Drugs 2008; 68 (4): 449-459
0012-6667/08/0004-0449/$53.45/0

Nilotinib

Greg L. Plosker and *Dean M. Robinson*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Contents

Abstract

▲ Nilotinib is an orally administered BCR-ABL tyrosine kinase inhibitor that has shown good clinical efficacy in imatinib-resistant or -intolerant, Philadelphia chromosome-positive, chronic myeloid leukaemia (CML) in a phase I/II trial. The phase I component of the trial established the dosage regimen used in the phase II part of the trial, which included several arms. Three of these arms, or phase II trials, evaluated nilotinib in each of the three phases of CML (chronic, accelerated or blast crisis).

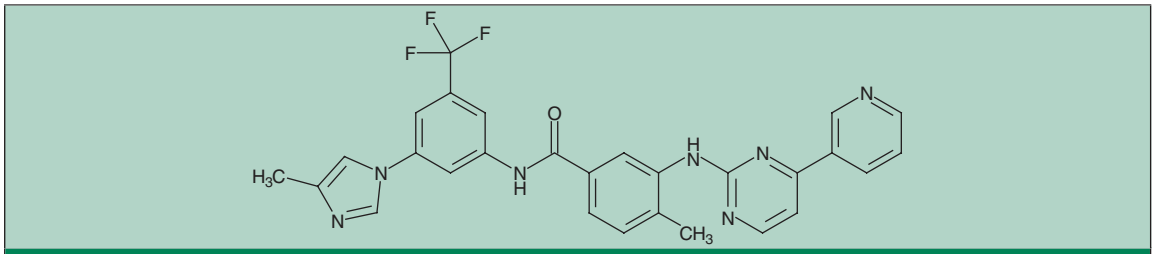
▲ In the phase II trial in patients with chronic-phase CML, major cytogenetic response (primary endpoint) was achieved in 48% of the 280 patients who received nilotinib and had a follow-up period of ≥6 months. Major cytogenetic response rates did not differ between imatinib-resistant and -intolerant patients, and nilotinib was effective in patients with BCR-ABL mutations (except T315I).

▲ Haematologic response rate (primary endpoint) was 47% in the phase II trial with nilotinib in patients with accelerated-phase CML (n = 119). Complete haematologic response was achieved in 26% of patients and 21% had no evidence of leukaemia or returned to chronic-phase CML. Major cytogenetic response, an important secondary endpoint in the trial, occurred in 29% of patients.

▲ Data from the phase II trial in patients with CML in blast crisis (n = 135) also showed promising results, with 39% of patients achieving haematologic response with nilotinib.

▲ Adverse events reported with nilotinib have generally been of mild to moderate severity. Grade 3 or 4 neutropenia and thrombocytopenia were reported in 29% of patients each.

Features and properties of nilotinib (AMN 107, Tasigna®)	
Indication	
Imatinib-resistant or -intolerant, Philadelphia chromosome-positive (Ph+), chronic myeloid leukaemia (CML) in chronic or accelerated phase	
Mechanism of action	
Inhibitor of BCR-ABL tyrosine kinase, including most imatinib-resistant BCR-ABL mutants	
Dosage and administration	
Recommended dose	400 mg twice daily
Route of administration	Oral
Special instructions	No food to be consumed for ≥2 h before or 1 h after administration
Pharmacokinetic profile (in patients with imatinib-resistant, Ph+ CML or acute lymphoblastic leukaemia)	
Time to peak serum concentration	3 h
Mean peak steady-state serum concentration (400 mg twice daily)	3.6 μmol/L
Mean trough steady-state serum concentration (400 mg twice daily)	1.7 μmol/L
Apparent elimination half-life (estimated from multiple-dose pharmacokinetic studies)	≈17 h
Adverse events	
Most frequently reported (regardless of causality)	Rash, nausea, pruritus, headache and fatigue
Myelosuppression or biochemical abnormalities	Neutropenia, thrombocytopenia, anaemia, AST and ALT elevations, hyperbilirubinaemia, increased lipase levels



Nilotinib

Chronic myeloid leukaemia (CML) accounts for 15% of adult leukaemias.[1] In the US in 2006, an estimated 4500 patients were diagnosed with CML and 600 patients died from the disease.[2] CML results from the clonal expansion of haematopoietic stem cells that have a reciprocal translocation between chromosomes 9 and 22.[1] The consequence of this translocation, referred to as the Philadelphia chromosome (Ph) and present in approximately 95% of patients with CML, is the formation of the chimeric protein BCR-ABL, in which the tyrosine kinase component of the ABL protein is activated.[1,3-6] This, in turn, results in enhanced cellular proliferation, inhibition of apoptosis and alteration of the adhesive properties of CML cells.

