Ponatinib: A Third-Generation Inhibitor for the Treatment of CML

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Abstract

The establishment of imatinib as the standard therapy for CML marked the beginning of a new era of treatment. Due to occurring intolerance and resistance against the drug, developing newer inhibitors was promoted. This led to the second-generation inhibitors dasatinib, nilotinib and bosutinib. Despite all achieved improvement, all first- and second-generation inhibitors are ineffective against the BCR-ABL T315I "gatekeeper" mutation. In order to overcome this issue and to further improve the inhibitory effect, the third-generation inhibitor ponatinib was developed. Various clinical trials have been launched to study the effect of ponatinib in the clinical setting. Based on positive phase 1 and phase 2 trials, ponatinib was approved for the second-line treatment of CML and Ph^+ ALL in December 2012 in the United States and in July 2013 in the European Union. Further trials investigate the potential effect of ponatinib in kinase-dependent subgroups of other malignancies. In conclusion, ponatinib has proved to be a powerful BCR-ABL inhibitor, which exhibits clinical activity both in BCR-ABL wild-type and mutant CML, including activity against the T315I mutation. Despite previous TKI failure, chronic-phase CML patients can achieve sustained remissions using the novel drug, offering a new therapeutic option in the treatment for CML.

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1 Resistance to Treatment in CML

The establishment of imatinib as the standard therapy for CML in 2001 (Druker et al. 2001) fundamentally changed the clinical course of this disease. For many patients, CML became a chronic disorder and patients experiencing a major molecular response (MMR) might not face a loss in life expectancy (Jain et al. 2013). However, this favorable prognosis is not true for all patients. Around 20–30 % of patients treated with imatinib do not respond adequately to treatment (primary resistance) or relapse after initial response to imatinib (secondary resistance) (Druker et al. 2006; de Lavallade et al. 2008).

Resistance against imatinib or newer Abl inhibitors is caused by various mechanisms that can occur in combination especially in advanced stages of disease (von Bubnoff et al. 2005; Lahaye et al. 2005; Nicolini et al. 2007). Patient-related causes for primary as well as secondary resistance are mainly noncompliance to the treatment regime (Darkow et al. 2007). However, inadequate serum levels can arise despite proper compliance from individual differences in the activity of imatinib-metabolizing enzymes such as CYP3A4. In addition, these enzymes can be induced by comedication and nutritional habits (Floyd et al. 2003).

At the cellular level, the ability of the malignant clone to transport drug out of the cell or to hinder drug influx can result in drug resistance. For example, the proteins ABCB1 and MDR-1 are considered responsible for the increased efflux of imatinib from CML cells (Kuwazuru et al. 1990; Mahon et al. 2003; Thomas et al. 2004).

Just as the BCR-ABL fusion protein represents the causative event for CML, it is also the main reason for the development of resistance (Shah and Sawyers 2003). Mutations of this fusion gene result in changes in critical amino acids, such that inhibitors become ineffective (Branford et al. 2003; Soverini et al. 2006). More than 90 different mutations of BCR-ABL in CML have been described in recent years (Soverini et al. 2011). However, the majority of observed mutations are limited to a small number of specific changes (one study found 14 mutations in 95 % of cases (Zhou et al. 2011) another 20 mutations in 88 % of cases (Branford et al. 2009)). Hence, these common mutations are clinically most relevant and have directed the development of second- and third-line inhibitors.

2 Second-Generation Inhibitors

After the approval of imatinib in 2002, second-generation BCR-ABL kinase inhibitors were developed. The need for these novel inhibitors became evident both from patients presenting with primary imatinib intolerance, or developing intolerance during treatment, and from the growing number of mutations in BCR-ABL, which confer imatinib resistance.

