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Advances in treatment of chronic myelogenous leukemia – new treatment options with tyrosine kinase inhibitors

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Abstract

Imatinib is considered standard therapy for patients with chronic myelogenous leukemia (CML), inducing a high rate of hematologic and cytogenetic responses. Despite these excellent results, several patients develop resistance to imatinib. Mechanisms of resistance are varied and include *BCR-ABL1* kinase domain mutations, decreased entry of imatinib into cells, acquisition of secondary genetic changes and activation of alternate signaling pathways. Second-generation tyrosine kinase inhibitors (TKI) (dasatinib, nilotinib) were developed as an alternative for patients that develop resistance or are intolerant to imatinib. Dasatinib is a dual Abl/Src kinase TKI that is structurally unrelated to imatinib and is approved for therapy of all phases of CML in patients who are resistant or intolerant to imatinib. Nilotinib is a compound related to imatinib that has greater specificity and improved binding characteristics, and has clinical activity in the setting of imatinib failure. Resistance to multiple TKIs does occur, particularly in patients with the T315I mutation. Several new agents are in development including new TKIs, aurora kinase inhibitors and homoharringtonine.

Keywords

Chronic myelogenous leukemia; imatinib; dasatinib; nilotinib; therapy

Introduction

Chronic myelogenous leukemia (CML) is a myelo-proliferative disorder (MPD) defined by the presence of the Philadelphia (Ph) chromosome (product of translocation t(9;22)(q34;q11)) and/or the chimeric gene *BCR-ABL1* [1–3]. The Ph chromosome is present in 95% of cases of CML and it gives rise to the *BCR-ABL1* gene, with the remaining 5% of cases having an alternative or occult translocation [2,4]. The translocation occurs in a primitive hematopoietic stem cell and the *BCR-ABL1* gene encodes a fusion protein (Bcr-Abl) that has deregulated tyrosine kinase (TK) activity and activates intracellular pathways

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that lead to increased cellular proliferation, resistance to apoptosis and genetic instability [1,3].

The clinical course of CML typically goes through three phases [4]. Most patients (90%) are diagnosed in chronic phase (CP), characterized by an increase in white blood cell counts with immature granulocytes in the peripheral blood, and up to 40% are asymptomatic at time of diagnosis. Left untreated the disease inexorably progresses to blastic phase (BP), defined by the presence of 30% or more blasts in the bone marrow and a clinical picture indistinguishable from acute leukemia. In most patients, the transition between CP and BP is gradual and manifested by an accelerated phase (AP) characterized by the development of a progressive increase in blast counts, cytopenias and acquisition of new chromosomal abnormalities [4].

Historically, patients with CML were treated with conventional chemotherapeutic agents, such as bu-sulfan and hydroxyurea. However, these drugs did not prevent progression and the disease was considered uniformly fatal [5]. The appearance of interferon-α was a great advance, as the drug could induce hematologic and cytogenetic remissions and improvements in survival, but it was poorly tolerated due to frequent side effects [6]. Hematopoietic stem cell transplantation (HSCT) is the only proven curative treatment for CML, but it is applicable in only a fraction of patients, mainly younger patients with a matched donor [7]. Therapy with tyrosine kinase inhibitors (TKIs) has changed the natural history of CML, which has gone from a potentially fatal disorder to one that can be easily controlled [8]. Nevertheless, not all patients respond equally to TKIs and there is a potential for development of resistance. Both newer TKIs and other non-ATP-competitive agents are being evaluated in patients with CML in particular those resistant to imatinib. This review focuses on the most recent clinical results of therapy in CML with the 2nd-generation TKIs (dasatinib, nilotinib) and on newer compounds currently under development.

Imatinib

Imatinib (STI-571; Glivec, Gleevec; Novartis, Basel, Switzerland) is a 2-phenylamino-pyrimidine compound which has activity as a TKI [Figure 1(A)] [9]. Imatinib binds to the inactive conformation of the Bcr-Abl TK, occluding its ATP-binding pocket and preventing its switch to the active conformation [10]. *In vitro* studies showed that imatinib inhibited the proliferation of *BCR-ABL1*-positive cells (concentration at which 50% of the enzyme is inhibited [IC50] is 250–280 nM) [11–13]. It was discovered later that imatinib is not selective for Bcr-Abl, also inhibiting other TKs including platelet derived growth factor receptor-α and -*β* (PDGFR-α/*β*) and C-Kit [14].