Most patients with CML are in the initial chronic phase at diagnosis, which is usually followed by progression to the accelerated phase and ultimately results in blast crisis.[3] If left untreated, patients diagnosed with CML have a life expectancy of ≈3–5 years.[1] However, the introduction of the BCR-ABL tyrosine kinase inhibitor imatinib, which demonstrated high overall survival and response rates after at least 5 years of follow-up,[7] has revolutionized the treatment of CML, and the drug has become the standard primary treatment for patients with this condition.[1]

While imatinib has shown good results in patients in chronic-phase CML,[7] response rates are lower and often transient in patients with more advanced disease.[8] In addition, disease progression occurs at an annual rate of 4% among patients with chronic-phase CML who are treated with imatinib.[9]

Resistance to imatinib can occur by various mechanisms, with the most common cause of acquired drug resistance being the emergence of point mutations in the kinase domain of the BCR-ABL protein, reducing the binding affinity of imatinib.[10-12] Other important mechanisms include amplification of Ph[13] and clonal evolution.[14] Dasatinib, an inhibitor of multiple tyrosine kinases including BCR-ABL, SRC-family, proto-oncogene protein c-KIT, ephrin A receptor and platelet-derived growth factor β kinases,[15] has shown promising results in the treatment of imatinib-resistant CML[16-19] and, until recently, has been the main treatment option in this setting.[1]

Nilotinib (Tasigna®)[1] is an orally administered, selective inhibitor of BCR-ABL tyrosine kinase, including most imatinib-resistant BCR-ABL mutants. This article provides an overview of the pharmacological properties of nilotinib and reviews the clinical trial data available on the efficacy and tolerability of the drug in patients with imatinib-resistant or -intolerant CML. Medical literature on the use of nilotinib in imatinib-resistant or -intolerant CML was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

- Nilotinib is an aminopyrimidine derivative that inhibits the tyrosine kinase activity of the chimeric protein BCR-ABL.[4,5] The unregulated activity of the ABL tyrosine kinase in the BCR-ABL protein

1 The use of trade names is for product identification purposes only and does not imply endorsement.

causes CML, and inhibition of tyrosine kinase activity is key to the treatment of the disorder.

- Nilotinib acts via competitive inhibition at the adenosine triphosphate (ATP)-binding site of the BCR-ABL protein in a similar manner to imatinib, although nilotinib has a higher binding affinity and selectivity for the ABL kinase.[5,12,20-22] Nilotinib binds to an inactive conformation of the protein in which the P-loop of ABL occupies a region that would be occupied by ATP in the active conformation.[6,21] Once bound to the ATP-binding site, nilotinib inhibits tyrosine phosphorylation of proteins involved in BCR-ABL-mediated intracellular signal transduction.[5,12,20-22]
- The inhibitory activity of nilotinib in CML cell lines is markedly higher than that of imatinib. In imatinib-sensitive CML cell lines, the inhibitory activity of nilotinib is 10–60 times that of imatinib.[5,12,21,22] For example, mean 50% inhibitory concentrations (IC_{50}) of cellular BCR-ABL autophosphorylation and proliferation of Ba/F3 BCR-ABL cells were 21 and 25 nmol/L, respectively, for nilotinib compared with 220 and 649 nmol/L for imatinib.[22] The inhibitory activity of nilotinib is also several-fold higher than that of imatinib in imatinib-resistant CML cell lines.[5,12,21]
- Nilotinib demonstrated inhibitory activity in 32 of 33 imatinib-resistant CML cell lines expressing mutant BCR-ABL kinases. The only BCR-ABL mutant that was not inhibited by nilotinib was T315I.[5,12,21,22] In patients with imatinib-resistant or -intolerant CML in chronic phase or accelerated phase who participated in phase II clinical trials, 39 different BCR-ABL mutations affecting 29 amino acids were noted in 39% of patients with chronic-phase disease and 58% of those with accelerated-phase disease.[23] Nilotinib was effective in patients with a range of BCR-ABL mutations associated with imatinib resistance, other than T315I, as well as in patients with BCR-ABL-independent resistance.

2. Pharmacokinetic Profile

Pharmacokinetic data on nilotinib are derived primarily from the phase I dose-escalation component of a phase I/II trial (see section 3 for further details). The phase I trial included 119 patients with imatinib-resistant, Ph+ chronic-phase CML or Ph+ acute lymphoblastic leukaemia (ALL).[24] Contributory data are also available from abstract reports in healthy volunteers.[25,26]

- In the phase I study, which involved administration of oral nilotinib at dosages of 50–1200 mg once daily, as well as 400 or 600 mg twice daily, all trough serum concentrations exceeded the IC_{50} for cellular phosphorylation of BCR-ABL including 32 of 33 BCR-ABL mutants.[24] At steady state, peak serum concentrations and area under the concentration-time curve (AUC) values increased with once-daily administration of nilotinib 50–400 mg but reached a plateau with higher doses, possibly as a result of saturation of gastrointestinal absorption.
- At steady state, drug exposure was 35% greater among patients who received 400 mg twice daily than among those who received 800 mg once daily.[24,27] Although a dose-proportional increase in drug exposure has been noted between 400 mg twice daily and 600 mg twice daily,[24] the increase in drug exposure is not clinically relevant.[27]
- At the recommended dosage of nilotinib 400 mg twice daily, the mean peak serum concentration of 3.6 μmol/L was achieved after a median time of 3 hours.[24] The serum trough concentration at steady state was 1.7 μmol/L at this dosage.
- Data from a large group of healthy volunteers (n = 92) showed that the bioavailability of nilotinib following single-dose administration (dosage not reported) was increased by 82% when taken with a high-fat meal compared with administration in the fasting state.[26]
- *In vitro*, ≈98% of nilotinib is bound to serum proteins.[27] The volume of distribution for nilotinib has not been reported; the blood-to-serum ratio is 0.68.[27]
- Oxidation and hydroxlyation are the main metabolic pathways in healthy volunteers, although nilotinib is the main circulating component in the serum.[27] Pharmacokinetic data from four healthy male volunteers who received a single 400 mg oral dose of ^{14}C-labelled nilotinib indicate that nilotinib represented >75% of total radioactivity at all time

points measured.[25] The major metabolite in serum or whole blood was the carboxylic acid derivative, although it represented only 7% of serum exposure and 4% of dose elimination in the faeces. None of the metabolites contribute significantly to the pharmacological activity of nilotinib.[27]

