Imatinib Mesylate

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Contents

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Abstract

Imatinib mesylate (Gleevec, Glivec [Novartis, Basel, Switzerland], formerly referred to as STI571 or CGP57148B) represents the paradigm of a new class of anticancer agents, so-called small molecules. They have a high selectivity against a specific molecular target known to be the cause for the establishment and maintenance of the malignant phenotype. Imatinib is a rationally designed oral signal transduction inhibitor that specifically targets several protein tyrosine kinases, Abl, Arg (*Abl*-related gene), the stem cell factor receptor (c-KIT), platelet-derived growth factor receptor (PDGF-R), and their oncogenic forms, most notably BCR-ABL. Imatinib has been shown to have remarkable clinical activity in patients with chronic myeloid leukemia (CML) and malignant gastrointestinal stroma tumors (GIST) leading to its approval for treatment of these diseases. Treatment with imatinib is generally well tolerated with a low incidence of severe side effects. The most common adverse events include mild to moderate edema, muscle cramps, diarrhea, nausea, skin rashes, and myelosuppression. Several mechanisms of resistance have been identified. Clonal evolution, amplification, or overexpression of BCR-ABL as well as mutations in the catalytic domain, P-loop, and other mutations have been demonstrated to play a role in primary and secondary resistance to imatinib, respectively. Understanding of the underlying mechanisms of resistance has led to the development of new second- and third-generation tyrosine kinase inhibitors (see chapters on dasatinib, nilotinib, bosutinib, and ponatinib).

Keywords

CML · Tyrosine kinase inhibitor · Imatinib

1 Introduction

Chronic myeloid leukemia (CML) is a clonal disorder of the hematopoietic stem cell. The clinical presentation often includes granulocytosis, a hypercellular bone marrow, and splenomegaly. The natural course of the disease involves three sequential phases—chronic phase (CP), progressing often through an accelerated phase (AP) into the terminal blast crisis (BC). The duration of CP is several years, while AP and BC usually last only for months. In the past, prior to the introduction of TKIs into the treatment of CML, median survival was in the range of 4–5 years (Hehlmann et al. 2007b; Sawyers 1999).

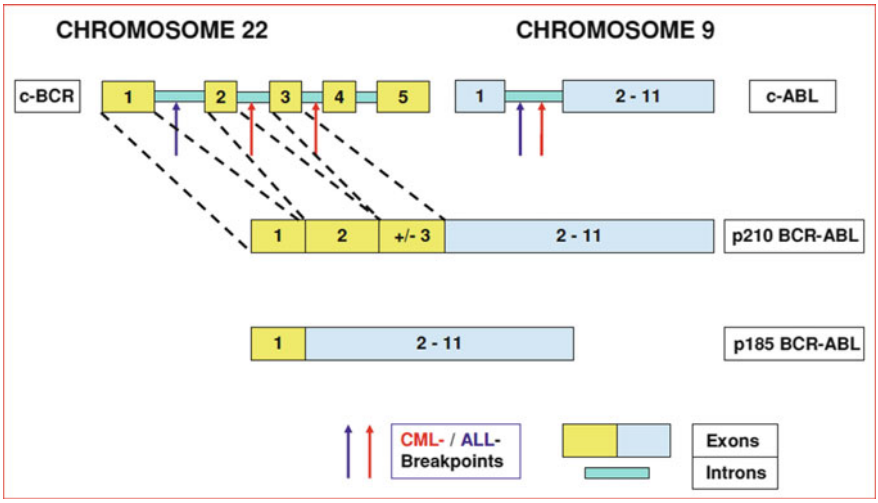

Fig. 1 Common breakpoints in CML and Ph^+ ALL: In CML, *BCR* breakpoints occur after the second or third exon, whereas in Ph^+ ALL, breaks can occur after the first exon. In *c-ABL,* a break occurs between the first and second exon (CML and Ph^+ ALL)

CML is characterized by the presence of the Philadelphia chromosome (Ph), a unique reciprocal translocation between the long arms of chromosomes 9 and 22, t(9:22), which is present in >90% of patients with CML and approximately 15–30% of ALL (Nowell and Hungerford 1960; Rowley 1973). On the molecular level, t(9:22) results in the generation of an oncogene, the BCR-ABL fusion gene, encoding the BCR-ABL protein which has constitutive tyrosine kinase activity (Konopka et al. 1984; Fig. 1).

Its causal role in the development of CML has been demonstrated in vitro as well as in several animal models (Daley et al. 1990; Heisterkamp et al. 1990; Lugo et al. 1990; Voncken et al. 1995).

The pathological effects of BCR-ABL include increased proliferation, protection from programmed cell death, altered stem cell adhesion, and possibly genetic instability that leads to disease progression (Deininger and Goldman 1998; Deininger et al. 2000).

Before the introduction of imatinib, standard therapy of CML was interferon-α alone or in combination with cytarabine (ara-C) leading to hematologic remissions in the majority of patients, but major cytogenetic responses—i.e., <35% Ph^+ metaphases—were only seen in 6–25% of patients (Hehlmann et al. 2007b). The only curative treatment of CML is allogeneic stem cell transplantation from an HLA-compatible donor. However, it is only an option for a part of the patients and still associated with considerable morbidity and mortality (Gratwohl et al. 1998; Hehlmann et al. 2007a).

The presence of BCR-ABL in >90% of CML patients and the identification of its essential role in the pathogenesis of the disease provided the rationale of targeting this fusion protein for treatment of CML.

In the nineties of the twentieth century, first data of compounds with an effect on tyrosine kinases were published (Levitzky and Gazit 1995). Tyrphostins and other similar compounds were shown to inhibit the ABL—as well as the BCR-ABL tyrosine kinase at micromolar concentrations but had only limited specificity (Anafi et al. 1993a, b; Carlo-Stella et al. 1999). This led to the rational design of further TKI with selective activity against the ABL tyrosine kinase, one of which was a 2-phenylaminopyrimidine called CGP57148B, later called STI571 or imatinib mesylate (Buchdunger et al. 1995, 1996; Druker and Lydon 2000; Druker et al. 1996).

