# Therapeutic options for chronic myeloid leukemia: focus on imatinib (Glivec®, Gleevec™)

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**Abstract:** Treatment options for chronic myeloid leukemia (CML) have changed dramatically during the last decades. Interferon-α treatment and stem cell transplantation (SCT) clearly improved survival over conventional chemotherapy and offered the possibility of complete and durable responses. With the advent of the small molecule inhibitor imatinib mesylate (Glivec®, Gleevec™) targeting the causative Bcr-Abl oncoprotein, the era of molecular cancer therapy began with remarkable success especially in chronic phase patients. Today, imatinib is the first-line treatment for CML. However, imatinib does not appear to be capable to eliminate all leukemia cells in the patients and pre-existing as well as acquired resistance to the drug has been increasingly recognized. To overcome these problems, several strategies involving dose escalation, combinations with other agents, and novel Bcr-Abl inhibitors have been developed.
**Keywords:** CML therapy, imatinib, SCT, novel kinase inhibitors

## Introduction

Basic research during the past decades has resulted in considerable advances in our knowledge of the biology underlying neoplastic disorders. This provides the basis for the development of molecular targeted therapies we are witnessing today. Several new molecular pharmaceuticals now pave their way to clinical practice. One of the best examples in this context is the development of new treatment strategies for chronic myeloid leukemia (CML), the first human malignancy which was linked to an acquired genetic abnormality (Nowell and Hungerford 1960; Rowley 1973). Biology, clinical presentation and diagnostics of CML have been extensively reviewed elsewhere (Faderl et al 1999a, b; Sawyers 1999; Barnes and Melo 2002; Vardiman et al 2002; Cortes 2004; Hughes et al 2006). In this review we present the current knowledge on CML treatment with focus on imatinib. For this, we searched MEDLINE from 1960 to May 2007 and used information obtained during the 46th, 47th, 48th annual meetings of the American Society of Hematology (San Diego, December 2004, Atlanta, December 2005, and Orlando, December 2006), and the 43th annual meeting of the American Society of Clinical Oncology (Chicago, June 2007).

## Cytoreductive chemotherapy

In 1953 busulfan was introduced into clinical practice. The substance rapidly became treatment of choice for CML based on its superiority compared to radiation therapy but was associated with a number of serious side effects including infertility and the risk of bone marrow aplasia, pulmonary, hepatic, and cardiac fibrosis (Silver et al 1999; Lee 2000). Subsequently, busulfan has been replaced by the less toxic Hydroxyurea (Hehlmann et al 1993; Chronic Myeloid Leukemia Trialists' Collaborative Group 1997) a substance that was introduced into clinical practice in the late 1960s and possesses a wide therapeutic window. Both chemotherapeutics provided symptomatic and hematologic improvement in the chronic phase and resulted in a somewhat prolonged

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survival. But none of these substances induces cytogenetic remissions in a significant proportion of patients.

## Interferon-α

Interferon-α was introduced in the 1980s (Talpaz et al 1983, 1986). In contrast to conventional cytoreductive chemotherapies Interferon-α was capable of inducing complete cytogenetic remissions in varying frequencies up to 26% in chronic phase patients (Silver et al 1999) and extending survival (Hehlmann et al 1994; Chronic Myeloid Leukemia Trialists' Collaborative Group 1997). Interferon-α was the first pharmacological treatment that significantly affected the diseases natural course. The latest updates of the major Interferon-α studies reported a 9-year or 10-year overall survival ranging from 27%–53% (Baccarani et al 2003). Major cytogenetic remissions (<35% $Ph^+$ metaphases) were associated with prolonged survival although most patients remain *bcr-abl* PCR positive if sensitive techniques are used (Hochhaus et al 1995, 1996, 2000). Patients that achieve a complete cytogenetic remission are likely to do very well and long term survivors are observed within this group of patients (Hehlmann et al 1994; The Benelux CML Study Group 1998; Bonifazi et al 2001).

However, side-effects limit the clinical utility of Interferon-α. These include fatigue, myalgias, arthralgias, headaches, weight loss, depression, diarrhea, neurological symptoms, memory changes, hair thinning, autoimmune diseases, and cardiomyopathy (Talpaz et al 1991; Sacchi et al 1995; Wetzler et al 1995; O'Brien et al 1996). Efforts to further improve results of Interferon-α included the retrieval for optimized dosing (Kluin-Nelemans et al 2004), the evaluation of pegylated Interferon-α (Michallet et al 2004), and the combination with other substances like Cytarabine (Guilhot et al 1997; Kantarjian et al 1999; Silver et al 2003; Kuhr et al 2003).

## Allogeneic stem cell transplantation

Until now allogeneic stem cell transplantation (SCT) is the treatment modality proven to cure more CML patients than all other treatment options. However, the utility of SCT is hampered by side-effects including immunodeficiency, infections, organ toxicity from the conditioning regiment, and acute as well as chronic graft versus host disease leading to significant treatment related mortality. The longest follow-up of patients who received matched sibling SCT has been reported by the European Group for Blood and Marrow Transplantation (EBMT) on 2628 patients treated between 1980 and 1990 (Gratwohl et al 2006). Overall survival at 20 years was 34% for all patients, 38% for patients who received transplants in first CR and 49% for those who had an EBMT risk score of 0–1. Several prognostic factors in CML patients receiving allogeneic SCT had been described, including age, interval from diagnose to HSCT, disease phase, donor-recipient sex match, and donor type (Gratwohl et al 1998; Passweg et al 2004).

The efficacy of allogeneic SCT for treatment of CML is largely related to alloimmune effects, as demonstrated by the excellent results of donor lymphocyte infusions (DLI) in case of post transplant relapse (Guglielmi et al 2002).

The best results from SCT have been obtained when the procedure was accomplished early in the disease course in young patients lacking significant co-morbidities with a suitable HLA-matched donor. Hence, young patients with high-risk CML and an optimal stem cell donor may have the greatest benefit from an early transplant.

Prior to the introduction of tyrosine kinase inhibitors into clinical practice, chronic phase was the most common single indication for allogeneic SCT. The considerable reduction in the numbers of transplants reported to the EBMT and the IBMTR since 1998/99 reflected efficacy, excellent duration of remissions, tolerability, and increased use of tyrosine kinase inhibitors in these patients (Gratwohl et al 2004; Giralt et al 2007). This resulted in the recommendation to treat all newly diagnosed adult patients with imatinib unless exceptional circumstances prevail (Baccarani et al 2006). Consequently, despite several improvements in the field of allogeneic SCT, its place is now as a salvage strategy for patients failing on imatinib therapy. In addition, with the advent of second-generation tyrosine kinase inhibitors such as dasatinib and nilotinib, the use of allogeneic SCT may be delayed further in the course of a patient's disease. In this regard superior estimated 2-year survival rates reported for subsequent treatment with nilotinib or dasatinib compared to allogeneic SCT in chronic phase but not in accelerated phase or blast crisis CML post-imatinib failure (Kantarjian et al 2007b) are interesting. However, valid long term survival comparisons between allogeneic SCT and non-transplant second line treatment approaches post-imatinib failure are not available at the moment.

The role of SCT as second- or third-line treatment in chronic phase CML is further assisted by the recently published results of the German CML III study. Herein 354 previously stratified adult patients with chronic phase CML eligible for allogeneic SCT were included. 135 patients had a matched sibling donor of which 91% received a transplant within a median of 10 months from diagnosis. 219 patients had no donor and received conventional drug treatment. With a median observation time of 8.9 years survival was significantly

superior for the conventional drug treatment, superiority being most pronounced in low risk patients. Although Interferon-α was used as primary conventional treatment in this trial, the main results are valid and relevant in the imatinib era, as the majority of patients switched to imatinib during the observation period of the study (Hehlmann et al 2007).

The decision to proceed to allogeneic SCT has to be based on a balance of risks. CML disease risk scores (Sokal et al 1984; Hasford et al 1998) and transplant associated risk scores for CML patients (Gratwohl et al 1998; Passweg et al 2004) provided assistance to this decision. However, patients included in historical analyses on which these scores are based were treated over a decade ago. With the improvements in HLA-matching, patient selection and supportive care, transplant outcomes are better today and specialized centers have shown nearly comparable results with related and unrelated donor transplants, especially in low risk patients (Weisdorf et al 2002) with a 3-year overall survival rate of 86% in matched related donor SCT for chronic phase CML (Radich et al 2003). The EBMT reported an improvement of the 2-year survival from 53% to 61% in the most recent years due to a reduction in transplant-related mortality from 41% to 30% in all patients and from 31% to 17% in low-risk patients (Gratwohl et al 2006). Outcome improvement of allogeneic SCT during the last decade is pronounced in patients with a low (0–1) risk score, where overall survival has increased to 80% in the more recent transplants. Unfortunately, improvements for patients in accelerated phase and blast crisis have been smaller (Gratwohl et al 2006).

Because SCT is mostly used as a salvage treatment after imatinib failure, the impact of imatinib treatment prior to allogenic SCT was of great interest. Imatinib treatment preceding allogeneic SCT neither increased transplantation-related morbidity nor mortality (Shimoni et al 2003; Kim et al 2004; Zaucha et al 2005; Bornhäuser et al 2006; Deininger et al 2006; Stylian et al 2006; Oehler et al 2007; Weisser et al 2007). Additionally, imatinib was found to control leukemia in patients relapsing after allogeneic transplant (Kantarjian et al 2002c; Olavarria et al 2003; DeAngelo et al 2004) and has also been studied as additional treatment early after allogeneic SCT in high risk Philadelphia chromosome positive leukemias (Carpenter et al 2007).

## Imatinib mesylate (Glivec®/Gleevec™)

### Development and early trials

Improvements in the understanding of the molecular mechanism underlying CML has led to the evolution of targeted therapies. In the early 1990s, Lyndon and Matter worked on the development of specific tyrosine kinase inhibitors. From this drug discovery program, imatinib was generated. Imatinib is a 2-phenylaminopyrimidin derivate (Figure 1) and was initially developed as a specific platelet-derived growth factor receptor (PDGFR) inhibitor, but was later found to inhibit autophosphorylation of Abl and c-Kit. The substance showed promising in vitro and in vivo activity in Bcr-Abl positive CML and ALL cell lines (Druker et al 1996; Buchdunger et al 1996). Imatinib binds to the ATP binding pocket and stabilizes the inactive form of the Abl kinase (Figure 3, left panel) (Schindler et al 2000). It functions as a competitive inhibitor of the Bcr-Abl tyrosine kinase leading to inhibition of proliferation, restoration of cell cycle control, induction of apoptosis and reversal of genetic instability in Bcr-Abl dependent cells in vitro (Gambacorti-Passerini et al 1997; Oetzel et al 2000; Jonuleit et al 1998; Jonuleit et al 2000; van der Kuip et al 2004).

