Impact of age on the outcome of patients with chronic myeloid leukemia in late chronic phase: results of a phase II study of the GIMEMA CML Working Party

Gianantonio Rosti, Ilaria Iacobucci, Simona Bassi, Fausto Castagnetti, Marilina Amabile, Daniela Cilloni, Angela Poerio, Simona Soverini, Francesca Palandri, Giovanna Rege Cambrin, Franco Iuliano, Giuliana Alimena, Roberto Latagliata, Nicoletta Testoni, Fabrizio Pane, Giuseppe Saglio, Michele Baccarani, Giovanni Martinelli

From the Institute of Hematology and Medical Oncology "Seràgnoli", University of Bologna, Bologna, Italy (GR, II, FC, MA, AP, SS, FP, NT, MB, GM); Istituto Europeo di Oncologia, Milan, Italy (SB); Division of Hematology and Internal Medicine, Department of Clinical and Biological Science, University of Turin, Turin, Italy (DC, GRC, GS); Division of Hematology, Hospital "Pugliese Ciaccio", Catanzaro, Italy (FI); Division of Hematology, University "La Sapienza", Rome, Italy (GA); CEINGE Biotecnologie Avanzate and Department of Biochemistry and Medical Biotechnology, University of Naples Federico II, Naples, Italy (RL, FP).

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Correspondence: Giovanni Martinelli, M.D., Molecular Biology Unit, Institute of Hematology and Medical Oncology "Seràgnoli", University of Bologna,Via Massarenti 9, 40138 Bologna, Italy. E-mail: gmartino@kaiser.alma.unibo.it

ABSTRACT

To assess the effect of age on response and compliance to treatment in patients with chronic myeloid leukemia (CML) we performed a sub-analysis within a phase II trial of the GIMEMA CML Working Party (CML/002/STI571). Since the WHO cut-off age to define an older patient is 65 years, among the 284 patients considered, we identified 226 (80%) younger patients (below 65 years) and 58 (20%) older patients (above 65 years) before starting imatinib. Response rates (hematologic and cytogenetic) were lower in the older age group but the probabilities of progression-free survival and overall survival (median observation time 3 years) were the same. Moreover, among complete cytogenetic responders, no differences were found in the level of molecular response between the two age groups. As might be expected, older patients experienced more adverse events, both hematologic and non-hematologic: this worsened compliance did not, however, prevent a long-term outcome similar to that of younger patients.

Key words: chronic myeloid leukemia, imatinib, older age.

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Older age constitutes a poor prognostic variable in patients with chronic myeloid leukemia (CML): the negative effect of age on long-term survival has been consistently observed with most effective therapeutic modalities, both pharmacological (busulfan, hydroxyurea and interferon) and allogeneic transplantation.[1-3] When recombinant interferon was the gold standard for CML treatment, poor compliance was clearly age-related.[4-6] Older patients had significantly worse side effects from interferon, although they had rates of complete hematologic response, complete cytogenetic response and overall survival similar to those of younger patients. Their poor prognosis may have been due at least in part to poorer tolerability and inadequate treatment delivery. Older patients were reported to tolerate only lower doses of interferon and dose adjustments were required more frequently. Conversely, other groups[7] reported no significant differences in interferon compliance between patients in different age groups, but the lower interferon dosage required in the elderly could have contributed to this finding.

The response to treatment and outcome of older patients with CML receiving effective treatment was not extensively investigated until the introduction of imatinib. Imatinib determines durable complete hematologic remissions in almost all Philadelphia chromosome-positive (Ph^+) patients with CML in early and late chronic phase.[8-16] Moreover, a major cytogenetic response is currently achieved in more than 80% of patients with early chronic phase disease and in more than 50% of those with late chronic phase disease.[17] In their series, Cortes *et al.*[18] showed that imatinib eliminated the negative effect of age on response and survival. Within the frame of a large phase II trial of the GIMEMA CML Working Party,[19] which enrolled 284 late chronic phase patients treated with imatinib (400 mg daily) after interferon failure, we evaluated responses, progression-free and

overall survival and compliance in patients younger and older than 65 years of age at enrollment.