Based on the positive results of phase 2 trials, the second-generation inhibitors dasatinib and nilotinib were approved as second-line therapy in imatinib-resistant or imatinib-intolerant CML and Ph^+ ALL (Kantarjian et al. 2007; Talpaz et al. 2006). In March 2013, bosutinib was also approved for second-line treatment. Recently, phase 3 trials (DAISION for dasatinib; ENESTnd for nilotinib) reported earlier and deeper remissions compared to imatinib in newly diagnosed, chronic-phase CML patients, as well as lower rates of progression to accelerated phase or blast crisis along with good tolerability of the drugs (Kantarjian et al. 2010, 2011; Saglio et al. 2010). These trials consequently led to the approval of both second-generation inhibitors, dasatinib and nilotinib, for the first-line treatment of CML. Although all second-generation inhibitors proved to be effective against a variety of known mutations, each of these inhibitors still faces a distinct spectrum of mutations, whose resistances they cannot overcome (Zhou et al. 2011; Branford et al. 2009) (Table 1).

Most notably, despite their differences, all first- and second-generation inhibitors are ineffective against the BCR-ABL T315I mutation. The exchange of threonine at position 315 for the more bulky isoleucine leads to a steric hindrance, inhibiting binding of all these inhibitors. Unable to bind the kinase, most Abl inhibitors lose their ability to block the BCR-ABL function. Twenty percent of patients who are imatinib resistant because of a BCR-ABL mutation bear the T315I "gatekeeper" mutation (O'Hare et al. 2007).

3 Ponatinib: A New Third-Generation Inhibitor

The small molecule ponatinib was developed specifically to overcome resistance based on the T315I mutation. The integration of a linear carbon–carbon triple bond into the structure of the molecule to link two functional groups avoids the blocking effect of the isoleucine in the context of the T315I mutation (Fig. 1). Furthermore, sites for interaction between the inhibitor and the kinase were optimized and are distributed over a wide range of protein residues. This increases the affinity and thereby reduces the required serum drug level. In addition, increased binding affinity ensures effectiveness of the inhibitor, even in those cases where one of the drug-binding site is lost, due to a mutation (Zhou et al. 2011).

Initial preclinical studies of ponatinib—formerly referred to as AP24534—revealed the activity of the drug as a pan-BCR-ABL inhibitor in biochemical assays, in cell lines as well as in mouse models. In contrast to the previously

Table 1 Resistance of BCR-ABL-mutations against first-, second- and third-generation inhibitors

	imatinib	dasatinib	nilotinib	bosutinib	ponatinib
WT	1,0	1,0	1,0	1,0	1,0
M244V	0,9	2,0	1,2	0,9	3,2
L248R	14,6	12,5	30,2	22,9	6,2
L248V	3,5	5,1	2,8	3,5	3,4
G250E	6,9	4,4	4,6	4,3	6,0
Q252H	1,4	3,1	2,6	0,8	6,1
Y253F	3,6	1,6	3,2	1,0	3,7
Y253H	8,7	2,6	36,8	0,6	2,6
E255K	6,0	5,6	6,7	9,5	8,4
E255V	17,0	3,4	10,3	5,5	12,9
D276G	2,2	1,4	2,0	0,6	2,1
E279K	3,6	1,6	2,0	1,0	3,0
E292L	0,7	1,3	1,8	1,1	2,0
V299L	1,5	8,7	1,3	26,1	0,6
T315A	1,7	58,9	2,7	6,0	0,4
T315I	17,5	75,0	39,4	45,4	3,0
T315V	12,2	738,8	57,0	29,3	2,1
F317L	2,6	4,5	2,2	2,4	0,7
F317R	2,3	114,0	2,3	33,5	4,9
F317V	0,4	21,3	0,5	11,5	2,3
M343T	1,2	0,9	0,8	1,1	0,9
M351T	1,8	0,9	0,4	0,7	1,2
F359I	6,0	3,0	16,3	2,9	2,9
F359V	2,9	1,5	5,2	0,9	4,4
L384M	1,3	2,2	2,3	0,5	2,2
H396P	2,4	1,1	2,4	0,4	1,4
H396R	3,9	1,6	3,1	0,8	5,9
F486S	8,1	3,0	1,9	2,3	2,1
L248R & F359I	1,2	13,7	96,2	39,3	17,7
Generation:	1st gen	2nd gen			3th gen.