Clinical results with imatinib

The early clinical studies with imatinib evaluated its efficacy in the treatment of patients with CML in CP that had failed prior therapy with interferon-α and in patients with advanced stages of the disease (AP and BP) [15–19]. These studies demonstrated the remarkable clinical activity of imatinib in CML in all phases, in particular in CP. These encouraging results were followed by a phase III trial, the IRIS (International Randomized Study of Interferon and **S**TI571) study, which randomized 1106 patients with untreated CP

CML to receive imatinib (400 mg daily) or interferon-α plus low-dose cytarabine [20]. After a median follow-up of 19 months, the rate of major cytogenetic response (MCyR, defined as 0–35% Ph+-metaphases in a conventional cytogenetic evaluation) was 87% in the imatinib arm *versus* 35% in the interferon arm (p <0.001). Similarly, the rate of complete cytogenetic response (CCyR, 0% Ph+-metaphases) was 76% *versus* 15% (p <0.001). At 18 months, the transformation free survival (TFS) was 97% *vs.* 91.5% (p <0.001). Therapy with imatinib was generally well tolerated. Most common side effects were superficial edema, nausea, diarrhea, rash and muscle cramps, and were usually mild or moderate in severity. Grade 3–4 cytopenias included neutropenia (17%) and thrombocytopenia (9%).

Recently, a 5 years update of the IRIS trial showed continued improvement in clinical results in patients receiving imatinib [8]. Overall, 382 patients remained on therapy with imatinib. The complete hematologic response (CHR), MCyR, and CCyR rates were 98, 92, and 87%, respectively. The event-free survival (EFS) was 83%, and TFS was 93% at 5 years. The rate of progression to AP/BP seemed to decrease with time, being 1.5% in the first year, 2.8% in the second year, 1.6% in the third year, 0.9% in the fourth year, and 0.6% in the fifth year. Importantly, cytogenetic and molecular responses had significant association with long-term outcomes. For patients achieving a CCyR within 12 months, the event-free survival at 5 years was 97%, *versus* 93% for patients with a partial cytogenetic response (PCyR, 1–35% Ph+ metaphases) and 81% for those without a MCyR (p <0.001). Patients who had a CCyR and a major molecular response (MMR, defined as a 3-log reduction in *BCR-ABL1* transcripts by real-time quantitative polymerase chain reaction) at 18 months of therapy had a 5-year overall survival (OS) of 100%. The estimated OS at 5 years for all patients in the imatinib arm was 87%, and was 95% considering CML-only deaths. The design of the study allowed crossover between arms and there was no difference in OS between imatinib and interferon-α with cytarabine cohorts. However, historical comparisons between imatinib and interferon-α based therapy have clearly shown an improvement in survival with the use of imatinib [21–23].

Resistance to imatinib

Despite these excellent results, several patients develop resistance to imatinib. In the latest update of the IRIS study at 7 years, 60% of patients who started on therapy with imatinib remain on the study [24]. The most common reason for discontinuation of imatinib was lack of efficacy and progression in 15% of patients. Resistance to imatinib can be classified into primary (never had a response to frontline therapy with imatinib) or secondary (achieved a response but then lost it) [25]. The incidence of resistance to imatinib in untreated CP CML is ~4% per year [8]. Patients with advanced stage have a much higher incidence of resistance, around 40% in AP and 90% in BP [26]. Consensus criteria for defining resistance to imatinib have been recently defined [27].

Mechanisms of resistance to imatinib are considered to be Bcr-Abl dependent or Bcr-Abl independent [25]. Bcr-Abl dependent resistance can be the result of Bcr-Abl protein overexpression or mutations in the kinase domain. Bcr-Abl overexpression is secondary to *BCR-ABL1* gene amplification and was identified both *in vitro* and *in vivo* [28]. Bcr-Abl overexpression is responsible for resistance in a small percentage of patients. *BCR-ABL1*

mutations are the most frequent mechanism of resistance to imatinib and other TKIs. They occur in 30–50% of patients, and are more common in patients who progress to AP and BP at time of resistance [28–32]. Mutations associated with imatinib resistance disrupt critical contact points between imatinib and the Bcr-Abl protein (e.g. Y253, T315) or induce a change in conformation from inactive to active, to which imatinib is unable to bind (e.g. H396) [28,33]. Some mutations induce mild to moderate resistance to imatinib while others are associated with a high degree of resistance. The P-loop mutations (in the phosphate binding loop, amino acids 244 to 255) and the gatekeeper T315I mutation are associated with a high level of resistance to imatinib [28,31,34].

Several other mechanisms of resistance to imatinib have been described in patients who do not have *BCR-ABL1* mutations. There is interpatient variability in imatinib concentrations [35,36]. Measuring the plasma concentrations of imatinib has been demonstrated to be useful by some investigators, showing a better outcome in patients who achieve higher plasma levels of imatinib [37,38]. Other reports have not found such a correlation, however [39]. Imatinib is transported into cells via the human organic cationic transporter-1 (OCT-1) [40]. Polymorphisms may affect the expression of OCT-1. There is *in vitro* and *in vivo* data suggesting that low OCT-1 expression is a potential mechanism of imatinib resistance by leading to decreased intracellular drug concentrations [41,42]. Clonal evolution and acquisition of secondary genetic changes may also be associated with resistance to imatinib, such as loss of p53 [43].

