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Leukemia (JP Dutcher, Section Editor)

Chronic Myeloid Leukemia: Overview of New Agents and Comparative Analysis

Preetesh Jain, MD, PhD
Hagop Kantarjian, MD
Jorge Cortes, MD[*]

Address
*Department of Leukemia, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 428, Houston, TX 77030, USA
Email: jcortes@mdanderson.org

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Opinion statement

Discovery of targeted BCR-ABL protein tyrosine kinase inhibitors (TKI) in the therapy of patients with chronic myeloid leukemia (CML) is perhaps the most popular success story in oncology. Imatinib is the most common TKI modality used as a frontline therapy in CML across the world. Lately, randomized control trials have shown that second-generation TKI, such as dasatinib and nilotinib, are superior to imatinib in terms of tolerability and efficacy. Therefore, second-generation TKI have been used increasingly as a first choice for patients with CML in chronic phase (CML-CP). Recently, ponatinib has shown significant efficacy against the most resistant cases (including those with T315I mutations) with CML. Omacetaxine is a non-TKI agent with a different mechanism of action and has shown benefit in resistant CML. Analysis of other novel agents and newer mechanisms affecting CML stem cells are under exploration. With these developments, the life expectancy of the majority of patients (>90 %) with CML-CP has become comparable to a healthy age-matched individual. The focus has now shifted to achieving faster and deeper responses, considering these parameters as a surrogate for long-term outcome and possibly cures in patients with CML. Adherence to therapy with TKI, proper monitoring by standardized techniques, and adequate use of the available therapies are established rules of managing patients with CML. However, even with these advances, problems of drug resistance, loss of response, kinase domain mutations, transformations in CML (accelerated and blast phase), and patient noncompliance prevail in the community practice. Early identification of resistant cases, feasibility for allogeneic stem cell transplantation (allo-SCT), and enrollment in clinical

trials with newer drugs is warranted. This article compares the efficacy and safety results of various TKI and non-TKI modalities and other novel pharmacological agents in the therapy of CML.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with unique biologic and clinical features. CML can present in three clinical phases: chronic phase (CML-CP), accelerated phase (CML-AP), and blast phase (CML-BP) [1, 2]. CML accounts for approximately 15–20 % of newly diagnosed cases of leukemias among adults in the United States. In 2012, approximately 5,430 patients were diagnosed with CML and 610 were estimated to die of this leukemia in the United States. Median age at diagnosis of CML is 64 years [3, 4]. CML is characterized by presence of a reciprocal chromosomal translocation [t(9;22)(q34;q11.2)] (Philadelphia chromosome (Ph) between the *C-ABL* (Abelson leukemia virus) oncogene (present in the long arm of chromosome 9) and the *BCR* (breakpoint cluster region) present in the long arm of chromosome 22 [5]. This results in a chimeric fusion protein, p210kDa BCR-ABL, although p185-p230kDa proteins can exist in CML depending upon the breakpoints [6, 7]. This is a constitutively activated protein tyrosine kinase causing abnormal activation of various intracellular signal transduction pathways (RAS/RAF/MAPK, PI3K-Akt, STAT5, JUN, MYC). This causes abnormal cell proliferation, genomic instability, initiation, and maintenance of CML clones [8]. Patients usually present with incidental detection of high white cell counts, anemia, and less frequently symptomatic with high white cell count, constitutional symptoms, and splenomegaly. Diagnosis is confirmed by documentation of Ph chromosome and BCR-ABL transcript in peripheral blood or bone marrow by routine chromosome banding analysis, FISH cytogenetics, and quantitative PCR techniques. Occasionally, other cytogenetic abnormalities or variant translocations also are associated with Ph. Additional chromosomal aberrations, in addition to the Ph chromosome, may develop over time—a process known as clonal evolution [9, 10•].

CML often is referred as the poster child for human race against cancers. Before the year 1998, the mainstays of therapy in CML were interferon alpha, busulfan, hydroxyurea, and allogeneic-SCT (with matched or unmatched donors). In 1996, a landmark discovery of selective ABL tyrosine kinase inhibitor in CML revolutionized the therapy of CML. In this study, a 92-98 % decrease in the number of BCR-ABL colonies grown from blood or bone marrow of patients with CML was observed with a selective ABL tyrosine kinase inhibitor without affecting any normal colonies [11]. Clinical efficacy of imatinib in patients with CML was first reported in 2001 [12]. Shortly after this, recognition of resistance developed paired with the discovery of point mutations in the kinase domain that rendered imatinib ineffective. Crystallographic analyses in the laboratory then led to development of second-generation TKIs, such as dasatinib and nilotinib. These two agents were first reported to have efficacy in patients who have failed imatinib or were resistant to imatinib [13–15]. Subsequently, second-generation TKIs were studied either alone or in comparison with imatinib in randomized, controlled trials in the frontline setting and demonstrated superior efficacy and tolerability [16–20]. Recently, results with bosutinib (second-generation TKI) [21•] and ponatinib [22••, 23] (third-generation TKI) also were reported in patients with refractory disease or as frontline therapy (in the case of bosutinib). Of note, ponatinib is the first TKI that has shown efficacy in patients with T315I mutations [24, 25]. Newer agents with different mechanism of action are in the pipeline for the therapy in CML [26, 27]. We have come a long way from a disease that was universally fatal to one that can be cured/controlled with oral medications.

