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ORIGINAL ARTICLE

Long-term outcome of chronic myeloid leukemia patients treated frontline with imatinib

F Castagnetti[1], G Gugliotta[1], M Breccia[2], F Stagno[3], A Iurlo[4], F Albano[5], E Abruzzese[6], B Martino[7], L Levato[8], T Intermesoli[9], P Pregno[10], G Rossi[11], F Gherlinzoni[12], P Leoni[13], F Cavazzini[14], C Venturi[1], S Soverini[1], N Testoni[1], G Alimena[2], M Cavo[1], G Martinelli[1], F Pane[15], G Saglio[16], G Rosti[1], M Baccarani[17]on behalf of the GIMEMA CML Working Party

For almost 10 years imatinib has been the therapeutic standard of chronic myeloid leukemia. The introduction of other tyrosine kinase inhibitors (TKIs) raised a debate on treatment optimization. The debate is still heated: some studies have protocol restrictions or limited follow-up; in other studies, some relevant data are missing. The aim of this report is to provide a comprehensive, long-term, intention-to-treat, analysis of 559 newly diagnosed, chronic-phase, patients treated frontline with imatinib. With a minimum follow-up of 66 months, 65% of patients were still on imatinib, 19% were on alternative treatment, 12% died and 4% were lost to follow-up. The prognostic value of BCR-ABL1 ratio at 3 months (⩽10% in 81% of patients) was confirmed. The prognostic value of complete cytogenetic response and major molecular response at 1 year was confirmed. The 6-year overall survival was 89%, but as 50% of deaths occurred in remission, the 6-year cumulative incidence of leukemia-related death was 5%. The long-term outcome of first-line imatinib was excellent, also because of second-line treatment with other TKIs, but all responses and outcomes were inferior in high-risk patients, suggesting that to optimize treatment results, a specific risk-adapted treatment is needed for such patients.

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INTRODUCTION

The evolution of chronic myeloid leukemia (CML) therapy has been determined by a remarkable flux of data coming from company-sponsored[1–11] or investigator-initiated[12–23] prospective studies; moreover, it has also been influenced by the report of retrospective analyses, which were not always planned in the original study design.[24–34] The update of the most important studies is frequently reported as a oral or poster presentation at international meetings,[35] but in full peer-reviewed reports, the median observation of the patients is shorter than 6 years,[1–34] with the exception of the German CML-Study IV, where it was 7.1 years.[36] Also, the studies of the CML Working Party of the Italian Group for Hematologic Diseases in Adults (GIMEMA) have been analyzed and reported with limited follow-up.[13,14,24] At present, the minimum follow-up of the patients enrolled in the GIMEMA studies is 66 months, with a median follow-up of 76 months. The response data are consequently solid, the outcome curves flattened and the relationships between baseline disease characteristics, response and long-term outcome could be calculated with greater accuracy. The aim of this report is to provide a comprehensive, detailed and intention-to-treat analysis of the long-term outcome of CML patients treated with first-line imatinib as a useful reference for the development of the current debates on the CML treatment optimization.[37–42] We analyzed the short- and the long-term probability of achieving cytogenetic and molecular milestones, and the prognostic value of disease risk, focusing in particular on Sokal score,[43] to understand if the baseline risk should be still considered as a candidate prognostic factor requiring a more careful warning, according to the 2013 European LeukemiaNet (ELN) recommendations,[41] or if it should require a different, risk-adapted and risk-specific, treatment.

MATERIALS AND METHODS

Five hundred and fifty-nine adult patients (18 years old or more) with newly diagnosed, chronic-phase Ph+ (Philadelphia-positive) and/or BCR-ABL1+ CML were enrolled between 2004 and 2007 in three multicentric prospective GIMEMA studies: the GIMEMA CML/021 phase 2 study of imatinib 400 mg two times daily (TD) in intermediate Sokal score patients (82 patients),[13] the GIMEMA CML/022 phase 3 study of imatinib 400 mg once daily (OD) compared with imatinib 400 mg TD in high Sokal score patients (112 patients)[14] and the GIMEMA CML/023 observational study of imatinib 400 mg OD (365 patients).[24] The intention-to-treat population of each study was analyzed and all the 559 enrolled patients were included in

