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Short Communication

Imatinib in hematology: A landmark in targeted therapy

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Imatinib mesylate, a tyrosine kinase inhibitor (TKI), represents a paradigm shift in the treatment of hematological malignancies. By specifically targeting the BCR-ABL1 fusion protein, Imatinib has transformed the prognosis of chronic myeloid leukemia (CML) and other hematological disorders. Its high efficacy and relatively mild toxicity profile have established it as a cornerstone in modern hematology.

1. Mechanism of Action

Imatinib competitively inhibits ATP binding to the tyrosine kinase domain of the BCR-ABL1 oncoprotein, which is formed by the Philadelphia chromosome translocation (t[9;22]). This inhibition halts aberrant tyrosine kinase activity, blocking downstream signaling pathways responsible for uncontrolled proliferation and survival of leukemic cells. Imatinib also targets other tyrosine kinases, including:

1. c-KIT**:** Overexpressed in gastrointestinal stromal tumors (GISTs) and some hematological malignancies.
2. PDGFR: Implicated in hypereosinophilic syndrome and myeloid/lymphoid neoplasms with eosinophilia.[1,2]

2. Applications in Hematology

1. Chronic myeloid leukemia (CML)**:** Imatinib is the first-line treatment for newly diagnosed CML in chronic phase. Key benefits include:

   (a) High response rates**:** Over 90% of patients achieve complete cytogenetic remission (CCyR) with durable molecular responses.
   (b) Improved survival: Long-term studies demonstrate survival rates exceeding 80% at 10 years, comparable to the general population.
   It is also effective in accelerated phase and blast crisis, though responses are less durable in advanced stages.

2. Acute lymphoblastic leukemia (ALL)**:** In Philadelphia chromosome-positive (Ph+) ALL, Imatinib is used in combination with chemotherapy. This approach has significantly improved remission rates and outcomes, including facilitating hematopoietic stem cell transplantation (HSCT) in eligible patients.
3. Hypereosinophilic syndrome (HES): For HES associated with PDGFR mutations, Imatinib induces rapid and sustained remissions. Doses as low as 100 mg daily are often sufficient for response.
4. Systemic mastocytosis**:** Imatinib is effective in systemic mastocytosis with D816V-negative c-KIT mutations. Its use is limited in D816V-positive cases due to resistance.

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5. Chronic eosinophilic leukemia (CEL)**:** In CEL with PDGFR rearrangements, Imatinib provides durable responses and symptom control, often transforming patient outcomes.

3. Adverse Effects and Management

Imatinib is generally well-tolerated, but adverse effects include:

1. Mild toxicities: Nausea, edema, muscle cramps, and fatigue.
2. Hematological toxicities: Neutropenia and thrombocytopenia, requiring dose modifications.
3. Rare toxicities: Hepatotoxicity, cardiac events, and gastrointestinal bleeding.

Proactive management of side effects and patient education ensure adherence, which is crucial for optimal outcomes.

4. Resistance Mechanisms

Resistance to Imatinib, observed in 20-30% of patients, may be primary (failure to achieve initial response) or secondary (loss of response). Mechanisms include:

- BCR-ABL mutations: Point mutations, such as T315I, interfere with drug binding.
- Gene amplification: Increased BCR-ABL expression.
- Alternate pathways: Activation of bypass signaling pathways.

To overcome resistance, second- and third-generation TKIs (e.g., dasatinib, nilotinib, and ponatinib) have been developed, offering options for resistant or intolerant cases.

5. Future Directions

Imatinib's success has paved the way for targeted therapies in hematology. Current research aims to:[3–5]

1. Refine treatment strategies: Tailored dosing and combination regimens to enhance efficacy and reduce resistance.
2. Expand indications: Investigating its role in other malignancies and rare hematological disorders.
3. Improve **monitoring:** Advanced molecular tools for detecting minimal residual disease (MRD) and guiding therapy.

6. Conclusion

Imatinib's introduction revolutionized the treatment of CML and other hematological malignancies, transforming fatal diseases into manageable chronic conditions. Its success underscores the potential of targeted therapy in hematology, inspiring ongoing innovations and improving patient outcomes worldwide.

7. Sources of Funding

None.

8. Conflict of Interest

None.

References

1. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999;340:1330–40. doi:10.1056/NEJM199904293401706.
2. Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. *Ann Intern Med*. 1999;131(3):207–19.
3. Kantarjian HM, Deisseroth A, Kurzrock R, Estrov Z, Talpaz M. Chronic myelogenous leukemia: a concise update. *Blood*. 1993;82(3):691–703.
4. Savage DG, Szydlo RM, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukemia seen at a referral centre over a 16-year period. *Br J Haematol*. 1997;96(1):111–6.
5. Speck B, Bortin MM, Champlin R, Goldman JM, Herzig RH, McGlave PB, et al. Allogeneic bone-marrow transplantation for chronic myelogenous leukaemia. *Lancet*. 1984;1(8378):665–8.

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