



Review Article

Use of Imatinib Mesylate in the Management of Chronic Myeloid Leukaemia

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Abstract

Imatinib mesylate (Enliven) is a synthetic tyrosine kinase inhibitor. It inhibits the break point cluster region (BCR)-Abelson (ABL) fusion protein that results from the chromosome abnormality known as the Philadelphia chromosome which leads to increased cell proliferation in chronic myeloid leukaemia (CML). Imatinib is approved for the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML). Response is good with high 5 years survival rate. It is well tolerated. Imatinib is also recommended for the treatment of Gastrointestinal stromal tumour (GIST), Philadelphia positive acute lymphoblastic leukaemia (ALL) and nephrogenic systemic fibrosis (NSF). Use of imatinib in CML is discussed in this review article.

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Introduction

Chronic myeloid leukaemia (CML) is a malignant myeloproliferative disorder of haematopoietic stem cells in bone marrow¹. It is characterized by chromosomal abnormality known as the Philadelphia chromosome, which results from a reciprocal translocation involving the abelson (ABL) oncogene from chromosome 9 being transferred to a region on chromosome 22 termed the break point cluster region (BCR). The resulting fused BCR-ABL gene produces a constitutively active tyrosine kinase that initiates multiple signaling pathways and causes decreased adhesion to bone marrow stromal cells and extracellular matrix, enhanced cell proliferation and reduced apoptosis². This leads to an increased number of granular leukocytes in bone marrow and peripheral blood.

There are three phases of the disorder. Chronic phase, accelerated phase and blast crisis CML.

Patients are usually diagnosed in the chronic phase of CML, which could last for 2-7 years with therapy in the pre-imatinib era. It then progresses to the accelerated phase, then finally to myeloid blast crisis, which is fatal. Treatments are less successful as the disorder progresses. Treatment options for CML include allogeneic haematopoietic stem cell transplantation (HSCT). Which may provide a complete response to CML. There is risk of transplant related mortality and morbidity⁴. Another gold standard of CML treatment was interferon-alpha. But this has been changed since imatinib was approved as first line therapy for CML in all phase.

Imatinib mesylate is a synthetic tyrosine kinase inhibitor. It inhibits the BCR-ABL fusion protein, the tyrosine kinase¹. Imatinib is also approved for the treatment of gastrointestinal stromal tumours

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(GIST), Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and nephrogenic systemic fibrosis (NSF)⁵.

Use of imatinib mesylate in the management of chronic myeloid leukaemia (CML) is discussed in this review article.

Pharmacodynamic Properties of Imatinib

Imatinib mesylate (Enliven) inhibits proliferation and induces apoptosis in Philadelphia chromosome positive CML cells⁶. It inhibits receptor tyrosine kinases for platelet derived growth factor and stem cell factor⁷. Imatinib normalizes bone marrow vascularity in CML patients⁸. It also reduces myelofibrosis in patients with CML⁹. Primary or acquired resistance to imatinib is common in patients with advanced CML, but less common in chronic phase CML¹⁰. Most involved mechanism of resistance is reactivation of BCR-ABL signaling through BCR-ABL gene amplification or mutation^{11,12}.

Pharmacokinetic Properties of Imatinib

Imatinib is administered orally and absorbed rapidly. Maximum plasma concentration is reached after 2 to 4 hours of ingestion. It is metabolized by liver and excreted via faeces. Bioavailability of imatinib is 98%.

Indications and Therapeutic Efficacy of Imatinib in Cml

Imatinib (Enliven) is indicated for the first line treatment of newly diagnosed patients with Philadelphia chromosome positive (Ph+) chronic phase chronic myeloid leukaemia (CML), Ph+ accelerated phase CML, Ph+ blast crisis CML. It is also indicated as second line treatment for Ph+ chronic phase CML patients after interferon- alpha failure. It is recommended for Ph+ CML paediatric patients with recurrence after Haematopoietic stem cell transplantation (HSCT) or CML refractory to interferon- alpha¹³.