- The apparent elimination half-life of nilotinib was ≈17 hours when estimated from multiple-dose pharmacokinetic studies.[27] More than 90% of an administered dose is eliminated in the faeces within 7 days, with almost 70% of the dose accounted for by the parent drug.
- Concomitant single-dose administration of nilotinib and ketoconazole (dosages not reported) in healthy volunteers resulted in a 3-fold increase in systemic exposure to nilotinib, suggesting that the metabolism of nilotinib was affected by the cytochrome P450 (CYP) 3A4 inhibitor.[26] In a similarly designed analysis, in which single doses of nilotinib and midazolam were co-administered, there was a 30% increase in systemic exposure to midazolam, suggesting that nilotinib may be a weak inhibitor of CYP3A4.[26]

3. Therapeutic Efficacy

The therapeutic efficacy of nilotinib in Ph+ CML has been evaluated in a phase I/II trial that included an initial phase I dose-escalation study conducted in a small number of centres,[24] followed by several phase II trials undertaken in a large number of centres worldwide.[28-30] Although the phase II component of the trial consisted of six arms, only three of these involved patients with CML as follows: (i) chronic-phase CML;[28] (ii) accelerated-phase CML;[29] and (iii) CML in blast crisis.[30] Data are also available for patients in any phase of CML who failed both imatinib and dasatinib therapy.[31,32] The other three arms included patients with Ph+ ALL or rare haematologic diseases, such as hypereosinophilic syndrome and systemic mastocytosis, and a discussion of these results is beyond the scope of the current article. To facilitate the discussion of the phase I/II study throughout this section and the remainder of the article, the individual components of the trial conducted in patients with CML are referred to as separate phase I and II trials. The phase I study[24] and the phase II trials in chronic-[28] and accelerated-phase[29] CML have been fully published, whereas studies in patients with CML in blast crisis[30] and in patients whose disease failed to respond to both imatinib and dasatinib therapy[31,32] are currently available as abstracts and/or posters.

All of the clinical trials included patients who had previously received imatinib therapy but were either unable to tolerate the drug or their disease was resistant to imatinib treatment (after ≥3 months of imatinib ≥600 mg/day). In patients with chronic-phase CML, imatinib resistance was defined as a lack of complete haematologic response after ≥3 months, a lack of any cytogenetic response after ≥6 months, a lack of major cytogenetic response after ≥12 months, or a relapse after a haematologic response or major cytogenetic response.[24,28] In patients with accelerated-phase CML, imatinib resistance was defined as disease progression from chronic-phase CML to accelerated-phase CML during imatinib therapy, or disease progression (≥50% increase in white blood cells [WBC], blasts, basophils or platelet counts) during imatinib therapy for accelerated-phase CML, or a lack of haematologic response in bone marrow after 4 weeks of imatinib therapy for accelerated-phase CML.[29] Across the clinical trials, imatinib intolerance was defined as patients without a major cytogenetic response who discontinued the drug because of grade 2–4 adverse events despite optimal supportive care.[28-30]

The phase I study was conducted in patients with CML or Ph+ ALL whose disease was resistant to imatinib.[24] Although it was designed to evaluate the safety and tolerability of nilotinib, haematologic and cytogenetic responses were also evaluated. These were defined as previously described in studies conducted with imatinib.[33,34] A major cytogenetic response included complete (0% Ph+ cells in metaphase) or partial (1–35% Ph+ cells in metaphase) cytogenetic response, and the definition remained the same across all stages of CML. Complete haematologic response was defined for CML patients in chronic phase as WBC count $<10 \times 10^9$/

L, platelet count <450 × 10^9/L, <5% myelocytes plus metamyelocytes, <20% basophils, absence of blasts and promyelocytes in peripheral blood, and absence of extramedullary involvement.

In general, these criteria for haematologic and cytogenetic response were also used in the phase II trials.[28-32] For patients with CML in accelerated phase or blast crisis, complete haematologic response was defined as neutrophil count ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L, basophils <5%, no myeloblasts in peripheral blood, <5% myeloblasts in bone marrow and no extramedullary disease.[29-32] Cytogenetic and haematologic response rates were primary endpoints or important secondary endpoints for all of the phase II trials.

On the basis of results of the phase I component of the trial,[24] the phase II trials in patients with CML used an oral nilotinib dosage of 400 mg twice daily, which could be increased to 600 mg twice daily if necessary and appropriate.[28-32]

Phase I Trial

The phase I trial included 119 patients with imatinib-resistant, Ph+ CML (n = 106) or Ph+ ALL (n = 13).[24] Patients were assigned to receive one of the following nilotinib dosage regimens: 50, 100, 200, 400, 600, 800 or 1200 mg once daily, or 400 or 600 mg twice daily. Dose escalation was allowed for patients with an inadequate response to initial nilotinib therapy and no significant adverse events. The median duration of nilotinib administration ranged from 4.9 to 5.1 months among patients with chronic- or accelerated-phase CML, but was shorter in patients with myeloid (2.9 months) or lymphoid (1.4 months) blastic-phase CML.