Some recent reports have focused on the role of other TK in mediating resistance to imatinib, in particular members of the Src family of kinases (SFK) [44–46]. Activation of Src kinases may promote cell growth and survival and lead to Bcr-Abl independence [45–47]. Overexpression of the SFK Lyn has been demonstrated in K562 cells resistant to imatinib, and lysate of blood cells of patients with BP CML resistant to imatinib were found to contain high levels of Lyn and Hck proteins [45].

Dasatinib

Dasatinib (formerly known as BMS-354825; Sprycel; Bristol-Myers Squibb, New York, NY) [Figure 1(B)] is an orally available, multi-targeted TKI structurally unrelated to imatinib [48]. Dasatinib binds to the ATP binding pocket of Bcr-Abl, and is capable of binding Bcr-Abl both in the active and inactive conformation [48,49].

Dasatinib is 325-fold more potent than imatinib *in vitro* against wild-type Bcr-Abl [50,51]. In cellular assays, dasatinib inhibited the proliferation of *BCR-ABL1* transfected BaF3 cells with IC50 values of 0.8 nM [51]. Dasatinib has activity against most imatinib-resistant *BCR-ABL1* mutants [50,51]. However, the T315I mutation is still highly resistant to dasatinib [50,51]. Similar to imatinib, dasatinib has activity against PDGFR-β (IC50 28 nM) and C-Kit (IC50 13 nM) [52,53]. In addition dasatinib also inhibits several members of the SFK, including Src (IC50 0.55 nM), Lck (IC50 1.1 nM), Fyn (IC50 0.2 nM), and Yes (IC50 0.41 nM) [52]. The activity of dasatinib *in vivo* was confirmed in mouse models of Ph+-leukemias with expression of different genotypes of *BCR-ABL1* [50]. Recently, dasatinib was approved by the FDA for use as a single agent for the treatment of patients with CML

(all phases) and Ph+-acute lymphoblastic leukemia (ALL) who have developed resistance or intolerance to imatinib.

Clinical results with dasatinib

Phase I study—Dasatinib was first evaluated in a phase I dose escalation study in patients with CML and Ph+-ALL that were resistant- or intolerant to imatinib [54] (Table I). A total of 84 patients (CP = 40, AP = 11, myeloid BP [MBP] = 23, lymphoid BP [LBP]/Ph+-ALL = 10) were treated with dasatinib with doses ranging from 15 to 240 mg daily, administered on a once daily or twice daily schedule.

Clinical results confirmed the activity of dasatinib as Bcr-Abl inhibitor. For patients in CP, a CHR was obtained in 92%, and a MCyR in 45% (35% CCyR). Similarly, patients in AP also had a high rate of CHR (45%) and MCyR (27%; 18% CCyR). Responses were durable, with 95% of patients in CP and 82% of patients in AP maintaining their response after a median follow-up of 12 and 5 months, respectively. Responses were also observed in patients with MBP with CHR in 35% and MCyR in 35% (26% CCyR). In patients with LBP/Ph+-ALL, the CHR rate was 70% and the MCyR rate was 80% (30% CCyR). Responses were of short duration in BP, with only one patient (10%) with LBP/Ph+-ALL still maintaining response after a median follow-up of 4 months, and only six patients with MBP still receiving the drug with a follow-up of 5 to 12 months. Sixty patients (71%) had *BCR-ABL1* mutations at the beginning of study, and clinical responses to dasatinib were observed among all *BCR-ABL1* mutations, with the exception of the T315I mutation. Pharmacokinetic and pharmacodynamic data supported a twice daily dosing schedule to achieve consistent TK inhibition over a period of 24 h, and the dose of 70 mg twice daily was chosen as the ideal dose to be pursued for further studies.

Phase II studies—A series of phase II studies (START studies; *S*rc-Abl *T*yrosine kinase inhibition *A*ctivity *R*esearch *T*rials) evaluated the efficacy of single agent dasatinib in patients with CML in CP (START-C), AP (START-A), MBP (START-B), and LBP/Ph+-ALL (START-L) that were resistant or intolerant to imatinib. Patients were treated with dasatinib at a dose of 70 mg twice daily, with dose escalation and reduction allowed for lack of response and toxicity, respectively. The results are summarized in Table I.

In the START-C trial, a total of 387 patients (288 = imatinib resistant; 99 = imatinib intolerant) in CP were treated with dasatinib [55]. A CHR was obtained or maintained in 91% of patients. Median duration of response was not reached after 18 months of follow-up. A MCyR was obtained or maintained in 59% of patients, with 49% achieving a CCyR. Only seven patients who achieved a MCyR progressed, and three of them had developed *BCR-ABL1* mutations (V299L, T315I, E459K). *BCR-ABL1* mutations were present at baseline in 40% of patients, and there was no difference in response rate between patients with and without mutations. Median daily dose was 101 mg, and dose reductions were required in 73% of patients and treatment interruption in 87%. At 15 months, the progression-free survival (PFS) was 90% and the OS was 96%.