Treatment options

Tyrosine kinase inhibitors (TKIs) are currently the first choice of therapy in every patient with CML-CP [10•, 28, 29]. Imatinib, dasatinib, nilotinib, bosutinib, and ponatinib are commercially available TKIs approved for various CML settings. Imatinib and second-generation TKIs are approved by the FDA for use as initial therapy. Bosutinib, ponatinib, and omacetaxine [30••] (the later a non-TKI drug) were all approved by FDA in 2012 for use in refractory patients with CML. Tables 1 and 2 provide a summary of efficacy and safety of various TKI and non-TKI modalities in the treatment of CML.

First-line treatments in CML in chronic phase (CML-CP) [10•, 31, 32]

Imatinib

Imatinib is a 2-phenylyaminopyrimidine BCR-ABL tyrosine kinase inhibitor. It was the first TKI approved for the treatment of CML in 2001, first for patients with resistance or intolerance to interferon alfa and then as frontline therapy [12]. Thus, among all the TKI, imatinib has the longest follow-up (approximately 14 years) and most mature safety and efficacy data in CML-CP. Imatinib blocks the binding of ATP to the BCR-ABL tyrosine kinase and competitively inhibit the tyrosine kinase activity of BCR-ABL-mediated signaling pathways. Inactivation of these pathways significantly reduces the excessive myeloid cell proliferation in CML. Imatinib also inhibits other kinases, such as ABL, c-Kit, PDGFR, DDR1, and NQO2.

Standard dosage The recommended initial adult dose of imatinib for the first-line treatment of CML-CP is 400 mg daily.Dose escalations to 600 mg to 800 mg daily (administered as 400 mg twice daily) were tested in clinical trials and used in settings where second-generation TKI were not available showing evidence of improvement in some patients, particularly those with cytogenetic resistance [33, 34]. Some studies investigated a starting dose of 600 mg to 800 mg, both in patients with resistance or intolerance to imatinib and in patients with no prior therapy. There is some increase in toxicity with the higher doses, but there is controversy about whether there is an improvement of outcome compared with the standard dose [35]. The recommended starting dose in children is 300 mg/m^2 once daily (maximum absolute dose, 400 mg) [36]. Imatinib tablets are taken orally with meals or with water to minimize gastrointestinal toxicity.

Efficacy data Imatinib was established as the "gold standard" for initial therapy of CML by the landmark IRIS trial (International Randomized Study of Interferon and STI571) [37]. In the IRIS study, 1,106 patients with untreated CML-CP were randomized to receive either a combination of interferon-α and low-dose cytarabine (IFN-α/Ara-C) or imatinib at 400-mg dose daily. After a median follow-up of 19 months, patients treated with imatinib arm fared signifi-

Table 1. Summary of the efficacy data for frontline TKI therapy in CML-CP

	IRIS [37]	DASISION [18]		ENESTnd [16]		BELA [21•]	
No. of patients (n)	Imatinib (553)	Imatinib (260)	Dasatinib (259)	Imatinib (283),	Nilotinib300 mg (282) and 400 mg (281)	Imatinib (252)	Bosutinib (250)
CCyR at 12 months	69 %	66 %	77 %	65 %,	80 and 78 %	68 and	70 %
CCyR at 24 months	NA	82 %	86 %	80 %	87 %	NA	NA
MMR at 12 months	NA	28 %	46 %	22 %,	44 % and 43 %	27 %	40 %
MMR at 24 months	NA	46 %	64 %	44 %	71 %	NA	NA
EFS	92 % at 18 months and 81 % at 8 years	92 % at 24 months	94 %	94 % at 24 months	96 % and 98 %	NA	NA
OS	97 % at 18 months and 93 % at 8 years	95 % at 24 months	95 %	96 %, at 24 months	97 % and 98 %	NA	NA
Comments	Imatinib was significantly better than IFN+Ara-C	Dasatinib achieved earlier and deeper CyR and MR with lower rate of transformations, better tolerability as compared to imatinib		Nilotinib achieved earlier and deeper CyR and MR with lower rate of transformations, better tolerability as compared to imatinib		Bosutinib achieved earlier and deeper MMR with lower rate of transformations, as compared to imatinib	

