Imatinib Mesylate in Polycythemia Vera.
A Status Report.

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Imatinib mesylate (STI571,Gleevec) targets the ATP-binding sites of the protein tyrosine kinase domains associated with Bcr-abl, platelet-derived growth factor receptors (PDGFR) and c-kit (1). Most recently imatinib has been shown to inhibit autonomous erythropoiesis in vitro in polycythemia vera (PV) (2) . Several clinical studies have shown that imatinib reduces phlebotomy requirements in PV (3-10), although none of these studies have followed the patients for longer periods on imatinib monotherapy . As one of the deliverables in WP9. CMPD this report summarizes the results obtained in clinical trials on imatinib mesylate in PV-patients and ongoing/planned studies of imatinib mesylate in PV within the European Leukemia Net.

Current status on Clinical Trials of Imatinib Mesylate in PV .

Table 1. Reported results on studies of imatinib mesylate in polycythaemia vera.

Study	No. of Patients	Dosage (mg/day)	Follow-up	Response Rate
Silver, 2003 (3)	15	400 –800	Median 6.8 mo; range 1-16mo	9/11 (CR = 4; PR = 2)
Jones & Dickinson, 2003 (4)	10	200 - 800	NR ; 14 and 6 mo for the first 2 pts	6/6
Cortes et al., 2003 (5)	2	400	32 and 63 weeks	2/2
Hasselbalch et al., 2003/2004 (6,7)	8	400 (300 – 800)	Median 12 mo range 6-12 mo	7/7
Silver et al 2004 (8)	27 (15 of these reported in (3))	400-800 mg	Median 11mo	13/23 (CR =5 PR = 8)
Borthakur et al 2004 (9)	9 (2 of these reported in (5))	400-800 mg	Median 4 mo (range 2-27 mo)	3/9
Kuriakose P et al 2004 (10)	5	400-800 mg	Median 6 mo (range 2-10)	3/5 (CR=2; PR =1)

Comments : In the series reported by Silver an increase in the dose of imatinib up to 800 mg was associated with a decline in the platelet counts in most of the patients not responding to 400 mg (3). Using a fixed dose of 400 mg/day for up to 12 months , the effect of imatinib mesylate on the leucocyte-and platelet count is highly unpredictable implying in some patients even an increase in the platelet count. Furthermore, even at 800 mg/daily some patients may not respond .Adding PEG-Intron may markedly reduce the counts within a few weeks . Unchanged or even increasing platelet counts in a subgroup of patients are very similar to the response patterns seen in patients with idiopathic and postpolycythemic myelofibrosis (7-11). Most recently, an imatinib mesylate sensitive phosphoprotein has been identified in leucocytes from four patients with PV . Tyrosine phosphorylation of a 170 kDa protein was reduced in a dose dependent manner after exposure to imatinib in all four patients. Furthermore, a reduction of tyrosine phosphorylation of several other proteins was recorded in two out of the four patient samples . Antibodies to known imatinib targets – C-kit, PDGFR – did not recognize the 170 kDa protein (12) . Accordingly, the effect of imatinib in PV may involve inhibition of tyrosine phosphorylation of several proteins being novel targets for imatinib therapy .

Conclusion : Imatinib mesylate effectively reduces the hematocrit in PV patients, whereas its effect upon the leucocyte-and platelet count is highly unpredictable at least when using a dose of dose of 400 mg per day. The pathogenesis behind the heterogeneous response to imatinib in PV is unknown but are currently being investigated in Pilot trials in Germany and Denmark together with studies on gene expression profiling before and during treatment of PV with imatinib. These studies are being extended to other European centers within European Leukemia Net in a common European Protocol for Imatinib Therapy of Polycythemia Vera.

Current Studies on Imatinib Mesylate in Polycythemia Vera in Europe.

1. Open-label Phase II Trial of Imatinib Mesylate (Glivec) in Patients with Polycythemia Vera. Principal Investigators: Dr. Eva Lengfelder, Dr. Andreas Hochaus , Mannheim,Germany.

2. A Phase II Pilot Study of Imatinib Mesylate (Glivec) in Polycythaemia Vera. Principal Investigator : Dr. Hans Hasselbalch , Odense, Denmark.

A common European protocol is planned to be elaborated with participation of other European Centers within the European Leukemia Net.

Presentations at Scientific Meetings :

Oral Presentation:

1. Hasselbalch HC. Imatinib Mesylate in the Treatment of Polycythemia Vera and Allied Disorders . Annual Meeting in the Danish Society of Haematology, March 2003.

2. Hasselbalch HC. Imatinib Mesylate in Polycythemia Vera. Status and Perspectives. International Meeting on Chronic Ph-negative Myeloproliferative Disorders. Rotterdam May 2004.

3. Lengfelder E. German PV activities: Efforts in the past and perspectives for the future. International Meeting on Chronic Ph-negative Myeloproliferative Disorders. Rotterdam May 2004.

4. Lengfelder E. Imatinib in Polycythemia V, a Phase II Study. Meeting of the German CML Study Group, Heidelberg June 2004.

5. Lengfelder E. Imatinib in Polycythemia V, a Phase II Study. Meeting of the German Süddeutsche Hämobastosegruppe, Mannheim November 2004.

Abstracts :

1. Hasselbalch HC, Petersen M, Bostrom H. Imatinib mesylate therapy reduces phlebotomy requirements in polycythemia vera. Blood 2003; abstract # 5087 .
2. Hasselbalch HC, et al. Imatinib mesylate in polycythemia vera. A Heterogeneous Response pattern but a consistent reduction in phlebotomy requirements. Blood 2004; abstract #

4747.

Publications :

1. Hasselbalch HC Bjerrum OW, Jensen BA, Toffner Clausen N, Hansen PB, Birgens H, Therkildsen MH, Ralfkiær E. Imatinib mesylate in idiopathic and postpolycythemic myelofibrosis. Am J Hematol 2003; 74: 238-242.

2. Hasselbalch HC, Larsen TS, Henriksen AS, Christiansen JH, Hansen PG, Pedersen NT, Kerndrup G, Pallisgaard N, Pedersen M, Nielsen PL, Bostrom H. Imatinib mesylates reduces phlebotomy requirements in polycythemia vera. Am J Hematol (submitted).

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8. Silver RT, Fruchtman SM, Feldman EJ, Spivak JL, Salvado AJ. Imatinib mesylate (GLEEVEC) is effective in the treatment of polycythemia vera: a multi-institutional clinical trial.Blood 2004; Abstract # 656.
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10. Kuriakose P, Shurafa MS. A phase II trial of imatinib mesylate (Gleevec) in myeloproliferative disorders. Blood 2004; abstract # 4765.
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