A total of 174 patients with CML in AP were treated in the START-A trial [56]. After a median follow-up of 14.1 months, a CHR was obtained in 45% of patients, with MCyR and

CCyR seen in 39% and 32%, respectively. The PFS and OS at 12 months were 66% and 82%, respectively. Dose reductions were required in 65% of patients and dose interruptions in 85%. The START-B trial treated 109 patients with MBP and the START-L trial treated 48 patients with LBP. The final results of both trials were recently combined in one report [57]. Most patients (90%) were resistant to imatinib. A major hematologic response (MaHR, defined as CHR plus no evidence of leukemia [NEL]) was obtained in 31% of patients with MBP (25% CHR) and 35% of patients with LBP (29% CHR). The median duration of MaHR was not reached in patients with MBP and was 4.9 months in patients with LBP. A MCyR was achieved in 33% of patients with MBP (26% CCyR) and 52% of patients with LBP (46% CCyR). The median PFS was 6.7 months in patients with MBP and 3.0 months in patients with LBP. The median OS was 11.8 months and 5.3 months in patients with MBP and LBP, respectively.

Overall, all these studies defined dasatinib as a very active agent in patients with CML in all phases who had failed or were intolerant to previous therapy with imatinib.

Dasatinib *versus* high dose imatinib—Dasatinib was also compared head-to-head with imatinib in a study of patients with CML in CP that failed therapy with imatinib (400–600 mg daily) (START-R trial) [58]. Patients were randomized 2:1 between dasatinib (70 mg twice daily) and high-dose imatinib (800 mg daily). A total of 150 patients were enrolled (dasatinib = 101; imatinib = 49). Approximately two-thirds of them had received imatinib at a dose of 600 mg daily. Overall, CHR rates were higher with dasatinib (93% *vs.* 82%, p = 0.034). There was also a higher rate of MCyR (52% *vs.* 33%, p = 0.023) and CCyR (40% *vs.* 16%, p = 0.004). There was no difference in the MCyR rate between imatinib and dasatinib in the subgroup of patients that had only received 400 mg of imatinib before being considered resistant (58% *vs.* 53%, p = non significant). Major molecular responses were also improved by switching to dasatinib (16% *vs*. 4%, p = 0.038). The survival outcomes favored dasatinib, and the hazard ratio for PFS was 0.14 (p <0.001). Dasatinib lead to more episodes of pleural effusion (all grades) (17% *vs.* 0%) and grade 3–4 cytopenias (neutropenia: 61% *vs.* 39%; thrombocytopenia: 56% *vs*. 14%).

Dasatinib dose optimization study—Based on the results of the START-C trial, where the median daily dose administered was 101 mg, but responses were still seen in the majority of patients, a randomized phase III study was conducted to evaluate what would be the optimal dose and schedule of dasatinib in patients with CML in CP [59]. A total of 670 patients with imatinib-resistant or –intolerant CML in CP were randomized between one of four dasatinib treatments: 100 mg once daily, 50 mg twice daily, 140 mg once daily, and 70 mg twice daily. With median treatment duration of 8 months, there was no difference in outcomes, with similar rates of CHR, MCyR, and CCyR. There was no difference in time to achieve a CyR and in PFS. Importantly, compared to the approved dose of 70 mg twice daily, the dose of 100 mg once daily lead to lower rates of pleural effusion (7% *vs*. 16%, p = 0.024), grade 3–4 thrombocytopenia (22% *vs*. 37%, p = 0.004), and fewer patients requiring treatment interruptions (51% *vs*. 68%) and dose reductions (30% *vs*. 55%). These results reflect *in vitro* data demonstrating that intermittent, but potent inhibition of Bcr-Abl is

sufficient to lead to apoptosis in CML cell lines [60]. As a consequence the approved dose of dasatinib for therapy of patients with CML in CP has changed to 100 mg once daily.

Managing toxicity of dasatinib—Therapy with dasatinib is relatively well tolerated. The most common side effects are cytopenias, specially neutropenia and thrombocytopenia. Cytopenias are more common in patients with advanced stages of CML (AP/BP) (grade 3–4: 80–90%) than in CP (grade 3–4: 50%) [55–57]. Besides the fact that many of the patients in AP/BP already have cytopenias at baseline, this high incidence may be a reflection of the rapid elimination of the malignant clone with few normal residual hematopoietic cells present to reconstitute hematopoiesis [57]. In general, most cytopenias are managed with treatment interruptions and dose reductions. Growth factor support (such as G-CSF and interleukin-11) can be used in this setting to decrease treatment interruptions [61].

