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Imatinib

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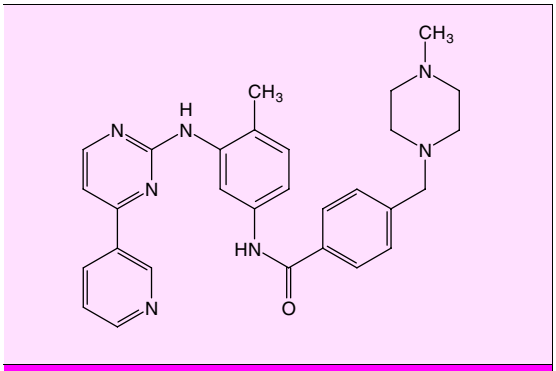
Contents

Abstract

▲ Imatinib inhibits the BCR-ABL tyrosine kinase created by the Philadelphia chromosome (Ph+) in chronic myeloid leukaemia (CML).
▲ Complete haematological responses were achieved in 88% of patients and major cytogenetic responses were detected in 49% of patients with chronic phase CML treated with oral imatinib 400 mg/day in a multicentre noncomparative study of 532 patients.
▲ Administration of oral imatinib 400 or 600 mg/day to 235 patients with accelerated phase CML in a multicentre noncomparative study resulted in haematological responses in 63% of patients and major cytogenetic responses in 21% of patients.
▲ 26% of the 260 patients with blast crisis CML receiving imatinib 400 or 600 mg/day in a multicentre noncomparative trial sustained a haematological response and 13.5% of patients had a major cytogenetic response.
▲ Imatinib 400 or 600 mg/day orally achieved a haematological response in 19 of 32 patients with Ph+ acute lymphoblastic leukaemia in a pilot study.
▲ Clinical improvement was demonstrated in 89% of 36 patients with gastrointestinal stromal tumours unresponsive to standard chemotherapy during treatment with 400 or 600 mg/day oral imatinib in a noncomparative phase II trial.
▲ Adverse events were frequent in clinical trials of imatinib but most events were mild or moderate in severity. Serious adverse events reported include severe fluid retention, cytopenias and hepatotoxicity.

Features and properties of imatinib (STI571, CGP 57148B)	
Approved Indications (in the US)	
Treatment of patients with chronic myeloid leukaemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-α therapy	
Mechanism of action	
Inhibits the BCR-ABL tyrosine kinase	
Approved dosages	
Chronic phase	400mg
Accelerated phase or blast crisis	600mg
Route of administration	Oral
Frequency of administration	Daily
Pharmacokinetic profile (400mg daily)	
Peak plasma concentration at steady state	2.3 mg/L
Time to peak plasma concentration	2-4h
Bioavailability	98%
Elimination half-life	≈18h
Adverse events	
Most frequent	Nausea, fluid retention, vomiting
Serious events	Severe fluid retention, thrombocytopenia, neutropenia, hepatotoxicity



Imatinib

Chronic myeloid leukaemia (CML) accounts for approximately 20% of all leukaemias and is identified by a chromosomal abnormality known as the Philadelphia chromosome (Ph+).[1,2] Exchange of segments from chromosomes 9 and 22 results in production of an abnormal protein tyrosine kinase called BCR-ABL, which causes uncontrollable proliferation and reduced apoptosis of white blood cells. Bone marrow transplantation and interferon-α (IFNα) have been the standard treatment options; however, many patients become refractory to or cannot tolerate IFNα therapy, and there has been no standard treatment for patients with the most aggressive stages of CML (accelerated phase and blast crisis).

Imatinib, a tyrosine kinase inhibitor with specific activity against the BCR-ABL tyrosine kinase, has been developed for the treatment of CML and its haematological and cytogenetic effects have been evaluated in a series of clinical trials.[3] The drug is also active against other abnormal tyrosine kinases including c-kit and has been evaluated in patients with gastrointestinal stromal tumours (GIST).[4-6]

