Nilotinib

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Abstract

Targeted therapy of Philadelphia chromosome-positive chronic myeloid leukemia (CML) using the tyrosine kinase inhibitor imatinib mesylate has been one of the most striking achievements in modern cancer medicine. However, while imatinib can establish long-term remission in many cases, resistance to or intolerance of imatinib is eventually experienced by a substantial number of patients. Subsequent advances have led to the development of novel tyrosine kinase inhibitors (TKIs). One such inhibitor, nilotinib, was rationally designed to increase its affinity and specificity for the oncogenic tyrosine kinase Bcr-Abl compared with imatinib and has been shown to be effective after imatinib failure. Recently, nilotinib has been shown to be more effective when used as first-line therapy of chronic phase CML.

Contents

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U. M. Martens (ed.), *Small Molecules in Oncology*, Recent Results in Cancer Research 201, DOI: 10.1007/978-3-642-54490-3_3,

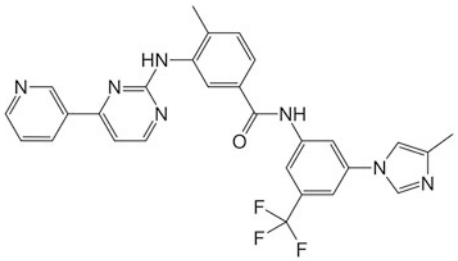
1 Introduction

Philadelphia chromosome-positive chronic myeloid leukemia (CML) cells are addicted to the oncogenic activity of tyrosine kinase Bcr-Abl, the molecular correlate of the Philadelphia chromosome (Druker et al. 1996). Imatinib mesylate (formerly STI571 or CGP5148B) is a specific inhibitor of Bcr-Abl and quickly replaced former therapy regimes as first-line therapy for CML in chronic phase (CP) because of its considerable antiproliferative activity against Bcr-Abl expressing cells (Druker et al. 2006). However, follow-up data in the landmark IRIS trial revealed a significant portion of patients to develop disease resistance to imatinib with an overall failure rate of 17 % after 5 years (Druker et al. 2006).

Secondary resistance most commonly arises as a consequence of point mutations within the kinase domain of Bcr-Abl (Gorre et al. 2001; O'Hare et al. 2007), with other mechanisms being less well-characterized (Apperley 2007). Over 100 mutations conferring varying degrees of resistance to imatinib have been detected in patients with CML, although seven mutations account for the majority of imatinib refractory cases (Ernst et al. 2011; Shah et al. 2002). In addition to secondary resistance, some patients never meet optimum response criteria to imatinib therapy. Moreover, patients in accelerated phase (AP) and blast phase (BP) are frequently resistant to imatinib and when they respond, responses are usually short-lived (Sawyers et al. 2002; Talpaz et al. 2002).

The high frequency with which CML recurs after discontinuation of therapy suggests that only a minute CML patient population might achieve a cure or at least long-term remission with tyrosine kinase inhibitors (TKIs) (Cortes et al. 2004; Mahon et al. 2010). Thus, prolonged therapy is required in most cases. However, despite its targeted mechanism imatinib therapy is not devoid of relevant side effects, sometimes compromising long-term therapy. The IRIS study showed imatinib discontinuation for various reasons in 30 % after 5 years (Druker et al. 2006), and Deininger and colleagues showed discontinuation of imatinib therapy due to adverse effects in 10 % of patients (Deininger et al. 2003).

Primary and secondary resistance to imatinib treatment as well as intolerance of therapy prompted the development of new generation TKIs. Recently, the second-generation TKIs nilotinib (Tasigna®) and dasatinib (Sprycel®) have been approved for first-line therapy of CML in chronic phase.



Chemical name:	4-Methyl-3-((4-(3-pyridinyl)-2-pyrimidinyl)amino) -N-(5-(4-methyl-1H-imidazol-1-yl)-3- (trifluoromethyl)phenyl)benzamide
Synonym:	AMN107
Molecular weight:	529.52
Molecular formula:	$C_{28}H_{22}F_3N_7O$

Fig. 1 Molecular structure and chemical characteristics of nilotinib

2 Structure and Mechanism of Action

Crystallographic analysis of the interaction between imatinib and the Abl kinase domain led to the rational development of nilotinib (formerly AMN107) by replacing an N-methylpiperazine group in imatinib (Manley et al. 2004; Weisberg et al. 2005) (for molecule structure see Fig. 1). Similar to imatinib, nilotinib is an orally bioavailable ATP-competitive inhibitor of the Abl kinase domain. It was shown to have a 10- to 50-fold increased potency against unmutated Bcr-Abl compared with imatinib. Importantly, nilotinib also has considerable activity against most imatinib-resistant Bcr-Abl mutations (Weisberg et al. 2005).