After demonstration of specificity in vitro, in cell-based systems as well as in different animal models, this compound was tested in several phase I and phase II studies (Druker et al. 2001a; Kantarjian et al. 2002a, b). Imatinib was shown to have very high rates of hematologic remissions in CP-CML patients previously treated with interferon-α as well as in advanced stages of the disease. Cytogenetic remissions were achieved in a considerable portion of patients. Based on these good results, imatinib was approved for treatment of CML patients in CP after treatment failure with interferon-α and the advanced stages, i.e., AP and BC (Cohen et al. 2002b).

The phase III (IRIS-) trial led to establishment of imatinib as standard for first-line therapy of CP-CML (Cohen et al. 2009; Dagher et al. 2002; Hochhaus et al. 2017). The very good clinical results for imatinib of the IRIS trial were reproduced by several large phase III studies, including the German CML IV trial (Hehlmann et al. 2017). Patients who optimally respond to imatinib or next-generation TKIs have a near-normal life expectancy and, in this population, the impact of comorbidities on survival outcomes is considered as greater than that of CML itself. However, lifelong treatment is still recommended (Saußele et al. 2015, 2016; Rea and Mahon 2018).

Currently, several trials investigate the effect of stopping imatinib or second-generation TKIs in patients reaching a very good long-lasting remission based upon the results of the so-called STIM trial where it could be shown that approximately half of patients stayed in a very good molecular remission after the end of the therapy (Mahon et al. 2010; Etienne et al. 2017; Mahon et al. 2016; Rea et al. 2017). This has prompted the development of a new concept in the evaluation of CML patients known as "treatment-free remission" (Saußele et al. 2016).

Other molecular targets of imatinib are the stem cell factor receptor (c-KIT) and platelet-derived growth factor receptor (PDGF-R) (Buchdunger et al. 1995, 1996, 2000; Heinrich et al. 2002a, b).

c-KIT is expressed in a variety of human cancers, including germ cell tumors, neuroblastoma, melanoma, small cell lung cancer, breast and ovarian cancers, acute myeloid leukemia, mast cell disorders as well as malignant gastrointestinal stroma tumors (GIST). While in most of these diseases, the exact role of c-KIT expression is not defined, in mastocytosis and GISTs activating mutations of c-KIT have been identified.

Based upon data of a single open-label phase II trial and two large phase III trials by the EORTC and SWOG, imatinib received approval for treatment of metastatic/unresectable GIST (Cohen et al. 2009; Dagher et al. 2002). In addition,

the role of neoadjuvant therapy and adjuvant treatment with imatinib after successful resection of primary GIST has been clearly demonstrated and led to its approval (Joensuu et al. 2012; von Mehren and Joensuu 2018). The duration of adjuvant imatinib therapy in patients with a substantial risk of recurrence should be at least 3 years. However, the optimal duration is unknown. As in CML, several resistance mutations in c-kit as well as in the PDGFRA have been identified in patients with GIST (von Mehren and Joensuu 2018).

Furthermore, imatinib has been successfully used in diseases with aberrant PDGF receptors. They have been shown to deregulate the growth of a variety of cancers, such as GIST; myeloproliferative disorders (Pardanani and Tefferi 2004), e.g., in hypereosinophilic syndrome (FIP1L1/PDGFRα-rearrangement), chronic myelomonocytic leukemia (CMML), harboring the activating translocations involving the PDGF receptor beta locus on chromosome 5q33 (FIP1/PDGFR-translocation); carcinomas; melanoma; gliomas; and sarcomas, including dermatofibrosarcoma protuberans (Barnhill et al. 1996; Greco et al. 2001).

In addition, in several non-malignant diseases, e.g., pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis imatinib, has a positive effect on the disease (Ogawa et al. 2017). Its role in the treatment of autoimmune disease has been investigated (Hoeper et al. 2013; Moinzadeh et al. 2013).

2 Structure and Mechanisms of Action

Imatinib mesylate is designated chemically as 4-[(4-methyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] aminophenyl] benzamide methanesulfonate. Its molecular formula is $C_{29}H_{31}N_7O.CH_4SO_3$, and its relative molecular mass is 589.7 (Fig. 2).

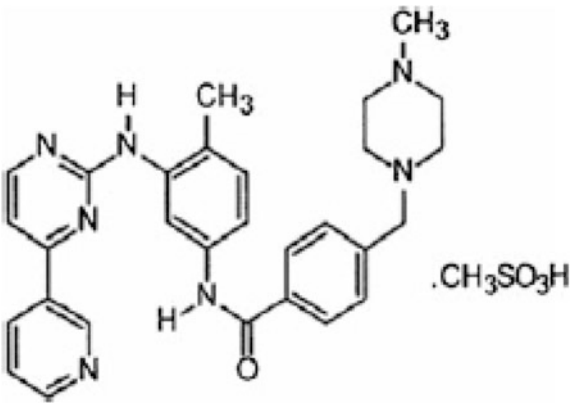

Fig. 2 Structure of imatinib mesylate (formerly STI 571 bzw. CGP57148)

Imatinib functions as a specific competitive inhibitor of ATP. It binds with high affinity at the ATP binding site in the inactive form of the kinase domain, blocks ATP binding, and thereby inhibits kinase activity by interrupting the transfer of phosphate from ATP to tyrosine residues on substrate proteins (Cohen et al. 2002a, b, 2005; Lyseng-Williamson and Jarvis 2001; Mauro et al. 2002).

Imatinib selectively inhibits all the ABL tyrosine kinases, including BCR-ABL, cellular homolog of the Abelson murine leukemia viral oncogene product (c-ABL), v-ABL, TEL-ABL, and Abelson-related gene (ARG). In addition, it was found to potently inhibit the tyrosine kinase activity of the α- and β-platelet-derived growth factor receptors (PDGF-R) and the receptor for stem cell factor (c-KIT; CD117). The concentrations required for a 50% kinase inhibition were in the range of 0.025 μM in in vitro kinase assays and approximately 0.25 μM in intact cells. Extensive screening did not show activity against other tyrosine kinases or serine/threonine kinases (Buchdunger et al. 1995, 1996, 2000, 2001; Deininger et al. 2005; Druker and Lydon 2000; Druker et al. 1996; Heinrich et al. 2002a; Okuda et al. 2001; Table 1).