1. Pharmacodynamic Profile

- Imatinib functions as a competitive inhibitor of ATP. It binds at the ATP binding site, blocks ATP binding and thereby inhibits kinase activity.[7]
- Cellular proliferation and tumour formation by BCR-ABL expressing cells were inhibited by imatinib *in vitro*. The concentration of imatinib required to inhibit cellular tyrosine phosphorylation by 50% (IC_{50}) was 0.25μM in BCR-ABL–expressing cell lines.[8] Inhibition was progressive and dose dependent with IC_{50} values ranging from 0.05 to 0.3μM in fresh and cultured cell lines from chronic phase CML, blast crisis CML and Ph+ acute lymphoblastic leukaemia (ALL) patients.[9] Incubation with imatinib at a concentration of 1μM resulted in a 92 to 98% decrease in the number of *BCR-ABL*-positive colonies formed in assays of peripheral blood or bone marrow cells cultured from patients with CML.[8] There was no induction of differentiation in some cell lines tested;[9] however, erythroid differentiation on K562 cells has been reported and is supported by findings that imatinib induced haemoglobin levels and the expression of CD11b in these cells.[8,10] The drug inhibited proliferation of leukaemic cells that expressed both the p210 and p190 BCR-ABL proteins but did not inhibit proliferation of BCR-ABL-negative cells.[8,9,11] The amplification of granulocyte-macrophage progenitors in CML was also reduced by imatinib.[12]
- Imatinib targets 3 tyrosine kinases, namely ABL, c-kit and platelet-derived growth factor (PDGF) receptors. All known forms of *ABL* oncogenes (*BCR-ABL*, *TEL-ABL* and *v-ABL*) are inhibited by the drug.[13-16] The kinase activity of c-kit, which is the receptor for stem cell factor (SCF) and is expressed by 70% of small cell lung cancers and by GIST, is inhibited by imatinib with similar potency as the BCR-ABL kinase ($IC_{50} \approx 0.1\mu M$) *in vitro*.[17-20] In cell-based assays, imatinib also selectively inhibited the kinase activity of PDGF receptors and PDGF- and SCF- mediated cellular events.[19,21-23]
- *In vitro* studies suggest that combinations of imatinib and other chemotherapy drugs (cytabarine, mafosfamide, etoposide, vincristine, IFNα, daunorubicin) with or without irradiation may be more useful than imatinib alone in the treatment of CML.[24-28] Imatinib has been reported to enhance the myeloid maturation activity of All-*trans*-retinoic acid (ATRA) in acute promyelocytic leu-

kaemia cells and to relieve the cyto-differentiation block in ATRA resistant cell lines.[29]

- Continuous treatment with imatinib eradicated 87 to 100% of BCR-ABL-induced tumours in mice.[16] In other animal studies, imatinib inhibited the growth of PDGF-mediated tumours in mice[16,21,23,30] including gliomas[31] and human prostate cancer cells.[32]
- The plasma protein α_1 glycoprotein (AGP) did not block the effect of imatinib on Ph+ cells *in vitro*.[33] Since CML is associated with significantly elevated plasma AGP levels at all disease stages compared with normal controls ($p < 0.05$), AGP isolated from CML plasma was examined for its ability to interact with imatinib and thus reduce drug efficacy. AGP samples from CML patients and normal subjects failed to block the antileukaemic effect of imatinib on CML progenitors *in vitro* even at AGP concentrations of up to 5 mg/ml (section 2).
- Diverse mechanisms of resistance to imatinib may explain why many patients in the advanced phases of CML obtain partial or complete responses with imatinib but then relapse.[34,35] Drug resistance was associated with reactivation of BCR-ABL signal transduction in studies of Ph+ relapsed patients.[36-38] In one study of 9 patients, this reactivation was associated with a substitution of a single amino acid in a threonine residue of the ABL kinase domain known to form a critical hydrogen bond with imatinib in 6 patients, and with progressive *BCR-ABL* gene amplification in 3 patients.[36] In other studies, *BCR-ABL* gene amplification was reported to be a possible mechanism of imatinib resistance in relapsed patients with late phase CML or ALL.[37,38] A variety of molecular and cytogenetic mechanisms of resistance which may lead to clonal selection of resistant cells and thus to haematological resistance to imatinib were detected in 7 of 33 imatinib-resistant CML patients.[39] *In vitro* studies on human Ph+ cell lines demonstrated that BCR-ABL overexpression, reduced uptake of imatinib by P-glycoprotein overexpression, excessive degradation or compensatory mutations in genes other than *BCR-ABL* are all possible mechanisms of resistance to imatinib.[40]

