Imatinib mesylate in the treatment of newly diagnosed or refractory/resistant c-KIT positive acute myeloid leukemia. Results of an italian multicentric phase II study.

We evaluated safety and efficacy of imatinib (600 mg) in 36 c-KIT+ acute myeloid leukemia patients not amenable to receive conventional chemotherapy. No patient achieved complete remission. One patient obtained a hematologic improvement (platelet increase with transfusion independence). Median overall survival was 3 months (0.5-44+). Non-hematologic toxicity was overall mild.

Haematologica 2007; 92:1721-1722. DOI: 10.3324/haematol.11345

The treatment of poor risk acute myeloid leukemia (AML), including elderly patients or those with poor performance status, or with refractory/relapsed disease, remains problematic due to the scarce efficacy and high toxicity of conventional chemotherapy.[1-5]

We investigated the efficacy and toxicity of imatinib in c-KIT$^+$ AML cases. Some authors reported responses in c-KIT$^+$ AML and high-risk myelodysplastic syndromes (MDS).[6,7] Nevertheless, whether c-KIT was the actual target in such cases is still unclear. The primary end-point was the response rate assessment. The secondary end-points were CR duration, overall survival at 12 months and type, frequency, severity, timing, and relatedness of adverse events (AE).

Thirty-six c-KIT$^+$ AML patients not amenable to conventional chemotherapy were enrolled in an open label phase II study. Patients aged over 18 years, with any FAB but M3 AML refractory or relapsed after conventional chemotherapy, as well as patients with previously untreated AML not conventional chemotherapy were eligible, provided that at least one of the known imatinib targets, PDGFR α or β, c-KIT (assessed by flow-cytometry) or *BCR-ABL1* (assessed by RT-PCR) was expressed. No core-binding-factor positive patients were enrolled. Treatment consisted of imatinib mesylate at the initial dose of 100 mg/day. If no major toxicity was observed, imatinib dosage was increased every second day up to a maximum of 800 mg/day. Therapy was assumed for at least two months and continued if a clinical response was observed. In cases of clear progression, the treatment could be withdrawn at any time at the physician's discretion. Clinical response was evaluated according to conventional criteria.[8]

All the 36 enrolled patients were evaluated for response. Only 1 out of 36 patients obtained a clinical response. She showed a hematologic improvement, with transient platelet increase and temporary transfusion independence. Conversely, Hb, WBC count and bone marrow blasts did not significantly improve. The clinical benefit lasted for approximately 4 months (Figure 1A). Intriguingly, this patient was the only one with expression of PDGFRB. While under treatment, blast cells progressively became PDGFRB negative, until progression occurred (Figure 1). On the contrary, CD117 was expressed and phosphorylated during the entire treatment duration. None of the other 35 patients (97%) responded. Of these patients, 21 (62%) and 7 (21%) interrupted imatinib for disease progression and adverse events respectively. Six out of 36 patients (17%) died during imatinib therapy, due to cerebral hemorrhagic stroke (2), disease progression (2) and multi organ failure (2).

