**Risk and early cytogenetic response to imatinib and interferon in chronic myeloid leukemia**

**GIANANTONIO ROSTI, ELENA TRABACCHI, SIMONA BASSI, FRANCESCA BONIFAZI, ANTONIO DE VIVO, GIOVANNI MARTINELLI, DANIELE ALBERTI, GIANLUCA FINCATO, GIUSEPPE SAGLIO, MICHELE BACCARANI ON BEHALF OF THE ITALIAN COOPERATIVE STUDY GROUP ON CHRONIC MYELOID LEUKEMIA**

**Chronic Myeloid Leukemia**

**Background and Objectives.** We compared the early cytogenetic response (CgR) to a combination of imatinib mesylate (Glivec®, Novartis Pharma, Basel, Switzerland) and a pegylated form of human recombinant interferon-α2b (pegIFN-α2b, PegIntron®, Schering Plough, Kenilworth, New Jersey, USA) with the relative risk, assessed according to either Sokal's or Euro scoring systems.

**Design and Methods.** Seventy-seven patients with early chronic phase, previously untreated, Ph-positive chronic myeloid leukemia (CML) received a combination of imatinib mesylate (400 mg/day) and pegIFN-α2b (3 consecutive cohorts treated with 50, 100 or 150 µg/weekly). Fifty-seven patients have completed the first 6 months of treatment and are evaluable for CgR.

**Results.** After 6 months of treatment, the overall major CgR rate was 89% and 90% in low risk patients (Sokal's and Euro Score, respectively), 76 and 59% in intermediate risk and 23% and 17% in high risk patients. These differences were significant (p=0.0001 for Sokal's Score and 0.001 for the Euro Score).

**Interpretation and Conclusions.** For the first time, these data suggest that the early CgR rate to an imatinib mesylate-based regimen is significantly risk-related.

**Key words:** chronic myeloid leukemia, imatinib, peginterferon.

Haematologica 2003; 88:256-259
http://www.haematologica.org/2003_03/88256.htm
©2003, Ferrata Storti Foundation

---

Chronic myeloid leukemia (CML) is a clonal malignancy characterized by an expansion of the myeloid compartment (chronic phase or CP) followed by a progressive loss of cell differentiation (accelerated phase or AP) and terminating in a picture of acute leukemia (blast crisis or BC).1 The disease is marked by a specific chromosome abnormality, the Philadelphia chromosome (Ph), which results from a reciprocal translocation between chromosome 9 and 22, leading to the formation of a new, leukemia-specific, bcr/abl gene.1 This hybrid gene codes for several constitutively active tyrosine kinase proteins (mainly p210, sometimes p190 or p230) which transform hematopoietic stem cells into leukemic cells.1 Imatinib mesylate, formerly CGP 57148B and STI571, is a novel therapeutic agent that has been designed to prevent p210-driven phosphorylation of downstream signal transduction messengers.2-4 Imatinib mesylate was shown to be effective for the treatment of AP and BP,5-7 and to be very effective in late CP patients who were resistant to or intolerant of interferon (IFN).8,9 At the 2002 American Society of Clinical Oncology meeting10 it was reported that imatinib mesylate was much superior to IFN, both in terms of cytogenetic response (CgR) and in terms of progression to AP and BC. Based on this study, imatinib mesylate will probably soon become the first line drug for treatment of CML and will compete even more with the indications for allogeneic stem cell transplantation (alloSCT). However an important piece of information on the possible relationship between response to an imatinib mesylate-based regimen and risk profile of CML is still lacking, mainly because the risk profile is calculated at diagnosis, whereas prior imatinib studies included mainly previously treated patients. The Italian Cooperative Study Group on CML has undertaken a pilot study of imatinib mesylate and pegIFN-α2b in previously untreated patients. This study has not been terminated yet, but since a relationship between risk and early CgR has emerged, it was felt worthy of an early release and a rapid report.

**Design and Methods**

Seventy-seven consecutive CML patients were enrolled between August 2001 and January 2002 in a multicenter phase II study of imatinib mesylate and pegIFN-α2b. The trial was approved by the Human Investigation Committee of each participating institution and written informed consent was obtained from...
all patients before study entry. All the patients had Ph+, bcr/abl positive CML in early CP and were previously untreated. Their median age was 47 years (range 18 - 68). The time from diagnosis to treatment ranged from 18 to 280 days (median 81).

During that period 30 of 77 patients received a short course of hydroxyurea. Treatment consisted of imatinib mesylate 400 mg daily for all patients while the dose of pegIFN-α2b was fixed at 50 µg weekly in the first cohort of 27 patients, at 100 µg weekly in the second cohort of 18 patients and at 150 µg weekly in the third cohort of 32 patients. The doses of either drug could not be increased but could be adjusted for safety and compliance according to specific protocol guidelines. Hematologic response (HR) was assessed monthly and CgR every 3 months, based on at least 20 evaluable marrow cell metaphases. The CgR was defined according to the percentage of Ph+ metaphases as complete (0% Ph+), partial (1-35% Ph+), minor (36-65% Ph+) and minimal or none (66-100% Ph+).

Complete and partial responses were pooled and defined as major CgR. The risk score was calculated using both available score systems, one of which (Sokal’s score) was derived from patients treated with conventional chemotherapy and the other (the Euro score) was generated from patients treated with IFN-based regimens.