Design and Methods

The general outline of the trial, (CML/002/STI571), inclusion criteria and response definitions have been published previously.[19-21] Briefly, late chronic phase Ph+ CML patients were eligible to be enrolled in the trial if resistant or intolerant to interferon. Patients received 400 mg of imatinib once daily until disease progression or until treatment intolerance. A complete hematologic response to treatment was defined as normalization of peripheral blood counts (white cell count $<10\times10^9$/L and platelet count $<450\times10^9$/L), with a normal white blood cell differential (up to 5% bands or metamyelocytes and occasional myelocytes). Cytogenetic studies were performed by standard banding techniques and at least 20 metaphases were analyzed. The cytogenetic response (CgR) was rated according to the proportion of Ph+ metaphases as complete (Ph+ 0), partial (Ph+ 1-35%), minor (Ph+ 36-65%), minimal (Ph+ 66-95) or none (Ph+ ≥96%). In patients who achieved a complete cytogenetic remission minimal residual disease was detected on peripheral blood samples by a standardized real time quantitative reverse transcriptase polymerase chain reaction method that was established in the framework of the UE concerted action and has been previously described.[19-21]

Statistic analysis

Means were compared with the t-test, and frequencies with the χ^2 test or Fisher's exact test, as appropriate. Overall survival and time to progression to accelerated or blastic phase were calculated by the product-limits method of Kaplan and Meier. The level of significance for all statistical tests was 0.05.

Discussion and Results

Hematologic, cytogenetic and molecular responses

Two hundred and eighty-four patients were treated with imatinib for chronic phase CML after treatment with interferon had failed. In accordance with the WHO, which defines patients ≥65 years as old, we stratified the whole series into two subgroups: 58 patients (20%) were 65 years of age or older and 226 (80%) were less than 65 years old at enrollment into the trial. The characteristics of the younger and older patients are compared in Table 1. The median age at enrollment was 74 (range 65-85) and 47 (range 17-63) years in the older and younger groups, respectively. The categories of enrollment were balanced between two age groups: a larger proportion of older patients than younger were enrolled because of intolerance to interferon treatment (52% versus 28%; p=ns). Table 2 presents the responses to treatment by age group: older patients had a significantly lower probability of complete hematologic response (CHR) and complete cytogenetic response (CCyR) compared to younger patients. In the older age group 31/58 patients (53%) obtained a CHR and 21/58 patients (36≥%) achieved a CCyR compared with 168/226 (74%) and 130/226 (58%) patients in the younger age group. Minimal residual disease was monitored by real time quantitative polymerase chain reaction analysis (PCR) in all patients who achieved a CCyR. Our purpose was to identify whether there was any difference in the amount of BCR-ABL transcript between patients in the two age groups, even though they were in cytogenetic remission. At baseline, the median BCR-ABL/β2M% ratio was 0.1340 and 0.0892 in the older and younger patients, respectively. We observed no significant difference in the kinetics of BCR-ABL transcript level reduction between older and younger patients who achieved CCyR during imatinib treatment, as shown in Figure 1. In fact, the median levels of BCR-ABL/β2M % were not different at any of the check-points up to the last analysis performed after 4 years on imatinib, when both groups had a BCR-ABL/β2M% ratio of 0.0007 (median value).

Table 1. Characteristics of younger and older chronic phase CML patients at enrollment.

	≥65 years	<65 years
Patients (%)	*58 (20%)*	*226 (80%)*
Characteristic	n (range)	n (range)
Sex		
Male (%)	48	53
Median age at the time of starting imatinib	74 (65-85)	47 (18-63)
Time from diagnosis to imatinib	40 (3-125)	37 (3-203)
Categories of enrollment	*n (%)*	*n (%)*
Hematologic resistance to interferon	4 (7)	40 (18)
Cytogenetic resistance to interferon	24 (41)	123 (54)
Intolerance to interferon	30 (52)	63 (28)

Table 2. Hematologic and cytogenetic responses in younger and older chronic phase CML patients treated with imatinib after failure of interferon treatment.