- Among 33 patients with blastic-phase CML, two (6%) had a complete haematologic response and six (18%) had a major cytogenetic response to nilotinib.[24] Thirteen patients (39%) experienced any haematologic response (complete response, marrow response or return to chronic phase) and nine patients (27%) had minor, minimal or major cytogenetic responses.
- Of the 56 patients with accelerated-phase CML, 26 (46%) had a complete haematologic response and 15 (27%) had a major cytogenetic response.[24] A total of 38 patients (74%) experienced any haematologic response and 31 (55%) had minor, minimal or major cytogenetic responses.
- Complete haematologic response was achieved by 11 of 17 patients (65%) with chronic-phase CML. Major cytogenetic response occurred in six patients (35%) and any cytogenetic response was reported in nine patients (53%).[24]
- A substantial proportion of patients with an inadequate initial response to nilotinib treatment responded to subsequent dose escalation.[24] Among 23 patients with accelerated or blastic-phase CML who had a dose escalation from 50–400 mg once daily to 600 mg daily or 400 mg twice daily, 13 (57%) had haematologic responses. Dose escalation was required by <10% of patients treated with once-daily doses of ≥600 mg.
- Among 91 patients with a baseline assessment for mutational status, nilotinib had similar efficacy in those with and in those without ABL mutations.[24]

Phase II Trial in Chronic-Phase Philadelphia Chromosome-Positive (Ph+) Chronic Myeloid Leukaemia (CML)

Efficacy data are available for 280 chronic-phase Ph+ CML patients with a follow-up period of ≥6 months who participated in a phase II trial of nilotinib in imatinib-resistant or -intolerant disease.[28] The primary endpoint of the trial was major cytogenetic response. The median duration of CML was 57 months; 69% of patients were deemed to have imatinib-resistant disease and 31% had imatinib intolerance. Most patients had received previous treatment with interferon-α (66%), hydroxyurea (83%) and/or cytarabine (25%).

- Major cytogenetic response occurred in 48% (95% CI 41.9, 53.9) of patients and results were similar in imatinib-resistant or -intolerant patients (figure 1).[28] Complete cytogenetic response was achieved in 31% (95% CI 26.0, 37.2) of patients. The median time to major cytogenetic response was 2.8 months and the projected survival at 1 year was 95%. Only 5 of 134 patients (4%) who achieved a

major cytogenetic response discontinued nilotinib over the subsequent 6-month period because of disease progression or death.

- Of 185 patients who did not have a baseline complete haematologic response, 137 patients (74%) had a complete haematologic response at ≥6 months of follow-up.[28] Complete haematologic response was achieved rapidly in this patient population (median 1 month).
- Major cytogenetic responses occurred in 42% of patients with BCR-ABL mutations and 51% of those without BCR-ABL mutations (figure 1); corresponding results for complete cytogenetic response were 23% and 35%.[28] A total of 182 patients had baseline assessment of BCR-ABL mutation status. Results showed that 77 patients (42%) had 28 different BCR-ABL mutations, including six patients (8%) who had more than one mutation; 105 patients (58%) did not have BCR-ABL mutations. Major cytogenetic responses were observed across all BCR-ABL genotypes other than T315I, which was identified in four patients (2.2%).[28]

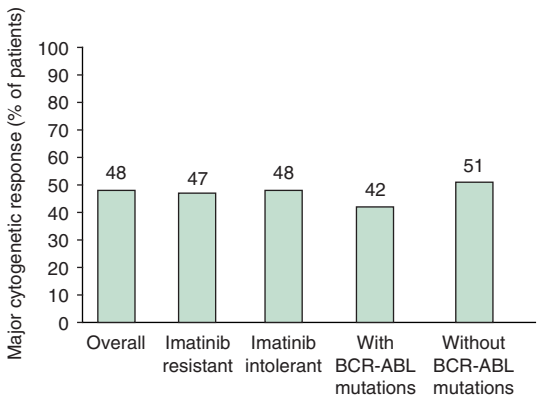


Fig. 1. Major cytogenetic responses with nilotinib in patients with chronic-phase, Philadelphia chromosome-positive, chronic myeloid leukaemia. Primary efficacy results for 280 patients with ≥6 months of follow-up in a phase II trial.[28] All patients were imatinib-resistant (n = 194) or -intolerant (n = 86) and received nilotinib 400 mg twice daily, which could be increased to 600 mg twice daily if necessary. BCR-ABL mutations were detected in 77 of 182 patients whose baseline status was available.

Phase II Trial in Accelerated-Phase Ph+ CML

A phase II study evaluated nilotinib in 119 imatinib-resistant (81%) or -intolerant (19%) patients with accelerated-phase Ph+ CML who had ≥6 months of follow-up.[29] The primary endpoint of the trial was haematologic response; cytogenetic response was an important secondary endpoint. The median duration of CML was 71 months and the median duration of prior imatinib use was 32 months. Most patients had also received previous treatment with hydroxyurea (92%) and/or interferon-α (58%). Patients were treated with nilotinib 400 mg twice daily, which could be increased to 600 mg twice daily if necessary. The median dose intensity of nilotinib was 790 mg/day.