cantly better than those treated with IFN-α/Ara-C. The rate of complete cytogenetic response (CCyR) was 76.2 % with imatinib vs. 14.5 % with IFN-α/Ara-C ($P<0.001$), and the freedom from progression to AP or BP at 18 months was 96.7 % vs. 91.5 %, respectively ($P<0.001$). Only 14.3 % of patients in the imatinib arm discontinued therapy or crossed over to the alternative arm, whereas 89.2 % patients discontinued therapy or crossed over to the imatinib arm from IFN- α/Ara-C combination. In an 8-year follow-up report of the IRIS study [38], the estimated event-free survival (EFS) rate was 81 % and the transformation-free survival (TFS) was 92 %. Considering only CML-related deaths the overall survival (OS) was 93 %. Only 55 % of patients enrolled in the IRIS study remained on imatinib therapy after 8 years; 45 % have discontinued therapy due to adverse events or unsatisfactory outcome or other reasons. Two other studies, one from Hammersmith hospital in UK [39] (n=204) and another population based study [40] from UK (n=68), have reported on imatinib 400 mg as a frontline modality in patients with CML-CP. The Hammersmith hospital study reported that at 5 years, cumulative incidences of complete cytogenetic response (CCyR) was 82.7 % and estimated OS and PFS were 83.2 % and 82.7 %, respectively. Twenty-five percent of the patients discontinued therapy due to side effects. In a few studies [41–43], imatinib was combined with interferon. One such study suggested a higher rate of the deeper responses with the combination [42]. However, other studies did not find such improvement in response and none of the studies reported an improvement in event-free or overall survival.

Table 2. Summary of the general pharmacological data on various drugs used in the treatment of CML

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib [22]	Omacetaxine
Therapeutic targets	ABL, Kit, PDGFR, DDR1, NQO2	SRC family, PDGFR,KIT, EPHA2	ABL, Kit, PDGFR, DDR1, NQO2, VEGF	ABL, SRC family	Pan BCR-ABL kinase and SRC kinase	Protein translation inhibitor
Recommended dose and route of ad ministration	400 mg daily orally	100 mg daily with dose adjustments	300 mg twice a day (frontline) or 400 mg twice a day (2nd line)	500 mg once a day	45 mg once a day	1.25 mg/m^2 sub cut twice a day (14 days as induction and 7 days as maintenance)
Main side effects [58]	Myelotoxicity, Periorbital edema, rash, nausea, skin pigmentation, elevated liver enzymes, diarrhea, myalgia, headache	Myelotoxicity, Thrombocytopenia, pleural effusions, QT prolongation, low phosphate, diarrhea	Elevated liver, pancreatic enzymes and glucose, prolonged QTc, skin rash, Myelotoxicity, diarrhea, myalgia, nausea	Diarrhea, Elevated liver enzymes, Myelotoxicity, edema, nausea, rash	Pancreatitis, Hepatotoxicity, Hypertension, rash, Myelotoxicity, Thrombocytopenia, edema	Myelotoxicity, Thrombocytopenia, fatigue, injection site reactions, infections, diarrhea
Cautions [48]	Pregnancy, severe CHF and prepubertal age group	Severe CHF, antiplatelet drugs and CYP3A4 inhibitors	Long QT syndrome, hypokalemia and low magnesium, pancreatitis	Hepatotoxicity, pregnancy, lactation, prolonged QTc	Hepatotoxicity, elderly, pancreatitis, thromboembolism, pregnancy, lactation, prolonged QTc	Elderly, myelosuppression, hyperglycemia, infections

High-dose imatinib (800 mg daily) was first reported in a single-institution study as an attempt to improve the rate, depth, and timing of responses. Among 114 patients treated with an initial dose of 800 mg daily, 90 % achieved a CCyR and 63 % an MMR [44]. Three trials then compared standard dose to high-dose imatinib [41, 45•, 46]. The tyrosine kinase inhibitor optimization and selectivity study (TOPS) included 476 patients [45•]. The high-dose imatinib cohort showed significantly superior CCyR and MMR rates at 6 months compared with standard-dose imatinib. However, at 12 months the differences were not significant and PFS and OS at 18 months did not differ between the two arms. In the German CML IV study, a superior MMR and superior PFS and OS at 12 months was noted in the imatinib high-dose arm compared with imatinib 400 mg [41]. Our group has reported that high-dose imatinib results in superior rate of CCyR, MMR, and CMR at 36 months (69 %, 69 %, and 55 % respectively) compared with a historical control treated with standard-dose imatinib [47]. This resulted in an improved TFS and EFS for those treated with high-dose imatinib. These results suggest that high-dose imatinib may have a role as initial therapy in instances where second-generation TKI are not feasible. Despite the higher incidence of some adverse events with use of high-dose imatinib, proper follow-up and management of adverse effects can help patients adhere to high-dose imatinib.