[1]Department of Experimental, Diagnostic and Specialty Medicine, Institute of Hematology 'L and A Seràgnoli', University of Bologna, 'S Orsola-Malpighi' University Hospital, Bologna, Italy; [2]Chair of Hematology, 'La Sapienza' University, Roma, Italy; [3]Chair of Hematology, University of Catania, Catania, Italy; [4]Oncohematology of the Elderly Unit, Oncohematology Division, IRCCS Ca' Granda – Maggiore University Hospital, Milano, Italy; [5]Chair of Hematology, University of Bari, Bari, Italy; [6]Hematology Unit, 'S Eugenio' Hospital, Roma, Italy; [7]Hematology Unit, Azienda Ospedaliera 'Bianchi-Melacrino-Morelli', Reggio Calabria, Italy; [8]Hematology Unit, 'Pugliese-Ciaccio' Hospital, Catanzaro, Italy; [9]Hematology Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [10]Hematology Unit, Azienda Ospedaliero Universitaria Città della Salute e della Scienza, Torino, Italy; [11]Hematology Unit, Azienda Ospedaliera 'Spedali Civili', Brescia, Italy; [12]Hematology Unit, 'Ca' Foncello' Hospital, Treviso, Italy; [13]Chair of Hematology, Torrette University Hospital, Ancona, Italy; [14]Chair of Hematology, Azienda Ospedaliero Universitaria Arcispedale S Anna, University of Ferrara, Ferrara, Italy; [15]Department of Biochemistry and Medical Biotechnologies, 'Federico II' University, Napoli, Italy; [16]Chair of Hematology, Department of Clinical and Biological Sciences, 'S Luigi Gonzaga' University Hospital, University of Torino, Orbassano (TO), Italy and [17]Department of Hematology and Oncology 'L and A Seràgnoli', University of Bologna, Bologna, Italy. Correspondence: Dr F Castagnetti, Department of Experimental, Diagnostic and Specialty Medicine, Institute of Hematology 'L and A Seràgnoli', University of Bologna, 'S Orsola-Malpighi' University Hospital, Via Massarenti, 9, Bologna 40138, Italy.
E-mail: fausto.castagnetti@unibo.it
Members of the GIMEMA Working Party on CML are listed before references.
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the present analysis. All the in- or off-study patients remained on active observation. The cutoff date for this analysis was 31 December 2013.

The chronic, accelerated or blastic disease phase (CP, AP, BP) were defined according to the ELN criteria.[41] The risk scores were calculated according to the Sokal,[43] Euro[44] and EUTOS[45] formulations. Complete cytogenetic response (CCyR), major molecular response ($MR^{3.0}$ or MMR, corresponding to BCR-ABL1^{IS} $\leqslant$0.1%) and deep molecular response ($MR^{4.0}$, corresponding to BCR-ABL1^{IS} $\leqslant$0.01% or undetectable disease with $\geqslant$10 000 ABL1 transcripts in all the replicates from the same sample) were defined according to the ELN criteria[40] and the International Scale (IS) standardized definitions of molecular response.[46] The early molecular response (EMR) was defined as a BCR-ABL1^{IS} $\leqslant$10% at 3 months or as a BCR-ABL1^{IS} $\leqslant$1% at 6 months.[41] Molecular tests were performed every 3 months until an MMR was achieved and confirmed, and then every 6 months. Cytogenetics was performed at the local laboratories by chromosome banding analysis of at least 20 marrow cell metaphases every 6 months until a CCyR was achieved and confirmed, and then every 12 months; to confirm a CCyR, a fluorescence *in situ* hybridization analysis on peripheral blood or bone marrow was accepted (CCyR was defined as $\leqslant$1% BCR-ABL1+ nuclei out of a least 200 nuclei).[41] If adequate molecular monitoring can be ensured, in case of stable MMR, cytogenetics can be spared.[41] All the responses were calculated on first-line imatinib; the responses to subsequent treatments were not counted.