	≥65 years n (%)	<65 years n (%)	p value
CHR	31 (53)	168 (74)	0.003
MCyR	31 (53)	168 (74)	0.003
CCyR	21 (36)	130 (58)	0.002

CHR: complete hematologic response; MCyR: major cytogenetic response; CCyR: complete cytogenetic response.

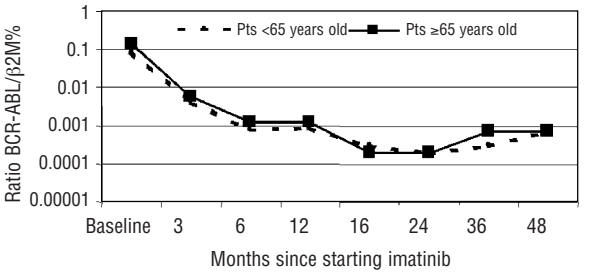

Figure 1. Pattern of molecular response in peripheral blood samples by treatment time. The transcript level is expressed as the ratio of BCR-ABL to β2-microglobulin × 100 and the values are medians. There was no significant difference in the level of BCR-ABL transcript between the two age groups during imatinib treatment and after 48 months of treatment the BCR-ABL/β2M % ratio was 0.0007 in patients ≥65 years old and in patients <65 years old.

Table 3. Older patients experienced more hematologic and non-hematologic side effects than did younger patients.

Hematologic toxicity	*≥65 years %*	*<65 years %*	*p value*
Neutropenia			
Grade III	35	27	
Grade IV	8	7	
Total	43	34	0.04
Thrombocytopenia			
Grade III	27	18	
Grade IV	6	2	
Total	33	20	0.02
Non-hematologic toxicity	%	%	
Grade III + IV	12	6	0.0001

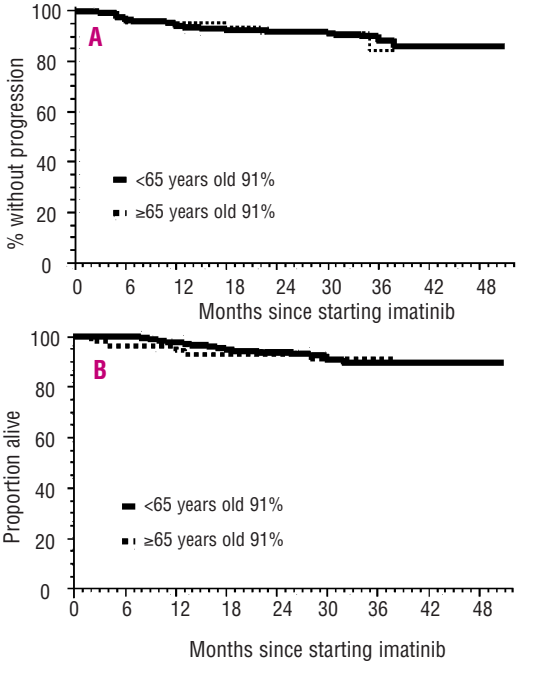

Figure 2. Disease free-progression (A) and overall survival (B) rates by age groups in chronic phase CML patients treated with imatinib. The overall survival curves were superimposed (91%).