Main side effects

The most common side effects include myelosuppression, edema/fluid retention (peripheral or periorbital), leg aches/muscle cramps, nausea, diarrhea, headaches, hyper or hypopigmentation of the skin, itchy rash, weight gain, elevated liver enzymes, myalgia, and growth retardation in prepubertal patients.

Contraindications

Known hypersensitivity. Avoid imatinib during pregnancy and patients with severe CHF and eosinophilic myocarditis need proper monitoring. Treatment with imatinib should be withheld when serum bilirubin is >3 times upper limit of normal (ULN), transaminases are >5 times ULN, and should be resumed with lesser dose when serum bilirubin is <1.5 times and transaminases <2.5 times ULN. Imatinib is withheld if absolute neutrophil count (ANC) is $<1 \times 10^9$/L and/or platelets are $<50 \times 10^9$/L; therapy is resumed when ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L.

Main drug interactions

Imatinib is metabolized by CYP3A4 enzyme and dose of imatinib is increased by 50 % when used with drugs which can induce CYP3A4, such as dexamethasone, rifampicin, and phenytoin [48].

Cost-effectiveness

Imatinib is the least costly and most widely available TKI among all the currently available TKIs. The average wholesale price of imatinib according to the *RED BOOK Online* (http://www.micromedexsolutions.com/micromedex2/librarian; Accessed 28 Feb 2013) is $7674.12 per month. Very inexpensive generic preparations of imatinib are available in certain countries and are routinely administered in large numbers of patients. In the United States, a generic formulation of imatinib is expected to become available in 2015.

Dasatinib

Dasatinib is a second-generation multityrosine kinase inhibitor. It was initially studied in patients with imatinib resistance or intolerance [14]. It is 300 times more potent than imatinib in preclinical studies and it can inhibit most imatinib-resistant BCR-ABL mutations, but it is not active against T315I

and some other mutations, such as F317V/L, and others rarely seen after imatinib therapy, such as T315A and V299L. It distinctly binds to the active and inactive ABL-kinase [49]. In addition, dasatinib inhibits SRC family kinases, c-KIT, ephrin receptors and platelet-derived growth factor receptor (PDGFR-β), among other tyrosine kinases.

Standard dosage Because of the short half-life, dasatinib was initially approved with a twice-daily administration schedule. However, randomized studies looking at different schedules of administration demonstrated that a once-daily schedule was associated with decreased toxicity (particularly pleural effusions and myelosuppression) with equivalent efficacy [50]. The recommended initial adult dose of dasatinib for CML-CP, either frontline or after imatinib failure, is 100 mg daily. Dose escalations to 140 mg daily can be considered to improve efficacy in nonresponders. In the advanced phases of the disease dasatinib is administered at 140 mg orally once daily. Dasatinib tablets are taken orally irrespective of meals or with water to prevent gastritis. Grapefruit juice is avoided while taking dasatinib.

Efficacy data Dasatinib is approved by FDA for use in imatinib resistant/intolerant CML patients in CP, AP, or BP [14, 35, 36]. Different single-arm and randomized trials have shown higher rates of CHR, CCyR, and MMR with dasatinib. START-R trial compared dasatinib 70 mg twice daily to high-dose imatinib (800 mg) in 150 imatinib resistant CML-CP patients. At 6 years, patients in the dasatinib arm showed significantly better responses and improvement in PFS [33, 51]. Subsequently, a study looking at different doses and schedules found that a dose of 100 mg once daily results in similar efficacy with reduced toxicity compared with 70 mg twice daily. Based on this study, 100 mg once daily became the standard dose. A complete cytogenetic response was achieved in 48 % of patients (44 % among patients with resistance to imatinib; 67 % among those intolerant), with 2-year progression-free survival of 80 % and overall survival of 91 % [52].