Eighty-three CML patients who failed on Interferon-α treatment or who could not tolerate the drug, were enrolled in the first phase I trial with imatinib. Imatinib doses of 25–1000 mg per day were evaluated. Dose limiting toxicity was not encountered, although at imatinib dosages above 750 mg per day a higher frequency of severe toxicities occurred. Notably, complete hematological remissions were reported in 53 of 54 patients receiving an imatinib dose of 300 mg or more per day and 31% of these patients achieved a major cytogenetic remission. Hematological responses usually occurred within the first month of treatment, whereas cytogenetic responses generally required at least 3 months of treatment (Druker et al 2001). Subsequently, open-label single-arm phase II trials were conducted in three different groups of CML patients, namely chronic phase after Interferon-α failure, accelerated phase, and blast crisis. Imatinib was administered orally once daily and initially all patients received 400 mg per day. Early in these trials, however, the imatinib dose was increased to 600 mg per day for patients with accelerated phase and with blast crisis and patients with resistant or progressive disease could receive doses up to 800 mg per day (administered as 400 mg twice daily). The excellent efficacy results of these phase II trials are summarized in Table 1. Overall these trials also affirmed the acceptable toxicity profile of imatinib. These data clearly supported the accelerated FDA approval of the substance for the treatment of advanced CML (in accelerated or blastic phase or in chronic phase after Interferon-α failure) in the year 2001, followed by the approval as first-line treatment for chronic phase CML in the year 2002 (Cohen et al 2002).

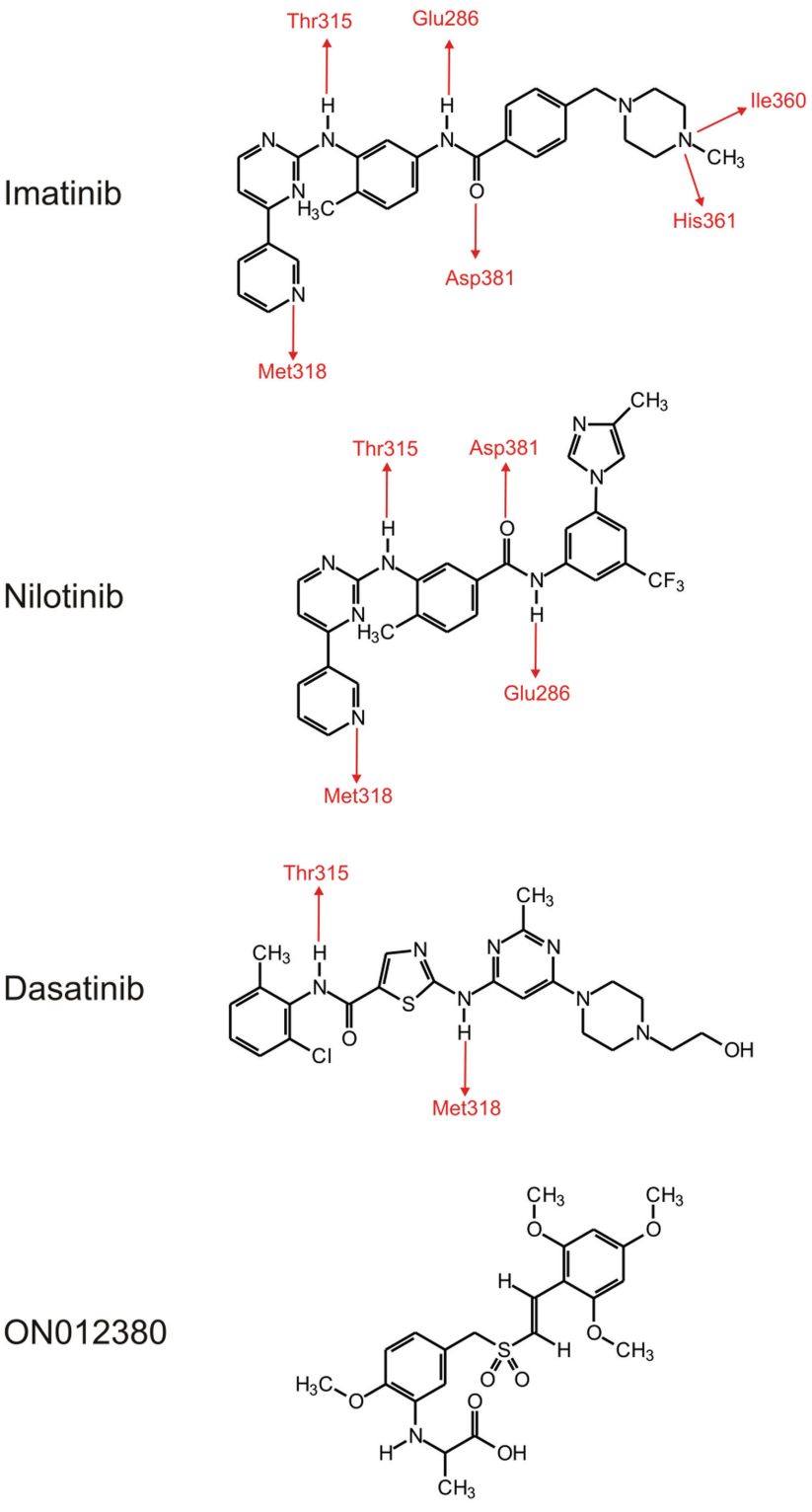


**Figure 1** Molecular structures of imatinib, nilotinib, dasatinib, and ON012380. The respective H-bond interactions with the Abl kinase domain are indicated in red. Derived from Weisberg et al (2006).

**Table 1** Efficacy of imatinib in early phase II trials

| | CML-CP, IFN failure | CML-AP | CML-BC |
|---|---|---|---|
| Hematological response | 88% | 63% | 26% |
| Major cytogenetic response | 49% | 21% | 13.5% |
| Complete cytogenetic response | 30% | 14% | 5% |

Adapted with permission from Cohen et al (2002).
**Abbreviations:** CML-CP, CML in chronic phase; IFN, interferon; CML-AP, CML in accelerated phase; CML-BC, CML in blast crisis.

## Results in chronic phase CML

The high complete cytogenetic remission rates, ranging from 41% to 64% with a 5-year progression-free survival of 69% and a 4-year overall survival of 86%–88% in different international trials with imatinib treatment in chronic phase CML patients resistant or intolerant to interferon-α further emphasized its exceptional potency (Kantarjian et al 2002a, b; Cervantes et al 2003; Kantarjian et al 2004a; Rosti et al 2004; Gambacorti et al 2005). The superiority of 400 mg imatinib daily over interferon-α combined with low dose cytarabine as first-line treatment in chronic phase CML was established in the International Randomized Study of Interferon and STI571 (IRIS), which included 1106 adult patients. The highly significant superiority after a median follow-up of 19 months with a complete hematological response rate of 95% versus 55%, a complete cytogenetic response rate of 76% versus 15%, an estimated one year 3 log reduction rate of the *bcr-abl* transcript in 39% versus 2%, and a survival free from progression to accelerated phase or blast crisis of 97% versus 91% ($p < 0.001$) profoundly changed CML treatment. Beside its surpassing efficacy the substance resulted in a clearly improved treatment compliance, quality of live and freedom from toxicity due to its lower rate of side-effects (O'Brien et al 2003; Hughes et al 2003). After a median follow-up of 60 months estimates of cumulative best rates of complete cytogenetic response among patients receiving imatinib in the IRIS trial were 87%, indicating that additional patients reach a complete cytogenetic response after more than 12-month of treatment. The estimated annual rate of treatment failure after the start of imatinib therapy was 3.3% in the first year, 7.5% in the second year, 4.8% in the third year, 1.5% in the fourth year, and 0.9% in the fifth year. The corresponding annual rates of progression to the accelerated phase or blast crisis were 1.5%, 2.8%, 1.6%, 0.9%, and 0.6%, respectively. This decrease in the proportion failing annually to imatinib treatment further supported that imatinib has to be regarded as standard of care first line treatment of CML (Druker et al 2006).

The 5-year overall survival rate of 89% for patients who received imatinib as initial therapy within the IRIS trial is higher than that reported in any previously published prospective CML trial. The IRIS trial allowed patients to cross over to the alternative treatment, and most patients in the Interferon arm either switched to imatinib or discontinued Interferon. Therefore, the intention-to-treat analysis found no significant difference in overall survival between the two study groups (Druker et al 2006). Randomized trials of interferon-α plus cytarabine, performed before the availability of imatinib, showed a 5-year overall survival of 68%–70% (Guilhot et al 1997; Baccarani et al 2002). As it seems unethical to withhold imatinib for patients failing on Interferon, such historical comparisons are the only way to study the impact of imatinib on survival. However, the magnitude of the survival advantage for therapy with imatinib over Interferon-α based therapies provides sufficient evidence for the superiority of this new drug (Roy et al 2006).

Despite the clinical use of imatinib for 9 years dose issues are not yet completely settled. The maximum tolerated dose was not identified in the early trials (Druker et al 2001). At 400 mg per day the blood concentration of imatinib was consistently higher than that required for 50% Bcr-Abl tyrosine kinase activity in vitro (Peng et al 2004; Schmidli et al 2005). 600 mg per day was likely to be more effective in accelerated and blastic phase CML and increasing the dose up to 800 mg per day can benefit a subgroup with either an inadequate cytogenetic response or disease progression (Kantarjian et al 2003a; Zonder et al 2003). Additionally, there is evidence that high dose imatinib (800 mg per day) results in superior response rate and progression free survival in patients with untreated early chronic phase CML than standard dose treatment (Aoki et al 2006).

Trials using high dose imatinib (Cortes et al 2003; Hughes et al 2004, 2005; Kantarjian et al 2004b) have not compared this approach with the standard dose of 400 mg on a randomized basis, thus the role of higher versus standard dose imatinib in the first-line treatment of chronic phase CML remains to be determined in the ongoing trials. However, from the pharmacologic point of view the simple one-dose-fits-it-all approach might not be optimal. Interestingly, mean through imatinib plasma levels were significantly higher in an imatinib treated group of patients with complete cytogenetic response than in the group without and higher in the group with major molecular response than in the group without (Picard et al 2007).