2. Pharmacokinetic Profile

- Absorption of oral imatinib is rapid, with mean maximum plasma concentration (C_{max}) reached within 2 to 4 hours, and 98% mean absolute bioavailability for the capsule formulation.[3,41] The bioavailability and other pharmacokinetic characteristics of imatinib were not clinically affected when imatinib was taken immediately after consumption of a fat-rich meal.[42]
- A mean C_{max} of 2.3 mg/L at steady state was obtained from 400 mg/day imatinib in 83 adult patients with chronic phase CML.[34] At steady state, the mean plasma trough concentration was 0.72 mg/L, which exceeds the IC_{50} of the drug required to inhibit proliferation of BCR-ABL-positive leukaemic cells obtained from patients with CML (section 1). The accumulation of drug at steady state increased by a factor of 1.5 to 2.5 with 400mg imatinib once daily.[3]
- The pharmacokinetics did not change significantly with repeated doses. The increase in administered dose (25 to 1000mg) was proportional to the increase in mean imatinib area under the plasma concentration-time curve (AUC).[3,34,41] The major *N*-desmethyl metabolite has a plasma AUC of 15% of the total AUC.[3] In *in vitro* experiments, plasma protein binding to predominantly albumin and α_1-acid glycoprotein was ≈95% at clinically relevant concentrations of imatinib (section 1).[3]
- The terminal elimination half-life of oral imatinib was approximately 18 hours, and that of the major active metabolite (*N*-demethylated piperazine derivative) was approximately 40 hours in healthy volunteers.[3] The major enzyme responsible for the metabolism of imatinib is cytochrome P450 (CYP3A4), although other isozymes (CYP1A2, CYP2D6, CYP2C9 and CYP2C19) play a minor role.

• Within 7 days, 81% of a radiolabelled dose was eliminated in faeces (68%) and urine (13%). Most of this dose was accounted for by metabolites with 25% of the dose accounted for by unmetabolised imatinib. Clearance of imatinib is expected to be 8 L/h for a 50-year-old patient weighing 50kg and will increase to 14 L/h for a 50-year-old patient weighing 100kg. It is not necessary to adjust the initial dosage based on bodyweight or age but treatment related toxicity will need to be monitored.

• Imatinib plasma concentrations may be altered when the drug is administered with inhibitors or inducers of CYP3A4 activity.[3,34] When imatinib is coadministered with drugs that inhibit CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin), its metabolism may be decreased. Healthy volunteers given imatinib and a single dose of ketoconazole had a 26% increase in mean C_{max} and a 40% increase in AUC of imatinib.[3]

• Drugs that induce CYP3A4 activity [e.g. dexamethasone, phenytoin, carbamazepine, rifampicin (rifampin), phenobarbital] may increase imatinib metabolism. Much lower plasma levels of imatinib than expected were reported in a single patient receiving imatinib and long term phenytoin.[3,34]

• CYP3A4 substrates (e.g. simvastatin, cyclosporin, pimozide) and other CYP3A4 metabolised drugs may have their plasma concentrations increased by imatinib.[3] The mean C_{max} of simvastatin doubled and its AUC increased by 3.5 fold when it was given with imatinib. Plasma concentrations of drugs that are substrates of CYP2C9 (e.g. warfarin), CYP2D6 and CYP3A4/5 may be increased by imatinib, since imatinib is a competitive inhibitor of these isoenzymes.

3. Therapeutic Trials

The haematological and cytogenetic responses to imatinib have been evaluated in multicentre noncomparative studies in adults with Ph+ CML in chronic, accelerated and blast phases.[3,34,35] As yet there are little data on response duration or the effect of the drug on patient survival. Some studies are not yet published; however, preliminary data are available in abstracts.[43-49]

Preliminary noncomparative studies are available on the efficacy of imatinib in patients with unresectable or metastatic GIST and other soft tissue sarcomas.[4-6]

In Patients with Chronic Phase Chronic Myeloid Leukaemia (CML)

Adult patients with chronic phase Ph+ CML (<15% blasts or basophils in the peripheral blood or bone marrow) were eligible for treatment with imatinib if IFNα therapy had failed.[3,34,49] IFNα failure was defined as haematological resistance, cytogenetic resistance, haematological or cytogenetic relapse, or severe intolerance.[34] The definition of a complete haematological response was a white blood cell count (WBC) $<10 \times 10^9$/L and platelet count $<450 \times 10^9$/L maintained for at least 4 weeks. The percentage of Ph+ metaphases in bone marrow determined the cytogenetic response: complete (no cells Ph+), partial (1 to 35% Ph+), minor (36 to 65% Ph+), and absent (>65% Ph+).[34,46]