Dasatinib (100 mg) was compared to imatinib (400 mg) in DASISION trial (Dasatinib versus Imatinib Study in Treatment-Naïve CML-CP Patients), a randomized, phase III, international study in newly diagnosed patients (n= 519) with CML-CP [18, 53••]. A higher percentage of patients randomized to dasatinib achieved a confirmed CCyR (77 % vs. 66 %, P=0.007) and MMR (46 % vs. 28 %, P<0.0001) at 12 months compared with imatinib. Safety profile was similar in both the arms with mild increase in pleural effusion and thrombocytopenia with dasatinib but a lower incidence of other adverse events, such as muscle cramps, peripheral edema, and gastrointestinal toxicity. A 2-year update of this study was recently reported and showed that dasatinib arm was similar to imatinib in terms of CCyR (86 % and 82 %). However, deeper molecular responses (MR4.5, equivalent to BCR-ABL transcripts ≤0.0032 %) were significantly more common in the dasatinib arm (17 % vs. 8 %). Patients treated with dasatinib also achieved faster responses and had a lower rate of transformation than those treated with imatinib. A survival benefit has not yet been shown with dasatinib in this trial [18]. Another phase II study comparing dasatinib and imatinib reported that the proportion of patients achieving a CCyR and MR at 12 months was superior with dasatinib without any difference in survival [17]. Our single institution trial shows that at 36 months, patients treated with dasatinib have CCyR and MMR of 78 % and 76 %, compared to 58 % and 44 %, respectively with imatinib [47]. Recently, it has been reported that

lack of achievement of BCR-ABL1/ABL1 transcript levels <10 % at 3 months is predictive of poorer CCyR at 2 years in patients treated with dasatinib [54].

Main side effects The most common side effects include myelosuppression especially thrombocytopenia and neutropenia, easy to manage pleural effusions (10-20 % cases) [55], intracranial bleed, QT prolongation, diarrhea, and headache. Fluid retention, skin rash, hypophosphatemia, and elevation in liver enzymes also can occur. Lymphocytosis especially with expansion of clonal cytotoxic T and NK cells has been reported with dasatinib therapy [53••, 56] and lymphocytosis was associated with higher rate of CCyR and pleural effusion. Rarely pulmonary hypertension [57] and cardiac dysfunction have been reported [58].

Contraindications Known hypersensitivity. Dasatinib interferes with platelet function [50] so it is recommended to avoid antiplatelet medications dasatinib when using dasatinib St. John's wort may decrease serum levels of dasatinib. Dasatinib is withheld if ANC is $<1\times10^9$/L and/or platelets are $<50\times10^9$/L and therapy is resumed until ANC $\geq1\times10^9$/L and platelets $\geq50\times10^9$/L. Fluid retention and pleural or pericardial effusions could be managed by prednisone 20 mg/day for 3 days and dasatinib could be restarted after recovery in lower doses. Discontinue dasatinib if pulmonary hypertension is confirmed. Rash due to dasatinib could be managed by withholding the drug for few days. Dose adjustments are not needed in renal and hepatic dysfunction.

Main drug interactions Dasatinib is metabolized by CYP3A4 enzyme and dasatinib should not be administered concomitantly with strong CYP3A4 inhibitors (such as azoles) [48].

Cost-effectiveness The average wholesale price according to the *RED BOOK Online* (http://www.micromedexsolutions.com/micromedex2/librarian; Accessed 28 Feb 2013) of dasatinib 100 mg daily is $10,298.56. Dasatinib is a very expensive medication compared with imatinib.

Nilotinib

Nilotinib is a second-generation tyrosine kinase inhibitor structurally derived from imatinib. Nilotinib is 30 times more potent than imatinib in preclinical studies. It can inhibit most imatinib-resistant BCR-ABL mutations, including F317L, V299L, and T315A mutations, but it is not active against T315I, E255K, and Y253 [59, 60]. It does not inhibit SRC family kinases but inhibits PDGFR, inactive BCR-ABL, c-KIT, DDR1, VEGF, and ephrin receptors.

Standard dosage The recommended initial adult dose of nilotinib for the first-line treatment of CML-CP is 300 mg twice daily, 12 hours apart. Dose escalations to 400 mg twice daily can be done in resistant cases. The standard dose for patients receiving nilotinib after imatinib resistance or intolerance is 400 mg twice daily. Nilotinib tablets are taken orally 1 hour before or 2 hours after food. Grapefruit juice is avoided while taking nilotinib.

Efficacy data Nilotinib has shown efficacy in patients with imatinib resistance and is approved by the FDA at a dose of 400 mg twice daily for this indication for patients in chronic or accelerated phase. A phase II study in 321 patients showed that at 24-month follow-up approximately 60 % of patients achieved MCyR and 44 % achieved CCyR, with an overall survival of 87 % [15]. Nilotinib was compared to imatinib (400 mg) in the ENESTnd trial (evaluating Nilotinib Efficacy and safety in Clinical Trials Newly Diagnosed patients), a randomized, phase III, international study in newly diagnosed patients (n=846) with CML-CP [16, 61, 62••]. Nilotinib 300 mg twice daily (n=282), nilotinib 400 mg twice daily (n=