## Results in accelerated phase and blast crisis

In patients with accelerated phase CML a daily dose of 600 mg resulted in a complete hematological response rate

of 37%, a complete cytogenetic response rate of 19%, and a 3-year progression free survival of 40% (Talpaz et al 2002; Silver et al 2004). 25% of patients with blast crisis CML treated with imatinib achieved a complete hematological remission, but progression free survival was rather short, with a median of 10 months or less and only about 7% remaining progression free after 3 years (Sawyers et al 2002; Silver et al 2004). Clearly, long-term results with imatinib in these advanced CML stages are less impressive than in the chronic phase. Allogeneic SCT can cure a significant proportion of advanced stage CML patients but it is toxic and can not be offered to every affected patient. Definitely, further improvements in accelerated and blastic phase of CML are desperately needed.

## Pharmacokinetics

Bioavailability of imatinib in healthy volunteers is 92% (86%–99%) with a mean plasma terminal half-live of 13.5 (±0.9) hours for imatinib and 20.6 (±1.7) hours for the pharmacologically active N-desmethyl metabolite (CGP74588) (Gschwind et al 2005). In a patient with short bowel syndrome, an 80% decrease in imatinib plasma level due to impaired absorption has been demonstrated (Beumer et al 2006). This indicates the importance of considering gastrointestinal anatomic abnormalities or disorders when imatinib is dosed. Imatinib is approximately 95% bound to human plasma proteins, mainly albumin and α1-acid glycoprotein (A1AGP). The drug is eliminated predominantly via the bile in form of metabolites, one of them (CGP74588) shows comparable pharmacological activity to the parent drug. The fecal to urinary excretion ratio is approximately 5:1 (Peng et al 2005). Cytochrome P-450 (CYP) enzymes reduce or alter the pharmacologic activity of many drugs and facilitate their elimination (Wilkinson 2005). Imatinib is metabolized mainly by CYP3A4 or CYP3A5 and can competitively inhibit the metabolism of drugs that are CYP3A4 or CYP3A5 substrates. Interactions may occur between imatinib and inhibitors or inducers of these enzymes, leading to changes in the plasma concentration of imatinib as well as co-administered drugs (Peng et al 2005). Hepatic and renal dysfunction may result in more variable and increased exposure to imatinib, although typically not necessitating dosage adjustment (Peng et al 2005). Currently monitoring imatinib plasma levels is not routinely performed. However, growing evidence suggests that maintaining adequate plasma levels correlates with best responses (Larson et al 2006; Picard et al 2007).

## Toxicity and adverse events

The exceptional efficacy and tolerable toxicity profile of imatinib was the reason for an FDA approval after a relatively short follow-up. Meanwhile, a longer follow-up has revealed some additional toxicities which were initially not reported. Although, imatinib remains a generally well tolerated drug, some of its toxicities need to be mentioned and carefully monitored for they sometimes demand especial measures by the clinician. Second generation tyrosine kinase inhibitors now provide an opportunity to overcome imatinib-induced toxicities in some of the patients.

### Hematological cytopenias

Myelosuppression is particularly common in CML patients treated with imatinib and it is more pronounced in patients with advanced disease. Myelosuppression can occur at any time during imatinib therapy, but it usually starts within the first weeks of treatment. In the IRIS trial grade 3 neutropenia was experienced by 11% of patients and grade 4 neutropenia occurred in 2% of patients. Grade 3 thrombocytopenia occurred in 6.9% of patients, and grade 4 thrombocytopenia in less than 1% of patients (Hughes et al 2003; O'Brien et al 2003). It was mandatory in the protocol to interrupt therapy with imatinib for grade 3 or 4 myelosuppression in chronic phase CML patients. This did not apply to patients with accelerated phase and blast crisis with grade 3 or 4 myelosuppression, because of the life-threatening nature of the disease. Thus, using these guidelines myelosuppression was more common in trials with BC- or AP-CML (AP-CML: neutropenia grade 3/4: 23/35% and thrombocytopenia grade 3/4: 31/12%, BC-CML: neutropenia grade 3/4: 16/48% and thrombocytopenia grade 3/4: 29/33%) (Sawyers et al 2002; Talpaz et al 2002).

Hematopoiesis in CML patients is mainly derived from Ph-positive stem cells and with disease progression the progenitor cell compartment gradually becomes dominated by the Ph-positive clone (Petzer et al 1996). Therefore, myelosuppression may reflect rather delayed recovery of the normal hematopoietic cell compartment than the toxicity on hematopoietic cells. Accordingly, in vitro and in vivo data indicate that imatinib does not severely affect normal hematopoiesis (Druker et al 1996; Deininger et al 1997). Further evidence that imatinib does not significantly suppress normal hematopoiesis results from the recovery of normal blood counts in patients with advanced-phase CML during continuous therapy with imatinib. These observations indicate that myelosuppression induced by imatinib is much more a consequence of the therapeutic effect on the leukemic clone than an inhibitory effect on the normal hematopoiesis.

Details in the management of imatinib-induced side effects have been reviewed elsewhere (Deininger et al 2003).

In brief, the aggressiveness of therapy has to be balanced against the risk of progression of the disease. Dose reductions below 300 mg per day are unlikely to assist in the recovery of normal hematopoiesis but may allow emergence of imatinib-resistant leukemic clones. To manage myelosuppression of grade 3 to 4 G-CSF is an option (Marin et al 2003). Temporary interruption of treatment is preferred to dose reduction in chronic phase CML (Deininger et al 2003). In patients with advanced-phase disease, it is unclear whether the best option is to continue therapy with imatinib in the face of severe myelosuppression and to manage complications aggressively (as is standard practice in the management of acute leukemia) or alternatively, to act as with patients in chronic phase. A published approach in that situation has been to not interrupt therapy or reduce doses on the basis of thrombocytopenia, but to appropriately support these patients with platelet transfusions. In case of clinically significant bleeding, imatinib has to be stopped immediately until the bleeding is controlled. Furthermore, bone marrow should be examined for cellularity and residual leukemia when absolute neutrophile counts (ANC) drop below 500/mm$^3$ (Deininger et al 2003). In patients whose marrow remains hypercellular or with blasts greater than 30%, imatinib should be continued. If the marrow is hypocellular and the ANC is less than 500/mm$^3$ for 2–4 weeks a reduction of the imatinib dose, the temporary interruption of treatment or the use of myeloid growth factors for approximately 2 weeks are generally practicable options (Deininger et al 2003).

## Nonhematological toxicities

The most common nonhematologic side effects in phase II and III trials were nausea, muscle cramps, fluid retention, diarrhea, musculoskeletal pain, fatigue, and skin rashes. Only few patients experienced nonhematologic grade 3–4 toxicity. The incidence of some specific side-effects was different according to the stage of CML. For example, vomiting and fluid retention were more prevalent in advanced-phase disease, whereas musculoskeletal symptoms and weight gain were more common in the chronic phase (Cohen et al 2002; Deininger et al 2003). In the meantime, longer follow-up has revealed some additional nonhematological toxicities which were initially not reported.

## Gastrointestinal side-effects

Nausea and occasionally vomiting are toxicities frequently seen with imatinib. These side-effects are usually dose-related and mild. They can be avoided in most patients when imatinib is taken with food, which does not alter the drugs pharmacokinetics. Patients with a history of esophagitis or hiatal hernia are advised to take the drug at least 2 hours before bedtime and 800 mg doses should be taken as 400 mg bid with two separate meals to avoid local irritant effects on the esophageal and the gastric mucosa. If nausea cannot be adequately controlled by such simple measures administration of antiemetics (eg, metoclopramide or ondansetrone) can provide better relief to the patients.

Diarrhea is another relatively common dose-related side-effect of imatinib. It is possible that diarrhea is caused by local irritant effects. Alternatively, the inhibition of c-Kit, which is highly expressed in the interstitial pace maker cells of Cajal, has been discussed (Deininger et al 2003; Popescu et al 2006). Diarrhea can easily be managed by antidiarrheal co-medications in most of the symptomatic patients.

## Fluid retention and cardiotoxicity

Mild fluid retention and edema (often in the periorbital region) are other common dose-related toxicities of imatinib, occurring in about 50%–70% of the patients (Cohen et al 2002). For periorbital edema no specific therapy is required in most of the cases. Serious generalized fluid retention is a much less common but a potentially life-threatening events which has been reported in less than 1% of chronic phase, but in 3% and 6% of patients in accelerated phase and blast crisis, respectively (Cohen et al 2002). It can present as pulmonary edema, pleural or pericardial effusion, ascites, anasarca, joint effusion, and cerebral edema. Live threatening events have been attributed to this fluid retention syndrome and one death occurred from cerebral edema (Ebnoether et al 2002). The underlying mechanism in such generalized imatinib-induced fluid retention and edema may be not consistent. One possible explanation could be the inhibition of targets that are responsible for the integrity of capillaries by imatinib. Mice with homozygous deletions of *PDGF-B* or *PDGFR-β* genes have defective blood vessels and edema (Lindahl et al 1997) and *abl/arg* double knockout mice also have edema (Koleske et al 1998), suggesting such a role for these tyrosine kinases. Additionally, a monoclonal anti-PDGFRβ antibody (CDP 860) used as anti-cancer agent in an early phase clinical trial in 8 cancer patients resulted in fluid retention in 7 cases (Jayson et al 2005).

Another mechanism which may be the cause of fluid retention in some patients is the development of severe congestive heart failure (CHF), possibly due to a Abl related toxic cardiomyopathy, that was just recently described (Kerkela et al 2006). However, evidence of the clinical significance of imatinib-induced cardiotoxicity is still small.

There is a need for further studies to evaluate cardiotoxicity in patients receiving the substance, taking into account dose levels of the drug, pre-existing cardiac conditions, and the use of additional cardiotoxic drugs (Schellings et al 2007). For this, Atallah et al reviewed all serious adverse events reported during various imatinib trials (Atallah et al 2007a). Among 1276 CML patients treated with imatinib, 22 patients (1.7%) were identified as having CHF by the Framingham criteria. Patients who developed CHF were significantly older compared with patients who did not develop such symptoms and 82% of the patients with CHF had previous medical conditions predisposing to cardiac disease. This reconfirmed some of the previously recognized risk factors for imatinib-induced fluid retention (female sex, age over 65, and a history of cardiac or renal insufficiency) (Deininger et al 2003). Indeed, the incidence of CHF per age group was nearly identical to that reported for the general population in the Framingham study (Atallah et al 2007a). Half of the patients who developed CHF continued imatinib therapy with dose adjustments and management for their CHF-symptoms with no further complications (Atallah et al 2007a).