• Complete haematological responses were obtained in patients with chronic phase CML treated with imatinib ≥300 mg/day in a phase I dose-ranging study.[34] 83 patients received 25 to 1000 mg/day of oral imatinib. Of the 54 patients treated with dosages ≥300 mg/day, 53 had complete haematological responses evident within 4 weeks of treatment. 51 of these patients maintained this response after median follow-up of 265 days (range 17 to 468 days). One patient progressed to the blast phase, and a second patient relapsed to the chronic phase. A major (complete or partial) cytogenetic response occurred in 17 (31%) of these 54 patients including complete cytogenetic remissions in 7 (13%) patients. *BCR-ABL* by fluorescence *in situ* hybridisation tested negative in 2 of these patients, and *BCR-ABL* messenger RNA by the polymerase chain reaction tested negative in 1 patient.

• Imatinib achieved haematological and cytogenetic responses in patients with late chronic phase CML in a phase II study.[3,49] 88% of the 532 patients who received imatinib 400 mg/day obtained a complete haematological response with a median response time of 0.7 months.[49] 49% of patients had a major cytogenetic response including 30% with a complete response and with a median response time of 2.9 months. Cytogenetic response rates were lowest for patients in the prior IFNα failure category of haematological resistance and highest in patients that were IFNα intolerant. Imatinib treatment was still being received by 93% of patients after a median treatment time of 8.3 months (range 0.5 to 10.5 months). The estimated 9-month probability (91%) of not progressing to the accelerated or blast phase was similar for all subgroups of IFNα failure. Blasts in peripheral blood <3%, platelets $<450 \times 10^9$ /L, haemoglobin ≥100g/L, WBC $<20 \times 10^9$/L, absence of splenomegaly and <2 years since diagnosis of CML were prognostic factors for cytogenetic response.

In Patients with Accelerated Phase CML

Accelerated phase CML was defined by the presence of ≥1 of the following: ≥15% but <30% blasts in peripheral blood or bone marrow, or ≥30% blasts plus promyelocytes in peripheral blood or bone marrow, or ≥20% basophils in peripheral blood, or nontherapy-related thrombocytopenia $<100 \times 10^9$/L.[45] Haematological responses were defined as no evidence of leukaemia in blood or bone marrow without full peripheral blood recovery, or return to chronic phase, and complete responses as <5% blasts in bone marrow with no circulating blasts with recovery of peripheral blood counts.[3,45]

• Haematological and cytogenetic responses were detected in Ph+ CML patients in the accelerated phase during treatment with imatinib 400 or 600 mg/day in a multicentre noncomparative phase II study.[3,48] The haematological response with duration of ≥4 weeks in 63% of the 235 patients included 28% with a complete response, 11% with no evidence of leukaemia (without full peripheral blood recovery) and 24% with a return to chronic phase.[3] 40% of patients had a cytogenetic response including a major response in 21% of patients (14% with complete response). The median duration of treatment was 7.9 months (range 0.2 to 13 months) at the time of analysis.[48] The estimated rates at 9 months of being progression-free and overall survival were 63 and 80%, respectively. Prognostic factors for improved time-to-progression were initial imatinib dose of 600 mg/day, baseline platelet count = 100×10^9/L and marrow blasts <15% (fig. 1).

In Patients with Blast Crisis CML or Ph+ Acute Lymphoblastic Leukaemia

Imatinib has shown haematological and cytogenetic activity in patients in myeloid blast crisis (>30% blasts in the peripheral blood or bone marrow) which is the terminal phase of CML.[3,35,47] In a pilot study, 38 patients with myeloid blast crisis received imatinib 300 to 1000 mg/day.[35] Complete haematological responses occurred in 4 (11%) of the 21 (55%) patients with a marrow response. Nine of these patients relapsed 42 to 194 days after initiation of treatment; however, 7 patients in remission were continuing therapy after 101 to 349 days of treatment.