281), and imatinib 400 mg once a day (n=283) were used in three separate cohorts. The primary endpoint was the rate of MMR at 12 months, which was achieved in more patients randomized to the nilotinib arms compared with those taking imatinib (44 % and 43 % vs. 22 %, $P<0.001$). Rates of 12 months CCyR were 80 %, 78 %, and 65 % respectively. There also was less progression to AP or BP noted in the groups randomized to nilotinib (0.7 %, 1.1 %, and 4.2 % in imatinib). A 3-year update of this study was recently reported confirming that nilotinib resulted in deeper molecular responses, with a widening difference in rate of MMR and $MR^{4.5}$, with a toxicity profile that was similar or better than imatinib [16]. The impact of early response also has been assessed in this study [63]. Patients with >10 % BCR-ABL transcript at 3 months had poorer outcomes regardless of the treatment received, but significantly fewer patients treated with nilotinib had >10 % BCR-ABL transcripts at 3 months compared with those treated with imatinib. Despite the earlier and deeper responses obtained with nilotinib, a survival benefit has not yet been observed. Nilotinib also is being studied in combination with pegylated interferon [64]. The combination with pegylated interferon appears to achieve deeper molecular responses as compared to nilotinib alone.

Main side effects The most common side effects with nilotinib include skin rash, electrolyte imbalance, hyperglycemia (not contraindicated in patients with diabetes), liver and pancreatic enzymes, pancreatitis, myelosuppression, fatigue, diarrhea, and headache. Nilotinib has a black box warning for QTc prolongation and sudden deaths. Rarely, peripheral vascular disease [65] and cardiac dysfunction has been reported.

Contraindications Patients with long QT syndrome, uncorrected hypokalemia and hypomagnesaemia, and patients with hypersensitivity to nilotinib. Treatment with nilotinib should be withheld when serum bilirubin is >3 times normal, liver enzymes >5 times normal, QTc>480 milliseconds, amylase or lipase >2 times normal, ANC<1,000/mm^3 or platelet counts <50,000/mm^3. Treatment can be resumed with dose adjustments when these adverse events resolved.

Main drug interactions Nilotinib is metabolized by CYP3A4 enzyme and concomitant administration of nilotinib with strong CYP3A4 inhibitors should be avoided [48].

Cost/cost effectiveness The average wholesale price according to the *RED BOOK Online* (http://www.micromedexsolutions.com/micromedex2/librarian. Accessed 28 Feb 2013) of nilotinib (300 mg or 400 mg twice daily) is $8,010.12 for 4 weeks.

Bosutinib

Bosutinib is a second-generation tyrosine kinase inhibitor drug. It can inhibit most imatinib-resistant BCR-ABL mutations except against T315I and V299L mutations. It also inhibits SRC and ABL family kinases and is more potent than imatinib. In contrast to other tyrosine kinase inhibitors used in CML, it has minimal activity against PDGFR and c-KIT.

Standard dosage Bosutinib is approved by FDA for patients with CML who have experienced resistance or intolerance to prior therapy. The recommended initial adult dose of bosutinib is 500 mg once daily. Dose escalations to 600 mg daily can be considered in resistant cases. Bosutinib tablets are taken orally with food.

Efficacy data Bosutinib was initially studied in imatinib resistant disease in a multicenter phase 1/2 study with 288 patients of CML-CP. After 2 years, 53 % had MCyR

and 41 % had CCyR with PFS of 79 % and OS of 92 % [66••]. Subsequently bosutinib has shown efficacy in patients (n=118) who have failed on imatinib, nilotinib, and dasatinib therapy. With a median follow-up of 28.5 months, 32 % achieved MCyR and 24 % CCyR. Durable responses were seen among patients with a variety of ABL mutations on dasatinib and nilotinib therapy [67•]. Bosutinib was then compared to imatinib (400 mg) in BELA trial [21•] (Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia)—a randomized, phase III, international study in newly diagnosed patients (n=502) with CML-CP. Bosutinib 500 mg per day (n=250) and imatinib 400 mg once a day (n=252) were compared. The primary endpoint in this study was CCyR at 12 months, which was similar in patients randomized to the bosutinib arm compared with those on imatinib (70 % and 68 %). However, the rate of MMR at 12 month was 41 % and 27 %, respectively, and patients randomized to bosutinib had a lower incidence of progression to AP or BP (2 % vs. 4 % with imatinib).

Main side effects The most common side effects with bosutinib include diarrhea (usually transient) and hepatotoxicity. Myelosuppression, nausea, vomiting, skin rash, and edema also can occur.