Thus, patients should be monitored closely for the presence of peripheral edema, rapid weight gain and other clinical signs of possible cardiac dysfunction. However, routine echocardiographic monitoring in otherwise asymptomatic patients treated with imatinib does not appear to be indicated. Cardiologic counseling and appropriate supportive measures (eg, salt-restriction, diuretics, ACE-inhibitors, beta blockers) should be initiated as soon as evidence for cardiac dysfunction occurs. In patients with severe fluid retention or cardiac dysfunction, imatinib has to be discontinued until the situation is adequately controlled with supportive measures (Deininger et al 2003). The decision whether imatinib should be reinitiated depends on the patients' disease risk and the availability of alternative treatment options. In cases with significant fluid retention not associated with cardiac dysfunction supportive treatment approaches also comprise salt restriction and diuretics as first line options. In very severe cases and in cases not responding to the first-line measures imatinib should be interrupted and sometimes glucocorticoids or occasionally thoracocentesis or pleurodesis might become necessary.

## Teratogenic and embryotoxic side-effects

Tyrosine kinases are critical signaling molecules for the cellular regulation of proliferation, differentiation, survival, function, and motility. Due to their fundamental role in cell biology possible adverse effects by a more or less specific inhibition of tyrosine kinases in pregnancy and early infancy could be expected. The importance of Abl for a proper embryonic development is underscored by the phenotype of *abl* knock out mice. These animals display increased perinatal mortality, runtedness, abnormal spleen, head, and eye development, and dysfunctions of the immune system (Schwartzberg et al 1991). Imatinib can be excreted with breast milk and preclinical data demonstrated the teratogenic and embryotoxic potential of the substance. Consequently, imatinib was not approved in breast feeding and pregnant women. Sexually active women in childbearing age that have to be treated with imatinib are advised to carefully exert contraception. Despite this advise, several pregnancies developed in women treated with imatinib during the last years with different outcomes being reported (Ali et al 2004; Ault et al 2006; Prabhash et al 2005; Choudhary et al 2006; Suppiah and Kalaycio 2006). A study on 180 pregnancies in women exposed to imatinib was recently presented (Pye et al 2006). Outcome data were shown for 125/180 (69%) cases. 63 pregnancies resulted in the birth of normal live infants. Thirty-five women underwent elective terminations, 3 following identification of fetal defects. The remaining group either had no defects or was of unknown status. There were 12 pregnancies with fetal abnormalities, resulting in 8 live and 1 still birth and 18 pregnancies ended in spontaneous abortion. Fetal abnormalities included among others several bony defects and cases with an exomphalos. Similar bony defects including exencephaly, encephaloceles and deformities of the skull bones had been described previously in animal models. Despite this, balancing the risk to the fetus of continuing imatinib against the risk to the mother of stopping treatment remains complex. Decisions have to be made on an individual basis after careful counseling of both parents (Pye et al 2006).

Male fertility is obviously preserved in at least some patients treated with imatinib. However, oligospermia and reduced sperm motility has been observed in animals and humans treated with imatinib (Seymour et al 2006). Clearly, one possibility for men desiring conception is the sperm cryopreservation before starting imatinib treatment.

## Musculoskeletal and metabolic side-effects

Painful musculoskeletal complaints are another common side-effect of imatinib. Muscle cramps occur mainly in the hands, feet, calves, and thighs. Despite the fact that ionized calcium and magnesium levels are usually normal in patients treated with imatinib, calcium and magnesium supplements, as well as quinine, can offer symptomatic relief to these

cramps (Deininger et al 2003) and the therapeutic effect of a chlordiazepoxide has recently been shown (Medeiros and Lipton 2006). The cause of this adverse effect is unclear. In some patients these symptoms coincide with clearance of leukemic cells from the bone marrow.

Hypophosphatemia and associated changes in bone and mineral metabolism have also recently been reported. These alterations appear to be dosage and age-dependent (Berman et al 2006; Joensuu and Reichardt 2006; Owen et al 2006). Serum phosphate levels were routinely measured in two clinical trials, including 403 patients. Hypophosphatemia of Common Toxicity Criteria grade 2 or higher was observed in 50% (33% had grade 2, 15% grade 3, and 1.5% grade 4) (Owen et al 2006). Chronic, untreated hypophosphatemia can result in impaired bone mineralization, rickets or osteomalacia. Therefore, it was advised to routinely monitor serum phosphate during imatinib therapy so that prompt phosphate replacement can be initiated (Owen et al 2006).

It was speculated, that imatinib negatively affects the formation and resorption of bone by inhibiting the PDGFR (Berman et al 2006). Prospective studies on calcium and bone metabolism demonstrated that altered bone remodeling and secondary hyperparathyroidism occurs early after the initiation of imatinib (Grey et al 2006). The most parsimonious explanation for these findings is that imatinib directly stimulates bone formation while restraining resorption (Dewar et al 2006). This effect might be explained by inhibition of macrophage-colony-stimulating factor (M-CSF) receptor c-fms, which is essential for osteoclast formation (Dewar et al 2006). An alternative explanation is that imatinib both inhibits the intestinal absorption of calcium (which induces secondary hyperparathyroidism) and the bone resorption (which abrogates the expected increase in this measure induced by parathyroid hormone). Both potential mechanisms involve direct skeletal effects of imatinib suggesting a role for imatinib -sensitive kinases in skeletal homeostasis in vivo (Grey et al 2006).

Imatinib might affect glucose homeostasis resulting in a reduced necessity for anti-diabetic treatment in some diabetic patients and hypoglycemia might be exacerbated in patients with gastrointestinal stromal tumors (GIST) exhibiting symptoms of non-islet cell-induced hypoglycemia. Physicians and patients should be aware of this potential adverse effect to carry out appropriate monitoring and adjustment of anti-diabetic treatment (Breccia et al 2004; Hamberg et al 2006).

Imatinib might also increase Levothyroxine replacement requirements in some hypothyroid patients, thus thyroid hormones should be additionally monitored after starting imatinib treatment in these patients (de Grot et al 2005, 2006).

### Cutaneous side-effects

Various imatinib-induced dermatologic side-effects have occurred including dermatitis, pigmentation anomalies, Sweet syndrome, pityriasis rosea-like eruptions, lichenoid reactions, erythema multiforme, acute generalized xanthematous pustulosis, and Stevens-Johnson Syndrome (Hsiao et al 2002; Rule et al 2002; Vidal et al 2002; Deininger et al 2003; Sanchez-Gonzalez et al 2003; Pavithran and Thomas 2005; Kuwano et al 2006; Martin et al 2006) and have been reviewed recently (Robert et al 2005; Scheinfeld 2006). In face of the clinical heterogeneity of the imatinib-induced cutaneous toxicities different pathomechanisms including direct toxic effects as well as hypersensitivity reactions are likely. Most skin reactions are mild and occur within the first 3 months of imatinib exposition. These cases often can easily be managed with antihistamines or topical steroids, but patients have to be followed closely. In more severe cases a short course of oral steroids can be used for treatment and imatinib should be interrupted temporarily. Severe cutaneous toxicities with desquamation are rare, but have been noticed in the context of imatinib treatment (Sanchez-Gonzalez et al 2003) including reports of Stevens-Johnson syndrome (Hsiao et al 2002; Rule et al 2002; Vidal et al 2002; Pavithran and Thomas 2005). In such cases, immediate discontinuation of imatinib and appropriate supportive care, including systemic steroids (eg, Prednisone at an initial dose of 1 mg/kg) are indicated. Depending on the clinical situation, it has been possible to restart imatinib after the rash has resolved. In such cases, Prednisone has typically been given at 1 mg/kg per day, tapering to 20 mg per day over several weeks and imatinib has been restarted at 100 mg per day and the dose increased by about 100 mg per week while tapering the steroids, assuming that the rash has not recurred (Deininger et al 2003). Nowadays for patients who had a severe skin reaction (eg, Stevens-Johnson syndrome) alternative treatment options should be considered first before restarting on imatinib.

### Hepatotoxicity

Imatinib-induced hepatotoxicity turned out to be less problematic than predicted from animal studies. However, different liver function test (LFT) abnormalities have been observed with imatinib, typical with an increase of transaminases, although increases in bilirubin have also been reported.

In general, grade 3 or 4 elevations in LFT are relatively rare. They have predominantly occurred in patients with advanced-phase disease in whom leukemic infiltration of the liver is a possible confounding factor (Deininger et al 2003). Rarely fatal cases of hepatic toxicity have been reported in patients treated with imatinib. One occurred in a patient in accelerated phase after prior bone marrow transplantation medicated with 600 mg imatinib and 3–3.5 g acetaminophen per day (Talpaz et al 2002; Cohen et al 2002). Whether this death was causally related to the combination of imatinib and acetaminophen is not known. Many other patients have taken these two drugs in combination safely. Nevertheless, caution is recommended and patients should be advised about the possible risk of taking imatinib together with higher doses of acetaminophen (Deininger et al 2003). The second cause of fatal liver failure was reported in a 61-year-old woman with polycythemia vera in spent phase/myelofibrosis who was included into a phase II trial evaluating the efficacy of imatinib in Bcr-Abl-negative myeloproliferative disorders (Lin et al 2003). Another patient was recently reported who died 3 days after liver transplant for the treatment of imatinib induced acute liver failure (Cross et al 2006).

Liver toxicity usually appears during the first few months of therapy but can also occur at later time points. The pathogenic mechanisms may not be homogenous and remain to be elucidated, though it appears to be a drug-induced inflammatory reaction on liver biopsies in some cases (Ohyashiki et al 2002; Ferrero et al 2006; Al Sobhi et al 2007; Dhalluin-Venier et al 2006).

Regarding hepatoxicity, monitoring of LFT should be performed routinely before imatinib treatment is started, every other week during the first month of therapy, and at least monthly thereafter (Deininger et al 2003). A practical approach to the management of imatinib-associated hepatotoxicity has been described in detail (Deininger et al 2003) and the interruption of imatinib in cases with grade 3–4 hepatotoxicity clearly is recommended. Additionally, Ferrero et al described a prompt regression of hepatotoxicity after the addition of steroids that allowed imatinib continuation and achievement of a complete cytogenetic response in three chronic phase patients (Ferrero et al 2006). Moreover, after a few months steroids were discontinued without recurrence of hepatotoxicity in spite of increased imatinib dosage in two patients up to 600 mg and 800 mg per day, respectively. Therefore, corticosteroids now can be regarded as a promising approach in imatinib-induced hepatotoxicity to avoid the permanent discontinuation of a very effective anti-neoplastic drug (Ferrero et al 2006). Anyway, as with other severe side effects second generation tyrosine kinase inhibitors now provide an opportunity to switch such patients to an alternative treatment, they are more likely to tolerate.

