Dasatinib or High-dose Imatinib for Chronic-phase Chronic Myeloid Leukemia After Failure of First-line Imatinib: a Randomized Phase 2 Trial

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Present study[8] is a randomized, international, open-label, phase II study conducted in CML-CP patients, with primary or acquired resistance to conventional doses of imatinib . Patients were randomized 2:1 to 140 mg dasatinib (n = 101) or 800 mg imatinib (n = 49). Patients were of atleast 18 years of age and had adequate organ functions. All patients were dasatinib-naïve. To avoid potential bias, patients with known specific BCR-ABL mutations with high resistance to imatinib were excluded. Treatment differences were analyzed retrospectively using the Agresti-Min exact test, and Time to treatment failure was analyzed using Kaplan-Meier method and an unstratified log rank test. The hazard ratio was computed using a Cox proportional hazard model.

Complete hematologic responses(CHR) were observed in 93% and 82% of patients receiving dasatinib and high-dose imatinib (P =.034), respectively. Dasatinib resulted in higher major cytogenetic response rates (MCR) (52%) than high-dose imatinib (33%) (P = .023); this included complete cytogenetic response (CCR) in 40% and 16% (P = .004). The degree of improvement in cytogenetic response from baseline (ie, no response to MCyR) was 3-fold higher, as well as responses were more durable for patients receiving dasatinib. Major molecular responses (MMR) were also more frequent with dasatinib (16% versus 4%; P = 0.038). Treatment failure (hazard ratio [HR], 0.16; P < .001) and progression-free survival (HR, 0.14; P < .001) both favored dasatinib.

Superficial edema (42% versus 15%) and fluid retention (45% versus 30%) were more common in imatinib group while pleural effusion was more common with dasatinib (17% versus 0%). Pleural effusions were successfully managed with dasatinib dose interruption, diuretics, and/or pulse steroid therapy. Grade 3 to 4 non hematologic toxicity was minimal. Cytopenias were more common and more severe in the dasatinib treatment group (grade 3-4 neutropenia: 61% versus 39%; grade 3-4 thrombocytopenia: 56% versus 14%); these were reversible and manageable with dose adjustments. Dose interruptions were required in 84 patients (83%) receiving dasatinib therapy (primarily due to hematologic toxicity [61%]), dose reductions were noted in 67 patients (66%), and dose escalations were made for 33 patients (33%). In high-dose imatinib group, 16 patients (33%) required dose interruptions while dose reduction was done in 5 patients (10%).

Table I. Studies on the treatment of patients with imatinib resistance using Dasatinib

Author	CML Phase	n	Haematological Response	Cytogenic Response	Grade II-IV toxicity (%)
George et al[10]	MBC LBC	74 42	MHR- (34) -(31)	MCR- (31) - -(50) CCR-(86)	diarrhoea(36& 31), Pleural effusion (28&14) pyrexia (16&19), nausea (16&24), vomiting (16&24)
Talpaz et al[11]	CP AP/BC ph+All	40 44	CHR 37/40 MHR 31/44	(45) (25)	Neutropenia, Pleural effusion, oedema, headache
Talpaz et al[12] START-A study	AP	107 evaluable	MHR 63 (59) CHR 35 (33) no evi of leukemia 28 (26)	MCR 33 (32) CHR 23 (22) PHR 10 (10)	Thrombocytopenia (79), neutropenia (69), diarrhea (46), oedema (27) Pleural effusion (16), rashes (8), gastronintestinal bleed (7)
Coutre et al[13] START-L study	L-BC Ph+ALL	42 36	MHR (31) CHR (26) MHR (42) CHR (31)	MCR (50) MCR (58)	Thrombocytopenia (82), neutropenia (76), diarrhea (30), Pleural effusion (13), rashes (17), nausea (23), fatigue (19)
Estrov et al[14]	Nilotinib failed CML	CP 1 AP 5 BC 5 2nd CP 1	CHR 1/1 CHR 4/5 CP 1, BMCR 1	Not given	Not given
Cortes et al[15] START-B study	M-BC	74	HR 39(53) MHR 24 (32) CHR 18 (24) No leukemia 6 (8)	MCR 22 (32) CCR 20 (27)	diarrhoea(7), Pleural effusion (9), rashes (11), nausea (4), oedema (14)

(Values in parentheses are percentages, CP chronic phase, AP-accelerated phase, BC blast crisis, L-BC-lymphoid blast crisis, HR-haematological response)

Comments

Results of the current study[8] suggest that dasatinib is more effective than high-dose imatinib in this Imatinib resistant CML-CP population. With a median follow up of 15 months, progression-free survival was significantly prolonged. Rates of major cytogenetic responses (including a >2-fold increase in complete CGR), favored dasatinib. In patients with no prior cytogenetic response to the conventional doses of imatinib, high-dose imatinib was also ineffective . But even in these, 50% achieved a major cytogenetic responses with dasatinib. Dasatinib was clearly superior in patients who failed or progressed on Imatinib

600 mg per day. But in subgroups only minimally resistant to imatinib like those failed or progressed on 400 mg imatinib per day, little difference was noted. Cytogenetic responses were more rapid for patients receiving dasatinib than for high dose (HD) imatinib (with complete cytogenetic response rates of 40% and 16%, respectively).

The toxicity profile seen for dasatinib group was similar to previous studies, but there are differences between dasatinib and HD imatinib group. Dasatinib was associated with a greater degree of myelosuppression, (mainly thrombocytopenia), possibly due to rapid clearance of BCR-ABL expressing malignant hematopoietic cells. Other explanation could be that, unlike imatinib, dasatinib is not a substrate of the p-glycoprotein pump, and therefore higher concentrations of dasatinib might be achieved in hematopoietic progenitor cells. In patients who experienced myelosuppression, recovery occurred after brief dose interruptions or reductions, occasionally requiring transfusions. Fluid retention was more common with imatinib, presented as superficial edema in imatinib and pleural effusion in dasatinib group. Dasatinib was associated with a significant prolongation in the time to treatment failure.

Dasatinib is a potent inhibitor of SRC/ ABL kinase inhibitor. Dasatinib's ability to overcome different forms of imatinib resistance is other possible mechanism. The only *BCR-ABL* mutation resistant to dasatinib in the current study is the ATP binding site mutation T315I [5]. Recent crystal structure studies suggest that dasatinib may be more effective in the P-loop resistance (to imatinib).[9] Table-1 provides review of previous studies with use of dasatinib in imatinib resistant patients.

Thus, data from above two studies suggest that Dasatinib represents a safe and effective therapy for CP-CML patients resistant to conventional imatinib doses with improved cytogenetic and molecular response rates and progression-free survival relative to high-dose imatinib. Dasatinib is also effective in patients with accelerated phase of CML. With the incidence of imatinib resistance increasing, the earlier use of dasatinib could prove beneficial by promoting an early response, and thereby potentially improving the prognosis for the patient, and/or by avoiding the development of treatment resistance.[16]

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