Other side effects of dasatinib that deserve mention include pleural effusions and bleeding episodes. Pleural effusions occur more commonly in patients receiving higher doses (>140 mg daily) and on a twice daily schedule [62]. The incidence of grade 1–4 pleural effusion can range from 10 to 30% [55–57,62]. The precise mechanism is not known, but it may involve dasatinib inhibition of PDGFRβ. It has been shown that PDGFRβ regulates interstitial fluid homeostasis by the phosphatidylinositol-3-kinase (PI3K) pathway [63]. Dasatinib induced pleural effusions are more common in patients with a previous history of cardiac disease and hypertension. In most cases (80%), pleural effusions are exudates. The management of pleural effusions induced by dasatinib includes treatment interruption, diuretics, corticosteroids, and thoracocentesis [62].

Dasatinib has also been shown to be associated with bleeding diathesis, in particular gastrointestinal (GI) bleeding [64]. The overall incidence is in the range of 23%, with grade 3 episodes occurring in 7% of patients [64]. Most episodes (69%) occur in the first 3 months of therapy and the GI tract is involved in 81% of cases [64]. In more than half of cases, platelets are above 30 $\times 10^9$/L [64]. Laboratory analysis has revealed that dasatinib induces platelet dysfunction with an aspirin-like effect, inhibiting platelet aggregation in response to arachidonic acid and epinephrine [65]. Patients on dasatinib are at an increased risk of bleeding even with normal platelet counts, and the use of concomitant platelet inhibitors should be avoided if possible.

Nilotinib

Nilotinib (formerly known as AMN107; Tasigna; Novartis, Basel, Switzerland) is a TKI structurally similar to imatinib [Figure 1(C)] [66]. Nilotinib was developed by modifying the methylpiperazinyl group of imatinib and improving its binding characteristics [66]. Nilotinib has a higher binding affinity and selectivity for the Bcr-Abl kinase than imatinib. It is more potent than imatinib in inhibiting TK activity of Bcr-Abl and 10–30 times more potent in inhibiting the proliferation of BaF3 cells transfected with the *BCR-ABL1* oncogene (IC50 25 nM) [66]. Nilotinib also showed efficacy in inhibiting CML cell lines expressing imatinib-resistant mutant Bcr-Abl kinases [51,67]. Mouse models of Bcr-Abl positive leukemias confirmed *in vivo* activity of nilotinib [66]. Nilotinib also inhibits, albeit with less potency than imatinib, the TK PDGFRβ (IC50 57 nM), and C-Kit (IC50 160 nM) [66]. Nilotinib has

no activity against SFK. Nilotinib is approved by the FDA for the treatment of patients with CML in CP and AP who are resistant or intolerant to imatinib.

Clinical results with nilotinib

Phase I study—A phase I dose escalation study in patients with CML and Ph+-ALL that were imatinib-resistant evaluated the safety and tolerability of nilotinib [68]. A total of 119 patients (CP = 17, AP = 56, BP = 33, Ph+-ALL = 13) were treated with doses of nilotinib ranging from 50 to 1200 mg once daily and 400 to 600 mg twice daily. Mutations of the *BCR-ABL1* gene were present in 37 of 91 patients who had a mutation analysis at baseline.

Pharmacokinetics showed that the half-life of nilotinib was 15 h, and there was saturation of plasma levels at doses of 400 mg or more when given once daily, probably secondary to saturation of GI absortion. A twice daily schedule was evaluated, and exposure at the steady state was higher with 400 mg twice daily than with 800 mg once daily. The mean through level at the steady state with 400 mg twice daily was 1.7 μM, which exceeds the IC50 values for inhibiting the wild-type Bcr-Abl kinase (20–50 nM) and most imatinib resistant mutants (19–709 nM) [67,68].

Nilotinib had meaningful clinical activity in patients with CML resistant to imatinib (Table II). The hematologic response (HR) rate (includes CHR, marrow response and return to CP) to nilotinib was 39% in BP, 74% in AP and 92% in CP. Cytogenetic responses were seen in 27% of patients with BP (MCyR 18%, CCyR 6%), 55% of patients with AP (MCyR 27%, CCyR 14%), and 53% of CP (CCyR 35%). Dose escalations improved the response rate in 13 of 23 patients who initially received doses of 50 to 400 mg daily. There was no difference in response rate among patients with and without *BCR-ABL1* mutations, but two patients with the T315I mutation did not respond, as expected.

Phase II studies—Following the results of the phase I study, several phase II studies were designed to evaluate the efficacy of nilotinib in patients with CML who were resistant or intolerant to imatinib (Table II). Patients were treated with nilotinib at a dose of 400 mg twice daily with the option of escalating the dose to 600 mg twice daily in case of no response.