### Pulmonary toxicity

Cases of interstitial lung disease (ILD) attributed to imatinib have been published (Bergeron et al 2002; Ma et al 2003; Rosado et al 2003; Isshiki et al 2004) and reviewed (Atallah et al 2007a). A lager series reported 27 cases of ILD in patients treated with imatinib (Ohnishi et al 2006). Eleven of those patients had a pre-existing lung disease. In most of the patients ILD was treated with steroids, with a complete resolution in 7 patients and an improvement in 16 patients. Four of the 11 patients in whom imatinib was reintroduced after ILD improved experienced relapsing ILD. Although ILD associated with imatinib is probably rare, physicians should be alert to it. Management should include appropriate supportive measures, steroids and the discontinuation of imatinib. A decision about the eventual reintroduction should be based on the individual clinical characteristics and course, but in severe cases not promptly responding to steroids switching to an alternative treatment would be prudent.

### Other side effects

Similar to conventional cytoreductive chemotherapy, imatinib can cause a tumor lysis syndrome, requiring an appropriate management including prophylaxis for patients who are at risk (Ali et al 2007).

Novartis reported a statistically significant increase of renal, bladder, and preputial/clitorial tumors in rats after 2 years of imatinib administration (Drug label). Additionally Roy et al (2005) suggested an increased incidence of urothelial carcinomas in their patient population. Despite these concerns there was no increase of urothelial tumors observed in 9500 patients enrolled on the various clinical trials (Pilot et al 2006).

## Drug interactions

Interactions may occur between imatinib and inhibitors or inducers of CYP3A4 and CYP3A5 enzymes leading to changes in the plasma concentration of imatinib as well as that of co-administered drugs (Peng et al 2005). Agents that inhibit CYP3A4/5 might result in increased levels of imatinib. This substance class includes several clinically important drugs (eg, clarithromycine, cyclosporine A, fluoxetine, erythromycine, indinavir, itraconazole, nelfinavir, ritonavir, saquinavir, sertraline, verapamil, and voriconazole).

Grapefruit juice is another inhibitor of CYP3A4 inhibitor, and patients should be cautioned against excessive intake (Deininger et al 2003). Allelic variants of the genes coding for the cytochrome P-450 have been shown to exert limited effects on imatinib pharmacokinetics (Gardner et al 2006). Although imatinib possesses a wide therapeutic window, caution still needs to be exercised, particularly in patients on higher imatinib doses or patients already experiencing dose related toxicities.

Plasma levels of some drugs, which are themselves metabolized by CYP3A4/5 also can be increased by imatinib (eg, cyclosporine A, simvastatin), which is particularly important in substances with a narrow therapeutic window. Conversely, drugs known to induce CYP3A4/5 may decrease the levels of imatinib. Major inductors of CYP3A4/5 include carbamazepine, dexamethasone, phenytoin, phenobarbital, rifampicin, St. John´s wort, and others.

In general, any co-medication with CYP3A4/5-inducing agents such as anticonvulsants and steroids should be used with caution and appropriate alternatives should be substituted if possible (Deininger et al 2003).

Imatinib is a weak inhibitor of CYP2D6 and CYP2C9. Therefore, drugs metabolized by these enzymes (eg, warfarin) should also be used with caution (Deininger et al 2003). Imatinib also has been shown to inhibit the O-glucuronidation in vitro, possibly increasing the effect of Acetaminophen.

## Resistance to imatinib

### Types of resistance

In principle, there are two types of imatinib resistance: (1) Primary resistance defined as a lack of response to initial imatinib-treatment. (2) Acquired or secondary resistance: that is loss of benefit of imatinib after initial response. In clinical studies imatinib failure was further subdivided into hematologic (lack of normalization of spleen size, peripheral blood counts, etc.), cytogenetic (lack of remission of Ph-positive cells), or molecular resistance (lack of a more than 3log reduction of Bcr-Abl transcript compared to a standardized baseline or a Bcr-Abl/Abl ratio of $\leq$0.1%).

### Molecular mechanisms

The mechanisms of resistance to imatinib in CML have been investigated extensively both in preclinical imatinib resistant cell line models (Issaad et al 2000; le Coutre et al 2000; Mahon et al 2000; Weisberg and Griffin 2001; Keeshan et al 2001; Barnes et al 2005) as well as in primary patient samples (Barthe et al 2001; Gorre et al 2001; Hochhaus et al 2002; Shah et al 2002; Roche-Lestienne et al 2002; von Bubnoff et al 2002; Branford et al 2004). In principle, failure to control CML by treatment with imatinib can be caused by three entirely different biological mechanisms (van der Kuip et al 2005). (1) imatinib fails to inhibit the kinase activity of Bcr-Abl effectively (target-dependent resistance). (2) Growth and survival of the malignant clone is independent of the Bcr-Abl kinase activity (target independent resistance). (3) The availability of the drug within the cell is not sufficient to inhibit the Bcr-Abl kinase activity (drug dependent resistance).

### Target dependent resistance

Despite continued treatment with imatinib, the kinase activity and the activation of Bcr-Abl downstream targets remain high. This can be caused by different mechanisms. First, amplification of the *bcr-abl* gene and consequently the production of a higher amount of Bcr-Abl protein has been observed in cell line models selected for imatinib resistance (le Coutre et al 2000; Mahon et al 2000; Weisberg and Griffin 2001). Multiple copies of the *bcr-abl* gene have also been detected in interphase nuclei from imatinib resistant CML patients by the use of a fluorescence in situ hybridization assay (Gorre et al 2001; Hochhaus et al 2002).

A much more frequent cause of target dependent resistance are single amino acid (AA) changes within the Abl kinase domain of Bcr-Abl that lead to an active Bcr-Abl kinase, but that reduce the binding affinity of imatinib to the protein (Gorre et al 2001; von Bubnoff et al 2002; Hochhaus et al 2002; Cowan-Jacob et al 2004). This reduced binding capacity can be caused by either direct or indirect mechanisms, allowing a classification of Bcr-Abl mutations into two groups (Table 2). (1) Mutations that directly impede the contact between Bcr-Abl protein and imatinib (Azam et al 2003): approximately 20 AA are involved in imatinib binding. Substitution of one of these can result in reduced affinity of imatinib to Bcr-Abl or in steric inhibition of the binding. Examples of mutations that inhibit imatinib binding are those that affect Thr315 and Phe317. The clinically important Thr315Ile mutation is viewed to be homolog to the Thr670Ile mutation in c-Kit, Thr674Ile in PDGFR-$\alpha$, and the Thr790Met mutation in EGFR in the sense of affecting the so-called gatekeeper threonine residue which is an important determinant of inhibitor binding to the kinase domains (Carter et al 2005). (2) Mutations that alter the spatial conformation of the protein leading to an indirect loss of imatinib binding affinity (Azam et al 2003): mutations in the nucleotide-binding loop (P-loop) and in the activation loop (A-loop) destabilize their arrangement such that imatinib cannot bind

**Table 2** Mechanisms, frequencies, and functional consequences on proliferation of relevant *bcr-abl* mutations

| Mutation | Mechanism of resistance | | Frequency in patients | | in vitro proliferation $IC_{50}$ [nM] | | |
|---|---|---|---|---|---|---|---|
| | direct | indirect | high | low or medium | Imatinib | Nilotinib | Dasatinib |
| wt | | | | | 260 | 13 | 0.8 |
| Met244Val | | + | | + | 2000 | 38 | 1.3 |
| Leu248Val | + | | + | | | 675 | |
| Gly250Ala | | | + | | 1350 | 48 | 1.8 |
| Gly250Glu (P-loop) | | + | | + | | | |
| Gln252His (P-loop) | | + | | + | 1325 | 70 | 3.4 |
| Gln252Arg (P-loop) | | + | | + | | | |
| Tyr253His (P-loop) | + | + | + | | >6400 | 450 | 1.3 |
| Tyr253Phe (P-loop) | | + | + | | 3475 | 125 | 1.4 |
| Glu255Lys (P-loop) | | + | | + | 5200 | 200 | 5.6 |
| Glu255Val (P-loop) | | + | | + | >6400 | 430 | 11 |
| Glu292Lys | | | | + | | | |
| Phe311Ile | | + | | + | | | |
| Phe311Leu | | + | | + | 480 | 23 | 1.3 |
| Thr315Ile | + | | + | | >6400 | >2000 | >200 |
| Phe317Leu | + | | + | | 1050 | 50 | 7.4 |
| Phe317Val | + | | | + | 350 | | 53 |
| Met343Thr | | + | | + | | | |
| Met351Thr | | + | + | | 880 | 15 | 1.1 |
| Glu355Gly | | | + | | 2300 | | 1.8 |
| Phe359Ala | + | | | + | | | |
| Phe359Val | + | | + | | 1825 | 175 | 2.2 |
| Val379Ile | | + | | + | 1630 | 51 | 0.8 |
| Met388Leu (A-loop) | | + | | + | | | |
| His396Arg (A-loop) | | + | + | | | | |
| His396Pro (A-loop) | | + | | + | 850 | 41 | 0.6 |
| Phe486Ser | | + | | + | | | |

Adapted from Ray et al (2007), Weisberg et al (2007), O´Hare et al (2005), and O´Hare et al (2007).
The $IC_{50}$ value is the concentration of inhibitor resulting in a 50% reduction of BaF3 cellular proliferation.

to the inactive kinase domain of Bcr-Abl anymore. Examples of mutations that destabilize the inactive conformation are those that affect residues Glu255, Tyr253, and Gly250 within the P-loop of the kinase domain (Schindler et al 2000; Shah et al 2002; Corbin et al 2003). In patients and in in vitro screens a set of more than 50 different point mutations leading to a more or less pronounced resistance to imatinib have been described (von Bubnoff et al 2002; Shah et al 2002; Hochhaus et al 2002; Azam et al 2003; von Bubnoff et al 2005). Most of these mutations are relatively rare, and the most common mutations (affecting Gly250, Tyr253, Glu255, Thr315, Met351, and Phe359) account for 60%–70% of all mutations. In patient samples and in in vitro generated mutants imatinib resistance was always associated with mutations within the kinase domain, including the activation loop, P-loop, and the hinge region that links the C- and N-terminal lobes of the kinase domain to form the ATP binding cleft. The localization of the most important mutations within the kinase domain is shown in Figure 2. In addition to these kinase domain mutations, both in laboratory-generated mutants and in patients, mutations were also identified in other regions outside the kinase domain. These regions, like SH3, SH2, and the linker between SH2 and the kinase domain are required to maintain the inactive conformation of the kinase (Hochhaus et al 2002; Azam et al 2003).

In vitro studies demonstrated that different imatinib resistant mutants can have different oncogenic potential, with a ranking list of the transforming capacity being Tyr253Phe, Glu255Lys>wtBcr-Abl>Thr315Ile>His396Pro>Met351Thr (Griswold et al 2006; Skaggs et al 2006). The two mutations with the greatest transforming ability (Tyr253Phe and Glu255Lys, both in the P-loop of the kinase domain) are also two of the most frequently detected mutations in patients. Importantly, P-loop mutations together with the Thr315Ile mutation are more frequently found in patients with advanced disease and seem to be closely associated with progression of patients from chronic phase to accelerated phase or blast crisis (Soverini et al 2006).

