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

transformation rate of approximately 10% over a 20-year period. Management of PV focuses on reducing the risk of thrombotic complications and alleviating symptoms. Phlebotomy is often the first-line treatment to reduce hematocrit levels, particularly in patients with high thrombotic risk. In cases where phlebotomy is insufficient or not tolerated, cytoreductive therapies, such as hydroxyurea, are commonly employed. However, approximately 25% of patients may experience inadequate responses or unacceptable side effects from hydroxyurea, necessitating alternative treatments. Ruxolitinib, a JAK2 inhibitor, has emerged as a promising option for patients who do not respond adequately to conventional therapies, demonstrating efficacy in reducing splenomegaly and symptom burden. In conclusion, PV is a complex hematological disorder with significant clinical implications. Early diagnosis and appropriate management are crucial to mitigate the risks associated with the disease. Ongoing research into novel therapeutic agents and treatment strategies continues to enhance our understanding and management of this condition, ultimately aiming to improve patient outcomes and QoL.

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TREATMENT OF MYELOFIBROSIS: PRESENT AND FUTURE

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Primary myelofibrosis (PMF) is a myeloproliferative neoplasm characterised by stem cell-derived clonal myeloproliferation often, but not always, accompanied by JAK2, CALR or MPL mutations. It is associated with bone marrow reticulin/collagen fibrosis, abnormal inflammatory cytokine expression, anaemia, hepatosplenomegaly, extramedullary haematopoiesis (EMH), constitutional symptoms, cachexia, risk of leukaemic transformation and shortened survival. Somatic mutations in MPN are classified as 'driver' and 'other' mutations. Driver mutations are JAK2, CALR and MPL, other mutations are ASXL1, SRSF2, U2AF1, IDH1/2, SF3B1, TET-2, DNMTA3A. SRSF2, ASXL1, and U2AF1-Q157 mutations indicate poor prognosis in PMF. RAS/CBL mutations predict resistance to ruxolitinib treatment. Type 1/like CALR mutation is associated with better survival. The hallmark of MF is the disruption of the JAK/STAT signalling pathway. **TREATMENT** In the treatment approach, allogeneic stem cell transplantation (ASCT) should first be positioned as a priority option. Then, treatment should be planned according to risk stratification for the control of anaemia and improvement of splenomegaly and related symptoms. The recommended treatment strategy is what we call risk-adaptive treatment, which is treatment according to risk groups and symptoms/symptoms. The general approach is observation in low-risk asymptomatic patients, treatment selection according to symptoms (constitutional findings, splenomegaly, anaemia) in the medium and low risk group, stem cell transplant-based treatment in the high risk group. If additional risk factors are present in the intermediate risk group, ASCT should be considered as an alternative and a patient-based approach should be taken as basis. In the absence of symptomatic splenomegaly, non-JAK inhibitor drugs may be preferred as first-line treatment for anaemia. Androgens, prednisone (can be used in addition to androgen therapy or alone), danazol, thymodomide, lenalidomide, erythropoiesis-stimulating agents (ESAs) can be used. Although luspatercept is approved for the treatment of anaemia associated with beta thalassaemia and low/intermediate risk MDS, it has been largely ineffective in MF patients. Response rates to each of these drugs range between 15-25%. In the 2nd step, JAK inhibitors, especially momelotinib and pacritinib, can be considered. These drugs exhibit erythropoietic activity as well as favourable effects on splenomegaly and systemic symptoms. Among the available JAKi, Momelotinib shows activity against all three major complications in MF, including anaemia, splenomegaly and constitutional symptoms. Ruxolitinib (RUX) is the first oral JAK1-2 inhibitor. It received FDA approval in 2011. Long-term data from the COMFORT-I/II studies showed a 30 per cent mortality reduction in intermediate-2/high-risk patients compared to the control group. COMFORT-I and II analyses found that a reduction in spleen size with ruxolitinib treatment correlated with longer survival. Fedratinib (FEDR) received FDA approval in 2019. In the JAKARTA study, FEDR was reported to significantly prolong patients' prognosis compared with placebo. Fedratinib is a treatment option for the treatment of symptoms and splenomegaly or for patients who are resistant or intolerant to ruxolitinib. It includes a warning regarding the potential risk of serious encephalopathy, including Wernicke's encephalopathy. Pacritinib is a selective JAK 2 inhibitor. It received FDA approval in 2022 in moderate-to-high patients. Momelotinib received FDA approval in 2023. JAK1, JAK2 and ACVR1 inhibitor; targets symptoms, splenomegaly and anaemia. The new therapies, complementary or independent with JAK inhibitors, aim to improve patients' responses and quality of life, going beyond current treatment limitations with a focus on improving anaemia, thrombocytopenia and fibrosis, with an impact on overall survival. One future combination appears to be Pelabresib + Ruxolitinib. In the MANIFEST II study, the $_{SVR35}$ response at week 24 was significantly higher in patients assigned to pelabresib+ruxolitinib compared to ruxolitinib alone (66% vs. 35%). At Week 24, at least one degree of improvement in bone marrow fibrosis was seen in 24.2% of patients who received ruxolitinib alone and 38.5% of patients who received pelabresib+ruxolitinib.In conclusion, PELA+RUX shows the potential to improve the four key features of MF with a significant reduction in splenomegaly, improvement in symptom score, improvement in anaemia and reduction in bone marrow (BM) fibrosis at Week 24.

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