Table 1 Inhibition of protein kinases by imatinib mesylate (formerly STI 571 bzw. CGP57148) (adapted from Deininger et al. 2005)

Protein kinase	Substrate phosphorylation IC50[a] (μM)	Cellular tyrosine phosphorylation IC50[a] (μM)
c-abl	0.2; 0.025	ND
v-abl	0.038	0.1–0.3
$p210^{BCR-ABL}$	0.025	0.25
$p185^{BCR-ABL}$	0.025	0.25
TEL-ABL	ND	0.35
PDGF-Rα and β	0.38 (PDGF-Rβ)	0.1
Tel-PDGF-R	ND	0.15
c-KIT	0.41	0.1
FLT-3	>10	>10
Btk	>10	ND
c-FMS	ND	>10
v-FMS	ND	>10
c-SRC	>100	ND
v-SRC	ND	>10
c-LYN	>100	ND
c-FGR	>100	ND
LCK	9.0	ND
SYK (TPK-IIB)	>100	ND
JAK-2	>100	>100
EGF-R	>100	>100

(continued)

Table 1 (continued)

Protein kinase	Substrate phosphorylation IC50[a] (μM)	Cellular tyrosine phosphorylation IC50[a] (μM)
Insulin receptor	>10	>100
IGF-IR	>10	>100
FGF-R1	31.2	ND
VEGF-R1 (FLT-1)	19.5	ND
VEGF-R2 (KDR)	10.7	ND
VEGF-R3 (FLT-4)	5.7	ND
TIE-2 (TEK)	>50	ND
c-MET	>100	ND
PKA	>500	ND
PPK	>500	ND
PKC α, β1, γ, δ, ε, ξ, η	>100	ND
Protein kinase CK-1, CK-2	>100	ND
PKB	>10	ND
P39	>10	ND
PDK1	>10	ND
c-RAF-1	0.97	ND
CDC2/cyclin B	>100	ND

ND not done, *PDGF-R* platelet-derived growth factor receptor, *Btk* Bruton tyrosine kinase, *TPK* tyrosine-protein kinase, *EGF-R* epidermal growth factor receptor, *IGF-IR* insulin-like growth factor receptor I, *FGF-R1* fibroblast growth factor receptor 1, *VEGF-R* vascular endothelial growth factor receptor, *PKA* cAMP-dependent protein kinase, *PPK* phosphorylase kinase; *PKC* protein kinase C, *CK* casein kinase, *PKB* protein kinase B (also known as Akt), *PKD1* 3-phosphoinoside-dependent protein kinase 1

[a]IC50 was determined in immunocomplex assays

Imatinib concentrations causing a 50% reduction in kinase activity (IC50) are given.

3 Preclinical Data

In vitro studies demonstrated specific inhibition of myeloid cell lines expressing BCR-ABL without killing the parental cell lines from which they were derived (Deininger et al. 1997; Druker et al. 1996; Gambacorti-Passerini et al. 1997). Continuous treatment with imatinib inhibited tumor formation in syngeneic mice as well as in a nude mouse model after inoculation of BCR-ABL-expressing cells in a dose-dependent manner, treated intraperitoneally or with oral administration of STI571, respectively (Druker et al. 1996; le Coutre et al. 1999). Activity on primary CML cells could be demonstrated, and a >90% reduction of BCR-ABL-expressing colonies in colony-forming assays from peripheral blood or bone marrow from CML patients was achieved at a concentration of imatinib of 1 μM while normal colonies did not show growth inhibition (Deininger et al. 1997; Druker et al. 1996; Gambacorti-Passerini et al. 1997).

4 Clinical Data in CML

4.1 Phase I Trials

In 1998, a phase I clinical trial with imatinib was initiated. This study was a dose escalation trial designed to determine the maximally tolerated dose, with clinical benefit as a secondary endpoint. 83 patients with CP-CML who had failed standard therapy with interferon-α (IFN-α) or were intolerant to it were enrolled. One-third of patients had signs of early progression to AP. They received escalating oral doses of imatinib, ranging from 25 to 1000 mg/day. Clinical features of patients were typical of the disease. Dose-limiting toxicity was not reached, although a higher frequency of severe toxicities was encountered at imatinib doses >750 mg/day. The most common adverse events were nausea (43%), myalgia (41%), edema (39%), and diarrhea (25%). After 29 patients were enrolled, therapeutic doses of 300 mg or more per day were reached. 53 of 54 patients achieved a complete hematologic response, reaching normal blood counts typically within four weeks of treatment. 51 of these 53 patients maintained normal blood counts after one year of therapy. Furthermore, these patients had a 31% rate of major cytogenetic responses (MCyR; <35% Ph^+ metaphases) and a 13% rate of complete cytogenetic responses (CCyR; eradication of Ph^+ bone marrow cells) (Druker 2008; Druker et al. 2001b).

In another phase I trial, patients with myeloid and lymphoid blast crisis and patients with relapsed or refractory Ph^+ lymphoblastic leukemia (ALL) were treated with daily doses of 300–1000 mg of imatinib. 55% of patients with myeloid blast crisis responded to therapy (45% of patients with <5% blasts in the bone marrow, and 11% reached a complete remission with full recovery of peripheral blood counts, respectively) but only in 18% response was maintained longer than one year.

Of 20 patients with Ph^+ ALL or lymphoid blast crisis, 70% responded, 20% reached a complete hematologic remission. Nevertheless, all but one relapsed between days 45 and 117 (Druker et al. 2001a).

Based on the results of the phase I trials, the use of imatinib was expanded to large phase II and phase III clinical trials.

4.2 Phase II Studies

Three open-label, single-arm phase II studies using imatinib as a single agent were conducted in patients with Ph^+ CML in three clinical settings: CML-CP after IFN-α failure or with intolerance to the drug, CML-AP, and CML-BC. Imatinib was administered orally once daily. Initially, all patients received 400 mg/day. Early in the study, however, the imatinib dose was increased to 600 mg daily for CML-AP and CML-BC trials. Patients with resistant or progressive disease receiving a dose of 400 or 600 mg/day could receive doses of 600 or 800 mg daily (administered as 400 mg twice daily).

