SYSTEMATIC REVIEW OF TYROSINE KINASE INHIBITORS (TKI) FOR THE TREATMENT OF CHRONIC MYELOID LEUKEMIA (CML) AND PHILADELPHIA-CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (PH+ ALL) WITH RESISTANCE TO AT LEAST ONE PRIOR TKI

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Former systematic reviews of TKI either did not distinguish between patients resistant or intolerant to prior TKI therapy or were limited to RCT or single outcomes of interest.
Methods: We compared efficacy and safety of TKI in CML and Ph+ ALL patients resistant to ≥1 prior TKI. Cochrane Library, EMBASE and MEDLINE database were searched from inception to May 2019 for randomized controlled, single-arm or observational trials enrolling ≥10 patients per treatment arm. Event proportions were meta-analyzed using a random-effects model. Subgroup analyses considered follow-up duration, T315I mutation, disease phase and therapy line.
Main results: Almost 2,000 patients from 30 publications reporting results on 26 studies were analyzed, with sample sizes ranging from 10 to >200 patients and median follow-up durations from 8-84 months. T315I mutation status and mortality in Ph+ ALL patients each were reported in only two trials. In CML patients, mortality and major molecular response (MMR) were similar. Based on a Bayesian approach, CTCAE grade 3/4 occurred in 67% of patients (95%-CI [0.48; 0.81]) and were comparable between bosutinib, dasatinib, nilotinib and ponatinib, while AE occurred less frequently under imatinib therapy.
Conclusion: The efficacy and safety of currently approved TKI in patients resistant to ≥1 prior TKI seem to be comparable. The low level of evidence of the available studies and the inadequate reporting were striking. The latter might improve with the implementation of the new European Medicines Agency registry. However, the performance of comparative RCT remains the responsibility of the regulatory authorities and pharmaceutical manufacturers.