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Genomics of Chronic Myeloid Leukemia (CML): Treatment Benefits and Future of Gene Therapy

Forat Jafar Ali Alkholeef [1],Ghadeer Abdullah Hassan Almustafa[1], Shatha Shabour Ahmad Alzaher[1], Ahmed Ali Alhamadah[2], Shereen Ali Buhalal[2], Haleema Saleh Alhazzom[3], Mahdi Saleh Ali Almarzooq [4], Ruqiyah Shafiq Baban[5], Ali Abdulmohsen Alobaid[6], Rabab Habib Almasoud [2], Abdulmonem Ahmed Albeladi[6], Taher Habib Almohaimeed[6], Haya Abdulhay Al Abdulhay[2], Kaltham Abdulhamid Ali Alomran[7], Adnan Abdulhamid Alomran[2]

1. Dammam primary healthcare centers
2.Prince saud ben jalawi hospital
3.Shaikh Hassan AlAfaleq Long-term Care hospital
4.Al jafr General Hospital in Alahsa
5.Eradah Complex for Mental Health Dammam
6.AL OMRAN GENERAL HOSPITAL
7.Maternity and Children's Hospital

ABSTRACT

Chronic Myeloid Leukemia (CML) is a hematological malignancy driven primarily by the BCR-ABL1 fusion gene, resulting from the translocation between chromosomes 9 and 22 (the Philadelphia chromosome). Advances in genomics have revolutionized CML management, with tyrosine kinase inhibitors (TKIs) offering remarkable clinical outcomes. This review explores the genomic underpinnings of CML, the benefits of current TKI-based treatments, and the potential role of gene therapy in shaping the future of personalized CML care. Emphasis is placed on novel gene-editing tools like CRISPR-Cas9 and their promise in eradicating leukemic stem cells and achieving treatment-free remission (TFR).
KEY WORDS
CHRONIC, ABL, CART CELL

1. Introduction

Chronic MyeloId Leukemia accounts for 15-20% of adult leukemias and has long been considered a model disease for targeted therapy due to its well-defined genetic hallmark, the BCR-ABL1 fusion gene. The advent of TKIs such as imatinib, dasatinib, and nilotinib has significantly improved survival rates and quality of life for patients. However, challenges such as drug resistance, persistence of leukemic stem cells, and lifelong dependency on medication necessitate the exploration of alternative therapies, particularly gene therapy(1).

2. Genomics of CML

2.1. The BCR-ABL1 Fusion Gene

The Philadelphia chromosome results in the formation of the BCR-ABL1 oncogene, which encodes a constitutively active tyrosine kinase responsible for uncontrolled cell proliferation and impaired apoptosis in hematopoietic stem cells. This genetic alteration is the primary driver of CML and the target of TKI therapy.

2.2. Secondary Mutations

Resistance to TKIs often arises from secondary mutations within the ABL1 kinase domain, such as the T315I mutation, which reduces drug binding affinity. Understanding these mutations through next-generation sequencing (NGS) is critical for guiding therapy choices(2).

2.3. Genomic Heterogeneity

While the BCR-ABL1 gene is central to CML, additional mutations in genes such as ASXL1, RUNX1, and DNMT3A contribute to disease progression, particularly in advanced phases (accelerated and blast crisis). Comprehensive genomic profiling can aid in risk stratification and personalized treatment approaches(3).

3. Current Treatment Strategies

3.1. Tyrosine Kinase Inhibitors (TKIs)

TKIs have transformed CML from a fatal disease into a manageable chronic condition.

- **First-Generation TKIs:** Imatinib, the first FDA-approved TKI, targets the ATP-binding site of the BCR-ABL1 protein, inhibiting its kinase activity.
- **Second- and Third-Generation TKIs:** Dasatinib, nilotinib, bosutinib, and ponatinib address resistance to imatinib and improve outcomes in patients with high-risk mutation(4).

3.2. Challenges with TKIs

Despite their efficacy, TKIs are not curative due to the persistence of quiescent leukemic stem cells, which evade therapy. Additionally, long-term TKI use is associated with adverse effects, financial burden, and decreased patient adherence.

4. Benefits of Genomic Insights in CML Treatment

4.1. Personalized Medicine

Genomic profiling allows for tailored treatment strategies, ensuring that patients receive the most effective TKI based on their mutation status.

4.2. Treatment-Free Remission (TFR)

Approximately 40-50% of patients achieve TFR after sustained deep molecular response (DMR) to TKIs. Genomic monitoring helps identify candidates for TFR and track minimal residual disease (MRD) (5).

5. Future of Gene Therapy in CML

5.1. Gene Editing with CRISPR-Cas9

CRISPR-Cas9 technology offers the potential to directly target and disrupt the BCR-ABL1 fusion gene in leukemic cells. Recent studies have demonstrated its ability to induce apoptosis in CML cells while sparing normal hematopoietic cells (6).

5.2. Eradication of Leukemic Stem Cells

Gene-editing tools can be used to modify signaling pathways and eliminate quiescent leukemic stem cells, overcoming one of the major limitations of TKI therapy.

5.3. RNA-Based Therapies

RNA interference (RNAi) and antisense oligonucleotides can silence the expression of BCR-ABL1 and other oncogenes involved in CML pathogenesis.

5.4. CAR-T Cell Therapy

Chimeric antigen receptor T-cell (CAR-T) therapy, while primarily used in acute leukemias, is being explored as a potential approach to target CML stem cells and achieve durable remission(7).

5.5. Gene Therapy Challenges

The implementation of gene therapy faces several obstacles, including:

- **Off-Target Effects:** CRISPR-Cas9 can inadvertently edit non-target genes, leading to unintended consequences.
- **Delivery Mechanisms:** Efficiently delivering gene-editing tools to hematopoietic stem cells remains a challenge.
- **Cost and Accessibility:** Gene therapy is currently expensive and may not be accessible to all patients.

6. Conclusion

Genomic advancements have significantly enhanced our understanding and treatment of CML, with TKIs offering unprecedented benefits in terms of survival and quality of life. However, the challenges of drug resistance and persistent leukemic stem cells underscore the need for innovative therapies. Gene therapy, particularly CRISPR-Cas9, holds immense promise as a curative approach by targeting the root genetic causes of CML. Future research should focus on optimizing gene-editing technologies and overcoming delivery and cost barriers to make these therapies widely available.

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