In 532 patients with CP-CML who had failed IFN-α therapy, 95% of patients reached a complete hematologic response, with CCR rates of 41% and major cytogenetic remission (MCR) of 60%. The estimated rates of freedom from progression to accelerated or blastic phase and overall survival at 6 years were 61 and 76%, respectively (Druker 2008; Hochhaus et al. 2008; Kantarjian et al. 2002a).

For patients in BC and with Ph^+ ALL, the studies confirmed the results of the phase I trial. Response rates were also high; however, relapses were seen frequently. The majority of patients in BC relapsed during the first year of treatment. Hematologic responses were observed in 52% of patients (n = 260) with myeloid BC, with a median response duration of 10 months. Interestingly, 48% of patients in this trial developed new cytogenetic abnormalities during treatment, demonstrating clonal evolution (Druker et al. 2001a; Ottmann et al. 2002; Sawyers et al. 2002).

The efficacy in patients with AP CML was intermediate between CP and BC. Of 181 patients with AP, 82% showed a hematologic response, 53% reached a CHR which was sustained in 69%. Major cytogenetic remissions were seen in 24% of patients with a CCR rate of 17% (Talpaz et al. 2002).

The treatment results in advanced phase CML and Ph^+ ALL underline the necessity of combination therapies with conventional chemotherapy as well as the use of second-generation tyrosine kinase inhibitors.

The results of the phase I and phase II trials led to the approval by the Food and Drug Administration (FDA) of imatinib for the treatment of CML in advanced phase and after failure of IFN therapy in CP CML (Cohen et al. 2002b; Deininger et al. 2005; Druker 2008).

4.3 Phase III Study (IRIS Trial)

In a landmark phase III study, the International Randomized Study of Interferon and STI571 (IRIS) trial, imatinib and the combination of IFN plus cytarabine were compared in newly diagnosed CP-CML patients. More than 1000 patients were accrued in less than 7 months. 553 patients were randomized to each of the two treatments, imatinib at 400 mg per day or interferon-α plus Ara-C. There were no significant differences in prognostic or clinical features between the two treatment arms. After a median follow-up of 19 months, patients randomized to imatinib had significantly better results for CHR, MCR, and CCR, as well as progression-free survival than patients treated with interferon-α plus Ara-C (O'Brien et al. 2003a, b).

The remarkable superiority of imatinib led to early disclosure of study results. Thereafter, most patients were crossed over from interferon-α plus Ara-C to the imatinib arm.

The IRIS trial is now a long-term follow-up study of patients who received imatinib as initial therapy. After a follow-up of 5 years, the overall survival for newly diagnosed CP patients treated with imatinib was 89%. An estimated 93% of imatinib-treated patients remained free from disease progression to the AP or BC. The estimated annual rate of treatment failure was 3.3% in the first year, 7.5% in

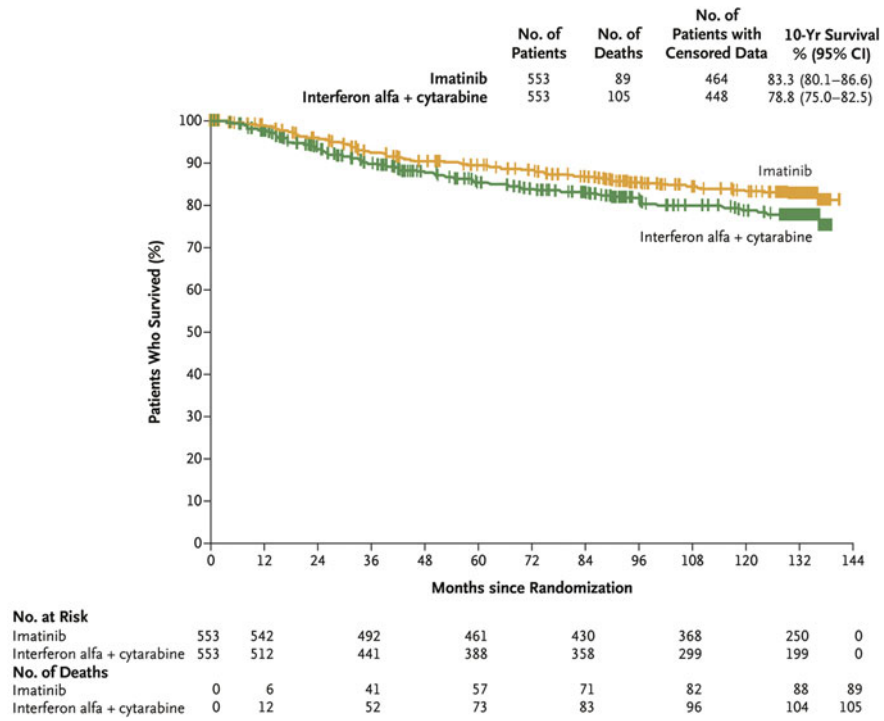

Fig. 3 Kaplan–Meier Estimated Overall Survival Rates at 10 Years in the Intention-to-Treat Population. Shown is the overall survival over time among patients assigned to each trial group. For the curve for the group of patients who had been randomly assigned to receive interferon alfa plus cytarabine, data include survival among the 363 patients who crossed over to imatinib (65.6%). These patients crossed over to imatinib after a median of 0.8 years of receiving interferon alfa plus cytarabine. In patients with no reported death (whether because they were known to be alive or because their survival status was unknown), survival was censored (tick marks) at the date of last contact. (Adapted from Hochhaus et al. NEJM 2017)

year two, 4.8% in year three, 1.5% in year four, and 0.9% in year five. The progression rate did not increase over time (Druker et al. 2006; Hochhaus et al. 2017; Fig. 3). Survival rates in the IRIS trial were especially high in patients who had a major molecular response at 12 months or 18 months and those with low Sokal scores. These results are consistent with previous reports from IRIS and other studies as, e.g., the CML IV trial showing that early response to TKI therapy is a valuable prognostic marker for long-term outcome (Hochhaus et al. 2017; Hehlmann et al. 2017).