### Results

Fifty-seven of 77 cases have completed 6 months of treatment and are evaluable for CgR at 3 and 6 months. They include all the 27 patients of the first cohort, 17/18 patients of the second cohort and 13/32 patients of the third cohort. Within 3 months all but 3 patients had achieved a complete HR. The CgRs are listed in Table 1. The relationship between CgR and risk is shown in Table 2, at 3 and 6 months, and overall. All the differences (Fisher’s exact test) are statistically significant, either with Sokal’s score or with the Euro score. The difference between the low and the high risk groups is quite impressive, with a complete CgR rate of 70% vs 8% with Sokal’s and of 65% vs none with Euro. The difference between the low and the intermediate risk groups is less significant, with a complete CgR rate of 70% vs 41% with Sokal’s score (p=0.05) and of 65% vs 36% with the Euro score (p=0.03).

### Discussion

We have found that the CgR rate to an imatinib mesylate-based treatment regimen is significantly affected by the risk profile, after 3 and 6 months...
of treatment. Although the results could be influenced to some extent by the co-administration of IFN which is known to be more effective in low risk patients than in the others, the data suggest that the early CgR rate to an imatinib mesylate-based regimen is higher and better in low risk patients than in the others.

In CML a relationship between response to treatment and risk is almost always found, but the strength of the relationship depends on the treatment. Conventional chemotherapy and IFN are virtually ineffective in AP and in BC but in CP they are much more effective in low risk cases, with a strong influence on long-term survival. Allogeneic stem cell transplantation (alloSCT) fails more frequently when it is performed in AP and especially in BC but in CP the results of alloSCT are not affected by the risk profile. Like alloSCT, imatinib mesylate is less effective in BC than in AP and in late CP. It was not, however, known whether in early CP, the response to imatinib mesylate was affected by risk as for IFN, or not affected as for alloSCT. The relationship that we have found has many explanations because low risk patients are less likely to have already developed one of the several mechanisms of imatinib mesylate resistance, namely bcr/abl amplification, overexpression or point mutation, and are more likely to have more normal hematopoietic cell left, which are required to sustain imatinib mesylate treatment and to achieve a CgR. More patients and especially a longer observation and treatment period are required to confirm these data and to understand whether this early relationship between CgR and risk will continue in the long term and will have an effect on survival. This may be very important because a response does not necessarily translate into long-term survival, as is the case with IFN. With IFN, high risk patients who achieve a complete CgR relapse and die earlier than low risk patients who achieve the same degree of CgR. It is important to clarify these issues as quickly as possible, because the introduction of imatinib has already produced a brisk decrease in the number of alloSCT which were reported to the European Registry, even before imatinib mesylate was registered in Europe. More information on the relationship between response to imatinib mesylate, survival and the risk profile of CML is clearly required.

References


Appendix
The following members of the Italian Co-operative Study Group on CML contributed to the study: N. Testoni, M. Amabile (Bologna), T. Barbui, R. Bassan (Bergamo), A. Peta, F. Iuliano (Catanzaro), G. Rege Cambrin, D. Cilloni (Torino-Orbassano), R. Fanin, M. Tiribelli (Udine), E. Gallo, M. Bertini (Torino, Ospedale Maggiore), P. Leoni, S. Rupoli (Ancona), A. Bosi, F. Leoni (Firenze), F. Lauria, M. Bocchia (Siena), V. Liso, G. Specchia (Bari), M. Gobbi, M. Migliino (Genova), M. Petrini, F. Papineschi (Pisa), F. Mandelli, E. Montefusco (Roma, Università “La Sapienza”), E. Morra, E. Pungolino (Milano), M. Baccadoro, D. Ferrero (Torino, Cattedra di Ematologia), F. Grignani, A. M. Liberati (Perugia), A. Capucci (Brescia), E. Abruzzese (Roma, Ospedale S. Eugenio).

Pre-publication Report & Outcomes of Peer Review

Contributions
All the authors contributed substantially to this study. GR, MB and GS contributed particularly to the conception and design of the study, GR and MB to drafting and reviewing the paper, FB to the statistical methods and analysis, and AdV to the database and analysis.

The skilled secretarial assistance of Katia Vecchi and Maira Marsili is gratefully acknowledged.

Funding
This study is supported by the Italian Ministry of University – MURST 40% (COFIN 1999 and 2000) and by the Bologna Section of the Italian Association Against Leukemia (BolognaAIL).

Disclosures
Conflict of interest: none.
Redundant publications: no substantial publications with previous papers.

Manuscript processing
This manuscript was peer-reviewed by two external referees and by Dr. Eduardo Olavarria, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Olavarria and the Editors. Manuscript received October 28, 2002; accepted February 4, 2003.

In the following paragraphs, the Editor-in-Chief summarizes the peer-review process and its outcomes.

What is already known on this topic
Complete cytogenetic responses to imatinib can be obtained in ≥ of patients with newly diagnosed CML. However, the durability of these responses is unknown. The kinetics of the early response seems to be of prognostic value although prognostic factors still remain unclear. The combination of interferon and imatinib is synergistic in vitro and should be explore in the clinical setting.

What this study adds
This study shows for the first time the prognostic value of the European Score in predicting response to the combination of imatinib and interferon. It also shows the feasibility of such a therapeutic combination.

Caveats
Data from this study are extremely preliminary and should be regarded with caution. No survival data is presented.