Relative activity ($IC50^{MUT}/IC50^{WT}$) of imatinib, dasatinib, nilotinib, bosutinib and ponatinib in the context of the respective mutation relative to the effectiveness against $BCR\text{-}ABL^{WT}$. Color code: *green* <2/sensitive; *yellow* 2, 1–4/moderately resistant; *orange* 4, 1–10/resistant; *red* >10/highly resistant. Note that ponatinib is the only inhibitor displaying activity against the common "gatekeeper" T315I mutation. Modified from Redaelli et al. (Redaelli et al. 2012)

approved first- and second-generation inhibitors, the activity profile of the new inhibitor included the T315I mutation. In addition, so-called "compound mutants", defined by the co-occurrence of several concurrent mutations within the

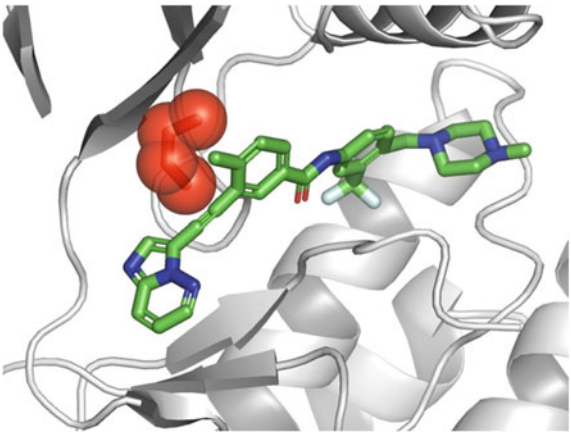

Fig. 1 Illustration of ponatinib in complex with the BCR-ABL protein. The *red spheres* represent the bulky side *chain* introduced by the T315I mutation. With kind permission of ARIAD Pharmaceuticals, Inc.

BCR-ABL fusion protein, were inhibited at a higher concentration by ponatinib (O'Hare et al. 2009).

In 2012, the first phase 1 trial for ponatinib in previously therapy-refractory patients was published (Cortes et al. 2012a). This study included 60 CML and 5 Ph^+ ALL patients. The CML cases included 43 patients in chronic phase (CP), 9 in accelerated phase (AP) and 8 in blast phase (BP) and represented a highly pre-treated collective (59/60 $\geq$ 2 TKIs; 41/60 $\geq$ 3 TKIs). Ponatinib was given once daily at doses ranging from 2 to 60 mg. Among the CP-CML patients, 98 % achieved a complete hematologic remission (CHR), 72 % achieved a major cytogenetic response (MCyR) and 44 % achieved a major molecular response (MMR). Given the refractory nature of CML in these patients and the high degree of pretreatment, these numbers were quite remarkable.

It should be highlighted that 12 of the 43 CP patients (28 %) carried the T315I mutation and therefore were refractory to first- or second-generation inhibitors. Under ponatinib therapy, 100 % of these T315I patients achieved a major hematologic response (MHR), 92 % achieved a MCyR and 67 % achieved a MMR.

Of the 13 refractory CML cases, which lacked any BCR-ABL mutation, rates for CHR, MCyR and MMR of 100, 62 and 15 %, respectively, were observed.

Patients with advanced CML (AP, BP) were analyzed together with the Ph^+ ALL cohort in this study and responded to ponatinib as well. A MHR was achieved in 36 %, MCyR in 32 % and MMR in 9 % of patients. Thus, the novel third-generation inhibitor showed a clinically significant effect even in advanced-phase CML.

In order to further investigate the primary response rates to ponatinib (45 mg once daily) and its safety, a phase 2 trial (PACE trial) was launched (Cortes J, et al. 2012b). Patients in all phases of CML (CP, AP and BP) and Ph^+ ALL, resistant or intolerant to dasatinib or nilotinib or with a known T315I mutation, were enrolled. To date, the recruitment of 449 patients has been completed and the follow-up assessment is still ongoing. Interim results were presented in December 2012

(Cortes J, et al. 2012b). In CP-CML patients (n = 267), the primary endpoint (MCyR at 12 months) was achieved in 56 % of cases. In particular, patients carrying a T315I mutation responded better than those who were included because of resistance or intolerance (70 % vs. 51 %). In the CP-CML cohort, progression-free survival (PFS) and overall survival (OS) after twelve months were 80 and 94 %, respectively. Furthermore, the study revealed that the response rates for MCyR, CCyR and MMR of those patients decreased depending on the number of previously applied TKIs.

The primary endpoint (MHR after 12 months) was achieved in 57 % of the AP CML and in 34 % of the group containing BP CML and Ph^+. Altogether, the interim results of the PACE trial confirm the efficacy of ponatinib in second-generation TKI-resistant or TKI-intolerant CML and PH^+ ALL patients at a dose of 45 mg daily. Importantly, the results confirm the efficacy of this new inhibitor against the "gatekeeper" T315I mutation.

Based on the two above-mentioned trials, ponatinib was approved for the second-line treatment of CML and Ph^+ ALL in December 2012 in the United States and in July 2013 in the European Union. The approval in the EU covers patients in all phases of CML

- Who are resistant to dasatinib or nilotinib.
- Who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate.
- Who carry the T315I mutation.

The same terms apply to the approval for the use in Ph^+ ALL except that nilotinib is not considered here.

A phase 3 trial (EPIC trial) opened in July 2012 strives to compare ponatinib (45 mg daily) with imatinib (400 mg daily) in first-line therapy of newly diagnosed CML in CP. This trial aims to enroll 528 patients, and the MMR at 12 months is defined as primary endpoint. Depending on the results of this study, ponatinib will potentially be approved for first-line therapy in CML.

The growing number of patients treated with ponatinib during clinical trials has now increased the overall experience in terms of safety and adverse effects. The interim results of the PACE trial reported the following non-hematologic adverse reactions in descending order of frequency: rash, stomach aches, headaches, dry skin, constipation, fatigue, fever, nausea, arthralgia, hypertension, increased lipase, pancreatitis and amylase increase. Hematologic adverse effects have been observed more frequently compared to other Abl kinase inhibitors (thrombocytopenia > neutropenia > anemia). Focusing on the serious adverse events of grades 3 and 4, the increase in lipase (11 % of CP-CML patients) and hematologic adverse effects (thrombocytopenia 34 %, neutropenia 16 %, anemia 8 %) have to be highlighted and should receive special attention (Cortes et al. 2012b).

In addition to the use of ponatinib in CML and Ph^+ ALL, other diseases could potentially benefit from the treatment with this new drug as well. Preclinical studies reported that ponatinib inhibits not only BCR-ABL but also RET, FLT3, KIT, SCR, as well as members of receptor kinase families VEGFR, FGFR and

PDGFR (O'Hare et al. 2009). Following these findings, in vitro as well as in vivo studies investigated the effect of ponatinib on AML as well as on breast cancer cells and carcinoma of the endometrium, bladder, stomach, colon, lung and medullary thyroid. In these neoplasms, ponatinib was shown to inhibit proliferation and additionally to induce apoptosis in FLT3-ITD-driven AML. The effect of ponatinib on diverse cancer cells gives rise to the hope that ponatinib could potentially be applied to kinase-dependent subgroups of other malignancies and that this novel TKI may prove therapeutic in additional cancer entities (Falco et al. 2013; Gozgit et al. 2011, 2012; Zirm et al. 2012).

In conclusion, ponatinib constitutes a powerful BCR-ABL inhibitor and has been approved for the treatment of CML patients resistant or intolerant to imatinib, dasatinib or nilotinib. It displays clinical activity both in wild-type and in BCR-ABL mutant CML, including activity against the T315I mutation. Ponatinib induces high rates of remission and simultaneously exhibits a good overall safety profile. Despite previous TKI failure, chronic-phase CML patients can achieve sustained remissions using the novel drug. For patients in advanced CML or Ph^+ ALL, ponatinib therapy can successfully bridge the time to allogeneic stem cell transplantation.

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