- Overall, the haematologic response rate was 47% (95% CI 38, 56) and the complete haematologic response rate was 26% (figure 2).[29] Among the 56 patients who achieved a haematologic response, the median time to haematologic response was 1 month. It should be noted that 30% of patients were not assessable for response, since at the time of data collection for this report, no second post-baseline efficacy assessment was available per protocol.
- Major cytogenetic response occurred in 29% (95% CI 21, 39) of patients and complete cytogenetic response was achieved in 16% of patients.[29] The median time to major cytogenetic response was 2 months and the median duration of response was 15.4 months. After 12 months, the estimated overall survival in all 119 patients was 79% (95% CI 70, 87).
- In the subset of 51 patients with baseline data available for mutational assessment, response to nilotinib therapy was observed in patients both with or without a baseline BCR-ABL mutation.[29]

Phase II Trial in Blastic-Phase Ph+ CML

Data are available from 135 patients with imatinib-resistant or -intolerant Ph+ CML in blast crisis who participated in another phase II trial and had at least 6 months of follow-up.[30] The majority of patients (n = 103) had myeloid disease and most of the remaining patients (n = 29) had lymphoid dis-

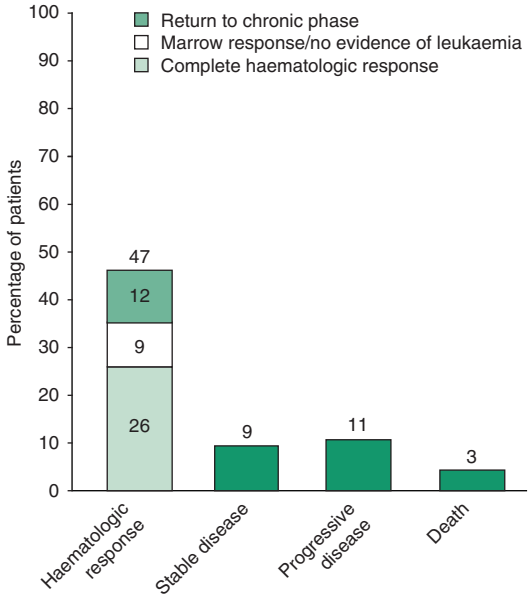


Fig. 2. Haematologic responses in accelerated-phase, Philadelphia chromosome-positive, chronic myeloid leukaemia. Primary efficacy results in 119 patients treated with nilotinib for ≥6 months in a phase II trial.[29] All patients were imatinib-resistant or -intolerant and received nilotinib 400 mg twice daily, which could be increased to 600 mg twice daily if necessary. In addition to the results shown, a further 30% of patients were not assessable for haematologic response.

ease. All patients were treated with nilotinib 400 mg twice daily for a median duration of ≈3 months; median dosage was 800 mg/day. The median duration of prior imatinib therapy was 15.9 months. Most patients (74%) had received prior hydroxyurea therapy and approximately one-third had received prior interferon.

- Haematologic response was reported in 52 of 135 patients (39%), including 33 patients (24%) who had complete haematologic response. These results were similar among patients with myeloid disease (39% haematologic response, 24% complete haematologic response) and those with lymphoid disease (38% and 28%).

Data From Patients Who Also Failed Dasatinib

Data are available from 67 patients with imatinib-resistant or -intolerant CML of any stage whose disease also failed to respond to dasatinib therapy.[31,32] Among the 67 evaluable patients, 27 were in chronic phase, 15 in accelerated phase and 25 in blast crisis (15 myeloid, 8 lymphoid, 2 not reported). All patients were treated with nilotinib 400 mg twice daily for a median duration of approximately 3 months; median dosage was 800 mg/day. Efficacy was evaluated in 55 patients with 4 months of follow-up: 22 patient in chronic-phase disease (17 without a complete haematologic response at baseline), 13 patients with CML in accelerated phase and 20 patients in blast crisis.

- Results of the study are presented in figure 3 and suggest that nilotinib may be useful to overcome dasatinib resistance in some patients.[31,32] In partic-

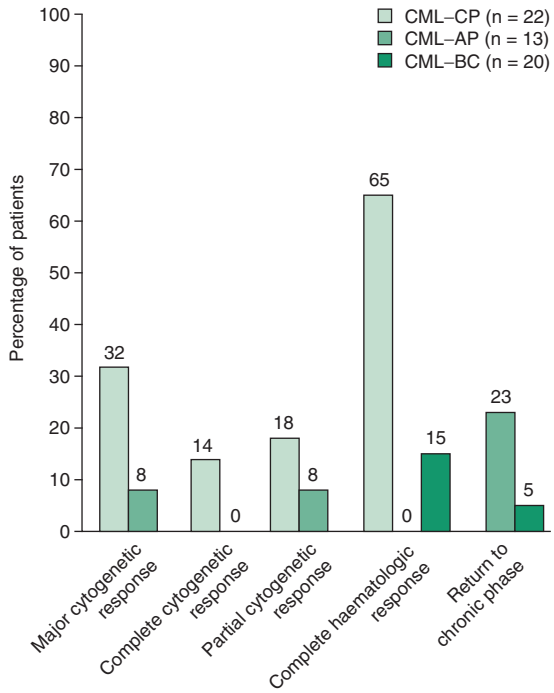


Fig. 3. Cytogenetic and haematologic responses in imatinib-resistant or -intolerant, Philadelphia chromosome-positive, chronic myeloid leukaemia (CML) patients who also failed dasatinib. Phase II efficacy data from 55 patients with CML in chronic phase (CP), accelerated phase (AP) or blast crisis (BC) who received nilotinib 400 mg twice daily, which could be increased to 600 mg twice daily if necessary.[31,32] All patients had 4 months of follow-up. Haematologic data for CML-CP relates to 17 patients who did not have baseline complete haematologic response.

