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

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

From the Institute of Hematology and Medical Oncology "L. and A. Seràgnoli", University of Bologna, St. Orsola-Malpighi Hospital, Bologna, Italy (GR, ET, SB, FB, AdV, GM, MB), Novartis Pharma, Origgio, VA, Italy (DA), Schering-Plough, Milano, Italy (GF) and Chair and Division of Internal Medicine, University of Torino, S. Luigi Gonzaga Hospital, Orbassano, Italy (GS).

Correspondence: Gianantonio Rosti, MD, Institute of Hematology and Medical Oncology "L. and A. Seràgnoli", St. Orsola-Malpighi Hospital, Bologna University, via Massarenti 9, 40138 Bologna, Italy.
E-mail: grosti@kaiser.alma.unibo.it

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 meeting[10] 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

Table 1. Cytogenetic response distribution by risk, after 3 and 6 months of treatment. Not evaluable means that metaphase yield was less than 20, due to a hypocellular marrow. Three of 57 cases (5%) could not be evaluated at 3 months and 10 of 57 (17%) at 6 months. Low risk cases are identified by a score <0.8 (Sokal's) or <781 (Euro); high risk ones are identified by a score >1.2 (Sokal's) or >1480 (Euro).The remaining patients are pooled in the intermediate (INT) risk group.

Cytogenetic response	*Sokal's risk*						*Euro risk*					
	Low		*Int*		*High*		*Low*		*Int*		*High*	
	3 mos.	*6 mos.*	*3 mos.*	*6 mos.*	*3 mos.*	*6 mos.*	*3 mos.*	*6 mos.*	*3 mos.*	*6 mos.*	*3 mos.*	*6 mos.*
Complete (Ph+ 0%)	11	15	3	6	1	1	12	16	3	6	0	0
Partial (Ph+ 1-35%)	9	5	9	6	1	1	10	5	8	6	1	1
Minor (Ph+ 36-65%)	2	2	2	1	3	1	2	3	4	0	1	1
Minimal or none (Ph+ 66-100%)	2	0	3	2	8	7	3	0	6	5	4	4
Not evaluable	3	5	0	2	0	3	2	5	1	5	0	0
Total	27	27	17	17	13	13	29	29	22	22	6	6

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[11] and the other (the Euro score) was generated from patients treated with IFN-based regimens.[12]

Table 2. The percentages of major and complete cytogenetic responses were calculated based on all cases, including those not evaluable because of an insufficient yield of metaphases. This occurred more frequently at 6 months (10 cases) than at 3 months (3 cases) and accounts for the fact that the improvement of the cytogenetic response at 6 months was less than expected. Excluding the non-evaluable cases, the major CgR rate at 6 months would be 91% (Sokal's Score) or 87% (Euro Score) in the low risk group, 80% (Sokal's Score) or 70% (Euro Score) in the intermediate risk group, and 20% (Sokal's Score) or 17% (Euro Score) in the high risk group. *p* values were calculated using Fisher's exact text.

	Sokal's risk				*Euro risk*			
	Low	*Int*	*High*	*p-value*	*Low*	*Int*	*High*	*p-value*
Major cytogenetic response								
At 3 months	74%	70%	15%	0.001	75%	50%	17%	0.01
At 6 months	74%	70%	15%	0.001	72%	54%	17%	0.03
Overall	89%	76%	23%	0.0001	90%	59%	17%	0.001
Complete cytogenetic response								
At 3 months	41%	18%	8%	0.06	41%	14%	–	0.02
At 6 months	55%	35%	8%	0.01	55%	27%	–	0.01
Overall	70%	41%	8%	0.001	65%	36%	–	0.002

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,[13-16] 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.[15,16] 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.[17] Like alloSCT, imatinib mesylate is less effective in BC than in AP and than in late CP.[5-9] 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,[18-20] and are more likely to have more normal hematopoietic cells left,[21,22] 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.[15,16] 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.[23] More information on the relationship between response to imatinib mesylate, survival and the risk profile of CML is clearly required.[24]