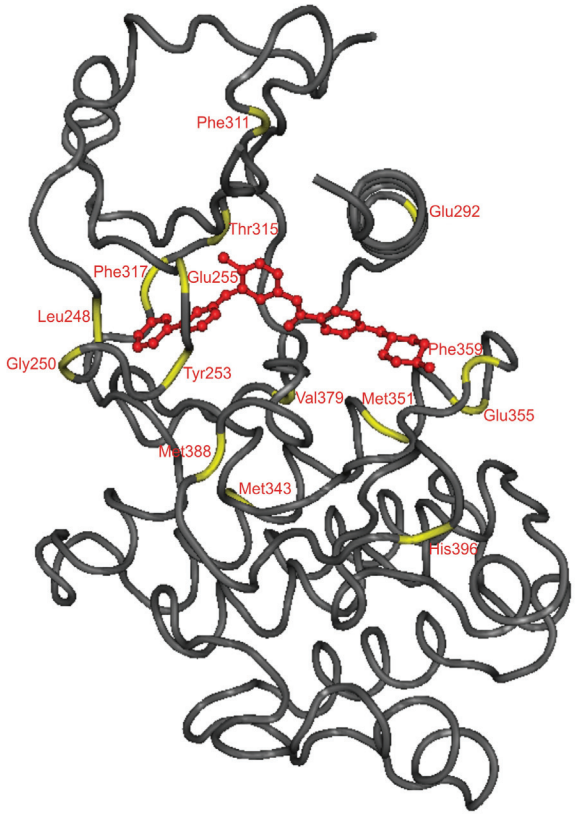


**Figure 2** Position of relevant AA substitutions within the Abl kinase causing resistance to imatinib. The structure of Abl is shown in its inactive status bound to imatinib. Relevant AA are highlighted in yellow. Derived from Nagar et al (2002).

Several studies suggest that imatinib resistant mutations can arise during imatinib treatment (Branford et al 2002; Muller et al 2002). However, highly sensitive screening assays (such as allele-specific oligonucleotide (ASO) PCR and the denaturing high – performance liquid chromatography (D-HPLC)) allowed the detection of low-level mutations in newly diagnosed and in pretreated, but imatinib-naive CML and ALL patients before imatinib treatment (Hofmann et al 2003; Willis et al 2005; Pfeifer et al 2007). Therefore, imatinib resistant mutations might also exist before imatinib treatment in a small sub-clone (<1%) of tumor cells.

## Target independent resistance

Bcr-Abl independence appears to be a rare phenomenon in patients with newly diagnosed chronic myelogenous leukemia (CML). Less than 5% of the patients do not respond to treatment with the standard dose of 400 mg per day imatinib (Kantarjian et al 2002a; O´Brien et al 2003). In contrast, patients with late stage CML more frequently exhibit primary resistance to Bcr-Abl inhibition. Only roughly 30% of patients with accelerated phase or blastic phase of CML respond to this treatment (Sawyers et al 2002; Talpaz et al 2002; Kantarjian et al 2004a; Silver et al 2004). Recent research has focused on the involvement of Bcr-Abl independent pathways that trigger the progression of the disease, in particular, the PI3K-mTOR pathway and the Src family kinases. Lyn and Src support cell survival and are also critical in development of some Bcr-Abl dependent leukemias (Lionberger et al 2000; Donato et al 2003; Dai et al 2004; Hu et al 2004). Bcr-Abl positive cells cultured in the continuous presence of imatinib show a reduced Bcr-Abl protein level and an increase of expression of Src kinases (Donato et al 2003). The role of Src kinases for imatinib resistance has been further supported by the finding that siRNA-mediated inhibition of Lyn expression significantly reduced proliferation and survival of imatinib resistant Bcr-Abl positive cells (Ptasznik et al 2004). The PI3K-mTOR pathway can be activated by imatinib treatment both in vitro and in vivo. PI3K activation was found to be a critical mediator of cell survival during the early onset of imatinib treatment before manifestation of mutations within the kinase domain leading to a robust resistance. This effect can be effectively antagonized by pharmacological inhibition of mTOR or AKT-specific siRNA treatment in vitro (Burchert et al 2005).

Recently, a potential role for autocrine GM-CSF secretion as a counterregulatory mechanism of Bcr-Abl positive cells to resist imatinib and nilotinib has been reported (Wang et al 2007).

## Drug dependent resistance

Cellular drug efflux pumps or trapping of the drug by binding proteins have been proposed to cause decreased intracellular levels of imatinib. An increase in the serum level of the A1AGP causing a decreased bioavailability of imatinib has been proposed as a mechanism favoring resistance (Gambacorti-Passerini et al 2000). The role of the A1AGP-imatinib binding and the thereby reduced distribution of imatinib from the blood for resistance is controversial. In vitro experiments using blasts from patients showed that A1AGP, at concentrations observed in patients, can reduce the concentration of imatinib roughly 10-fold (Gambacorti-Passerini et al 2003). However, there is no correlation between elevated A1AGP levels with imatinib resistance, despite the fact that about 50% of CML patients have higher A1AGP level (le Coutre et al 2002).

Drug transporters play a major role in the regulated transport of drugs across the cellular membrane and therefore in determining drug bioavailability and intracellular drug concentrations. It has become evident that transporter

proteins contribute substantially to the cellular uptake and efflux of imatinib: in vitro experiments have demonstrated that in leukemic cells the uptake of imatinib is strongly temperature-dependent corroborating an active transport process (Thomas et al 2004). Imatinib is a substrate of the human organic cation transporter 1 (hOCT1), but not for hOCT2 or hOCT3 (Thomas et al 2004). Imatinib clearance is most strongly associated with the multi drug resistance transporter P-glycoprotein the gene product of the multi drug resistance gene 1 (*MDR1*), also termed as *ABCB1* (Illmer et al 2004) and by the breast cancer resistance protein BCRP (*ABCG2*; Ozvegy-Laczka et al 2004; Burger et al 2004). Interestingly, imatinib is both a substrate and an inhibitor of BCRP (Burger et al 2004; Houghton et al 2004). This is the reason why BCRP mediated resistance to imatinib is attenuated by imatinib induced reduction of BCRP expression (Nakanishi et al 2006).

## Strategies to overcome resistance

Further understanding of the reasons of transient responses and complete resistance to imatinib has provided the opportunity to develop strategies that are able to overcome resistance. These include imatinib dose escalation, combining imatinib with other agents, and novel Bcr-Abl inhibitors.

### Novel Bcr-Abl inhibitors

Expanded knowledge on the different mechanisms of imatinib resistance clearly aids in the development of novel tyrosine kinase inhibitors. One goal was to identify compounds that bind to and inhibit Abl kinase but are less affected by *bcr-abl* point mutations. In particular, crystal structure analysis of the Abl-imatinib complex (Figure 2) has been helpful in the identification of potential critical residues that hinder the interaction of imatinib with mutated Bcr-Abl (Schindler et al 2000).

### Nilotinib (Tasigna™)

Nilotinib (Tasigna™, AMN107) is an anilinopyrimidine derivative structurally related to imatinib (Figure 1). Similar to imatinib, nilotinib binds to Abl in its inactive conformation. Nilotinib exerts a significantly higher potency on wild type Bcr-Abl (Weisberg et al 2005 and 2006) and most imatinib-resistant Bcr-Abl mutants are effectively targeted by nilotinib (Table 2). However, clones carrying the Leu248Val, Tyr253Cys, Tyr253His, Glu255Lys, Lys285Asn, and Thr315Ile mutations are markedly resistant, even at high doses in vitro (Weisberg et al 2007; Inokuchi 2006; Ray et al 2007).

For nilotinib, antileukemic activity and a relatively favorable safety profile have been demonstrated in patients with imatinib-resistant CML in an international phase I trial (Kantarjian et al 2006a). In addition, promising phase II results have been reported (Kantarjian et al 2006b; Giles et al 2006a; Ottmann et al 2006; Giles et al 2007a; le Coutre et al 2007). After its approval in Switzerland the manufacturer now is hoping to launch its second-generation Bcr-Abl inhibitor, nilotinib, in the very near future in other countries. Recently nilotinib was reported to possess a very low rate of cross-intolerance in imatinib-intolerant patients (Jabbour et al 2007). Thus approval of nilotinib clearly will expand therapeutic options for imatinib-intolerant or imatinib-resistant patients.

### Dasatinib (Sprycel™)

The pyridol [2,3-d] pyrimidine dasatinib (Sprycel™, BMS-354825, Figure 1) is another novel Abl-targeted kinase inhibitor, which additionally displays an inhibitory activity against Src kinases.

Compared with imatinib, dasatinib is more potent and binds to the active conformation of the Abl kinase domain (Figure 3, middle panel). In addition, dasatinib showed in vitro activity against 14 of 15 imatinib-resistant *bcr-abl* mutations. The gatekeeper mutation Thr315Ile mutation was the only resistant variant of Abl (Table 2) (Shah et al 2004). Meanwhile, other *bcr-abl* mutations have been reported to confer resistance towards dasatinib in vitro (eg, Val299Leu, Thr315Ala, and Phe317Val) (Burgess et al 2005; Shah et al 2006a).

Acquired resistance in patients treated with dasatinib seems almost invariably associated with a small set of tyrosine kinase domain mutations. Thus, once the malignant clone is fully committed to Bcr-Abl, activating a Bcr-Abl independent transformation program appears to be difficult, leaving tyrosine kinase mutations as the most important escape mechanism for the neoplasia. This experience is strikingly different from that in patients with acute myeloid leukemia (AML) developing acquired resistance to FLT-3 inhibitors (O´Hare et al 2007).