ular, almost one-third of patients in chronic phase had a major cytogenetic response and up to approximately one-quarter of those in accelerated phase or blast crisis had a haematologic response (either complete haematologic response or return to chronic phase).

4. Tolerability

Tolerability data for nilotinib are available from the clinical trials discussed in section 3. This section focuses primarily on tolerability data from the phase II trial in patients with imatinib-resistant or -intolerant CML in chronic phase.[28] Tolerability data are available from 280 patients who participated in this study and received nilotinib 400 mg twice daily, increasing to 600 mg twice daily if necessary. Additional data are also briefly presented from the phase I dose-escalation trial[24] and other phase II studies[29-32] with nilotinib.

- The most common adverse events reported in the phase I study with nilotinib in patients with imatinib-resistant CML or Ph+ ALL were mild to moderate rashes, transient and clinically insignificant elevations of indirect bilirubin levels, and myelosuppression, which was an important dose-limiting adverse event.[24] Grade 3 or 4 neutropenia occurred in 9% of patients who received nilotinib 400 mg twice daily and in 22% of those receiving 600 mg twice daily.
- Tolerability data from 280 imatinib-resistant or imatinib-intolerant patients with chronic-phase CML who participated in a phase II trial are presented in figure 4.[28] The most frequently reported non-haematologic adverse events (regardless of causality) were rash, nausea, pruritus, headache and fatigue, which were generally of mild to moderate severity. The median duration of therapy was 261 days and the median dose intensity was 797 mg/day. Since the planned dosage of 400 mg twice daily was almost achieved, this suggests that nilotinib was generally well tolerated.
- Among haematologic adverse events in patients with chronic-phase CML, the most frequently reported grade 3 or 4 abnormalities were neutropenia and thrombocytopenia, both of which occurred in 29% of patients.[28] The median duration of neutropenia was 15 days, whereas thrombocytopenia persisted for a median of 22 days. Dosage interruptions and reductions were required in 10% and 19% of patients; platelet transfusions or haematopoietic growth factors were used in 10% and 5% of patients.
- Other laboratory abnormalities were generally mild to moderate in severity in chronic-phase CML patients.[28] Grade 3 or 4 elevations in AST or ALT levels were reported infrequently (1% and 4% of patients). Grade 3 or 4 indirect hyperbilirubinaemia occurred in 9% of patients and elevated lipase levels were reported in 14% of patients; 1% of patients developed pancreatitis. Recent data suggest that the most likely cause of nilotinib-induced indirect hyperbilirubinaemia is the combined effect of inhibition of uridine diphosphate glucuronosyl-transferase 1A1 activity by nilotinib and genetic polymorphism.[35]

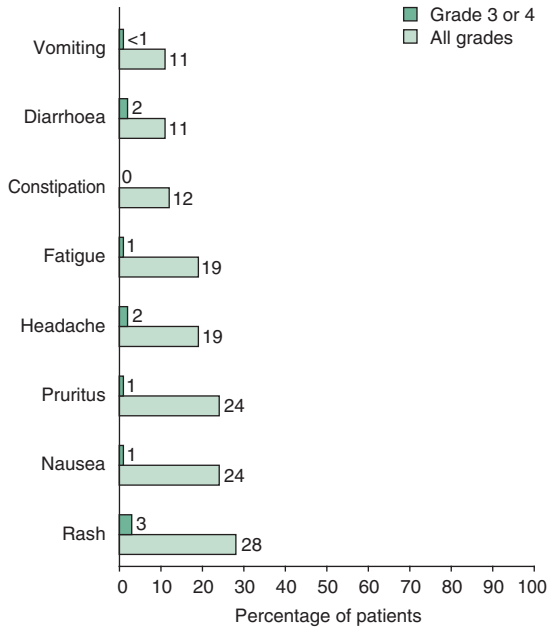


Fig. 4. Tolerability data for nilotinib in chronic-phase, Philadelphia chromosome-positive, chronic myeloid leukaemia. Incidence of adverse events, regardless of causality, among 280 patients in a phase II trial.[28] All patients were imatinib-resistant or -intolerant and received nilotinib 400 mg twice daily, which could be increased to 600 mg twice daily if necessary. Only non-haematologic adverse events (all grades) reported in >10% of patients are shown.