The baseline performance status of all patients was assessed using the Eastern Cooperative Oncology Group (ECOG) score.[47] Overall survival (OS), progression-free survival (PFS) and event-free survival (EFS) were calculated from the date of treatment start until death at any time and for any reason (OS), until death or progression to AP or BP at any time (PFS) or until death, progression to AP or BP, failure on imatinib or imatinib treatment discontinuation for any cause (except treatment-free remission) (EFS), respectively, whichever came first. Failures were retrospectively defined according to the current ELN criteria;[40] as the ELN criteria changed over time, not all the failures according to the 2013 ELN criteria were followed by a change of treatment. Probabilities of OS, PFS and EFS were calculated using the Kaplan–Meier method.[48] The times to response were calculated from the date of treatment start until the first achievement of the response. Cumulative incidences of response were calculated under consideration of competing risks[49,50] defined by AP, BC and death. After careful revision of all cases with progression to AP or BP, of the causes of death and of the remission status before death, deaths were classified as leukemia-related or -unrelated (deaths because of other causes): a death

Table 1. Patient characteristics at diagnosis

Patients, *N*	559
Age (years); median (range)	52 (18–84)
Age $>$70 years, *N* (%)	66 (12)
Gender male, *N* (%)	336 (60)
ECOG $\geqslant$1, *N* (%)	118 (21)
Hb level (g/dl); median (range)	12.2 (6.4–17.5)
PLT count (10^3/μl); median (range)	352 (100–4920)
WBC count (10^3/μl); median (range)	54.8 (1.2–500.0)
Peripheral blasts (%); median (range)	1.0 (0–9.5)
Eosinophils (%); median (range)	2.0 (0–15.0)
Basophils (%); median (range)	2.0 (0–19.0)
Spleen (cm); median (range)	1 (0–24)
Palpable spleen, *N* (%)	324 (58)
Sokal score,[43] N *(%)*	
Low	219 (39)
Intermediate	216 (39)
High	124 (22)
Euro score,[44] N *(%)*	
Low	243 (43)
Intermediate	277 (50)
High	39 (7)
EUTOS score,[45] N *(%)*	
Low	519 (93)
High	40 (7)
CCA/Ph+ present, *N* (%)	21 (4)
Variant translocations present, *N* (%)	30 (5)
Derivative 9 deletions present, *N* (%)	60 (11)
BCR-ABL1 transcript type, N *(%)*	
e13a2	203 (36)
e14a2	290 (52)
e13a2/e14a2	60 (11)
Other transcripts	6 (1)
Imatinib dose, N *(%)*	
400 mg	423 (76)
800 mg	136 (24)

Abbreviations: CCA/Ph+, clonal chromosome abnormalities in Philadelphia-positive cells; ECOG, performance status according to the Eastern Cooperative Oncology Group grading; EUTOS, European Treatment and Outcome Study; Hb, hemoglobin; PLT, platelet; WBC, white blood cells.