Most of the side effects of imatinib were mild to moderate, with the most common being edema, muscle cramps, diarrhea, nausea, skin rashes, and myelosuppression (Druker et al. 2006; Hochhaus et al. 2017). Serious adverse cardiac events were reported in 7.1%. No new safety signals were observed after the 5-year analysis. Quality of life was far better in patients treated with imatinib (Hahn et al. 2003).

Table 2 Results from the IRIS trial (Druker et al. 2006; O'Brien et al. 2003a, b)

Timepoint of follow-up	First-line treatment	Estimated cumulative rate of CHR (%)	Estimated cumulative rate of MCR (%)	Estimated cumulative rate of CCR (%)	Progression-free survival (PFS) (%)	Freedom from progression to AP or BC (%)	OAS (%)	References
18 months	IFN + Ara-C *n* = 553	55.5	22.1	8.5	73.5	91.5		O'Brien et al. (2003a, b)
	Imatinib *n* = 553	95.3*	85.2*	73.8*	92.1	96.7		O'Brien et al. (2003a, b)
60 months	Imatinib	98	92	87	83	95.0	89.4	Druker et al. (2006)
10.9 years	Imatinib	98.6	89	82.8		92.4	83.3	Hochhaus et al. (2017)

*Statistically significant difference to treatment with IFN + Ara-C ($p = 0.001$)

Rates of hematologic and cytogenetic responses are shown in Table 2. A recent update at 10.9 years showed an estimated overall survival of 83.3% which is similar to the rate of 84% reported among patients who were treated with imatinib-based regimens in the German CML IV study, which was initiated shortly after IRIS to investigate alternative dosing strategies and drug combinations in patients with newly diagnosed CML in first chronic phase (Hehlmann et al. 2017). The estimated EFS at 10.9 years was 79.6%.

The estimated rate without progression to AP or BC is 93%. A CCR was achieved by 456 of 553 (82%) of patients on first-line imatinib (O'Brien et al. 2008).

Monitoring of residual disease by quantitative RT-PCR in complete cytogenetic responders showed that the risk of disease progression was inversely correlated with the reduction of BCR-ABL mRNA compared with pre-therapeutic levels (Hughes et al. 2003). The rates of major molecular remissions as well as the depth of molecular responses increase over time with a downward trend of relapse (O'Brien et al. 2008).

Investigation of pharmacokinetics in the imatinib-treated patients showed a correlation between imatinib trough plasma concentrations with clinical responses, EFS, and adverse events. Patients with high imatinib exposure had better rates of CCR, major molecular responses, and event-free survival (Larsen et al. 2008).

The results of the IRIS trial have led to FDA approval of imatinib for first-line treatment of patients with CP-CML in 2002 (Cohen et al. 2002b, 2005; Druker et al. 2001b).

5 Treatment Recommendations for the Use of Imatinib in Chronic Phase CML

Based upon the results achieved in the phase I, II, and III trials with imatinib, expert panels of the European Leukemia Net and the NCCN have developed guidelines for monitoring and treatment of CP-CML with imatinib (http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf; Baccarani et al. 2013; http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf; Table 3).

While the IRIS trial was performed, new guidelines for CML treatment were published and new BCR-ABL1 inhibitors dasatinib, nilotinib, bosutinib were developed. Nilotinib, dasatinib and bosutinib have been approved as first-line therapies in patients with CML in chronic phase based on results from phase III trials showing higher response rates than the comparator imatinib.

In case of suboptimal response to imatinib, a mutation analysis should be performed and treatment with a 2nd generation TKI such as dasatinib, nilotinib, bosutinib or third-generation TKI as ponatinib should be discussed as they are approved in this setting (see according chapters). Furthermore, the option of allogeneic stem cell transplantation should be considered. New third-generation TKI are currently under investigation.

Table 3 Response definitions to first-line treatment with TKIs (any TKI) (adapted from Baccarani et al. 2013)

Timepoint	Optimal response	Warning	Treatment failure
Baseline	NA	High risk or CCA/Ph^+ Major Route	NA
3 months	BCR-ABL1 $\leq$ 10% and/or Ph^+ $\leq$ 35%	BCR-ABL1 > 10% and/or Ph^+ 36–95%	Non-CHR and/or Ph^+ > 95%
6 months	BCR-ABL1 < 1% and/or Ph^+ 0	BCR-ABL1 1–10% and/or Ph^+ 1–35%	BCR-ABL1 > 10% and/or Ph^+ > 35%
12 months	BCR-ABL1 $\leq$ 0.1%	BCR-ABL1 > 0.1–1%	BCR-ABL1 > 1% and/or Ph^+ > 0
Any time point	BCR-ABL1 $\leq$ 0.1%	CCA/Ph^- (−7, or 7q−)	Loss of CHR/CCgR
			Confirmed loss of MMR[a]
			Mutation
			CCA/Ph^+

CHR complete hematologic response
CCgR complete cytogenetic response (absence of Ph^+)
MMR major molecular response (ratio BCR-ABL/ABL > 0,10)
CCA/Ph^+ clonal chromosome abnormalities in Ph^+ cells
CCA/Ph^- clonal chromosome abnormalities in Ph^- cells
[a]In 2 consecutive tests, of which one with a BCR-ABL1 transcripts level $\geq$ 1%

6 Imatinib in Combination with Other Drugs

In order to further optimize the efficacy of imatinib in CML, a number of approaches have been investigated in phase II trials. Increase in the dose of imatinib monotherapy to 800 mg/d in CP-CML has shown earlier complete cytogenetic responses but is associated with more side effects (Cortes et al. 2003; Hehlmann et al. 2011; Hehlmann et al. 2017). In addition, imatinib in combination with other agents, such as interferon-α, cytarabine, and homoharringtonine, has been examined. Patients treated with combination therapy reached faster cytogenetic remission, but also experienced higher rates of toxicity, in particular myelotoxicity (Baccarani et al. 2003, 2004; Gardembas et al. 2003). Several major phase III trials compared standard dose imatinib with increased doses and combinations with cytarabine or interferon. In these trials, the induction of faster cytogenetic as well as molecular remissions could be shown in patients receiving higher dosages of imatinib. However, the increased dosage if imatinib as well as when used in combination with cytarabine was more toxic than standard dose (Hehlmann et al. 2017; Preudhomme et al. 2010).