Adverse effects

Older patients experienced more adverse events, both hematologic and non-hematologic, than did younger patients. In fact, older patients experienced more grade III and grade IV neutropenia (p=0.04) and thrombocytopenia (p=0.02) (Table 3). The incidence of grade III and IV extra-hematologic adverse events was also significantly higher in older patients (12%) versus younger ones (6%) (p=0.001). Overall, 6% of older patients definitely abandoned imatinib due to adverse events as compared to 2% of younger ones. With a median follow-up of 36 months (range, 12-54 months), the rate of progression to accelerated and blastic crisis was 12% in older patients and 10% in younger ones. The progression-free survival and the overall survival were not different between the two age groups (Figure 2). Older age constitutes a poor prognostic factor for outcome in patients with Ph-positive CML.[1-3] Significantly, the most widely employed staging systems for CML, the Sokal score and the Euro score[22] include age within the variables that can negatively influence the survival of CML patients. Older age was associated with a higher incidence of poor performance status, hepatomegaly and anemia. Until recently, the response and survival of elderly CML patients managed with effective treatment modalities has not been widely explored. Our analysis is focused on investigating the influence of age on responses (hematologic, cytogenetic and – for the first time – molecular) in a subset of aging patients with CML in late chronic phase after unsuccessful interferon therapy. Older patients had a lower probability of CHR (53%) compared to younger ones (74%). Cortes *et al.*[18] reported a higher probability of CHR (94%) in both groups of patients using the same criteria to define a CHR. The differences in CHR rates probably reflect a difference in the ability to assure high dose intensity between a single, very experienced center and a multi-institutional, national trial. The 53% CHR rate in older patients in our study, significantly lower than that reported by Cortes *et al.* (94%), might also be explained by the different threshold ages chosen for defining patiens as elderly (60 years by Cortes *et al.*, 65 years in the present study). The probability of CCgR was lower in elderly patients (36%) than in younger ones (58%) (p=0.02). We investigated the kinetics and the level of molecular response in patients who obtained a CCgR and found no difference. Despite differences in the hematologic and cytogenetic response rates between the two groups, with a median follow-up of 36 monts, survival free from accelerated or blastic phase and overall survival of the two groups were the same. These results were obtained notwithstanding the higher incidence of adverse events (both hematologic and extra-hematologic): it is, however, well known that most ima-

tinib-related adverse events can be managed without jeopardizing treatment end-points significantly. In conclusion, this study demonstrates that the poor prognostic influence of older age in patients with CML in chronic phase appears to be minimized in those treated with imatinib. Our data confirm the results of Cortes *et al*. in patients treated in late CP after failure of interferon treatment: fewer responses but the same long-term outcome for older patients. Finally, in the era of targeted therapies in hematology and oncology, it would be reasonable to define *old* patients on the basis of partially or completely age-independent reproducible indicators of *fragility* rather than simply according to years of age.