The definition of a complete haematological response is a white blood cell (WBC) count

<10x10⁹/L, Platelet count <450x10⁹/L, maintained for at least 4 weeks. Complete cytogenetic response define no Philadelphia cells in bone marrow¹⁴.

Adverse Events of Imatinib and its Management

Non haematological adverse events are oedema, nausea, diarrhoea, abdominal pain, skin rash, fatigue, musculoskeletal pain, joint pain, headache and hepatotoxicity. Severe oedema with pleural effusion, pericardial effusion, pulmonary oedema and ascitis can occur in 1-5% of patients.

Haematological adverse events are neutropenia, thrombocytopenia and anaemia. These are more in accelerated phase and blast crisis CML than in chronic phase CML¹³.

Haemoglobin levels were decreased in most chronic-phase CML patients, but returned to normal values with continuation of imatinib treatment¹⁵. Cytopenic events (Neutropenia and thrombocytopenia) can be managed by reducing the dose or by interrupting the treatment with imatinib. Permanent discontinuation of imatinib may be required in few cases. Non-haematological adverse events are also generally manageable. Dose reduction or temporary discontinuation of imatinib may improve the condition. Diuretics can be used for oedema with good result^{13,14}.

Dosage and Administration of Imatinib

Dose is 400mg orally once daily in patients with chronic phase CML. In patients with accelerated phase or blast crises CML, initially 600mg/day is recommended. Circumstances that may permit an increase in the dose from 400 to 600mg/day or from 600 to 800mg/day include disease progression, failure to achieve satisfactory haematological response after ≥3 months of treatment or a cytogenetic response after 6-12 months or loss of haematological or cytogenetic response. Dosage of imatinib 400 or 600mg/day should be taken once daily. A dose of 800mg/day should be split in two (400 mg twice daily) doses. The tablets should be taken with a meal and a large glass of water.

For paediatric patients, the recommended dose is 200mg/m²/day, may be increased up to 340mg/m²/day under same circumstances as those described for adults. The dose may be given as single daily dose or split in two doses.

For hepatic insufficiency, the decreased recommended dose is 300-400mg/day. Caution is recommended for patients with severe renal insufficiency¹³.

Place of Imatinib in The Management of Cml

Incidence of CML is 1-2 cases per 100,000 population per year and 0.74 cases per 100,000 population die from the disease each year¹³. CML can affect any age group including children, although the median age at diagnosis is between 50 and 60 years¹. Immediate goals of CML treatment are to stabilise blood counts and to achieve a haematological or cytogenetic response. The ultimate goal is the removal of all BCR-ABL transcripts (molecular remission)¹⁶.

Allogeneic haematological stem cell transplant (HSCT) is the potentially curative treatment for CML. It needs suitable human leukocyte antigen-matched donor and is usually restricted to younger patients, age \leq 30 years, with a better chance of disease free survival³. The procedure is associated with a high risk of morbidity and mortality. The 100 day mortality risk after transplantation is 15%⁴. Outcomes of transplantation also depend on the stage of CML. The 5 years survival rate for matched related donor transplants is 75% but decreases to 40% with accelerated phase CML and 10% in blast crisis CML¹³. Hydroxycarbamide allows only haematological response and does not affect the percentage of Ph⁺ cells in the bone marrow. Interferon-alpha is administered subcutaneously. Cytogenetic response can be achieved with interferon-alpha, but it is not well tolerated by all patients. Response is better with addition of cytarabine to interferon-alpha treatment^{3,13}.

Imatinib inhibits BCR-ABL tyrosine kinase in Ph⁺ CML patients. Study in patients with chronic phase Ph⁺ CML, who failed interferon-alpha

therapy, almost all patients who received imatinib 400mg/day achieved a complete haematological response after a median duration of treatment of 18 months. Given the high response rate for chronic phase Ph⁺ CML patients who received imatinib, it has been suggested that most patients should attempt initial therapy with imatinib. It is generally well tolerated in over all clinical trials¹⁷.

Conclusion

The effectiveness of imatinib has been compared with that of interferon-alpha, other CML therapeutic agents and bone marrow transplantation. Imatinib provide more health benefits. Though imatinib is costly it is more effective and well tolerated.

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