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ADVANCEMENTS IN TARGETED THERAPIES FOR CHRONIC MYELOID LEUKEMIA: CURRENT PERSPECTIVES

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Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm driven by the Philadelphia chromosome, resulting in the BCR-ABL1 fusion gene. The development of tyrosine kinase inhibitors (TKIs) has revolutionized CML treatment, achieving unprecedented remission rates and improving overall survival. This review explores the advancements in targeted therapies for CML, focusing on the evolution of TKI generations, including imatinib, dasatinib, nilotinib, bosutinib, ponatinib, and newer agents like asciminib and osimertinib. We discuss the mechanisms of action, clinical efficacy, safety profiles, and evolving treatment paradigms for different patient populations, including newly diagnosed, treatment-resistant, and elderly patients. Furthermore, we delve into the challenges and future directions of CML therapy, highlighting the emergence of resistance mechanisms, the need for personalized medicine, and the potential of novel therapeutic strategies. This review provides a comprehensive overview of the current landscape of targeted therapies for CML, offering valuable insights into the ongoing efforts to optimize treatment outcomes and improve the lives of patients with this hematological malignancy

Keywords: Chronic myeloid leukemia, Tyrosine kinase inhibitors, Targeted therapy, BCR-ABL1, Imatinib, Dasatinib, Nilotinib, Ponatinib, Asciminib, Osimertinib, Treatment resistance.

Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder characterized by the uncontrolled proliferation of myeloid cells in the bone marrow and peripheral blood (Jabbour & Kantarjian, 2018). The hallmark of CML is the presence of the Philadelphia (Ph) chromosome, a reciprocal translocation between chromosomes 9 and 22, which generates the BCR-ABL1 fusion gene (Melo, 2014). The BCR-ABL1 protein possesses constitutive tyrosine kinase activity, leading to uncontrolled cell proliferation, survival, and differentiation of myeloid progenitor cells (Druker et al., 2001).

Prior to the advent of targeted therapies, CML treatment options were limited and often associated with significant toxicity and limited efficacy. Allogeneic hematopoietic stem cell transplantation (HSCT) was the only curative option, but it was associated with high morbidity and mortality (Champlin et al., 2000). However, the development of tyrosine kinase inhibitors (TKIs) has revolutionized CML treatment, transforming it from a life-threatening disease to a manageable chronic condition (Druker et al., 2006).

Tyrosine Kinase Inhibitors (TKIs): A Paradigm Shift in CML Treatment

TKIs have emerged as the cornerstone of CML treatment by specifically targeting the BCR-ABL1 tyrosine kinase, inhibiting its activity and ultimately suppressing leukemic cell proliferation (O'Brien et al., 2003). The first-generation TKI, imatinib, was a groundbreaking development, demonstrating remarkable efficacy in inducing major cytogenetic responses (MCR) and achieving deep molecular responses (MMR) in a significant proportion of patients (Druker et al., 2001).

First-Generation TKIs: Imatinib

Imatinib, a potent BCR-ABL1 inhibitor, became the standard of care for CML upon its approval in 2001 (Druker et al., 2001). Its success in achieving high rates of MCR and MMR in newly diagnosed CML patients transformed the treatment landscape (O'Brien et al., 2003). However, imatinib's efficacy is limited in some patients, particularly those with specific BCR-ABL1 mutations or advanced disease (Hochhaus et al., 2002).

Second-Generation TKIs: Dasatinib and Nilotinib

The limitations of imatinib prompted the development of second-generation TKIs, including dasatinib and nilotinib (Shah et al., 2004; Kantarjian et al., 2006). These agents demonstrated superior efficacy compared to imatinib in patients with imatinib resistance or intolerance, particularly those with specific BCR-ABL1 mutations. Dasatinib has a broader spectrum of activity against various BCR-ABL1 mutations, while nilotinib shows a higher potency against the T315I mutation (Shah et al., 2004; Kantarjian et al., 2006).