References

1. Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999;340:1330-40.
2. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the ABL tyrosine kinase on the growth of BCR/ABL positive cells. Nature Med 1996;2:561-6.
3. Buchdunger E, Zimmermann J, Mett H, Meyer T, Muller M, Druker B, et al. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. Cancer Res 1996;56:100-4.
4. Druker BJ. Perspectives on the development of a molecularly targeted agent. Cancer Cell 2002;1:31-5.
5. Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood 2002;99:3530-9.
6. Talpaz M, Silver RT, Druker BJ, Goldman JM, Gambacorti-Passerini C, Guilhot F, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99:1928-37.
7. Kantarjian HM, Cortes J, O'Brien S, Giles FJ, Albitar M, Rios MB, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood 2002;99:3547-53.
8. Druker BJ, Talpaz M, Resta M, Bin Peng RN, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031-7.
9. Kantarjian HM, Sawyers CL, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002;346:645-52.
10. Druker BJ. STI571 (Gleevec/Glivec, Imatinib) versus interferon (IFN) + cytarabine as initial therapy for patients with CML: results of a randomized study. Program and abstracts of the American Society of Clinical Oncology 38th Annual Meeting; May 18-21, 2002; Orlando, Florida. Proc Am Soc Clin Oncol;2002[abstract 1].
11. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, et al. Prognostic discrimination in "good risk" chronic granulocytic leukemia. Blood 1984; 63:789-99.
12. Hasford J, Pfirmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon α. J Natl Cancer Inst 1998;90:850-8.
13. Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-α n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response. The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. Lancet 1995;345:1392-7.
14. Guilhot F, Chastang C, Michallet M, Guerci A, Harousseau JL, Maloisel F, et al. Interferon α-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. N Engl J Med 1997;337:223-9.
15. Italian Cooperative Study Group on Chronic Myeloid Leukemia and Italian Group for Bone Marrow Transplantation. Monitoring treatment and survival in chronic myeloid leukemia. J Clin Oncol 1999;17:1858-68.
16. Bonifazi F, de Vivo A, Rosti G, Tiribelli M, Russo D, Trabacchi E, et al. Chronic myeloid leukemia and interferon α: a study of complete cytogenetic responders. Blood 2001;98:3074-81.
17. Gratwohl A, Hermans J, Goldman JM, Arcese W, Carreras E, Devergie A, et al. Risk assessment for patients with chronic myeloid leukemia before allogeneic blood or bone marrow transplantations. Lancet 1998;352:1087-92.
18. Weisberg E, Griffin JD. Mechanism of resistance to the ABL tyrosine kinase inhibitor STI 571 in BCR/ABL-transformed hematopoietic cell lines. Blood 2000;95:3498-505.
19. Mahon FX, Deininger MW, Schultheis B, Chabrol J, Reiffers J, Goldman JM, et al. Selection and characterization of BCR/ABL positive cell lines with differential sensitivity to the tyrosine kinase inhibitor STI 571: diverse mechanisms of resistance. Blood 2000;96:1070-9.
20. Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao P, et al. Clinical resistance to STI 571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 2001;293:876-80.
21. Verfaillie CM, Bhatia R, Miller W, Mortari F, Roy V, Burger S, et al. BCR/ABL negative primitive progenitors suitable for transplantation can be selected from bone marrow of most early chronic phase but not accelerated phase chronic myel-

ogenous leukemia patients. Blood 1996;87:4770-9.
22. Frassoni F, Podestà M, Piaggio G, Rosti V, Pitto A, Benvenuto F, et al. Normal primitive haemopoietic progenitors are more frequent than their leukaemic counterpart in newly diagnosed patients with chronic myeloid leukaemia but rapidly decline with time. Br J Haematol 1999;104:538-45.
23. Goldman JM, Druker BJ. Chronic myeloid leukemia: current treatment options. Blood 2001;98:2039-42.
24. Gratwohl A, Baldomero H, Urbano-Ispizua A. Transplantation in chronic myeloid leukemia. Lancet 2002;359:712-3.

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. Miglino (Genova), M. Petrini, F. Papineschi (Pisa), F. Mandelli, E. Montefusco (Roma, Università "La Sapienza"), E. Morra, E. Pungolino (Milano), M. Boccadoro, 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.