Dasatinib-induced hematologic and cytogenetic responses in patients with CML or Ph-positive ALL intolerant or resistant to imatinib (Talpaz et al 2006). Clinical efficacy was further established in 4 single-arm studies, including a total of 445 extensively pretreated patients with CML in different phases or Ph-positive ALL. Initial dose of dasatinib was 70 mg twice daily. The substance was generally well tolerated; however, dose interruptions due to cytopenias or nonhematologic toxicities were not uncommon. Of note, pleural effusions

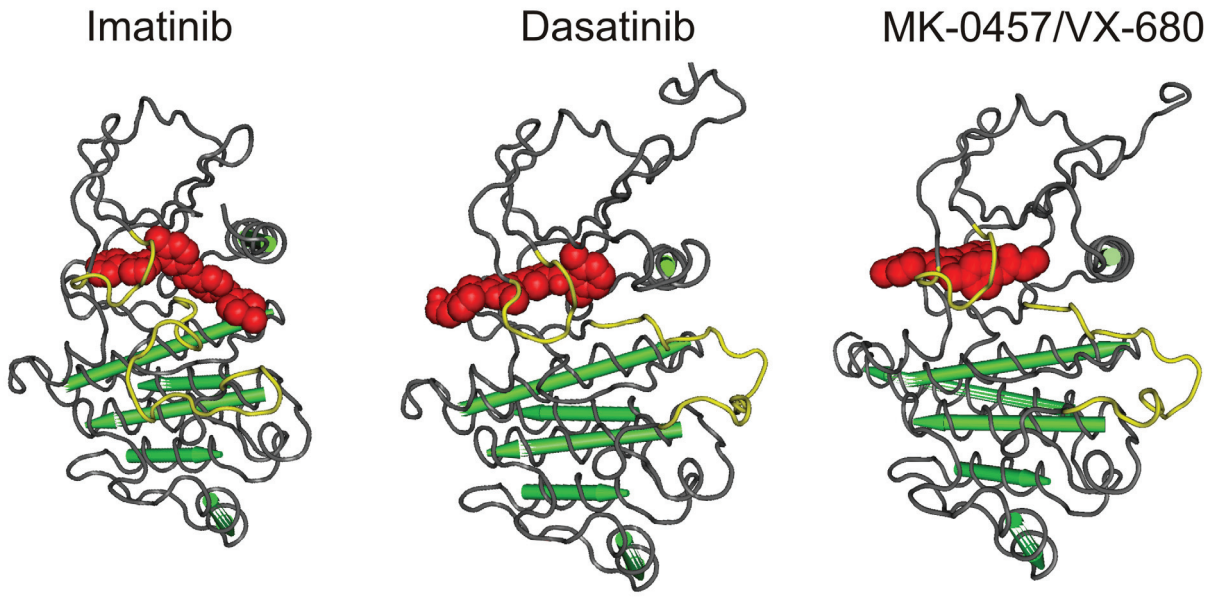


**Figure 3** Structure of the Abl kinase in complex with imatinib (red, left panel), dasatinib (red, middle panel), and MK-0457 (red, right panel). The positions of the P-loop and the activation loop are indicated in yellow. Imatinib binds and stabilizes the inactive conformation of Abl (left panel) whereas dasatinib binds to the active conformation of the Abl kinase which is similar for Src and Abl (middle panel). MK-0457 (left panel) is not fully buried in the kinase domain and is anchored to this domain by 4 hydrogen bonds to sequence-invariant elements within the active form of Abl. Derived from Nagar et al (2002), Tokarski et al (2006), and Young et al (2006).

occurred more often as expected from the prior experience with imatinib. Clearly, the observed adverse events have to be noticed but might be considered partially acceptable in light of the available alternative therapeutic options in these patients. The observed pleural effusions were reversible with dose interruption and diuretic or steroid administration. In chronic phase CML patients´ treatment resulted in 90% complete hematologic responses and 52% major cytogenetic responses after 8 month of follow-up and only 2% of the patients achieving major cytogenetic responses progressed or died (Hochhaus et al 2007). In accelerated phase, 81%, 64%, and 39% of patients achieved overall, major and complete hematologic responses, respectively, while 33% and 24% attained major and complete cytogenetic remissions at 8 months minimum follow-up. Of 69 patients who achieved a major hematologic remission only 7 progressed and 66% of patients are estimated to be alive and progression-free after 10 months (Guilhot et al 2007). In patients with blast crisis, dasatinib induced major hematologic responses in 34% and 31% of myeloid blast crisis and lymphoid blast crisis, respectively. Of note, 31% and 50% of these patients achieved a major cytogenetic response. Responses were rapid and durable and 86% of patients with a major cytogenetic response were complete cytogenetic responders (Cortes et al 2007). Importantly, comparable response rates were achieved by patients with or without *bcr-abl* mutations conferring imatinib resistance in these trials. So far available evidence clearly indicates that dasatinib is effective in overcoming resistance and intolerance to imatinib and in June 2006 the FDA granted accelerated approval to dasatinib for use in the treatment of adults with chronic phase, accelerated phase, and myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy, including imatinib. Towards the recent publication of a randomized comparison of high-dose imatinib (800 mg per day) versus standard dose dasatinib (140 mg per day) after failure of first-line imatinib in an international phase II trial the latter treatment option clearly appears favorable. With a median follow-up of 15 months, complete hematologic responses were observed in 93% and 82% of patients receiving dasatinib and high-dose imatinib ($p = 0.034$), respectively. Dasatinib resulted in significantly higher major (52% versus 33%) and complete (40% versus 16%) cytogenetic response rates. Major molecular responses (16% versus 4%) were also more frequent with dasatinib. Additionally, treatment failure and progression-free survival favored dasatinib (Kantarjian et al 2007a). However, the majority of these patients have failed to treatment with 600 mg imatinib before entering the trial. Therefore, the question whether dasatinib is superior to dose escalation of imatinib is not definitely settled.

Data from a trial of 4 different dose schedules, including the standard dose of $2 \times 70$ mg per day, scrutinized the optimal dosage of dasatinib. All dosing levels had similar efficacy as

reflected by hematologic and cytogenetic responses, but the 100 mg once a day schedule had a favorable adverse event profile with a reduced incidence of cytopenias (Hochhaus et al 2006). Rapid, complete cytogenetic responses to dasatinib 100 mg per day have been observed in a high percentage of patients in an ongoing trial with dasatinib as first-line treatment for chronic phase CML (Atallah et al 2007b).

### Bosutinib (SKI-606)

Bosutinib (SKI-606) is a 4-anilino-3-quinolinecarbonitrile Src/Abl kinase inhibitor. Bosutinib can bind to and inhibit several imatinib-resistant Abl mutants, but not Thr315Ile (Soverini et al 2007; Weisberg et al 2007). Initial clinical trials are underway on both sides of the Atlantic and the substance already showed evidence of efficacy in imatinib resistant or intolerant patients with cytogenetic responses and complete hematologic responses across a range of BCR-ABL mutations (Cortes et al 2006; Gambacorti-Passerini et al 2007).

### INNO-406

INNO-406 (NS-187) is an orally available, dual Abl/Lyn kinase inhibitor which is structurally related to imatinib and nilotinib but much more potent than imatinib in vitro. Numerous Bcr-Abl mutants, but not Thr315Ile, are sensitive to the substance (Weisberg et al 2007). INNO-406 showed encouraging evidence of clinical activity in imatinib-resistant patients in a phase I trial (Craig et al 2007) and is currently evaluated in ongoing trials. Unlike imatinib this new Abl inhibitor appears to cross the blood–brain barrier in a murine model system (Yokota et al 2007).

### ON012380

Unlike imatinib, the Abl inhibitor ON012380 (Figure 1) was specifically designed to block the substrate binding site rather than the ATP binding site. A feature that gives the advantage that the previously described imatinib-resistant mutants are unlikely to be resistant to this novel inhibitor, due to their different binding sites. As expected, in vitro studies confirmed this assumption and ON012380 has been shown to inhibit wild-type and all tested imatinib-resistant kinase domain mutations, including the Thr315Ile mutation, with an $IC_{50}$ of less than 10nM (Gumireddy et al 2005). Besides Abl, ON012380 showed inhibitory activity against PDGFR kinases and the Src family member Lyn.

### Aurora kinase inhibitors

Aurora kinases (AK) are essential for the regulation of mitotic chromosome segregation and cytokinesis. Aberrant AK activity has been described in many human tumors (Matthews et al 2006). Bcr-Abl stimulates several signal transduction pathways, including the Janus kinase 2 (JAK2) pathway. The activation step of JAK2 involves phosphorylation of the critical Tyr1007 residue (Xie et al 2001). One major effect of the JAK2 activation by Bcr-Abl is the increase in c-Myc expression (Xie et al 2002) which is important for leukemia induction (Sawyers et al 1992). Samanta et al (2006) identified JAK2 as a potentially important therapeutic target for CML. MK-0457 (VX-680), a small molecule inhibitor targeting AK, FLT-3 and JAK2 and with the ability to block cell cycle progression and induce apoptosis in diverse human tumor types (Harrington et al 2004) has been shown to possess preclinical and clinical activity in CML harboring Thr315Ile mutated Bcr-Abl without significant extramedullary toxicity in preliminary trials (Bergstrom et al 2006; Giles et al 2006b; Shah et al 2006b; Giles et al 2007b). These fascinating results may indicate the possibility to develop targeted treatment approaches interacting with Bcr-Abl-induced pathways rather than Bcr-Abl itself. However, MK-0457 has also been shown to bind to and inhibit the Abl kinase (Young et al 2006; Buser et al 2007; Cheetham et al 2007) in a mode that accommodates the substitution of the bulkier isoleucine for threonine at residue 315 (Figure 3, left panel), but the relative contributions of AK, JAK-2, and Bcr-Abl inhibition in the activity of MK-0457 have not been elucidated (Giles et al 2007b).

Whatever the key mechanism of MK-0457 action in Thr315Ile Bcr-Abl positive CML is, the observations of Giles et al and others may set the starting point for a breakthrough in the management of patients with the Thr315Ile mutation, for whom presently no other effective targeted therapy exists (Martinelli et al 2007).

### Combination of imatinib with other substances

#### Interferon-α

Interferon-α is clinically effective in the treatment of CML with a different mechanism of action than imatinib and its combination with imatinib might facilitate eradication of leukemic cells. Interestingly, the addition of pegylated interferon-α in CML patients with a durable imatinib-induced complete cytogenetic remission was shown to improve molecular response (Hardan et al 2006). This observation is encouraging in the attempt of using combined modality approaches in the treatment of CML patients. The interest in combination therapies using these agents has resulted in the design of clinical trials referring to this (eg, the German CML IV trial) (Hehlmann et al 2005) with early results already reported (Gardembas et al 2003; Baccarani et al 2004).

Despite promising efficacy enhanced toxicity due to such combinations clearly remains an issue of concern.

### Farnesyltransferase inhibitors

Preclinical studies have demonstrated the activity of farnesyltransferase inhibitors (FTI) such as lonafarnib as single agents against Bcr-Abl positive cells from CML patients and Bcr-Abl-induced leukemia in a mouse model (Peters et al 2001). Lonafarnib also inhibits proliferation of imatinib-resistant CML cell lines and primary cells from imatinib-resistant patients (Hoover et al 2002). In addition, some in vitro studies suggest that lonafarnib may reduce the number of dormant, possibly imatinib-insensitive CML stem cells when combined with imatinib (Jorgensen et al 2005). In a recently published pilot study, the efficacy of this FTI was investigated in a cohort of 13 CML patients in chronic and accelerated phase who had failed prior imatinib and interferon-α therapy (Borthakur et al 2006). Two patients had a transient hematological response (Borthakur et al 2006). Lonafarnib has also been combined with imatinib in a phase I study with 22 patients who had failed imatinib therapy. Roughly 30% of patients achieved hematological remission (Cortes et al 2004).

