Risk of Bias Assessment

Two of us (S.Y. and J.M.S.) independently extracted data according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and conducted the risk of bias assessment using the Cochrane Collaboration tool. Any disagreement was resolved by consensus with another one of us (Y.D.) after group discussion and a full text review. The following information was extracted from the individual trials: journal of publication, publication year, clinical trial registration number, inclusion and exclusion criteria, sample size, median age, gender, previous systemic treatment, experimental and control TKI, risk stratification of study population (using the Hasford[24] or Sokal[25] risk score), treatment responses, survival outcomes, and median follow-up intervals. The statistical data extracted included the CCyR and MMR (using the definition from European LeukemiaNet[23]), progression to AP/BC, PFS, OS, ABL1 KD mutation, relative risk (RR), 95% confidence intervals (95% CIs), and P values. Additionally, any updated data were extracted from the abstracts (American Society of Hematology and American Society of Clinical Oncology) or ClinicalTrials.gov (https://clinicaltrials.gov/). The authors of each trial were interviewed for complementary information, if needed.

Outcomes

The primary outcome measures in the present study were the CCyR and MMR rates at 12 months of TKI treatment. The secondary outcomes included the PFS, OS, progression to AP/BC, and ABL1 KD mutation rates at 12 months of TKI treatment.

Statistical Analysis

Statistical analyses were performed as described in a previous meta-analysis.[26] In brief, we used RevMan, version 5.3 for Window, for the meta-analytic calculations. Cochran's Q statistic was used to estimate the total percentage of variation across each study due to heterogeneity rather than chance, and the I^2 statistic [$100\% \times (Q - df)/Q$] was used to quantify the heterogeneity.[27] The funnel plot method was applied to assess for publication bias. A 2-sided P value $< .05$ without correction for multiplicity was considered statistically significant in the RR analysis. We performed intention-to-treat analyses stratified by the allocated TKI treatments for the primary and secondary outcomes. A meta-regression model was used to assess the statistical significance of the RR differences between the subgroups.

Results

Search Results

Our initial literature search yielded a total of 184 relevant abstracts. Of the 184 studies, 143 were excluded as being irrelevant according to the abstract review, and the full text of 41 studies was assessed. Of the 41 studies, 13 imatinib studies, 2 retrospective studies, and 3 meta-analyses were excluded. Also, 4 studies of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia and 11 duplicates or follow-up studies were excluded. After a careful eligibility review, 8 randomized controlled trials (2 of