Contraindications Patients with hypersensitivity to bosutinib. Withhold treatment when serum bilirubin is >3 times normal, liver enzymes >5 times normal, ANC<1,000/mm^3, and platelet counts <50,000/mm^3. Treatment can be resumed with dose adjustments when these adverse events resolved. Avoid in pregnancy and breastfeeding.

Main drug interactions Bosutinib is metabolized by CYP3A4 enzyme and the use of strong CYP3A4 inhibitors should be avoided when possible on patients treated with bosutinib.

Cost/cost effectiveness The average wholesale price according to the *RED BOOK Online* (http://www.micromedexsolutions.com/micromedex2/librarian. Accessed 28 Feb 2013) of bosutinib is $9,817.50 for 30 days.

Ponatinib

Ponatinib is a third-generation multitargeted tyrosine kinase inhibitor. It can inhibit most imatinib-resistant BCR-ABL mutations, including T315I [23]. Up to 20 % of patients with imatinib resistant patients with CML develop T315I mutation, where threonine is substituted by isoleucine at codon 315 of the ABL gene; isoleucine is a bulky residue that also eliminates the hydrogen bond and avoids the binding of TKI to high affinity ATP binding pocket. Ponatinib has a unique carbon-carbon triple bond, which avoids the steric hindrance caused by T315I and inhibits the BCR-ABL kinase. Ponatinib also causes inhibition of VEGFR, PDGFR, FGFR and SRC kinase, KIT, RET, and FLT3.

Standard dosage Ponatinib is approved by FDA for patients with CML in CP, AP, or BP with resistance or intolerance to prior tyrosine kinase inhibitor therapy. The recommended initial adult dose of ponatinib is 45 mg once daily. Ponatinib is taken orally.

Efficacy data Ponatinib was tested in a phase I dose escalation trial where 60 refractory CML patients were enrolled [22••]. Forty-three of these patients were in chronic phase and 12 had a T315I mutation. The majority of these patients were previously treated with two or more TKIs. The rate of MCyR was 72 % (CCyR 63 %), and MMR was 44 %. Among the 12 patients with T315I mutations, 100 % of the patients achieved a complete hematological re-

sponse, 92 % had a major cytogenetic response (75 % CCyR), and 67 % had MMR. In advanced phase disease, 36 % and 32 % of the 22 patients with AP or BP-CML had major hematological and cytogenetic response respectively. Ponatinib is further studied in the PACE trial (Ponatinib Ph+ALL and CML Evaluation)—a phase II, international study in refractory patients (n=449) with CML. Forty-six percent of the patients achieved CCyR (including those with T315I mutations) [25].

Main side effects The most common side effects with ponatinib include pancreatitis (elevation of serum lipase) and hepatotoxicity. Ponatinib has a black box warning for arterial thrombosis and hepatotoxicity. Myelosuppression (thrombocytopenia grade 3 or more, neutropenia and anemia), cardiac dysfunction, thromboembolism, hypertension, nausea, vomiting, skin rash, and edema also can occur.

Contraindications No absolute contraindications exist for the use of ponatinib. Caution must be exercised in patients with impaired liver functions, those with cardiac dysfunction, and thromboembolism.

Main drug interactions Ponatinib is metabolized by CYP3A4 enzyme.

Cost/cost-effectiveness The average wholesale price according to the *RED BOOK Online* (http://www.micromedexsolutions.com/micromedex2/librarian. Accessed 28 Feb 2013) of ponatinib is $11,496 for 30 days at a dose of 45 mg daily.

Non-TKI agent

Omacetaxine (Homoharringotonine)

Omacetaxine is a drug derived from an alkaloid *cephalotaxus harringtonia*. It is a protein translation inhibitor and has a different mechanism of action from that of TKIs. Omacetaxine inhibits protein synthesis by binding to ribosomal A subunit and thus preventing the correct positioning of amino acid side chains of incoming aminoacyl-tRNAs [68].

Standard dosage Omacetaxine mepesuccinate is administered as subcutaneous injections 1.25 mg/m^2 twice daily for 14 days consecutively (days 1–14) of a 28-day cycle until hematological response or 6 cycles and then (days 1–7) of a 28-day cycle as maintenance therapy [30••].

Efficacy data It is approved by the FDA for therapy in resistant (two or more TKI) or intolerant cases with CML in chronic or accelerated phase. A phase II study (Omacetaxine 202 study) in 62 refractory (2TKI) and 60 with (3TKI) patients with CML-CP and T315I mutations reported that 77 % of the patients had CHR, 23 % patients achieve MCyR, and 16 % had CCyR. The median progression free-survival was 7.7 months [30••, 69, 70]. Seventeen patients were in accelerated phase and approximately 30 % had major hematological response. Median months of survival in the two and three TKI groups were 12.0 and 24.6 months.