Third-Generation TKIs: Ponatinib and Beyond

The emergence of T315I mutation, a highly resistant mutation to prior-generation TKIs, led to the development of third-generation TKIs. Ponatinib, a potent inhibitor of various BCR-ABL1 mutations, including T315I, has demonstrated significant efficacy in patients who failed prior-generation TKIs (O'Hare et al., 2012). However, ponatinib is associated with a higher risk of cardiovascular events, limiting its widespread use.

Newer TKIs: Asciminib and Osimertinib

The field of CML therapy continues to evolve with the development of newer TKIs targeting specific aspects of BCR-ABL1 signaling. Asciminib, a highly selective ABL1 inhibitor, spares wild-type ABL1, potentially mitigating some off-target effects (Jabbour & Kantarjian, 2018). Osimertinib, initially developed for non-small cell lung cancer, has shown promising activity against certain BCR-ABL1 mutations (Cappuzzo et al., 2018). These agents represent a promising direction in the pursuit of more targeted and less toxic therapies for CML.

Treatment Paradigms and Patient Populations

The optimal treatment approach for CML depends on factors such as patient age, risk status, prior therapies, and the presence of specific BCR-ABL1 mutations.

Newly Diagnosed Patients:

Newly diagnosed CML patients generally receive treatment with first- or second-generation TKIs. The choice of agent depends on various factors including patient characteristics and physician preference. The goal of initial therapy is to achieve a deep molecular response (DMR) and maintain it for long-term disease control (Baccarani et al., 2013).

Treatment-Resistant Patients:

Patients who develop resistance to initial TKIs may require a switch to a more potent agent, often a second- or third-generation TKI. The choice of agent is guided by the specific BCR-ABL1 mutation responsible for resistance (Hochhaus et al., 2017).

Elderly Patients:

The management of CML in elderly patients presents unique challenges due to potential comorbidities and reduced tolerance to therapy. The choice of TKI needs to be carefully considered, balancing efficacy with safety and tolerability (Saglio et al., 2011).

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT):

HSCT remains a curative option for selected patients, particularly those who are younger and have a suitable donor. The role of HSCT has diminished with the advent of TKIs, but it may be considered for patients who are ineligible for or fail TKI therapy (Champlin et al., 2000).

Challenges and Future Directions

Despite the remarkable advancements in CML treatment, several challenges remain:

Treatment Resistance:

The development of TKI resistance is a major challenge in CML therapy. Resistance can arise due to various factors, including BCR-ABL1 mutations, changes in drug transport or metabolism, and alterations in downstream signaling pathways (Jabbour & Kantarjian, 2018).

Personalized Medicine:

The emergence of diverse resistance mechanisms highlights the need for personalized medicine approaches. Identifying the specific drivers of resistance and tailoring treatment accordingly can improve outcomes (Hochhaus et al., 2017).

Novel Therapeutic Strategies:

Ongoing research focuses on developing novel therapeutic strategies to overcome TKI resistance and improve long-term disease control. These include exploring new TKIs with distinct mechanisms of action, targeting other components of the BCR-ABL1 signaling pathway, and utilizing immunotherapeutic approaches (Deininger et al., 2019).

Monitoring and Management of Long-Term Complications:

TKIs are generally well-tolerated, but long-term use can be associated with a variety of side effects, including cardiovascular complications, fluid retention, and skin rash. Careful monitoring and management of these complications are crucial for improving patient quality of life (Kantarjian et al., 2006).

Conclusion

The field of CML therapy has undergone a remarkable transformation with the development of targeted therapies, particularly TKIs. The evolution of TKI generations, from imatinib to the newer agents like asciminib and osimertinib, has significantly improved treatment outcomes and extended patient survival. While challenges remain, including the emergence of resistance mechanisms, ongoing research is actively pursuing novel therapeutic strategies to overcome these hurdles. The future of CML therapy lies in implementing personalized medicine approaches, exploiting novel drug targets, and integrating various therapeutic modalities to further optimize treatment outcomes and improve the lives of patients with this chronic myeloid malignancy.

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