

## ***Selected Summary***

### **Dasatinib Induces Significant Hematologic and Cytogenetic Responses in Patients with Imatinib-resistant or-intolerant Chronic Myeloid Leukemia in Accelerated Phase**

FRANCOIS GUILHOT, JANE APPERLEY, DONG-WOOK KIM, EDUARDO O. BULLORSKY, MICHELE BACCARANI, GAIL J. ROBOZ, SERGIO AMADORI, CARMINO A. DE SOUZA, JEFFREY H. LIPTON, ANDREAS HOCHHAUS, DOMINIK HEIM, RICHARD A. LARSON, SUSAN BRANFORD, MARTIN C. MULLER, PRASHEEN AGARWAL ASHWIN GOLLERKERI, AND MOSHE TALPAZ. *Blood* 2007 May 15;109(10):4143-50.

#### **SUMMARY**

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of haematopoietic stem cells. Its incidence is 1 per 1,00,000 population in the West. According to 6 population based cancer registries (covering <0.3 % of the total population), the incidence in India varies from 0.8 to 2.2 per 1,00,000 population for men and 0.6 to 1.6 per 100,000 population for women.<sup>1</sup> The median age of onset is 38-40 years in India as compared to 50 years in the west. There is a slight male preponderance.

The disease is characterized by an insidious onset of symptoms, progressive splenomegaly, marrow hypercellularity, anaemia, leucocytosis, and cytogenetically by the presence of Philadelphia (Ph) chromosome t(9;22)(q34;q11) in 90-95 % of patients.

In the formation of Ph chromosome, ABL proto-oncogene is translocated from chromosome 9 (q34.1) to BCR gene in chromosome 22 (q11.2). The resultant fusion gene BCR-ABL transcribes a chimeric 8.5 mRNA which in turn is translated into a novel protein p210 kDa termed as p210. The latter through increased tyrosine kinase activity changes normal hematopoietic cells into CML cells.<sup>2</sup>

Imatinib mesylate is currently the standard of care for all patients of CML. This drug acts by binding to ATP binding pocket of BCR-ABL fusion chimeric protein, and stabilizes the inactive form of BCR-ABL. Treatment with imatinib results in complete hematological remission rate of 95% and major cytogenetic response rate of >80% in newly diagnosed chronic phase CML patients.<sup>3</sup> Response rates are lower in patients with late chronic phase or those with advanced disease (accelerated phase and blast crisis).<sup>4</sup> Thus, resistance to imatinib, especially in later stages of CML, represents an important clinical problem. In CML-AP, 40-50% patients develop imatinib resistance after 2 years and 75%

after 4 years of treatment. About 4% of patients become intolerant to imatinib.<sup>5</sup> Current treatment options for patients who are imatinib-resistant are higher dose of imatinib (600-800 mg daily),<sup>4</sup> allogeneic stem cell transplantation (limited by availability of HLA-identical sibling donor, transplant related morbidity and mortality) and newer drugs e.g. dasatinib or nilotinib. Dasatinib is a novel, potent, oral, multitargeted kinase inhibitor of BCR-ABL. The drug has shown 325-fold greater potency compared to imatinib and has activity against 21 of 22 imatinib-resistant mutants of BCR-ABL tested and is a potent inhibitor of the SFKs causing imatinib resistance.<sup>6</sup>

Present study is an open-label, single-arm, multinational, phase 2 study, primarily aimed to determine the major hematologic response (MaHR) and overall hematologic response (OHR) rates to dasatinib in imatinib-resistant/intolerant CML-AP patients.<sup>7</sup> Secondary objectives were – duration of hematologic responses, the hematologic and cytogenetic response rates, and the assessment of the safety and tolerability of dasatinib. Baseline mutational analyses were also performed to assess responses to dasatinib in the context of specific BCR-ABL mutations.

Eligibility criteria included - patients age 18 years or older; those with Ph<sup>+</sup> or BCR-ABL positive CML-AP having primary or acquired hematologic resistance or intolerance to imatinib therapy. Accelerated phase of CML, Imatinib resistance and Imatinib intolerance was defined as per the standard Guidelines. Patients received dasatinib 70mg twice daily (140 mg total daily dose).

At 8 months of minimum follow-up, response rates were : OHR- 81%, MaHR- 64%, and complete HR-39% whereas 33% and 24% attained major and complete cytogenetic remission (CCR). Of 69 patients who achieved MaHR, 7 progressed. At 10

months, 76% of patients are estimated to be alive and progression-free. Though, the median progression-free survival (PFS) had not been reached till the analysis, 14 deaths were recorded. Among them 5 were as a result of documented disease progression while 6 deaths occurred more than 30 days after dasatinib was discontinued. Responder rates for the 60% of patients with baseline BCR-ABL mutations did not differ from the total population.

Dasatinib was well tolerated. The most frequent adverse effects were diarrhoea (50%), headache (28%), pyrexia (23%), fatigue (23%), nausea (22%), and peripheral edema (22%). Pleural effusion occurred in 25 (23%) patients; this was grade 3 to 4 in 3 (3%) patients but most were uncomplicated, resolved with temporary dose interruption, diuretics, and, in some cases, with pulse steroids. The most common (= 5%) grade 3 to 4 non hematologic adverse effects related to treatment were diarrhoea (6%) and gastrointestinal bleeding (7%). Grade 3-4 hematological toxicities were –

leucopenia (5%), neutropenia (7%), thrombocytopenia (23%), and anemia in 5%. Cytopenias were manageable through dose modification.

**Comments:**

In this study significant hematologic, cytogenetic and molecular responses were seen following dasatinib therapy in patients with imatinib resistance or intolerance and dasatinib was generally well tolerated. The latter is important since most of these patients were heavily pretreated, the median time from original diagnosis of CML to study entry was more than 5.5 years. Among the 69 patients who achieved good hematologic responses, 7 had progressed. Dasatinib was generally well tolerated in this study. At 8 months' follow-up, only 6% of patients had withdrawn from therapy as a result of drug-related toxicities. Findings from this indicate that dasatinib represents a potent new therapeutic option for patients with accelerated phase as well as for patients with imatinib resistance or intolerance.<sup>7</sup>