Appendix

The following members of the GIMEMA Working Party on CML actively participated in this study: G. Lucarelli and G. Polimeno (Acquaviva delle Fonti); P. Galieni and C. Bigazzi (Ascoli Piceno); V. Liso and G. Specchia (Bari); V. Zampaglione (Biella); P. Coser, and R. Quaini (Bolzano); E. Abruzzese (Roma); M. Gobbi and M. Miglino (Genova); E. Pogliani, C. Gambacorti Passerini and M. Miccolis (Monza); M. Lazzarino, E. Orlandi and S. Merante (Pavia); P. Bernasconi and R. Invernizzi (Pavia); R. Fanin and M. Tiribelli (Udine); D. Russo and M. Malagola (Brescia); G. Alimena , E. Montefusco and M. Breccia (Roma); G. Rossi and A. Capucci (Brescia); F. Nobile, M. Martino and E. Oliva (Reggio Calabria); L. Gugliotta and P. Avanzini (Reggio Emilia); P. Fattori (Rimini); G. Leone and S. Sica (Roma); L. Annino (Roma); M. C. Petti (Roma); E. Conte (Roma); A. M. Carella (Genova and San Giovanni Rotondo); M. Longinotti and S. Pardini (Sassari); E. Gottardi , M. Fava (Orbassano); L. Cavanna, D. Vallisa and E. Trabacchi (Piacenza); A. Bacigalupo (Genova); B. Rotoli, and L. Luciano (Napoli); F. Ferrara and E. Schiavone (Napoli); V. Mettivier (Napoli); A. Tabilio, C. Mecucci and D. Falzetti (Perugia); G. Visani and G. Nicolini (Pesaro); T. Barbui, U. Giussani and R Bassan (Bergamo); V. Rizzoli and L. Mangoni (Parma); M. Bocchia (Siena); E. Volpe and F. Palmieri and N. Cantore (Avellino); M.C. Michieli (Aviano); S. Amadori and A. Cantonetti (Roma); A. Levis, and M. Pini (Alessandria); E. Angelucci and E. Usala (Cagliari); A. Cuneo and G.L. Scapoli (Ferrara); E. Curioni and F. Radaelli (Milano); R. Marasca and G. Leonardi (Modena); E. Morra and E. Pungolino (Milano); V. Montefusco (Milano); A. Peta (Catanzaro); P Leoni and S. Rupoli (Ancona); A. Bosi and S. Santini (Firenze); R. Giustolisi and F. Stagno and P. Guglielmo (Catania); F. Porretto (Palermo); A. Liberati and E. Donti (Perugia); A. Zaccaria, E. Zuffa and B.Giannini (Ravenna); P. Mazza and M. Cervellera (Taranto); D. Ferrero and C. Della Casa (Torino); M. Candela and G. Danieli (Ancona); S. Morandi and C. Bergonzi (Cremona); A. Gabbas and D. Noli (Nuoro); G Semanzato and L. Trentin (Padova); S. Mirto, S. Tringali and D. Turri (Palermo); V. Abbadessa, G. Marini and Caracciolo (Palermo); M. Musso and F. Porretto (Palermo); A. D' Emilio (Vicenza); A. Bonati (Parma); M. Petrini, F. Parineschi and R. Fazzi (Pisa); F. Ricciuti and M. Pizzuti (Potenza); E. Gallo and P. Pregno (Torino); F. Gherlinzoni and C. Tecchio (Treviso); A. Ambrosetti and V. Meneghini (Verona); R. Di Lorenzo and G. Fioritoni (Pescara); G. Quarta, and M. Girasoli (Brindisi); E. De Biasi (Castelfranco Veneto); M. Monaco and E. Capussela (Foggia); A. Gallamini and M.A. Pistone (Cuneo); A. De Blasio (Latina); C. Musolino (Messina); S. Luatti, C. Nicci, E. Montanari, G. Marzocchi, F. Buontempo, T. Grafone, E. Ottaviani, C. Terragna, S. Colarossi, A. Gnani, M. Palmisano, and M. Renzulli (Bologna).

Author Contributions

GR: data analysis and interpretation, manuscript writing; II: data analysis and interpretation, manuscript writing; SB: data analysis and interpretation; FC: data analysis and interpretation; MA: data analysis and interpretation; DC: collection and assembly of data; AP: data analysis and interpretation; SS: data analysis and interpretation; FP: collection and assembly of data; GRC: collection and assembly of data; FI: collection and assembly of data; GA: collection and assembly of data; RL: collection and assembly of data; NT: data analysis and interpretation; FP: data analysis and interpretation; GS: data analysis and interpretation; MB: final approval of manuscript; GM: conception and design.

Conflict of Interest

The authors reported no potential conflicts of interest.