7 Imatinib: Other Targets

Other molecular targets of imatinib are the platelet-derived growth factor receptor (PDGF-R) and the stem cell factor receptor (c-KIT) (Buchdunger et al. 1995, 2000; Heinrich et al. 2002a).

Aberrant PDGF receptors have been shown to deregulate the growth of a variety of cancers, such as myeloproliferative disorders (Pardanani and Tefferi 2004), e.g., in hypereosinophilic syndrome (FIP1L1/PDGFR-rearrangement) (Jovanovic et al. 2007), CMML involving the 5q33 translocations (Jovanovic et al. 2007), carcinomas, melanoma, gliomas, and sarcomas, including dermatofibrosarcoma protuberans (Barnhill et al. 1996; Greco et al. 2001).

c-KIT is expressed in a variety of human malignancies, including germ cell tumors, neuroblastoma, melanoma, small cell lung cancer, breast and ovarian cancer, acute myeloid leukemia, mast cell disorders, and malignant GIST.

In most of these diseases, the exact role of c-KIT expression is not defined in mastocytosis and GISTs, activating mutations of c-KIT have been identified (Heinrich et al. 2003a, b).

In approximately 60% of cases of GIST, there are mutations in *c-kit*[105] in the juxtamembrane domain. In most of the remaining cases, mutations in exon 13 and exon 9 have been found. The mutations lead to constitutive activation of the receptor without its ligand (Lux et al. 2000). Imatinib at a dosage of 400 mg once or twice daily was investigated in the EORTC 62,005 and S0033 trials. Both studies confirmed the benefit of imatinib 400 mg once daily, which was first reported in the B2222 study, (CR rates 3–6%, PR rates 45–48%, and SD rates 26–32%) (Verweij et al. 2004; Casali et al. 2015; Demetri 2002). No OS difference (47–55 months) was demonstrated between the 400 and 800 mg doses, establishing 400 mg once daily as the standard dose. Pooled analysis of the two EORTC trials showed that patients with exon 9 mutations treated with the higher imatinib dose had a longer PFS. These patients should therefore receive 2 mg × 400 mg, if tolerated. In the BFR14 trial patients were randomly assigned to stop therapy after 1, 3, or 5 years. Patients who stopped therapy had a shorter PFS compared with those who remained on treatment. These data support uninterrupted treatment with imatinib (von Mehren and Joentsuu 2018).

After approval of imatinib in metastatic GIST, the role of adjuvant treatment after successful resection was investigated.

In two of three randomized trials, adjuvant imatinib administered for 1 or 2 years improved recurrence-free survival compared with observation or placebo. However, an overall survival benefit was not demonstrated in either study. In the third trial, GIST patients with a high risk for relapse were randomized to receive adjuvant imatinib for 1 or 3 years after surgery, respectively. After a median follow-up of 7.5 years, patients who received 3 years of imatinib had longer recurrence-free survival while OS was comparable between both arms. In all three studies, patients with KIT exon 11 deletion mutations had the most benefit from adjuvant imatinib (Corless et al. 2014; Joensuu et al. 2012). Two further phase III trials are ongoing.

Table 4 Randomized trials that led to approval of imatinib (FDA) for advanced GIST (modified from von Mehren and Joentsuu 2018)

Trial/reference	Line of therapy	Allocation group	Median PFS	Median OS
B2222 van Oosterom et al. (2001), Blanke et al. (2008)	Imatinib, first line	Imatinib 400 versus 600 mg	20 versus 26 months (p = 0.371)	57 versus 57 months; HR, 0.87 (p = 0.551).
S0033 Demetri et al. (2002), Verweij et al. (2004)	Imatinib, first line	Imatinib 400 mg daily versus 400 mg twice daily	18 versus 20 months (p = 0.13)	55 versus 51 months; HR, 0.98; (95% CI, 0.79 to 1.21) (p = 0.83).
EORTC Casali et al. (2015)	Imatinib, first line	Imatinib 400 mg daily versus 400 mg twice daily	1.7 versus 2.0 years; HR, 0.91; (95% CI, 0.79–1.04) (p = 0.18)	3.9 years in both arms; HR, 0.93; (95% CI, 0.80–1.07) (p = 0.31)

Patients with a substantial risk for relapse should be treated for at least 3 years with imatinib. However, the optimal duration remains unknown. Mutation analysis of kit and PDGFRA is mandatory prior to initiation of adjuvant therapy because GISTs with PDGFRA D842 V mutation or lacking a mutation in KIT or PDGFRA are unlikely to benefit from adjuvant imatinib (see for review von Mehren and Joensuu 2018) (Table 4).

8 Side Effects/Toxicity

Hematologic side effects of imatinib are shown in Tables 5 and 6. Grade 3 or 4 neutropenia, thrombocytopenia, or anemia was seen in all phase II trials and the phase III study. While grade 3/4 neutropenia occurred in first-line treatment of CP-CML in about 17%, in accelerated and blastic phase, it could be detected in approximately 60% of patients. In addition, in advanced phase, CML thrombocytopenia and anemia are more frequently than in CP-CML (first or second line).

Typical non-hematologic side effects in phase II trials of imatinib in CML are shown in Table 5 (Cohen et al. 2002b, 2005; Guilhot 2004). In the IRIS trial, most of the side effects of imatinib were mild to moderate, with the most common being edema, muscle cramps, diarrhea, nausea, skin rashes, and myelosuppression as shown in Table 5 (Druker et al. 2006; O'Brien et al. 2003b).

