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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.

Understanding these molecular mechanisms helps in managing side effects and improving patient outcomes. Monitoring for these adverse effects and adjusting treatment accordingly is essential to minimize long-term toxicity while maintaining treatment efficacy. The concept of TFR, where patients discontinue TKI therapy after achieving sustained molecular remission, is gaining ground. Studies such as EURO-SKI, ENESTfreedom, and DASFREE have demonstrated that certain patients can safely stop treatment without relapse, provided they remain MRD-negative. Selecting the right candidates for TFR is critical, and patients must be closely monitored for minimal residual disease (MRD). Even after discontinuation, immunological changes and potential relapse mechanisms must be carefully tracked. In special populations such as pregnant women, pediatric patients, and the elderly, TKI therapy requires careful consideration. TKIs are contraindicated in pregnancy due to potential teratogenic effects, and fertility preservation options should be discussed with male patients. In pediatric CML patients, concerns about growth and development arise, and TKI dosing must be adjusted for optimal treatment without affecting growth. Elderly patients or those with comorbidities may require lower doses and closer monitoring to minimize toxicity while ensuring adequate therapeutic effects. This summary highlights key aspects of TKI therapy in CML, including treatment selection, resistance mechanisms, side effects, treatment discontinuation strategies, and considerations for special populations. Each of these factors plays a significant role in optimizing treatment and improving patient outcomes.

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THE EVOLVING ROLE OF PROTEASOME INHIBITORS IN CANCER TREATMENT

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Recent developments in tumor immunology have led to a shift from chemotherapy to targeted therapy, focusing on blocking the pathways that drive cancer. An important aspect of this approach is the personalization of treatment, as the same cancer can present different immunopathologies in different individuals. Genetic mutations or variations in gene expression serve as determinants for identifying molecules that should be targeted in treatment. This has given rise to the concept of personalized therapy. One of the key therapeutic pathways is the proteasome system. This system is essentially a circular enzyme system that helps eliminate substances that may pose a threat to the cell. Its primary role is to process and degrade intracellular antigens and present them to CD8 T lymphocytes, in conjunction with the Major Histocompatibility Complex (MHC I) and Class II genes. The proteasome system carries out this function with the help of the endoplasmic reticulum (ER) and autophagy. Proteins that are continuously produced in the body are corrected within the ER if they misfold, in order to prevent potential antigenic properties. If the amount of misfolded proteins in the ER increases, it overwhelms the ER's capacity, resulting in a condition known as ER stress. In this case, the misfolded proteins are sent to the proteasome system for degradation, or alternatively, the autophagic pathway is activated through the enzyme Beclin to eliminate these faulty proteins. These mechanisms are essential for maintaining cellular integrity and survival. This survival strategy applies not only to healthy cells but also to cancer cells. In fact, proteasome inhibition is increasingly being used in the treatment of various cancers, including Multiple Myeloma. When the proteasome system is inhibited, cancer cells are unable to eliminate toxic or misfolded substances, leading them toward apoptosis. Proteasome inhibition can occur at different levels within the body and is not limited to the nucleus. Different proteasomes are responsible for degrading different substances. Thus, rather than aiming to completely eliminate the proteasome system, future cancer treatments are focusing on the selective inhibition of specific proteasomes. Research is ongoing in this direction, with the goal of developing more targeted and effective therapies for cancer.

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IMPROVING TREATMENT OPTIONS IN POLYCYTHEMIA VERA: FROM INTERFERON TO NEW AGENTS

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Polycythemia Vera (PV) is a chronic myeloproliferative neoplasm characterized by the overproduction of red blood cells, often accompanied by increased white blood cells and platelets. The disease is primarily driven by mutations in the Janus kinase 2 (JAK2) gene, specifically the JAK2 V617F mutation, which is present in approximately 95% of patients. The clinical presentation of PV includes a range of symptoms that significantly impact the quality of life (QoL) of affected individuals. Common symptoms include fatigue, pruritus, headaches, and visual disturbances, which are often attributed to the hyper viscosity of the blood resulting from increased red blood cell mass. The diagnosis of PV is based on the World Health Organization (WHO) criteria, which include elevated hemoglobin or hematocrit levels, the presence of the JAK2 mutation, and evidence of bone marrow hypercellularity. Diagnostic challenges may arise due to overlapping features with other myeloproliferative neoplasms, necessitating comprehensive blood evaluations and sometimes bone marrow biopsies. The disease is associated with a significant risk of thrombotic events, including stroke and myocardial infarction, which can occur in up to 26% of patients. Furthermore, the risk of transformation to more severe forms of hematological malignancies, such as acute myeloid leukemia (AML) or myelofibrosis, is notable, with studies indicating a