• Approximately 1% of patients (3 of 280) in the large phase II trial in chronic-phase CML had a corrected QT (QT_c) interval that was increased from baseline by >500 msec.[28]

• Fluid retention, oedema and weight gain, which can occur commonly with imatinib[8] and dasatinib,[36] were infrequently reported among nilotinib recipients. In the phase I trial in 119 patients treated with nilotinib, there were no reports of fluid retention, oedema, weight gain or pleural effusion.[24] In the phase II trial in 280 patients, pleural effusion, pericardial effusion and pulmonary oedema of any grade were reported in three patients (≈1%) [all grade 1 or 2].[28]

• Of the 280 patients with chronic-phase CML enrolled in the phase II trial, 86 (30.7%) had imatinib intolerance.[28] Among these 86 patients, cross intolerance, defined as the occurrence of any grade 3 or 4 nilotinib-induced toxicity previously reported in the same group of patients receiving imatinib, was infrequent, occurring in only two patients (2.3%).

• The tolerability profile of nilotinib, including biochemistry and haematologic abnormalities, was similar in the phase II trial in 119 patients with imatinib-resistant or -intolerant CML in accelerated phase[29] to that in the large phase II trial in patients with chronic-phase disease. Rash (22% of patients), pruritus (20%), constipation (11%), headache (10%), fatigue (10%) and nausea (10%) were the most frequently reported non-haematologic adverse events regardless of causality, and grade 3 or 4 adverse events were uncommon.[29] Grade 3 or 4 anaemia, neutropenia and thrombocytopenia occurred in 13%, 21% and 35% of patients, respectively. There were no clinically significant changes in the QT_c interval, nor were any episodes of Torsades de pointes observed.

• Tolerability data from the other phase II trials,[30-32] including fluid retention events and QT_c interval prolongation, were similar to those reported in the phase II studies in patients with chronic- or accelerated-phase CML.

5. Dosage and Administration

In patients with chronic- or accelerated-phase imatinib-resistant or -intolerant Ph+ CML, the recommended dose of oral nilotinib is 400 mg twice daily.[27] No food should be consumed for at least 2 hours before or 1 hour after administration.

US prescribing information includes a boxed warning on sudden death and the propensity for nilotinib to cause QT_c interval prolongation.[27] Nilotinib should not be used in patients with hypokalaemia, hypomagnesaemia or long QT syndrome. Hypokalaemia and hypomagnesaemia must be corrected prior to nilotinib administration and should be periodically monitored.

Local prescribing information should be consulted for dosage reduction guidelines, dosage recommendations in special populations, contraindications and precautions.

6. Nilotinib: Current Status

Nilotinib continues to undergo evaluation in phase II and III clinical trials in CML and has recently been approved by the US FDA for the treatment of adults with chronic- or accelerated-phase Ph+ CML who are resistant or intolerant to prior treatment, including imatinib. Nilotinib received its first regulatory approval in Switzerland and has recently been approved in the EU. Results to date from phase I and II trials indicate that nilotinib is effective and generally well tolerated when used for its approved indications.

Acknowledgements and Disclosures

The manuscript was reviewed by: **P. le Coutre**, Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum, Medizinische Klinic m.S. Hämatologie und Onkologie, Berlin, Germany; **G. Rosti**, Department of Haematology and Oncology "L. and A. Seràgnoli", University of Bologna, Bologna, Italy.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes based on any comments received were made on the basis of scientific and editorial merit.