The CP study recruited 321 patients (71% imatinib-resistant). After 2 years follow-up, the MCyR was 58% (CCyR 42%) [69,70]. Responses were durable, and 84% of patients who achieved MCyR were maintaining their response at 18 months. Responses were observed in patients with and without *BCR-ABL1* mutations. The estimated OS at 18 months was 91%. In the AP study, 138 patients were enrolled; 80% were imatinib resistant [71]. The HR rate was 56%, with a CHR obtained in 30%. At 1 year, 78% of patients maintained their HR. MCyR and CCyR occurred in 32% and 19% of patients, respectively. After 18 months, 69% of patients maintained MCyR. Estimated OS at 1 year was 82%.

The results of the phase II studies conducted in BP and Ph+-ALL were also encouraging, but response rates and duration were lower [72,73]. In the BP study, 135 patients were treated. The HR rate was 38% (CHR 25%). After a median treatment duration of 84 days, only 16 patients (12%) were still on study. In the Ph+-ALL study 41 patients were treated, and the

CHR rate was 24%. After a median treatment duration of 53 days, only 2 patients (5%) remained on the study.

Managing toxicity of nilotinib—Therapy with nilotinib is very well tolerated. The most common hematological toxicities include neutropenia (grade 3–4; 30–40%) and thrombocytopenia (grade 3–4; 28–40%) [70,71]. Non-hematological toxicity is usually mild (grade 1–2), with less than 2% of patients experiencing grade 3–4 toxicity, most commonly rash, diarrhea, nausea, fatigue, and headache [70,71]. Grade 3–4 biochemical laboratory abnormalities include elevated lipase (15–16%), elevated total bilirubin levels (3–7%), hypophosphatemia (12–15%), and hyperglycemia (12%) [70,71]. Usually biochemical abnormalities are transient and without associated clinical symptoms. Elevated bilirubin levels are most commonly due to unconjugated bilirubin. The $(TA)_7$ polymorphism of the promoter region of the gene of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), the enzyme responsible for glucoronidation of bilirubin in humans, is clinically associated with Gilbert's syndrome and the development of nilotinib induced hyperbilirubinemia [74]. Most of the time, toxicities induced by nilotinib are managed with temporary interruptions and dose reductions as necessary. Nilotinib has also been shown to increase the corrected QT interval by Fredericia's formula (QTcF). QTcF prolongation is uncommon, occurring in only 2.5% of patients [70,71]. Sudden deaths have been reported, however, and clinicians should be aware of potential drug interactions that might increase the risk of QTcF prolongation [68]. Key points of dasatinib and nilotinib are summarized in Table III.

Future therapies in chronic myelogenous leukemia

Besides dasatinib and nilotinib, there are other drugs in development for treatment of patients with imatinib-resistant CML, in particular for patients with the T315I mutation (Table IV). For more details, the reader is referred to recent reviews [75,76].

New tyrosine kinase inhibitors

There are several new TKIs in pre-clinical and clinical trials for treatment of patients with CML. Bosutinib (also known as SKI-606) is an orally available dual Abl/Src inhibitor which is more potent than imatinib in inhibiting Bcr-Abl (IC50 13 nM) but has no activity against PDGFRβ (IC50 370 nM) and C-Kit (IC50 6,000 nM) [77]. Two phase II trial have demonstrated the efficacy of bosutinib in patients with CP and advanced CML resistant to imatinib, also demonstrating activity against most *BCR-ABL1* genotypes resistant to imatinib [78–80]. In patients with CML in CP resistant to imatinib, the CHR rate was 79% and the MCyR rate was 40% (CCyR 29%) [78]. Bosutinib has as excellent toxicity profile, with few patients developing cytopenias (neutropenia grade 3–4; 13%, thrombocytopenia grade 3–4; 23%) and episodes of fluid retention (grades 1–4; 10%) [78]. This is probably secondary to its decreased activity against PDGFRβ and C-Kit. The most common side effects were diarrhea (grade 3–4; 8%), nausea, and vomiting [78,79]. INNO406 is a TKI that targets wild type and most mutant genotypes of *BCR-ABL1* and also has specific activity against the SFK Lyn, with no activity against other SFK members [81,82]. INNO-406 is 25 to 55 times more potent than imatinib *in vitro* (IC50 11–22 nM) [81,82]. In a phase I study, INNO-406 was

shown to have clinical activity in patients with imatinib-resistant or -intolerant Ph+-leukemias with a good tolerance profile [83].

Aurora kinase inhibitors

Aurora kinases are serine/threonine kinases that regulate several mitotic processes during cell division [84]. Aurora kinases are overexpressed in several malignancies, and may lead to aneuploidy and carcinogenesis [85]. Aurora kinase inhibitors (AKIs) have been developed for therapy in CML, and their mechanism of action involves simultaneous targeting of both aurora kinases and Bcr-Abl. The first AKI to be developed was MK-0457, and responses were seen in patients with CML with the T315I mutation [86,87]. Most common toxicities included myelosuppression, alopecia, and mucositis [86,87]. More recently, the AKI PHA-739358 and XL-228 are being evaluated in phase I and phase II studies in patients with CML. These drugs have *in vitro* and *in vivo* activity against CML cells harboring the *BCR-ABL1* T315I mutation [88,89]. Clinical studies are being conducted in patients with CML refractory to other TKIs, and clinical responses have been seen in patients who developed the T315I mutation [90,91]. There is also *in vitro* data suggesting that these drugs may synergize with imatinib, forming the rationale for future studies with combined therapy [92].