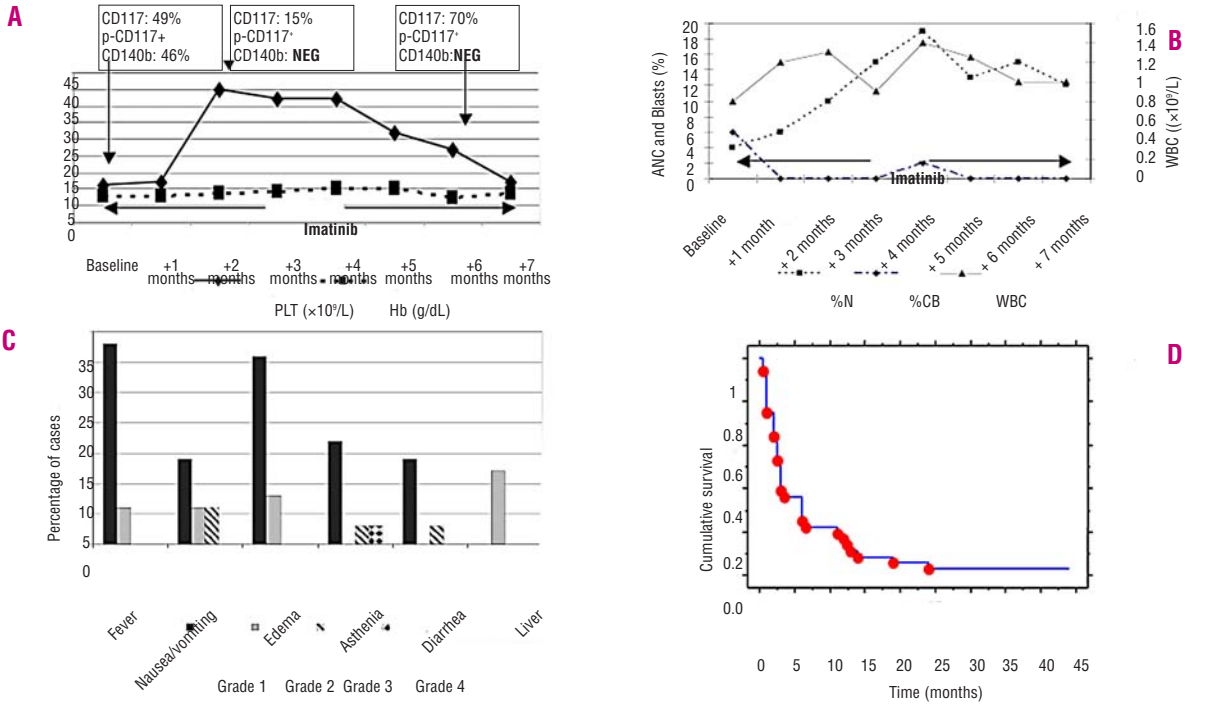

Figure 1. A. Platelet count improvement in the single responder was associated with CD140 (PDGFRB) expression but not with c-KIT phosphorylation. p-CD117: phosphorylated c-KIT (assessed by flow cytometry). **B.** Hb and WBC count as well as ANC and blast percentage did not significantly vary during treatment. **C.** Extra-hematologic treatment toxicity (WHO scale). **D.** Overall survival of patient population. Kaplan-Meier Cumulative Survival Plot for OS (months); Censor Variable: death.

The median treatment duration was 31 days (range 2–311), at a median dosage of 600 mg/day (range 200–800). Only 53% of patients assumed imatinib for at least 4 weeks. The other patients withdrew from the study within 4 weeks of therapy due to disease progression, or died within this period while on therapy. The median overall survival was 3 months (0.5-44+) (Figure 1B). Imatinib was overall well tolerated. Treatment outcome and toxicity are summarized in Table 1 and Figure 1C respectively.

The effect of imatinib on AML and myelodysplastic syndromes was previously evaluated in other studies. Kindler *et al*., reported 5/21 clinical responses, including 2 CR.[7] However, the study population was slightly different from ours and clinical responses were observed in patients with limited marrow/peripheral blood involvement.[7] Furthermore, CR was only achieved in patients starting imatinib during hematopoietic reconstitution after chemotherapy. In some instances, responses were recorded after prolonged imatinib administration, a rare event in our series. In another study, Cortes and Colleagues obtained results more similar to our own.[6]

However, whether c-KIT is not a good candidate as therapeutic target in AML or whether imatinib was not able to completely inhibit its function is not known. It is unlikely, however, that D816- c-KIT mutations played a role since these are rare in unselected AML. In our series, responses were not observed despite c-KIT de-phosphorylation during treatment, while the single responder showed p-CD117$^+$ when PLT count increased. Furthermore, other possible targets may be relevant in AML rather than c-KIT, including c-FMS which can be inhibited by imatinib.[9,10] On the other hand, the biologic and clinical role of PDGFRB inhibition should also be further investigated in AML.

We conclude that imatinib is not effective as single agent in the treatment of c-KIT$^+$ AML, though further studies might indicate possible indications in specific AML subsets.

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Funding: this work was supported in part by AIRC, BolognAIL, FIRB/RFO (Prof. M Baccarani), Fondazione Cassa di Risparmio, and Fondazione del Monte di Bologna e Ravenna grants.

Additional information on this trial are available upon request (pierpaolo.piccaluga@unibo.it).

Key words: imatinib mesylate, acute myeloid leukemia, c-KIT, PDGFRB, targeted therapy.

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Table 1. Treatment and outcome.

Treatment duration	
Median (days, range)	31 (2-311)
≤2 weeks	2 (5.6%)
2-4 weeks	6 (17.6%)
4-8 weeks	8 (23.5%)
≥ 8 weeks	10 (29.4%)
Median treatment dosage (mg, range)	600 (200-600)
Clinical response	
Complete response	0
Hematologic improvement	1
No response	35
Stable disease	1
Progression	21
Death during treatment	6
Withdrawn due to toxicity	7
Causes of death during treatment	
Multi-organ failure	2
Leukemic progression	2
CNS hemorrhage	2
Median overall survival, months (range)	3 (0.5-44+)

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