References

1. Kantarjian HM, Smith TL, McCredie KB, Keating MJ, Walters RS, Talpaz M, et al. Chronic myelogenous leukemia: a multivariate analysis of the associations of patient characteristics and therapy with survival. Blood 1985;66:1366-35.
2. Kantarjian H, Keating M, McCredie K. Old age is a sign of poor prognosis in patients with chronic myelogenous leukemia. Southern Med J 1988;80:1233-35.
3. Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian, HM. The biology of chronic myeloid leukaemia. N Engl J Med 1999;341: 164-72.
4. Cortes J, Kantarjian H, O'Brien S, Robertson LE, Pierce S, Talpaz M. Result of interferon-alpha therapy in patients with chronic myelogenous leukemia 60 years of age and older. Am J Med 1996;100:452-5.
5. Hilbe W, Apfelbeck U, Fridrik M, Bernhart M, Niessner H, Abbrederis K, et al. Interferon-alpha for the treatment of elderly patients with chronic myeloid leukaemia. Leuk Res 1998;22:881-6.
6. Kantarjian HM, Smith TL, O'Brien S, Beran M, Pierce S, Talpaz M. Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-α therapy. The Leukemia Service. Ann Intern Med 1995; 122:254-61.
7. Shepherd PC, Richards SM, Allan NC.Progress with interferon in CML--results of the MRC UK CML III study. Bone Marrow Transplant 1996;17Suppl 3:S15-8.
8. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344:1038-42.
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. International STI571 CML Study Group. N Engl J Med 2002;346:645-52.
10. 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.
11. 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; 99:3547-53.
12. Baccarani M, Martinelli G, Rosti G, Trabacchi E, Testoni N, Bassi S, et al. Imatinib and pegylated human recombinant interferon-α2b in early chronic-phase chronic myeloid leukemia. Blood 2004;104:4245-51.
13. Ottmann OG, Druker BJ, Sawyers CL, Goldman JM, Reiffers J, Silver RT, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood 2002;100:1965-71.
14. Sureda A, Carrasco M, de Miguel M, Martinez JA, Conde E, Sanz MA, et al. Imatinib mesylate as treatment for blastic transformation of Philadelphia chromosome positive chronic myelogenous leukemia. Haematologica 2003;88:1213-20.
15. Cervantes F, Hernandez-Boluda JC, Steegmann JL, Conde E, Alvarez-Larran A, Lopez-Jimenez J, et al. Imatinib mesylate therapy of chronic phase chronic myeloid leukemia resistant or intolerant to interferon: results and prognostic factors for response and progression-free survival in 150 patients. Haematologica 2003;88:1117-22.
16. Colombat M, Fort MP, Chollet C, Marit G, Roche C, Preudhomme C, et al. Molecular remission in chronic myeloid leukemia patients with sustained complete cytogenetic remission after imatinib mesylate treatment. Haematologica 2006;91:162-8.
17. Muller MC, Gattermann N, Lahaye T, Deininger MW, Berndt A, Fruehauf S, et al. Dynamics of BCR-ABL mRNA expression in first-line therapy of chronic myelogenous leukemia patients with imatinib or interferon /araC. Leukemia 2003; 17:2392-00.
18. Cortes J, Talpaz M, O'Brien S, Giles F, Beth Rios M, Shan J, et al. Effects of age on prognosis with imatinib mesylate therapy for patients with Philadelphia chromosome-positive chronic myelogenous leukemia. Cancer 2003;98:1105-13.
19. Rosti G, Martinelli G, Bassi S, Amabile M, Trabacchi E, Giannini B, et al. Molecular response to imatinib in late chronic phase chronic myeloid leukemia. Study Committee, Italian Cooperative Study Group for Chronic Myeloid Leukemia; Writing Committee, Italian Cooperative Study Group for Chronic Myeloid Leukemia. Blood 2004;103:2284-90.
20. Iacobucci I, Rosti G, Amabile M, Poerio A, Soverini S, Cilloni D, et al. Comparison between patients with Ph^+ chronic phase chronic myeloid leukemia who obtained a complete cytogenetic response within 1 year of imatinib therapy and those who achieved such a response after 12 months of treatment. J Clin Oncol 2006;24:454-9.
21. Martinelli G, Iacobucci I, Rosti G, Pane F, Amabile M, Castagnetti F, et al. Prediction of response to imatinib by prospective quantitation of BCR-ABL transcript in late chronic phase chronic myeloid leukemia patients. Ann Oncol 2006;17:495-502.
22. Kantarjian HM, Keating MJ, Smith TL, Talpaz M, McCredie KB. Proposal for a simple synthesis prognostic staging system in chronic myelogenous leukemia. Am J Med 1990;88:1-8.