Homoharringtonine

Homoharringtonine (cephalotaxine, HHT) is a natural alkaloid extract from the seeds of the evergreen tree *Cephalotaxus harringtonia K. Koch var harringtonia* [93]. HHT was first isolated and developed in China and used for treatment of CML and AML in that country [94,95]. Before the development of imatinib, HHT was one of the most efficient agents for salvaging patients that were resistant to interferon-alpha [96]. HHT exerts antitumoral activity by disrupting protein synthesis and inducing apoptosis by down regulating the anti-apoptotic protein myeloid cell leukemia-1 (Mcl-1) [97]. Currently, HHT is being re-evaluated in the treatment of patients with CML who are resistant to imatinib and other TKIs. A single center phase II trial demonstrated activity of subcutaneous HHT in patients with CML in CP that were refractory to previous therapy with TKIs [98]. Patients received an initial i.v. loading dose of 2.5 mg/m^2 over 24 h followed by 1.25 mg/m^2 s.c. twice daily for 14 days until remission [98]. Six patients were treated, 5 achieved a CHR and 3 had a CyR (CCyR = 1, minor CyR = 2) [98]. A semisynthetic formulation of HHT (omacetaxine mepesuccinate) has been developed [99]. An international phase II trial with omacetaxine is being conducted in patients with CML who harbor the T315I mutation [100]. The outcome for 55 patients has been reported (CP = 32, AP = 14, BP = 9). Sixty-four percent of patients in CP had disappearance of the T315I clones, and 20% had a MCyR. HHT has a different mechanism of action that allows it to exert antitumoral effects in cells that have escaped control from TKIs.

Conclusions

Although it is clear that therapy with imatinib has dramatically changed the outcomes for patients with CML, a fraction of patients will develop resistance. The development of novel TKIs has helped improve treatment outcomes for these patients. However, resistance is still a problem, even with second generation compounds. Further research into the mechanisms

of resistance and developing compounds that are able to overcome them will no doubt continue to improve the outcome of patients with this disease.

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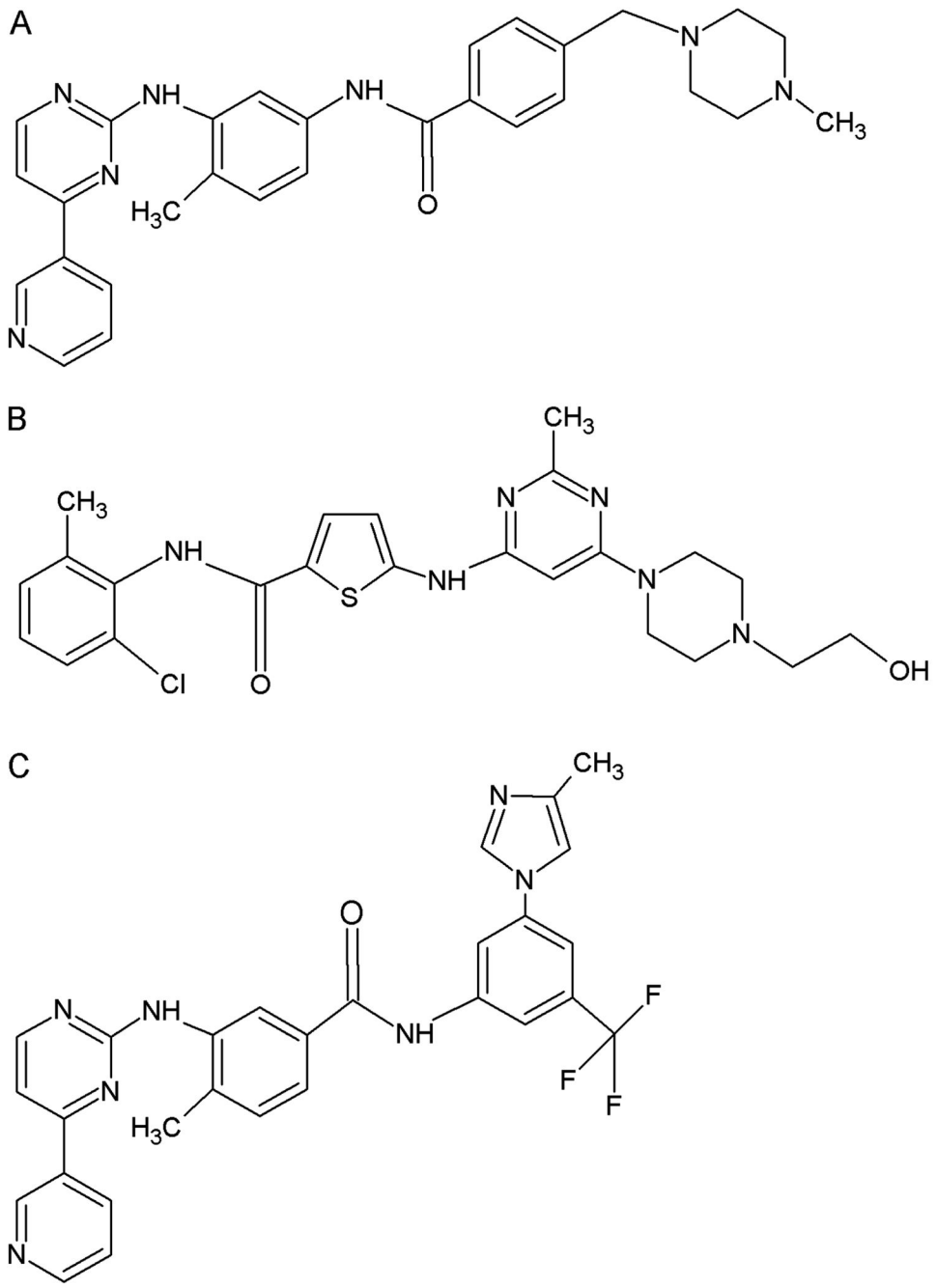