Recently, it has been suggested that imatinib may cause cardiotoxicity (Kerkela et al. 2006). However, a preexisting condition predisposing to congestive heart failure (CHF) could not be excluded in these patients. Furthermore, a follow-up

Table 5 Adverse events >10% in the phase II CML trials (Guilhot 2004; Cohen et al. 2002a, b)

Reported or specified term	CML-CP[a] after IFN-failure/ intolerance		CML-AP[b]		CML-myeloid BC[b]	
	N = 532		*N* = 235		*N* = 260	
	Dosage: 400 mg		Dosage 600 mg: *n* = 158		Dosage 600 mg: *n* = 223	
			Dosage 400 mg: *n* = 77		Dosage 400 mg: *n* = 37	
	All grades (%)	Grades 3/4%	All grades (%)	Grades 3/4%	All grades (%)	Grades 3/4%
Hematologic adverse events						
Anemia		4		36		50
Neutropenia		33		58		62
Thrombocythemia		16		42		58
Non-hematologic AEs						
Nausea	60	2	71	5	70	4
Fluid retention	66	3	73	6	71	12
Superficial edema	64	2	71	4	67	5
Other fluid retention	7	2	7	2	22	8
Muscle cramps	55	1	42	0.4	27	0.8
Diarrhea	43	2	55	4	42	2
Vomiting	32	1	56	3	54	4
Hemorrhage	22	2	44	9	52	19
GI hemorrhage	2	0.4	5	3	8	3
CNS hemorrhage	1	1	2	0.9	7	5
Musculoskeletal pain	35	2	46	9	43	9
Skin rash	42	3	44	4	35	5
Headache	34	0.2	30	2	27	5
Fatigue	40	1	41	4	29	3
Arthralgia/joint pain	36	1	31	6	25	4
Dyspepsia	24	0	21	0	11	0
Myalgia	25	0.2	22	2	8	0
Weight gain	30	5	14	3	5	0.8
Pyrexia	17	1	39	8	41	7
Abdominal pain	29	0.6	33	3	31	6
Cough	17	0	26	0.9	14	0.8
Dyspnea	9	0.6	20	7	14	4
Anorexia	6	0	17	2	14	2
Constipation	6	0.2	15	0.9	15	2
Nasopharyngitis	18	0.2	16	0	8	0
Night sweats	10	0.2	14	1	12	0.8
Pruritus	12	0.8	13	0.9	8	1
Epistaxis	5	0.2	13	0	13	3

(continued)

Table 5 (continued)

Reported or specified term	CML-CP[a] after IFN-failure/ intolerance		CML-AP[b]		CML-myeloid BC[b]	
	N = 532		*N* = 235		*N* = 260	
	Dosage: 400 mg		Dosage 600 mg: *n* = 158		Dosage 600 mg: *n* = 223	
			Dosage 400 mg: *n* = 77		Dosage 400 mg: *n* = 37	
	All grades (%)	Grades 3/4%	All grades (%)	Grades 3/4%	All grades (%)	Grades 3/4%
Hypokalemia	5	0.2	8	2	13	4
Petechiae	1	0	5	0.9	10	2
Pneumonia	3	0.8	8	6	12	6
Weakness	7	0.2	9	3	12	3
Upper respiratory tract infection	15	0	9	0.4	3	0
Dizziness	13.0	0.2	12	0	11	0.4
Insomnia	13	0.2	13	0	10	0
Sore throat	11	0	11	0	8	0
Ecchymosis	2	0	6	0.9	11	0.4
Rigors	8	0	11	0.4	10	0
Asthenia	6	0	11	2	5	2
Influenza	10	0.2	6	0	0.8	0.4

CP chronic phase, *AP* accelerated phase; *BC* blast crisis, *AE* adverse event
[a]Adverse events considered possibly related to treatment
[b]All adverse events regardless of relationship to treatment

Table 6 Most frequently reported AEs: first-line imatinib at 7-year follow-up: (Druker et al. 2006; O'Brien et al. 2008)

Most common adverse events (by 5 years)	All grade AEs patients (%)	Grade 3/4 AEs patients (%)
Superficial edema	60	2
Nausea	50	1
Muscle cramps	49	2
Musculoskeletal pain	47	5
Diarrhea	45	3
Rash/skin problems	40	3
Fatigue	39	2
Headache	37	<1
Abdominal pain	37	4
Joint pain	31	3
Elevated liver enzymes	5	5
Hematologic toxicity		
Neutropenia	60.8	17
Thrombocytopenia	56.6	9
Anemia	44.6	4

Only serious adverse events (SAEs) were collected after 2005. Grade 3/4 adverse events decreased in incidence after years 1–2

examination of the Novartis database of imatinib clinical trials including >5600 years of exposure to imatinib found an incidence of CHF in imatinib recipients of 0.2% cases per year with a possible or probable relationship to the drug. In the IRIS trial, the incidence of cardiac failure and left ventricular dysfunction was estimated at 0.04% per year in the imatinib arm compared to 0.75% in interferon-a- and ara-C-treated patients (Hatfield et al. 2007). The final analysis after a median follow-up of 10.9 years showed cardiac SAEs, regardless of study drug relationship in 7.1% of patients treated with frontline imatinib. Serious events of a second neoplasm could be seen in 11.3%. No new safety signals were observed since the 5-year analysis (Hochhaus et al. 2017).

In an early trial in GIST, adverse events were similar to CML patients and included edema, fluid retention, nausea, vomiting, diarrhea, myalgia, skin rash, bone marrow suppression, bleeding, and elevations in aspartate aminotransferase, alanine aminotransferase, or bilirubin. Gastrointestinal bleeding or intratumoral hemorrhage occurred in seven patients (5%) and was not correlated with thrombocytopenia or tumor bulk. Other non-hematologic side effects included fatigue and gastrointestinal complaints which were usually mild to moderate. The most common laboratory abnormality was anemia. Fluid retention and skin rash were reported more often in patients treated with 800 mg/day. Based upon these data, escalation of imatinib dosing up to 800 mg/day for patients with progressive disease was approved (Blanke et al. 2008; Heinrich et al. 2008). However, 26% of patients receiving imatinib for 3 years in the adjuvant setting discontinued treatment for causes other than relapse (Joensuu et al. 2012).

9 Clinical Pharmacology and Drug Interactions

Imatinib AUC is dose proportional at the recommended daily dose range of 400 and 600 mg. Within 7 days, approximately 81% of the dose is eliminated, 68% in feces, and 13% in urine.