References

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: chronic myelogenous leukemia. V.2.2007 [online]. Available from URL: www.nccn.org/professional/physician-gls/PDF/cml.pdf [Accessed 2007 Apr 23]
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin 2006; 56: 106-30
3. Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999 Apr 29; 340 (17): 1330-40
4. Weisberg E, Manley P, Mestan J, et al. AMN107 (nilotinib): a novel and selective inhibitor of *BCR-ABL*. Br J Cancer 2006 Jun 19; 94 (12): 1765-9
5. Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell 2005 Feb; 7 (2): 129-41
6. Deininger MWN, Druker BJ. Specific targeted therapy of chronic myelogenous leukemia with imatinib. Pharmacol Rev 2003; 55 (3): 401-23
7. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006 Dec 7; 355 (23): 2408-17
8. Moen MD, McKeage K, Plosker GL, et al. Imatinib: a review of its use in chronic myeloid leukaemia. Drugs 2007; 67 (2): 299-320
9. Silver RT, Talpaz M, Sawyers CL, et al. Four years of follow-up of 1027 patients with late chronic phase (L-CP), accelerated phase (AP), or blast crisis (BC) chronic myeloid leukemia (CML) treated with imatinib in three large phase II trials [abstract no. 23]. Blood 2004 Nov 16; 104 (11 Pt 1): 11a
10. Walz C, Sattler M. Novel targeted therapies to overcome imatinib mesylate resistance in chronic myeloid leukemia (CML). Crit Rev Oncol Hematol 2006 Feb; 57 (2): 145-64
11. Druker BJ. Circumventing resistance to kinase-inhibitor therapy. N Engl J Med 2006 Jun 15; 354 (24): 2594-6
12. O'Hare T, Walters DK, Stoffregen EP, et al. *In vitro* activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. Cancer Res 2005 Jun 1; 65 (11): 4500-5
13. le Coutre P, Tassi E, Varella-Garcia M, et al. Induction of resistance to the Abelson inhibitor STI571 in human leukemic cells through gene amplification. Blood 2000 Mar 1; 95 (5): 1758-66
14. Hochhaus A, Kreil S, Corbin AS, et al. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. Leukemia 2002; 16: 2190-6
15. Jabbour E, Cortes J, Kantarjian H. Dasatinib for the treatment of Philadelphia chromosome-positive leukaemias [published erratum appears in Expert Opin Investig Drugs 2007 Jul; 16 (7): 1135]. Expert Opin Investig Drugs 2007 May; 16 (5): 679-87
16. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med 2006 Jun 15; 354 (24): 2531-41
17. Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic phase chronic myeloid leukemia after failure of imatinib therapy. Blood 2007 Mar 15; 109 (6): 2303-9
18. Guilhot F, Apperley J, Kim D-W, et al. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. Blood 2007 May 15; 109 (10): 4143-50
19. Cortes J, Rousselot P, Kim D-W, et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. Blood 2007 Apr 15; 109 (8): 3207-13
20. Verstovsek S, Golemovic M, Kantarjian H, et al. AMN107, a novel aminopyrimidine inhibitor of p190 Bcr-Abl activation and of in vitro proliferation of Philadelphia-positive acute lymphoblastic leukemia cells. Cancer 2005 Sep 15; 104 (6): 1230-6
21. Golemovic M, Verstovsek S, Giles F, et al. AMN107, a novel aminopyrimidine inhibitor of Bcr-Abl, has *in vitro* activity against imatinib-resistant chronic myeloid leukemia. Clin Cancer Res 2005 Jul 1; 11 (13): 4941-7
22. Manley PW, Mestan J, Cowan-Jacob S, et al. AMN107: inhibitory profile against non-mutated and mutated forms of the Bcr-Abl tyrosine kinase [abstract no. 5985]. Presented at the 96th Annual Meeting of the American Association for Cancer Research; 2005 Apr 16-20; Anaheim (CA)
23. Mueller MC, Branford S, Radich J, et al. Response dynamics to nilotinib depend on the type of BCR-ABL mutations in patients with chronic myelogenous leukemia (CML) after imatinib failure [abstract no. 7024]. Plus poster presented at the 43rd Annual Meeting of the American Society of Clinical Oncology; 2007 Jun 1-5; Chicago (IL)
24. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med 2006 Jun 15; 354 (24): 2542-51
25. Kagan M, Tran P, Fischer V, et al. Safety, pharmacokinetics, metabolism, and mass balance of [14C]-AMN107, a novel aminopyrimidine inhibitor of Bcr-Abl tyrosine kinase, in healthy subjects [abstract no. 4887]. Blood 2005 Nov 16; 106 (11 Pt 2): 302b
26. Tanaka C, Smith T, Kantarjian H, et al. Clinical pharmacokinetics (PK) of AMN107, a novel inhibitor of Bcr-Abl, in healthy subjects and patients with imatinib resistant or intolerant chronic myelogenous leukemia (CML) or relapsed/refractory Ph+ acute lymphocytic leukemia (Ph+ ALL) [abstract no. 3095]. J Clin Oncol 2006 Jun 20; (18 Pt 1 Suppl. 24): 144s
27. Novartis Pharmaceuticals Corporation: East Hanover (NJ). Tasigna® (nilotinib capsules): US prescribing information [online]. Available from URL: http://www.fda.gov/ [Accessed 2007 Nov 29]
28. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective Bcr-Abl tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood 2007 Nov 15; 110 (10): 3540-6
29. le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated phase chronic myelogenous leukemia. Blood 2008 Feb 15; 111 (4): 1834-9
30. Ottmann O, Larson R, Kantarjian H, et al. Nilotinib monotherapy in patients with imatinib-resistant or -intolerant Ph+ chronic myelogenous leukemia (CML) in blast crisis (BC) or relapsed/refractory Ph+ acute lymphoblastic leukemia (ALL) [abstract no. 0556]. Plus poster presented at the 12th Congress of the European Hematology Association (EHA); 2007 Jun 7-10; Vienna
31. Giles F, le Coutre P, Bhalla K, et al. Nilotinib therapy after dasatinib failure in patients with imatinib-resistant or -intolerant chronic phase and accelerated phase Philadelphia-positive chronic myelogenous leukemia [abstract no. 0554]. Plus poster

presented at the 12th Congress of the European Hematology Association (EHA); 2007 Jun 7-10; Vienna

32. Giles FJ, le Coutre P, Bhalla K, et al. A phase II study of nilotinib administered to patients with imatinib resistant or intolerant chronic myelogenous leukemia (CML) in chronic phase (CP), accelerated phase (AP) or blast crisis (BC) who also failed dasatinib [abstract no. 7038]. Plus poster presented at the 43rd Annual Meeting of the American Society of Clinical Oncology; 2007 Jun 1-5; Chicago (IL)
33. Kantarjian HM, Cortes J, O'Brien S, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood 2002 May 15; 99 (10): 3547-53
34. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002 Feb 28; 346 (9): 645-52
35. Singer JB, Shou Y, Giles F, et al. UGT1A1 promoter polymorphism increases risk of nilotinib-induced hyperbilirubinemia. Leukemia 2007 Nov; 21 (11): 2311-5
36. Bristol-Myers Squibb: Princeton (NJ). Sprycel® (dasatinib): US prescribing information. [online]. Available from URL: http://www.fda.gov [Accessed 2007 Dec 6]

Correspondence: *Greg L. Plosker*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz