

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