Figure 1.

Tyrosine kinase inhibitors currently available for the treatment of CML. Imatinib (A), Dasatinib (B), Nilotinib (C).

Table I

Phase I and II clinical trials with dasatinib [54–57].

			% Response		
				Cytogenetic response	
Study	**Disease stage**	***N***	**CHR**	**Major**	**Complete**
Phase I	CP	40	92	45	35
	AP	11	45	27	18
	MBP	23	35	35	26
	LBP/Ph+ ALL	10	70	80	30
START-C	CP	387	91	59	49
START-A	AP	174	45	39	32
START-B	MBP	109	25	33	26
START-L	LBP	48	29	52	46

AP, accelerated phase; CHR, complete hematological response; CP, chronic phase; LBP, lymphoid blast phase; MBP, myeloid blast phase; Ph+-ALL, Philadelphia-positive acute lymphoblastic leukemia.

Table II

Phase I and II clinical trials with nilotinib [68–73].

			% Response			
			Hematologic response		Cytogenetic response	
Study	**Disease stage**	***N***	**HR**	**CHR**	**Major**	**Complete**
Phase I	CP	17	92	92	35	35
	AP	56	74	51	27	14
	BP	33	39	6	18	6
	Ph+-ALL*	10	10	–	–	–
Phase II	CP	321	NR	76	58	42
	AP	134	56	30	32	19
	BP	135	38	25	–	–
	Ph+-ALL	41	27	24	–	–

AP, accelerated phase; BP, blastic phase; CHR, complete hematological response; CP, chronic phase; HR, hematological response; NR, not reported; Ph+-ALL, Philadelphia-positive acute lymphoblastic leukemia.

*Three patients with Ph+-ALL who had persistent molecular signs of ALL were enrolled.

One of these patients entered a complete molecular remission.

Table III

Summary of key points for dasatinib and nilotinib.

Dasatinib
Approved for
CP
AP
BP
Dose
CP – 100 mg once daily
AP/BP – 70 mg twice daily
BCR-ABL1 mutations with decreased sensitivity (other than T315I)
F317L
V299L
E255K/V
Q252H
Common toxicities
Myelosuppression
Fluid retention
Pleural effusion
Platelet dysfunction
Bleeding diathesis
Nilotinib
Approved for
CP
AP
Dose
CP/AP – 400 mg twice daily
BCR-ABL1 mutations with decreased sensitivity (other than T315I)
Y253H
E255K/V
F359C/V
Common toxicities
Myelosuppression
Hyperbilirubinemia
Elevations of amylase and lipase
Hyperglicemia

AP, accelerated phase; BP, blastic phase; CP, chronic phase.

Table IV

Selected new agents in development for CML.

Tyrosine kinase inhibitors
Bosutinib
INNO-406
AP24534
SGX393
Aurora kinase inhibitors
PHA-739358
XL228
AT9283
KW-2449
ABL switch pocket inhibitors
DCC-2036
DP-2494
Inductor of apoptosis
Omacetaxine mepesuccinate (Homoharringtonine)
Heat shock protein 90 inhibitor
17,AAG
Phosphatase (PP2A) activator
FTY720
Farnesyl transferase inhibitors
BMS214662
Rac GTPase inhibitors
NSC23766
Histone deacetylase inhibitors
LAQ824
Panobinostat (also known as LBH589)
Depsipeptide (FK228)

CML, chronic myelogenous leukemia.