### Hypomethylating agents

Promotor hypermethylation may also play a role in progression of CML (Zion et al 1994; Nguyen et al 2000). 5-aza-2′-deoxycytidine (decitabine, DAC), a hypomethylating agent, has been investigated in CML. In early clinical trials, this compound was used as single agent at doses of 50–100 mg/m$^2$ over 6 hours every 12 hours for 5 days every 4–8 weeks (Kantarjian et al 2003b). 55% (28 of 55) patients in accelerated phase and 28% (18 of 64) patients in blast crisis achieved a hematological response. Because of its myelosuppressive effect, with infections occurring in 34% of patients, lower dosages of decitabine are now favored. A dose of 15 mg/m$^2$ daily for 10 days was given to 35 patients with imatinib failure; 12 in chronic phase and 17 in accelerated phase. Complete hematological response was reported in 12 patients, 7 patients had a partial hematological response (Issa et al 2005). In a phase II study with the same schedule, 28 patients were enrolled, 25 with imatinib resistance. Complete hematological response was observed in 32% (Oki et al 2007). Interestingly, the response rate was higher in patients without Bcr-Abl kinase domain mutations (53% versus 14%).

### Other agents

Combination strategies involving imatinib and other agents are currently under investigation. These include PI3K/mTOR inhibitors, *bcr-abl* RNA interference, histone deacetylase inhibitors, and others. Phosphatidylinositol 3-kinase (PI3K) and its downstream substrate mTOR are critical for survival and proliferation of Bcr-Abl transformed cells. The mTOR inhibitors rapamycin (Sirolimus) and RAD001 (Everolimus) have been shown to inhibit proliferation in CML cell lines, and it has been demonstrated that rapamycin and imatinib act synergistically in Bcr-Abl transformed cell lines (Ly et al 2003; Mohi et al 2004). Concerning the Thr315Ile mutation, conflicting data have been reported on the effects of imatinib and rapamycin. Mohi et al (2004) found these compounds to act synergistically on that imatinib resistant phenotype, whereas Ly et al (2003) and Dengler et al (2005) found no effect of imatinib or rapamycin in Thr315Ile Bcr-Abl positive cells. Combination treatment of imatinib with mTOR inhibitors could be effective in cases where Bcr-Abl mutants do not cause complete resistance to imatinib (Dengler et al 2005).

Decreasing the protein expression of a target kinase is also capable of restoring sensitivity to imatinib in cells over-expressing *bcr-abl* as well as in cells expressing a mutant *bcr-abl* variant conferring partially resistance to imatinib. In vitro experiments demonstrated that cells expressing the His396Pro variant of Bcr-Abl reverted to an imatinib sensitive state upon reduction of the Bcr-abl protein content with breakpoint specific siRNAs (Wohlbold et al 2003).

## Treatment strategies 2007

The treatment options presently available for chronic phase CML include hydroxyurea, interferon-α, interferon-α plus cytarabine, imatinib, dasatinib, and allogeneic SCT (SCT). Nilotinib is currently approved in Switzerland but expected to be available in other countries in the very near future. Up to now allogeneic SCT is the only treatment option providing definitive cure in about 50% of the patients eligible for the procedure. However, the treatment related risks clearly exceed the risk of disease progression upon treatment with imatinib. Imatinib 400 mg per day is well tolerated and clearly superior to any other treatment up to 6 years of observation. This hopefully will end up in an excellent long-term outcome but to date follow-up with imatinib is not sufficient to draw firm conclusions on the 10-year or 20-year results. Prospective studies comparing 400 mg daily with a higher dosage of imatinib have been initiated to optimize treatment in chronic phase CML but 400 mg per day remains today's standard of care. First line allogeneic SCT may still be an option exclusively for very young patients with unfavorable disease characteristics.

Clearly, response to imatinib treatment and tolerability has to be monitored appropriately. The definition of an appropriate response is dependent on the extent of remission at certain time points after initiation of treatment. For this, specific recommendations have been issued (Deininger et al 2003; Baccarani et al 2006; Branford et al 2006; Hughes et al 2006). However, even close monitoring will not always detect relapse early, as some patients have progressed directly to accelerated phase or blast crisis, even from complete cytogenetic remission (Deininger 2005). Definition of response, treatment failure, suboptimal response, and recommendation for appropriate action for patients with early chronic phase CML treated with 400 mg imatinib per day have been presented by Baccarani et al in 2006 (Table 3). A complete hematologic response (CHR) is defined as follows: Platelet count $<450 \times 10^9$/L, WBC count $<10 \times 10^9$/L, differential without immature granulocytes and with less than 5% basophils, nonpalpable spleen. The level of cytogenetic response (CgR) is classified as follows, according to the morphologic cytogenetic evaluation of at least 20 marrow metaphases: Complete CgR 0% $Ph^+$, partial or major CgR 1%–35% $Ph^+$, minor CgR 36%–65% $Ph^+$, minimal CgR 66%–95% $Ph^+$, no CgR $>$ 95% $Ph^+$. Molecular response (MolR) is assessed in the peripheral blood and a complete MolR indicates Bcr-Abl transcript nonquantifiable and nondetectable. A major MolR is defined as more than 3log reduction of Bcr-Abl transcript compared to a standardized baseline or a Bcr-Abl/Abl ratio of $\leq$0.1%). Complete CgR and major MolR should be confirmed on two subsequent occasions.

In cases of failure or suboptimal response, the options available are either dose escalation of imatinib, dasatinib, investigational TK-inhibitors (eg, nilotinib), allogeneic SCT, or interferon-α. If possible allogeneic SCT should be offered to patients before the disease progresses to an accelerated or blastic phase. However, the 2-year survival rates for second-line treatment with nilotinib or dasatinib are superior compared to allogeneic SCT in chronic phase, but not in accelerated phase or blast crisis CML post-imatinib failure (Kantarjian et al 2007b). Nevertheless, valid long-term survival comparisons between allogeneic SCT and non-transplant second line treatment approaches post-imatinib failure are not available at the moment. Individual treatment decisions in patients failing or suboptimally responding on imatinib should appropriately take the patient's individual situation and risk factors into account. Therefore, Kantarjian et al (2007b) developed a novel risk score in this group of patients, comprising splenomegaly and hematologic failure as independent poor prognostic factors. Of note, patients with target-independent mechanisms of imatinib resistance will most likely not obtain a sustained benefit from specific Abl kinase inhibitors, and today these patients should proceed to allogeneic SCT if possible.

In a patient appearing with "warning signs", standard treatment is still 400 mg imatinib, but physicians should be alert that the patient might become eligible for alternative treatment approaches as lined out above.

Monitoring of imatinib blood concentrations are not recommended routinely, but they could be desirable in cases of

**Table 3** Definition of failure and suboptimal response in first-line imatinib treatment (400 mg)

| | Failure | Suboptimal response | Warning signs |
|---|---|---|---|
| at diagnoses | NA | NA | High risk, del9q<br>ACAs in $Ph^+$ cells |
| 3 months after diagnosis | No HR | Less than complete HR | |
| 6 months after diagnosis | Less than complete HR<br>No CgR ($Ph^+$ >95%) | Less than partial CgR ($Ph^+$ >35%) | |
| 12 months after diagnosis | Less than partial CgR ($Ph^+$ >35%) | Less than complete CgR | Less than major MolR |
| 18 months after diagnosis | Less than complete CgR | Less than major MolR | |
| Anytime | Loss of complete HR[1]<br>Loss of complete CgR[2]<br>Mutation[3] | ACA in $Ph^+$ cells[4]<br>Loss of major MolR[4]<br>Mutation[5] | Any rise in transcript level<br>OCA in $Ph^-$ cells |

Adapted with permission from Baccarani M, Saglio G, Goldman J, et al. 2006. Evolving concepts in the management of chronic myeloid leukemia:recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*, 108:1809–20. Copyright © 2006 American Society of Hematology.

[1]to be confirmed on 2 occasions unless associated with progression to AP/BC.

[2]to be confirmed on 2 occasions unless associated with loss of complete hematologic remission or progression to AP/BC.

[3]high level of insensitivity to imatinib (eg, Thr315Ile).

[4]to be confirmed on 2 occasions unless associated with loss of complete hematologic remission or complete cytogenetic remission.

[5]low level of insensitivity to imatinib.

**Abbreviations:** NA, not applicable; ACA, additional cytogenetic aberrations in $Ph^+$ cells; OCA, other chromosomal abnormalities in $Ph^-$ cells; HR, hematologic remission; CgR, cytogenetic remission; MolR, molecular remission.

failure and in patients who must take drugs interfering with the imatinib metabolism via cytochrome P-450 or have experienced severe drug-related adverse effect (Baccarani et al 2006).

In patients presenting with early blast crisis at the time of diagnosis initial treatment with imatinib (600 mg per day) or another tyrosine kinase inhibitor (based on mutational analysis) has been proposed (Baccarani et al 2006) followed by allogeneic SCT. In patients failing to respond to imatinib an alternative targeted approach or appropriate induction chemotherapy might be used to induce remission before transplant. Since remissions achieved with imatinib (600 mg per day) in accelerated phase CML clearly tend to be longer than in blastic crisis, a more prolonged trial with imatinib might be possible in these patients. However, whenever possible, allogeneic SCT should be discussed and planned in such cases.

## Conclusions

Research has led to the understanding of the molecular mechanisms underlying CML and allowed the development of effective targeted therapies. Imatinib is a breakthrough not only for treatment of CML patients but also for the understanding how to advance targeted therapies for treatment of other malignant diseases. In addition, unraveling the molecular mechanisms of imatinib resistance allowed the rapid development of second line drugs effective for the treatment of patients failing on imatinib therapy.

Cure of CML is not yet achieved by blocking the Bcr-Abl kinase. It remains the major challenge to completely eradicate the neoplastic cell clone in CML patients. However, the high number of potential drugs proven to inhibit or kill the Bcr-Abl positive cells allows the testing of innovative hypotheses in clinical studies to finally achieve this goal.

## Acknowledgments

The authors are supported by the Robert Bosch Foundation. We are grateful to Dr Liza Bacchus and Ms Maike Sonnenberg for critical reading of the manuscript.

## Disclosures

The authors have no conflicts of interest to disclose.

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