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## CHANGING IMAGE OF TKIS: ORIGINAL, BIOSIMILAR AND GENERIC OPTIONS

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BCR-ABL is a 210 kDa protein that is required for the proliferation of CML-specific myeloid cells and has sustained kinase activity. Kinase activity provides uncontrolled signal transduction related to cell proliferation, apoptosis and adhesion. Although there are many tyrosine kinase enzymes, imatinib is especially effective on ABL, c-kit and PDGF-R-dependent tyrosine kinases. The advantage of TKI is that it inhibits more than one receptor and therefore the possibility of signaling is increased. Another advantage is that these compounds offer ease of use to patients since they are used orally. In general, TKIs are well tolerated in clinical practice compared to the toxicity of cytostatic drugs. Side effects are usually mild (grade 2 and lower) and occur early in treatment. Due to the emergence of imatinib resistance and intolerance, second generation TKIs were developed (Dasatinib, Nilotinib and Bosutinib). In nonclinical models, they are 30 to 300 times more potent than Imatinib and can inhibit most imatinib-resistant BCR-ABL mutations. Patients with the T315I mutation respond only to treatment with the third-generation TKI Ponatinib. The crystal form of a drug's active ingredient may cause differences in solubility, stability, density, melting point, processability. The original imatinib is produced in b-crystalline form, generics are mostly in crystalline form and have been observed to be less stable at room temperature than the b-form. Several in vitro and in vivo studies comparing the pharmacological properties of the reference molecule and generics have proven that both forms are equivalent. The high financial burden of these treatments can be a serious problem for both patients and patients. With the emergence of generic imatinib, the reimbursement policies of many countries have changed and generic drugs have become an alternative treatment option for CML patients. In addition to their possible positive effects, there are concerns about these drugs, including bioequivalence, efficiency, effectiveness, safety, tolerability, adherence, permanence and healthcare costs, due to the use of generic imatinib in healthcare systems. In many countries other than the USA and in Turkey, CML patients can access more than one generic imatinib, and this competitive environment generally results in significant cost reductions. In general, the efficacy and safety profiles of generic and original imatinib were found to be similar in almost all studies. In light of these results, it is possible to say that generic drugs have a generally manageable toxicity profile and are not inferior to the original molecule in terms of effectiveness. Two pharmaceutical equivalent or pharmaceutical alternative drugs containing the same active ingredient in the same molar dose are considered bioequivalent if their bioavailability (rate and degree of absorption) is within predetermined acceptance limits. Generic pharmaceutical products are placed on the market if they are therapeutically equivalent to the reference product containing the same active substance in the same molar dose. Considering the data in the literature, both in vitro and in vivo studies have shown that generic drugs are comparable to the original imatinib in terms of bioequivalence and bioavailability. In most studies, generic drugs have shown similar results in terms of efficacy and safety, both in newly diagnosed patients and after switching from the original.

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## OPTIMIZATION OF TKI SELECTION IN CML: BALANCING EFFICACY, SAFETY, AND PATIENT PREFERENCES

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The long-term results from key studies such as ENESTnd, DASISION, and BFORE have helped guide first-line treatment decisions in chronic myeloid leukemia (CML). These studies compare the efficacy of different TKIs, including imatinib, dasatinib, and nilotinib, showing the potential benefits of second-generation TKIs in achieving deeper and faster molecular responses. Early molecular response (EMR) is a crucial prognostic factor, as patients who achieve EMR are more likely to have better long-term outcomes. Risk scores such as Sokal, EUTOS, and ELTS play a role in determining the appropriate first-line TKI, with higher-risk patients potentially benefiting from second-generation TKIs due to their more aggressive nature. Second-generation TKIs, including nilotinib, dasatinib, and bosutinib, offer enhanced potency over imatinib but come with distinct safety profiles. Nilotinib has demonstrated superior efficacy in terms of molecular response, but it is associated with cardiovascular risks, including QT prolongation. Dasatinib, while effective in achieving rapid molecular responses, can lead to pulmonary complications like pleural effusion. Bosutinib, which is less commonly used, has a more favorable gastrointestinal side effect profile but may have less activity in some resistant CML cases. Management of cardiovascular, pulmonary, and metabolic side effects is crucial in selecting the appropriate TKI for each patient, particularly for those at higher risk of cardiovascular or pulmonary issues. TKI resistance, primarily due to BCR-ABL1 kinase domain mutations, presents a challenge in CML treatment. Mutations such as T315I are particularly problematic as they confer resistance to most TKIs. Ponatinib, a third-line treatment, is highly effective against T315I and other mutations, but it carries significant cardiovascular risks, necessitating careful monitoring. Asciminib, a newer drug that targets BCR-ABL1 through allosteric inhibition, offers a promising alternative for patients with resistance to other TKIs, as it bypasses common mutations like T315I and is associated with a different side-effect profile. Off-target inhibition of kinases by TKIs is a significant contributor to their side-effect profiles. For instance, nilotinib has been linked to glucose metabolism disturbances, leading to hyperglycemia, whereas dasatinib may cause pulmonary hypertension due to PDGFR inhibition.