Cytochrome P450 (CYP3A4) is the major enzyme responsible for imatinib metabolism, and both imatinib and CGP74588 appear to be potent in vitro CYP2D6 inhibitors. Imatinib plasma concentrations may be altered when the drug is administered with inhibitors or inducers of CYP3A4. When CYP3A4 inhibitors, e.g., itroconazole, ketoconazole, erythromycin, or clarithromycin, are co-administered with imatinib, its metabolization may be decreased. CYP3A4 inducers, such as dexamethasone, phenytoin, rifampicin, carbamazepine, phenobarbital, may increase imatinib metabolism. Furthermore, increased plasma concentrations of drugs which are substrates of CYP3A4, e.g., simvastatin, cyclosporine, and others, may be the result of imatinib use (Cohen et al. 2002b, 2005; Lyseng-Williamson and Jarvis 2001; Mauro et al. 2002).

In a small number of children with Ph^+ ALL imatinib plasma levels as well as of its metabolite CGP74588 were measured. Imatinib plasma levels were similar to those in adult patients. However, AUC of CGP74588 was only 5–24% of the parent

drug's AUC, and it was eliminated much faster than in adults indicating a lesser role of the metabolite in antileukemic activity (Marangon et al. 2009).

In the phase III (IRIS) trial, the correlation of imatinib pharmacokinetics and the response to treatment as well as to side effects could be shown (Larsen et al. 2008).

10 Biomarkers

10.1 CML

10.1.1 Disease Progression and Imatinib Resistance

Resistance to imatinib includes de novo resistance and relapse after an initial response. The frequent and durable responses in CP-CML are caused by the selective inhibition of BCR-ABL by imatinib. In accelerated and blastic phase CML as well as in Ph^+ ALL, the combination of high numbers of proliferating tumor cells and genomic instability may lead to secondary genetic alterations, independent of BCR-ABL (von Bubnoff et al. 2003). In the majority of patients who respond to imatinib and then relapse, reactivation of the BCR-ABL tyrosine kinase could be shown. This indicates that BCR-ABL-dependent mechanisms either prevent imatinib from reaching its target or render the target insensitive to BCR-ABL. In the former category are mechanisms such as increased drug efflux through the multidrug resistance gene or protein binding of imatinib while the latter include mutations in the catalytic domain, the P-loop, and other mutations (Druker 2008; Gorre et al. 2001). Over 70 point mutations have been demonstrated to play a role in primary and secondary resistance to imatinib, respectively (Hochhaus et al. 2011; Fig. 4).

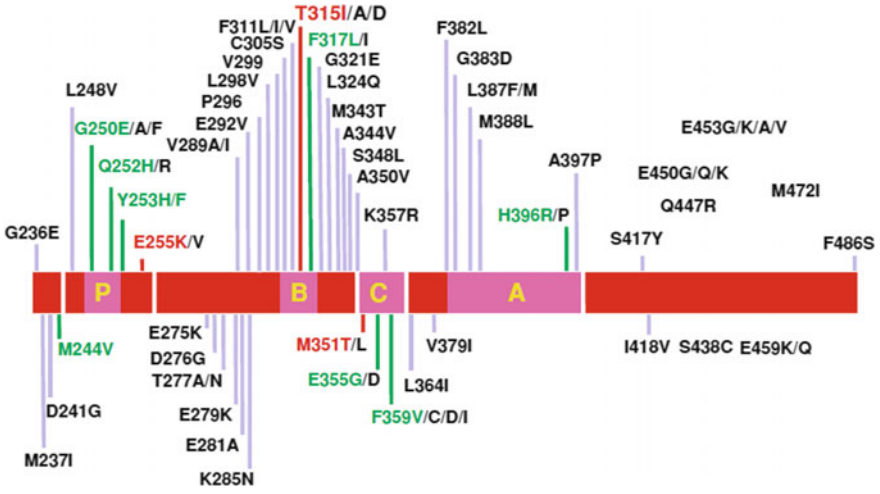

Fig. 4 Map of BCR-ABL kinase domain mutations associated with clinical resistance to imatinib (adapted from Branford and Hughes 2006). *P* P-loop, *B* imatinib binding site, *C* catalytic domain, *A* activation loop. Amino acid substitutions in *green indicate* mutations detected in 2–10% and in *red* in >10% of patients with mutations.

Gene amplification or overexpression of BCR-ABL as reason for resistance is seen occasionally (Shah et al. 2008; Shah and Sawyers 2003).

Understanding the underlying mechanisms of resistance has led to the development and investigation of new second- and third-generation tyrosine kinase inhibitors (Mueller 2009; Schiffer 2007) (see chapters bosutinib, dasatinib, nilotinib, and ponatinib).

10.2 GIST

Other molecular targets of imatinib are the platelet-derived growth factor receptor (PDGF-R) and the stem cell factor receptor (c-KIT) (Buchdunger et al. 1995, 2000; Heinrich et al. 2002a).

In GISTs, activating mutations of c-KIT and PDGF-R have been identified (Heinrich et al. 2003a, b).

In approximately 60% of cases of GIST, there are mutations in *c-kit*[105] in the juxtamembrane domain. In most of the remaining cases, mutations in exon 13 and exon 9 have been found. The mutations lead to constitutive activation of the receptor without its ligand (Lux et al. 2000). The mutational status is being used for the choice and duration of adjuvant therapy. In case of a PDGFRA D842V mutation, no adjuvant therapy is indicated. In the presence of wild-type kit, the situation has to be discussed on an individual base. In exon-11 and all mutations except exon-9 mutations, adjuvant therapy should be performed with 400 mg imatinib while in the presence of exon-9-mutations, 800 mg/d should be used (Joensuu et al. 2012; von Mehren and Joentsuu 2018).

11 Summary and Perspectives

The development of imatinib mesylate resembles the progress made in molecular biology over the past 30 years and has changed the landscape of cancer treatment leading toward causative treatment not only of CML and GIST but also for other malignancies.

After identification of the critical role of BCR-ABL in the pathogenesis of CML, less than 15 years went by until the development of imatinib which became the standard of care for patients in CP-CML. It has specific activity against a limited number of targets and has been shown to be highly effective not only in CML but also in other hematologic malignancies and solid tumors such as GIST. Side effects of treatment are mild to moderate. In addition to the originator product, after running out of the patent rights there are several generic versions of imatinib available in the EU and in the USA. The understanding of mechanisms of resistance and disease progression has furthermore lead to the development of second- and third-generation tyrosine kinase inhibitors which are even more effective in first-line therapy of CP-CML and have each a distinct profile of side effects.

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