Main side effects Major side effects are in the form of manageable grade 3/4 hematologic toxicity including thrombocytopenia (76 %), neutropenia (44 %), and anemia (39 %). It also can cause injection site reactions, edema, fatigue, diarrhea, and infections.

Contraindications No specific contraindications. It can cause glucose intolerance, so caution should be observed among patients with uncontrolled diabetes.

Main drug interactions It can cause myelosuppression, so caution should be observed with the concomitant use of anticoagulants, aspirin and among patients with diabetes.

Cost/cost-effectiveness The average wholesale price according to the *RED BOOK Online* (http://www.micromedexsolutions.com/micromedex2/librarian. Accessed 28 Feb 2013) of omacetaxine is $28,056 for 14 days (twice daily administration).

Other novel agents

DCC-2036 (switch pocket inhibitor)

This compound acts via a non-ATP competitive mechanism and prevents the activation of ABL kinase by blocking an essential conformation change in the switch pockets [71]. It is highly selective for ABL kinase, FLT3 and SRC family kinases. A phase I trial was reported in (n=30) very refractory patients with CML (including T315I mutants). Ten dose levels were assessed. The median tolerated dose was 150 mg orally BID. Two of 19 patients in CML-CP had CyR. Four of eight patients in AP had responses [72].

Aurora kinase inhibitors – Tozasertib (MK-0457), Danusertib (PHA-739358), KW2449 (Oral agent)

These compounds block various aurora kinases and ABL kinases. Specifically, tozasertib prevents the binding of isoleucine at the "gate keeper" area and thus is mechanistically relevant in T315I mutations [73–75]. A recent phase 1/2 study has reported that 8/18 patients with T315I mutation CML had hematological responses on treatment MK-0457 [76]. Clinical benefit with danusertib also was observed with some hematological responses in very refractory patients with CML (T315I) in AP or in BP (n=12) in a phase I trial and three patients had CyR [77].

Heat shock protein 90 (Hsp 90) inhibitors – Geldanamycin, Ganetespib (STA-9090)

These compounds bind to the ATP binding domain of Hsp90 and promotes the degradation of BCR-ABL protein kinase in the cells [78, 79]. They are in phase I trials in CML (with T315I mutations).

GNF-2 (allosteric ABL kinase inhibitor agent)

This compound is in preclinical study. It stabilizes the ABL kinase in an inactive configuration [80].

Autophagy inhibitors – Hydroxychloroquine

In this process, the protective effect of autophagy on dormant stem cells is abrogated by inhibiting autophagy [81, 82]. Hydroxychloroquine is being studied in comparison to imatinib among patients with CML who are in major cytogenetic response and have residual disease to eliminate stem cells of CML (CHOICES trial).

Inhibition of PML (promyelocytic leukemia protein)

This protein is shown to protect CML stem cells. Inhibition of PML by arsenic trioxide has been suggested to inhibit CML stem cells [83].

Other agents

Hedgehog pathway inhibitors [84, 85], PP2A activators (e.g., Fingolimod) [86, 87], HDAC inhibitors (e.g., Panobinostat) [88] and lipoxygenase path-

way inhibitors (e.g. Zileuton) [89], Wnt-1/beta catenin pathway inhibitors [90], and glycogen synthase kinase 3β (GSK3) SB216763, a specific inhibitor of GSK3 [91, 92] are being investigated, with a main focus of eliminating the leukemic stem cell responsible for persistence of the disease.

Conclusions

These are exciting times in the treatment of CML. Superior safety and efficacy of second-generation TKIs as initial therapy has been shown from randomized, controlled, clinical trials. The increased availability of newer agents offers more opportunities but also risks for the patients as there might be an increased temptation to rapidly switch from one drug to the next for questionable "suboptimal responses" or adverse events that could be managed properly while remaining with the same original therapy. With proper management, early discontinuation should be less than 10 % rather than the nearly 30 % reported in the first 2–3 years from the randomized trials of second generation TKIs versus imatinib. Significant challenges still exist in managing patients with blast phase, patients with resistance to multiple TKIs, and those with compound BCR-ABL mutations [93]. Considerations on stopping therapy for TKI in asymptomatic patients who have remained in long-term remission are underway [94•]. Newer therapeutic molecules with unique mechanisms of action have a potential to eliminate dormant leukemic stem cells and resistant CML clones and are in clinical trials [95, 96]. Still, with the available tools today, very few patients should die of CML.

Conflict of Interest

Preetesh Jain declares that he has no conflict of interest.
Hagop Kantarjian received research support from Ariad, Pfizer, Chemgenex, BMS and Novartis.
Jorge Cortes is a consultant to Ariad, Teva, and Pfizer.

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