

From the 48<sup>th</sup> Annual Meeting of the American Society of Hematology

## CML patients with imatinib-resistant mutations responsive to dasatinib and nilotinib

**B**oth dasatinib (Sprycel) and nilotinib (AMN107) have induced hematologic and cytogenetic remissions in a significant proportion of imatinib (Gleevec)-resistant patients with chronic myelogenous leukemia (CML) harboring BCR-ABL mutations, except T315I. Recent clinical data on these agents, and emerging information about mutational status, were the subjects of a number of key presentations at the meeting.

Nilotinib has produced encouraging results in CML patients who have progressed after treatment with both imatinib and dasatinib; in accelerated-phase CML patients resistant to or intolerant to imatinib; and up front in newly diagnosed, mostly low-risk CML patients.

In an open-label multicenter phase II study of 42 patients reported by Francis Giles, MD, of M. D. Anderson Cancer Center, Houston, approximately one third of chronic-phase CML patients achieved a major cytogenetic response after failure with both imatinib and dasatinib.

After a median of 81 days of treatment with nilotinib (400 mg twice daily), 5 of 13 chronic-phase patients (39%) achieved new complete hematologic responses, whereas major cytogenetic responses were seen in an additional 5 patients in chronic phase. Two accelerated-phase patients (22%) returned to chronic phase; three blast-crisis CML patients (18%) had complete hematologic responses, one patient returned to chronic phase, and five had stable disease.

Studies of dasatinib after imatinib failure were similar. Baccarani et al reported data from a 15-month follow-up of the phase II CA180-013 (START-C)

trial. Response rates to dasatinib (70 mg twice daily) have improved over time, and progression-free survival is 90%. Complete hematologic responses were achieved in 91% of chronic-phase patients, and major cytogenetic responses were observed in 59%, they indicated.

### Type of genetic mutation is key to response

The dynamics of response to nilotinib and dasatinib appears to depend on the individual type of mutation, which could form the basis for individual dose adaptation, according to investigators from the University of Heidelberg, Mannheim, Germany.

“Resistance to imatinib is a problem, especially in advanced CML,” said Professor Andreas Hochhaus. “We know that about 50% of patients with resistance to imatinib carry mutations to BCR-ABL, and this is the reason for resistance in this cohort.”

### Study parameters

Martin C. Müller, MD, and colleagues sought to establish a relationship between the type of preexisting BCR-ABL mutations associated with imatinib resistance and the efficacy of dasatinib in patients with CML and Philadelphia chromosome-positive ALL. Their study involved blood samples from 395 patients being treated with dasatinib and followed for a median of 14 months. This group included 201 chronic-phase, 78 accelerated-phase, 51 myeloid blast crisis, and 65 lymphoid blast crisis/ALL patients.

Prior to treatment with dasatinib, 46 different BCR-ABL mutations were detected in 202 patients. Patients were monitored in 3-month intervals to determine how the pre-

existing genetic mutations responded to treatment and whether new mutations emerged.

Patients with BCR-ABL mutations responded well to dasatinib, Dr. Müller reported. Complete hematologic response was achieved in 92% of chronic-phase, 55% of accelerated-phase, 38% of myeloid blast crisis, and 37% of lymphoid blast crisis/ALL patients. Complete cytogenetic responses were observed in 48% of chronic-phase, 33% of accelerated-phase, 27% of myeloid blast crisis, and 48% of lymphoid blast crisis/ALL patients.

Researchers noticed two response patterns in the treatment population. First, some patients experienced a decrease in BCR-ABL expression and the proportion of the mutated clone simultaneously, whereas others experienced a decrease in BCR-ABL followed by a decrease of the mutated clone after a delay of 4–6 months. Thirteen patients developed new mutations associated with resistance to dasatinib, including T315I, which is highly resistant to both imatinib and dasatinib. Second, clinical response to dasatinib was associated with the cellular IC<sub>50</sub> of the pretreatment mutation, with significantly more responses seen in patients with mutations with low IC<sub>50</sub> levels.

Similarly, in the phase II study of nilotinib in 142 imatinib-resistant patients, 24 different BCR-ABL mutations were found in 44% of patients with chronic-phase and 61% of those with accelerated-phase CML. Among patients in chronic-phase and accelerated-phase CML, 7% and 15% had multiple mutations.

Hematologic responses were observed in 70% of patients with mutations and 88% of patients without mu-

tations. Within 3 to 6 months, complete cytogenetic responses were reported in chronic-phase patients whose genetic mutations were sensitive to nilotinib (according to IC<sub>50</sub>). Nilotinib was also effective in patients with certain P-loop mutations (mutations of the phosphate binding loop of the tyrosine kinase domain), Dr. Hochhaus continued. In the presence of P-loop mutations, the time to hematologic response to nilotinib is prolonged.

“We found that nilotinib is efficacious in all but one of these mutations [T315I],” Dr. Hochhaus said. “We observed efficacy in patients with mutations but also in patients without mutations. Clearly, the study demonstrated that BCR-ABL is still the driving force of proliferation in CML, even in patients without specific mutations.”

Both dasatinib and nilotinib may play an important therapeutic role for patients with CML who have become resistant to imatinib, the investigators concluded. “However, we noted that response depends on the type of genetic mutation, which may signal a method for individualizing each patient’s dose,” Dr. Müller revealed.

“We are now focusing on the best time to switch patients from imatinib to another tyrosine kinase inhibitor,” Professor Hochhaus added. “In the future, we may use combinations of tyrosine kinase inhibitors to avoid the selection of mutant clones.”

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Müller MC, Erben P, Schenk T, et al. Response to dasatinib after imatinib failure according to type of preexisting BCR-ABL mutations; Hochhaus A, Erben P, Brandford S, et al. Hematologic and cytogenetic response dynamics to nilotinib (AMN107) depend on the type of BCR-ABL mutations in patients with chronic myelogenous leukemia (CML) after imatinib failure; Giles F, le Coutre P, Bhalia K, et al. A phase II study of nilotinib, a novel tyrosine kinase inhibitor administered to patients with imatinib resistant to intolerant chronic myelogenous leukemia (CML) in chronic phase (CP), accelerated phase (AP) or blast crisis (BC) who have also failed dasatinib therapy. Papers presented at the 48<sup>th</sup> Annual Meeting and Exposition of the American Society of Hematology; December 9–12, 2006; Orlando, Fla. Abstracts 748, 749, and 2170.