Nilotinib exerts its inhibitory activity on Bcr-Abl by binding to an inactive conformation of the kinase and preventing its change to an active conformation. In addition to Bcr-Abl, nilotinib also inhibits tyrosine kinases KIT, platelet-derived growth factor receptor (PDGFR), and discoidin domain receptor 1 (DDR1). Nilotinib was also found to inhibit the non-tyrosine kinase NAD(P)H:quinone oxidoreductase (NQO2) (Rix et al. 2007). Whether these interactions impact clinical activity or the toxicity profile of nilotinib remains unknown.

3 Preclinical Data

Nilotinib was shown to be more potent than imatinib at inhibiting proliferation of Bcr-Abl expressing murine and human cells in culture. Autophosphorylation of Bcr-Abl in cells exposed to nilotinib was lower than in cells exposed to imatinib (Golemovic et al. 2005; Weisberg et al. 2005). Consistently, nilotinib was shown

Table 1 Categorized sensitivity to nilotinib of clinically relevant Bcr-Abl mutations recovered in unbiased mutational screens

Sensitivity	IC_{50} (nM)	Bcr-Abl mutations
High	100	M237I, M244V, K247N, G250A, G250E[a], G250V, Q252H, E255D, E255R, L273F, E275K, D276G[a], E281K, E285N, K285N, V289L, E292K[a], N297T, F311L, F317C, F317L[a], FF317V[a], D325N, S348L, M351T, E355A, E355G, H375P, V379I, L387F, M388L, L387F, L387M, H396P, H396R, T406I, W430L, E431G
Medium	200	L284V[a], G250E[a], Y253F, E255K[a], D276G[a], E282K, E292K[a], F311, F317L[a], F317R, F359, A380S, F486S
Low	1,000	L248V[a], Y253C, Y253H[a], E255K[a], E255V[a], K285, F317V[a], F359C, F359I[a]
None	>2,000	T315I, T315V, L248R

Of note, the extent of sensitivity depends not only on the position of the mutation but also on the specific substitution

[a]Denotes mutations that fall into two different categories, based on different values reported. Values are from references (Bradeen et al. 2006; von Bubnoff et al. 2006; O'Hare et al. 2005; Ray et al. 2007; Redaelli et al. 2012; Weisberg et al. 2006)

to significantly prolong survival and reduce tumor burden in a CML mouse model (Golemovic et al. 2005; Weisberg et al. 2005).

Importantly, nilotinib retained its inhibitory activity against most Bcr-Abl mutants resistant to imatinib with the exception of the T315I-, T315V-, and L248R-mutations (Table 1).

4 Clinical Data

4.1 Nilotinib Phase I Trial

A phase I dose escalation study showed higher steady-state levels when nilotinib was administered twice daily (Kantarjian et al. 2006). The median time to peak concentration was three hours after administration, reaching a mean peak concentration of 3.6 μM at steady-state level at 400 mg twice daily. Increase in steady-state levels was dose-dependent and achieved by day 8 with a mean serum trough level at steady state of 1.7 μM at 400 mg twice daily and of 2.3 μM at 600 mg twice daily. These trough levels exceeded the 50 % inhibitory concentration for phosphorylation of unmutated Bcr-Abl as well as of 32 out of 33 Bcr-Abl mutants. The half-life of nilotinib was 16 h. Nilotinib absorption but not elimination was shown to be increased when taken after a light or high-fat meal (Tanaka et al. 2009). Results were consistent with pharmacokinetic analyses in healthy volunteers (Kagan et al. 2005; Tanaka et al. 2009).

Table 2 Efficacy of nilotinib in chronic phase (*CP*), accelerated phase (*AP*), myeloid blastic phase (*MBP*), and lymphoid blastic phase (*LBP*) of Ph-positive chronic myeloid leukemia (*CML*) with imatinib resistance or intolerance

	CP (n = 321)	AP (n = 137)	MBP (n = 105)	LBP (n = 31)
Overall HR (%) (CHR + MR/NEL + RTC)	–	55	54	59
CHR (%)	–	31	24	21
MR/NEL (%)	–	12	–	–
RTC (%)	–	12	–	–
MCyR (CCyR + PCyR) (%)	59	32	38	52
CCyR (%)	45	21	30	32
PCyR (%)	14	11	8	20
Continuous HR (%)	–	49	51	21
Continuous MCyR (%)	–	66	44	0
Progression-free survival (%)	57	33	–	–
Overall survival (%)	78	70	32	10

Numbers are based on references (Giles et al. 2012, 2013; le Coutre et al. 2012). Time of analysis was 48 months after initiation of nilotinib therapy for CML in CP and 24 months for CML in AP or BP. *HR* hematologic response; *CHR* complete hematologic response; *MR/NEL* marrow response/no evidence of leukemia; *RTC* return to chronic phase; *MCyR* major cytogenetic response; *CCyR* complete cytogenetic response; *PCyR* partial cytogenetic response;—not reported/applicable

4.2 Nilotinib Second- and Third-Line Therapy

Nilotinib was first used as second-line therapy in the context of imatinib resistance or intolerance (Kantarjian et al. 2006). Phase II trials have been conducted to study nilotinib administration in patients with CML in CP, AP, or BC resistant to or intolerant of imatinib (Table 2).

The first phase II trial published in 2007 included patients with CML in CP (Kantarjian et al. 2007). The last update reported on 321 patients, 70 % of which were resistant to and 30 % intolerant of imatinib (Giles et al. 2013). Median CML duration before study entry was 58 months (range, 5–275). Mean duration of prior imatinib treatment was 32 months (range, <1–94), and median follow-up was 1,555 days. Seventy percent of patients had discontinued nilotinib at 48 months, mostly due to disease progression (n = 96, 30 %) or adverse events (n = 66, 21 %). At 24 months, 190 patients (59 %) had achieved a major cytogenetic response (MCyR) (Kantarjian et al. 2011a), and no additional patients achieved a MCyR between months 24 and 48 (Giles et al. 2013). Remission rates in patients resistant to and intolerant of imatinib were comparable. Most patients achieving a MCyR also achieved a complete cytogenetic response (CCyR) (45 %). Progression-free survival at 48 months was 57 % (95 % CI, 51–64 %) with only very few patients progressing to AP or BP (3 %). The estimated overall survival rate at

48 months was 78 %, and a median survival time was not reached. The median administered nilotinib dose of 789 mg/day (range, 151–1,110) was close to the planned initial dose of 800 mg/day, indicating excellent tolerability.

Another phase II trial analyzed the efficacy of nilotinib after failure of both imatinib and dasatinib in 39 patients with CML in CP (Giles et al. 2010). The median CML duration before initiation of nilotinib therapy was 89 months. Complete hematological response (CHR) and MCyR were achieved in 79 and 43 %, respectively. Although most patients in the study were included due to intolerance to dasatinib treatment (67 %), most had also failed to attain a MCyR (79 %), despite a median duration of dasatinib exposure of 7 months. The estimated overall survival at 18 months was 86 %.

The efficacy of nilotinib in patients with CML in AP and imatinib resistance or intolerance was also studied in a phase II study (le Coutre et al. 2008). Overall, 137 patients with a follow-up of at least 24 months or after early discontinuation were evaluated (le Coutre et al. 2012). The majority of patients were imatinib resistant (80 %), while 20 % had imatinib intolerance. The median duration of CML was 71 months, and the median duration of prior imatinib therapy was 28 months. Nilotinib was administered for a median of 264 days (range, 2–1,160), and the median dose intensity was 780 mg/day (range, 150–1,149). A hematologic response was confirmed in 55 % of patients with 31 % attaining a CHR and 32 % a MCyR (most of which were complete). At 24 months, 49 and 66 % of responders had maintained a hematological and MCyR, respectively. Response rates were similar in patients with resistance and intolerance. The estimated OS and PFS at 24 months were 70 and 33 %, respectively. At the time of analysis, 85 % of patients had discontinued nilotinib treatment, mostly due to disease progression (44 %) with only 10 % discontinuing due to drug-related AEs.

The efficacy of nilotinib in patients with CML in BP was analyzed in 136 patients enrolled in a phase II study (Giles et al. 2008), 105 of which were in myeloid blastic phase (MBP) and 31 in lymphoid blastic phase (LBP). The median duration of prior imatinib therapy was 490 days (range, 1–3,267), and the majority of patients were enrolled due to imatinib resistance (82 %). At 24 months, major hematologic responses were observed in 60 and 59 % of patients in MBP and LBP, respectively, with corresponding figures for MCyR of 38 and 52 % (Giles et al. 2012). The median respective duration of MCyR was 10.8 and 3.2 months. Overall survival was 27 % (MPP 32 %, LBP 10 %). In conclusion, nilotinib was shown to have significant efficacy in patients with CML after failure of imatinib therapy, including patients with advanced phase CML, although in such cases response rates and duration were significantly lower compared with CML in CP.

4.3 Nilotinib First-Line Therapy

The randomized, open-label, multicenter phase III trial Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients (ENESTnd) evaluated nilotinib as first-line therapy in patients with CML in CP (Saglio

et al. 2010) by comparing imatinib 400 mg once daily to nilotinib 300 mg twice daily or nilotinib 400 mg twice daily in 283, 282, and 281 patients, respectively. In the most recent update with a follow-up time of 4 years significantly more patients treated with nilotinib 400 mg twice daily (73 %) and nilotinib 300 mg twice daily (76 %) had reached a major molecular response (MMR) than patients treated with imatinib (56 %). The molecular response at 4 years was also deeper in patients on nilotinib 300 mg and nilotinib 400 mg than in patients on imatinib, with 56 and 50 % versus 32 % of patients achieving a molecular response of Bcr-Abl $\leq$ 0.01 % expressed on the international scale (Bcr-Abl^{IS}; MR^{4}), respectively. Similarly, rates of Bcr-Abl $\leq$ 0.0032 % (MR$^{4.5}$) were significantly higher in patients on nilotinib 300 mg and nilotinib 400 mg than in the imatinib arm (40 and 37 % vs. 23 %, respectively). The difference in depth of molecular response across arms became more apparent on longer follow-up (Kantarjian et al. 2011b; Larson et al. 2012, 2013). Rates of progression to AP or BP were significantly lower in patients on nilotinib 300 mg and nilotinib 400 mg than in patients on imatinib (3.3, 2.2, and 6.9 %, respectively). While not statistically significant, overall survival was higher in both nilotinib arms compared with the imatinib arm (94.3, 96.7, and 93.3 % of patients on nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib 400 mg once daily, respectively).

In conclusion, nilotinib has shown superior efficacy to imatinib in first-line therapy of CML in CP.

4.4 Resistance to Nilotinib

In vitro screening assays showed nilotinib to render a reduced spectrum of mutant clones compared with imatinib (Bradeen et al. 2006; von Bubnoff et al. 2006; Ray et al. 2007). In the majority of cases, resistance was conferred by mutations within the P-loop of the Bcr-Abl kinase domain, only partly overlapping with the spectrum of mutations conferring resistance to other TKIs. This is reflected in the significant efficacy of nilotinib after previous failure of other TKIs (Giles et al. 2013).

Recently, the Bcr-Abl mutational profile during nilotinib versus imatinib treatment was assessed in 846 patients treated in the ENESTnd trial (Hochhaus et al. 2013). No mutations were detected at baseline in either group. Significantly more patients treated with imatinib developed Bcr-Abl mutations at 3 years than patients treated with nilotinib. Most mutations in the imatinib group retained sensitivity to nilotinib. The most frequent mutations in the nilotinib group were Y253H-, E255K/V-, and F359C/V. Notably, T315I, which is resistant to either agent, was acquired at comparable rates in both groups. Of note, fewer patients treated with nilotinib progressed to advanced disease or lost response to treatment compared with those treated with imatinib.

In conclusion, nilotinib is a potent inhibitor of the majority of imatinib-resistant Bcr-Abl mutant isoforms, with the exception of T315I and some mutations mapping to the P-loop.

5 Toxicity

In phase II and phase III studies investigating nilotinib efficacy, a high dose intensity was reached and discontinuation of nilotinib due to grade 3 and 4 adverse events was rare (Table 3), indicating that nilotinib has an overall favorable toxicity profile (Giles et al. 2012, 2013; Larson et al. 2012; le Coutre et al. 2012).

Among the most frequently reported, non-hematological events of any grade were rash and headache. Grade 3 and 4 adverse events were uncommon, with rash being the only non-hematological grade 3/4 adverse event observed in more than 2 % of patients. Notably, rates of drug-related fluid retention syndromes and gastrointestinal events were higher with imatinib than with nilotinib. Also, grade 3 and 4 neutropenia were more frequent in the imatinib group. With regard to already known toxicities, the safety profile of nilotinib showed only minimal change over a 4 year follow-up period (Larson et al. 2013).

In patients receiving nilotinib as second-line therapy, adverse events were expectedly higher, with grade 3 and 4 abnormalities mainly consisting of hematological toxicities. In patients treated with second-line nilotinib 400 mg twice daily for CML in CP, AP, and BP rates of grade 3/4 anemia were 11, 27, and 47 %, respectively. Rates of grade 3/4 neutropenia were 32, 42, and 68 %, respectively. Grade 3/4 thrombocytopenia was documented in 30, 42, and 63 % of patients, respectively (Giles et al. 2012, 2013; le Coutre et al. 2012).

Non-hematological biochemical laboratory abnormalities included lipase, alanine transaminase, and bilirubin elevations as well as hyperglycemia. These were often self-limited, rarely leading to treatment interruption or discontinuation.

In preclinical analyses, nilotinib was shown to prolong QTc-duration, making frequent ECG-monitoring mandatory. In particular, caution is warranted when drugs either inhibiting CYP3A4 or causing QTc prolongation themselves such as amiodarone or digoxin are administered. However, after 4 years of follow-up in the ENESTnd study, nilotinib induced no QTc prolongation $\geq$500 ms and no episodes of Torsade de Pointes were reported (Larson et al. 2013), thus markedly minimizing the risk previously adjudicated to nilotinib regarding QTc interval prolongation.

An alarming and new finding made after long follow-up of nilotinib-treated patients was an increase in the incidence of peripheral artery occlusive disease (PAOD). In patients treated with nilotinib 300 and 400 mg twice daily as first-line therapy for CML in CP 1.4 and 1.8 % of patients developed PAOD compared with 0 % in the imatinib group (Larson et al. 2013). PAOD did not lead to study discontinuation, and most patients had preexisting risk factors for PAOD at study entry. These data are confirmatory of the initial reports by Aichberger et al. and our groups showing severe cases of PAOD in nilotinib-treated patients (Aichberger et al. 2011; le Coutre et al. 2011; Quintás-Cardama et al. 2012). In addition, a higher proportion of nilotinib-treated patients as compared with imatinib-treated patients developed cardiac and cerebrovascular events, indicating a general risk of atherosclerosis in the context of nilotinib treatment. Recently, a prospective

Table 3 Adverse events (%) with nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib 400 mg once daily as reported from patients with CML in CP treated in a phase III trial with a minimum follow-up of 3 years (Larson et al. 2012)

	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Imatinib 400 mg once daily
Study drug-related AEs	91.0	96.4	93.6
AEs leading to discontinuation	10.0	14.1	11.4
Study drug-related AEs leading to discontinuation	9.3	12.6	10.4
AEs leading to dose reduction/ interruption	57.3	66.4	50.0
Hematologic toxicity grade 3/4			
Anemia	3.9	4.7	5.7
Neutropenia	11.8	10.8	21.4
Thrombocytopenia	10.4	12.3	8.9
Non-hematologic toxicity (any grade)			
Symptomatic QT prolongation	1.8	1.4	2.5
Pancreatitis	1.8	2.2	0.7
Hepatotoxicity	1.4	4.0	2.5
Fluid retention	18.6	23.5	56.4
Effusions	1.8	0.7	1.8
Rash	41.2	46.9	22.1
Significant bleeding	2.9	4.3	1.4
CNS hemorrhage	0.4	0.7	0.4
Gastrointestinal hemorrhage	2.5	4.0	1.1
Ischemic heart disease	3.2	4.0	1.1
Peripheral arterial occlusive disease	1.4	1.1	0
Grade 3/4 laboratory abnormalities			
AST elevation	1.4	2.9	1.4
ALT elevation	4.3	9.4	2.5
Bilirubin (total) elevation	3.9	7.9	0.4
Lipase (plasma) elevation	7.5	7.9	3.9
Glucose elevation	6.1	5.4	0
QTc prolongation			

(continued)

Table 3 (continued)

	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Imatinib 400 mg once daily
Absolute QTcF $\geq$ 480 ms	0	0.4	0.7
Absolute QTcF $\geq$ 500 ms	0	0	0.4
QTcF $\geq$ 60 ms change from baseline	0.4	1.1	0.4

Abbreviations AE adverse event; *CNS* central nervous system; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase

analysis compared the rates of PAOD in nilotinib- versus imatinib-treated patients (Kim et al. 2013). Significantly more patients on nilotinib first- and second-line therapy than on first-line imatinib therapy showed a pathological ankle-brachial index (26, 35.7, and 6.3 %, respectively). Clinically obvious PAOD was documented only in patients exposed to nilotinib. In addition, elevation of both cholesterol and LDL levels was observed in patients receiving nilotinib. Thus, noninvasive monitoring for PAOD as well as careful assessment of risk factors is warranted in patients treated with nilotinib. In detail, we presently recommend pretherapy ankle-brachial-index testing as well as control of biochemical risk factors and to repeat these tests annually.

In summary, nilotinib has a favorable safety profile with few severe adverse events, most of which can be controlled by dose reduction or interruptions. Caution is warranted especially in patients at increased cardiovascular risk due to a small but sizeable risk of PAOD.

6 Drug Interactions

Therapy with TKIs usually requires prolonged, if not lifelong administration to maintain CML remission, which increases the risk of drug–drug interactions over the course of the lives of patients with CML. This becomes particularly relevant for those patients that require additional therapy for other comorbidities.

Nilotinib is metabolized by the cytochrome P450 enzyme CYP3A4. Thus, inhibitors of CYP3A4 can result in higher nilotinib exposure, as shown when co-administered with ketoconazole or grapefruit juice (Tanaka et al. 2011; Yin et al. 2010). Conversely, drugs inducing expression of CYP3A4 such as rifampicin lead to significantly lower nilotinib exposure (Tanaka et al. 2011).

Nilotinib itself inhibits CYP2C8, CYP2C9, CYP2D6, CYP3A4, UGT1A1, and Pgp. Therefore, caution should be exercised when drugs metabolized by these enzymes, including vitamin K-antagonists, are administered with nilotinib (Haouala et al. 2011).

7 Biomarkers

Several endpoints have been used in trials studying the efficacy of TKIs for treatment of CML, including hematological, cytogenetic, and molecular response. Monitoring guidelines suggested by The European Leukemia Net define an optimal response to imatinib therapy as reaching CHR at 3 months and a partial cytogenetic response (PCyR) at 6 months. At 12 months, a CCyR should be reached and at 18 months an optimum response is defined as reaching an MMR (Baccarani et al. 2009). Importantly, similar criteria are not available to monitor response to second-generation TKIs such as nilotinib. Several studies suggest that more stringent criteria for both cytogenetic and molecular response at early time points (e.g., 3 months) are best suited to define optimal response and failure to nilotinib or dasatinib therapy in the frontline setting (Jain et al. 2013).

A topical issue regarding TKI therapy in CML is the possibility of treatment discontinuation in patients achieving very deep levels of response (e.g., Bcr-Abl undetectability). This has been demonstrated in patients receiving imatinib therapy. A prospective trial assessed discontinuation of imatinib in patients achieving long-term complete molecular remission (Mahon et al. 2010). At 12 months follow-up, 41 % of patients remained in complete molecular remission. All patients that required re-initiation of therapy due to molecular relapse remained sensitive to imatinib. Another trial included 40 patients with CML in CP who had sustained undetectable minimal residual disease for at least 2 years (Ross et al. 2013). At 24 months, 47.1 % remained in stable treatment-free remission. These data indicate that it is safe to discontinue TKI therapy in patients who have maintained deep molecular remission over an extended period of time (Mahon 2012). Given the opportunity of achieving deeper and faster molecular responses with second-generation TKIs, this issue may be even more relevant in patients starting CML therapy with nilotinib. Preliminary data indicate that similar conclusions might be drawn regarding discontinuation of second-generation TKIs, but larger studies are warranted (Rea et al. 2011).

8 Summary and Perspectives

In summary, nilotinib is a rationally designed second-generation TKI with significant efficacy in treating patients with CML. It is currently approved for patients with CML both newly diagnosed as well as after imatinib failure.

An unsolved issue is how individual risk factors, disease status, comorbidities, and Bcr-Abl mutation status should guide the choice of TKI therapy given the fact that several of them in addition to nilotinib are currently approved for the same indication. Data from the ENESTnd study indicate that nilotinib appears to be superior both from an efficacy and tolerability point of view compared with imatinib, most strikingly, in preventing progression to AP or BP. As therapy for advanced phase CML is still very deficient, most efforts when treating patients

with CML in CP should be focused on preventing progression to AP or BP. A potential added benefit of using nilotinib over imatinib as frontline therapy in CML in CP is the induction of deep and fast molecular responses in a larger number of patients, which might facilitate future TKI interruption strategies.

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