• Of the 260 patients in a multicentre phase II trial, 26% obtained a sustained (>4 weeks) haematological response including 4% with a complete response, 3% with no evidence of leukaemia and 19% with a return to chronic phase.[3,47] A higher response rate was reported in the previously untreated patients (31%) than in the previously treated patients (19%) and also in the 600 mg/day group (29%) than the 400 mg/day group (11%).[3] Median duration of haematological response was 6.6 months at the time of analysis, and median survival for previously untreated and treated patients with CML were 7.1 and 5.2 months, respectively.[47] Haematological response at 3 months

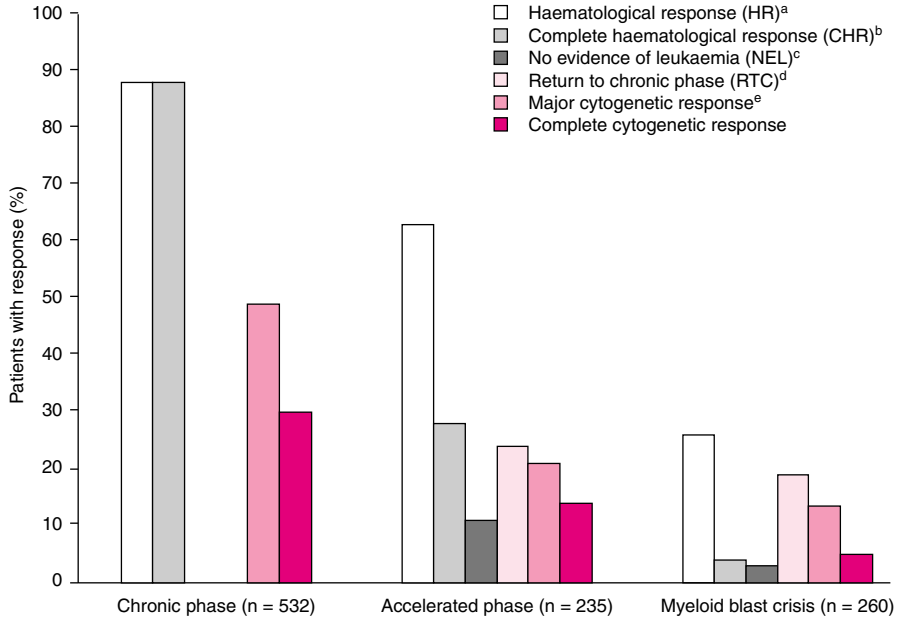


Fig. 1. Haematological and cytogenetic responses with imatinib 400 or 600 mg/day in chronic phase, accelerated phase and myeloid blast crisis chronic myeloid leukaemia in 3 multicentre noncomparative studies.[3]

a. Haematological response is total of CHR, NEL and RTC.

b. CHR in patients in the chronic phase included no extramedullary involvement, WBC $<10 \times 10^9$/L, platelets $<450 \times 10^9$/L, <20% basophils, <5% myelocytes and metamyelocytes, and no blasts or promyelocytes in blood. In patients in the accelerated or blast phases, CHR was defined as no extramedullary disease, ANC $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, <5% blasts in BM and no blasts in PB.

c. In patients in the accelerated phase or blast crisis, NEL was defined as for CHR in these groups with the exception of an ANC $\geq 1 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L.

d. In patients in the accelerated phase or blast crisis, RTC was defined as no extramedullary disease other than spleen and liver, <15% blasts in BM and PB, <30% blasts and promyelocytes in BM and PB and <20% basophils in PB.

e. Major cytogenetic response combined both complete and partial responses. Complete response was defined as 0% Philadelphia positive metaphases (Ph+) and partial response was defined as 1 to 35% Ph+.

ANC = absolute neutrophil count; **BM** = bone marrow; **PB** = peripheral blood; **WBC** = white blood cells.

was a significant prognostic factor for survival; age ≥60 years, haemoglobin ≥100g/L, <50% blasts in peripheral blood, and platelets $\geq 100 \times 10^9$/L were advantageous prognostic factors for haematological response. Cytogenetic responses in 26% of patients included 13.5% with major responses (5% with a complete response) [fig. 1].

• Haematological responses were achieved in patients with Ph+ ALL (refractory to or relapsed from standard chemotherapy) treated with imatinib in pilot studies.[35,44] Preliminary data in one study report that 19 (59%) of 32 patients with Ph+ ALL achieved a haematological response after 4 weeks of treatment with imatinib 400 or 600 mg/day.[44] In a dose-escalating pilot study (imatinib 300 to 1000 mg/day) 14 (70%) of 20 Ph+ ALL patients demonstrated a haematological response including a complete response in 4 (20%) of patients.[35] This response typically occurred within 1 week of starting therapy; however, 12 of these 14 patients relapsed after 42 to 123 days of therapy (median 58 days). Cytogenetic responses were demonstrated in

3 of the patients including 2 complete responses. Relapsed patients remained Ph+.

In Patients with Metastatic Gastrointestinal Stromal Tumours

• Imatinib has shown activity in patients with unresectable metastatic GISTs including patients unresponsive to standard chemotherapy.[4-6] 35 patients with GISTs with expression of c-kit were randomised to 400 or 600 mg/day imatinib in a phase II trial.[4] After 1 to 3 months, 54% (19) of patients had partial responses, 34% (12) had stable disease and 11% (4) had disease progression. Clinical improvement was demonstrated in 89% of initially symptomatic patients with no differences between dosage groups. Of the patients with positive [^{18}F]fluorodeoxyglucose (^{18}FDG) PET scans, 89% had ≥50% decrease in uptake values. Reduced ^{18}FDG uptake after 8 days was associated with clinical improvement in the majority of patients.[5] Median survival time has not been established; however, a patient with advanced resistant GIST has maintained a response for more than 11 months.[6]

4. Tolerability

• Adverse events were reported in the majority of patients treated with imatinib during clinical trials; however, most events were mild to moderate in severity.[3,34] Nausea, vomiting, oedema, muscle cramps, diarrhoea and headache were the most frequently reported adverse events (fig. 2).[3,34,35,43-45] One percent of patients in chronic phase, 2% in accelerated phase and 5% in blast phase CML discontinued the drug because of drug-related adverse events.[3]

• Fluid retention ranged from mild oedema to severe fluid retention and was more common with the higher imatinib dosage (600 mg/day) and age ≥65 years.[3] One to 5% of patients receiving imatinib experienced severe fluid retention including pleural effusion, pericardial effusion, pulmonary oedema, ascites, rapid weight gain and severe

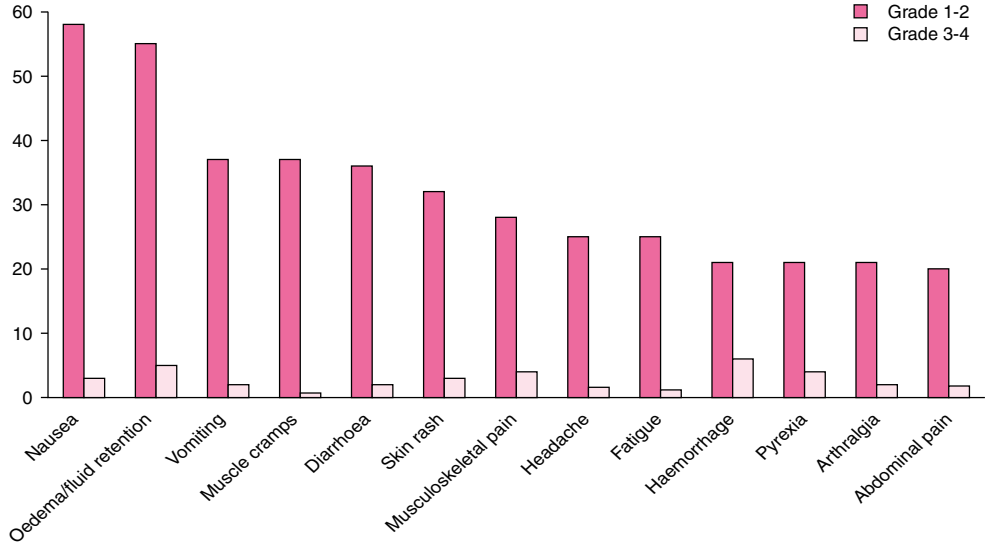


Fig. 2. Tolerability of oral imatinib 400 or 600 mg/day in 1027 patients with chronic myeloid leukaemia (CML). Combined incidence of grade 1 and 2 or grade 3 and 4 adverse events experienced by >20% of patients in 3 multicentre noncomparative studies. Adverse events are included regardless of suspected relationship to treatment. Fluid retention includes superficial oedema and other fluid retention events such as pleural effusion, ascites, pulmonary oedema and pericardial effusion.[3]

superficial oedema. Interruption of imatinib treatment, diuretics and other supportive care measures usually managed these events. One death was reported in a blast crisis patient with pleural effusion, congestive heart failure and renal failure.[3]

• Thrombocytopenia and neutropenia frequently occurred in patients treated with the drug in clinical trials and were more common at higher dosages (≥750mg) and in the blast crisis and accelerated phase than in the chronic phase (fig. 3).[3,6,34,43,45] Permanent discontinuation of imatinib treatment may be required in a few patients; however, reducing the dosage or interrupting treatment will usually manage these cytopenic events.[3] Blast crisis and accelerated phase patients had a higher incidence of anaemia than chronic phase patients (fig. 3).[3] Haemoglobin levels were decreased in most chronic phase CML patients but returned to or exceeded baseline values with continued therapy.[34]

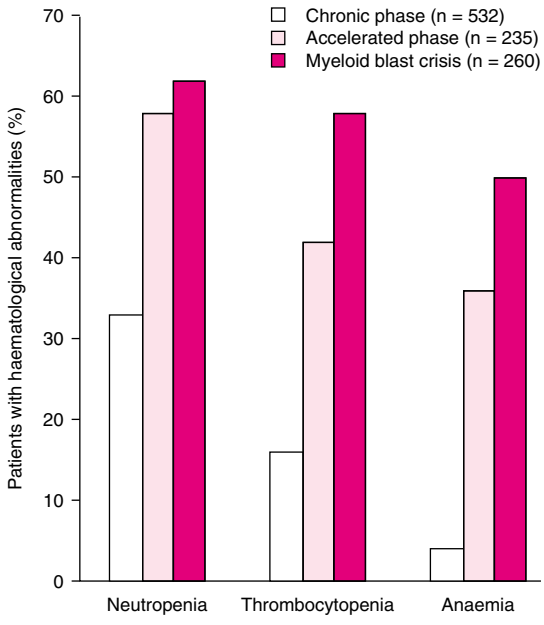


Fig. 3. Percentage of patients with chronic myeloid leukaemia (CML) exhibiting grade 3 or 4 haematological abnormalities during treatment with 400 or 600 mg/day oral imatinib in 3 multicentre noncomparative clinical trials.[3] Haematological grades 3 or 4 are defined as neutropenia (<0.5-1.0 × 10^9/L), thrombocytopenia (<10-50 × 10^9/L) and anaemia (haemoglobin <65-80 g/L).

• Hepatotoxicity was reported with severe elevation of transaminases or bilirubin in 1.1 to 3.5% of patients receiving imatinib.[3] Laboratory abnormalities resulted in <0.5% of patients discontinuing treatment permanently; however, most abnormalities were managed with dosage reduction or interruption (median duration of episode ≈1 week). One death due to liver failure occurred within 11 days of therapy in a patient who had taken paracetamol (acetaminophen) regularly.[3,45]

• Rapid tumour lysis may have been responsible for tumour bleeding in 3 (15%) patients with GISTs receiving imatinib in a clinical trial.[5]

5. Imatinib: Current Status

Imatinib is a tyrosine-kinase inhibitor that has been approved in the US and is being reviewed for registration in many other countries. It is indicated for the treatment of patients with CML in blast crisis, accelerated phase or chronic phase after failure of IFNα therapy. The effectiveness of imatinib is based on the rate of haematological and cytogenetic responses, as completed controlled studies demonstrating increased survival or improvement in symptoms are not available. Although most patients experienced adverse events at some time during treatment with the drug, these events were mild to moderate.

The efficacy of imatinib in inhibiting other receptor tyrosine kinases such as c-kit in GIST or in other solid tumours is being studied.[4,5] Ongoing studies include the use of imatinib in combination with other chemotherapy protocols in CML or Ph+ ALL and in children with refractory or relapsed Ph+ leukaemias. Other studies will examine the pharmocokinetics of the drug in patients with liver impairment and in those receiving concomitant medications including paracetamol and CYP2D6 substrates.[50]

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