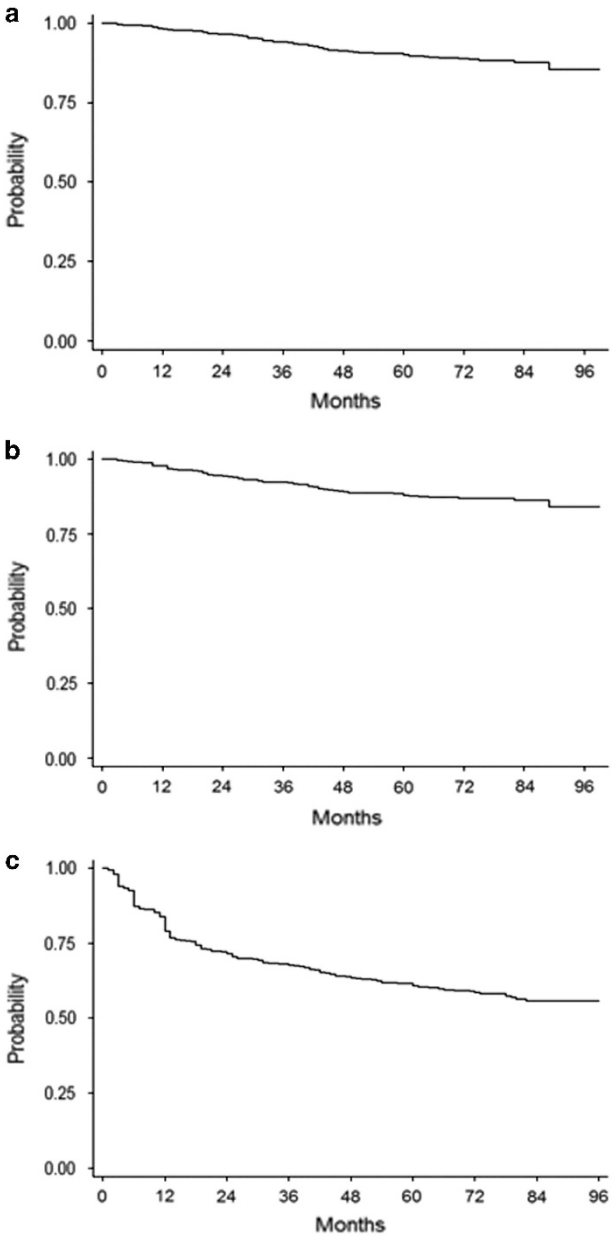

Figure 1. Outcome of all the 559 enrolled patients. (**a**) OS: the 6-year estimated OS was 89% (95% CI: 86–91%). (**b**) PFS: the 6-year estimated PFS was 87% (95% CI: 84–89%). (**c**) EFS: the estimated 6-year EFS was 58% (95% CI: 54–62%).

was defined leukemia-unrelated if a progression to AP or BP did not occur, the final cause of death was identified and a condition of CCyR and/or MMR was documented within 6 months before death. All other deaths were classified as leukemia-related. The cumulative incidence of leukemia-related death (LRD) was estimated considering the competing risk of leukemia-unrelated death.[49,50] Patients who underwent allogeneic stem cell transplantation were not censored at transplant. The 23 patients lost to follow-up were censored at the date of last contact. Survival comparisons were made by the log-rank test. Comparisons between cumulative incidences were performed by the Gray test.[51]

RESULTS

Baseline characteristics

The baseline characteristics of the enrolled patients are shown in Table 1. The male patients were 60%. The median age was 52 years (range 18–84 years); 12% of patients were older than 70 years. A palpable spleen was detected in 58% of patients; a large palpable spleen, more than 10 cm below the costal margin, was reported in 18% of patients. Additional chromosome abnormalities in Ph+ cells (CCA/Ph+) were detected in 4% of patients (6% of evaluable patients). High-risk patients were 22% by Sokal,[42] 7% by Euro[43] and 7% by EUTOS[44] score. Three hundred and five patients (55%) received a pretreatment with hydroxyurea for < 3 months. The starting imatinib dose was 400 mg OD in 76% of patients and 400 mg TD in 24% of patients. Twenty-three patients (4%) were lost to follow-up after 7 to 81 months. All the other patients were followed until death or 2013, with a median follow-up of living patients of 76 months (range 66–99 months).

Outcome

The EFS, PFS and OS are shown in Figure 1. All curves but that of EFS tended to flatten after 3 years. The 6-year survival probabilities were: 58% (95% confidence interval (CI): 54–62%) for EFS, 87% (95% CI: 84–89%) for PFS and 89% (95% CI: 86–91%) for OS, respectively. The estimated 6-year cumulative incidence of LRD was 5% (95% CI: 4–8%).

The outcome by Sokal score, including the 6-year estimated probabilities of EFS, PFS, OS and LRD, is shown in Table 2. The curves are shown in Figure 2. Almost all these estimates were significantly better in Sokal low- and intermediate-risk patients compared with that in high-risk ones. The same relationship between outcome and risk was also found according to the Euro and EUTOS risk scores (Supplementary Tables 1 and 2, and Supplementary Figures 1 and 2). The cumulative incidence of LRD according to the Sokal, Euro and EUTOS score is shown in Supplementary Figure 3.

A worse baseline performance status (ECOG $\geqslant 1$, compared with ECOG 0) was associated with a significantly lower OS (Figure 3) and with a significantly higher probability of leukemia-unrelated death (data not shown). The impact of baseline ECOG on the OS was confirmed in a multivariate Cox analysis (data not shown).

Response

Patients achieving an EMR at 3 and 6 months were 82% and 76%, respectively. The EMR at 6 months, unlike the EMR at 3 months, was significantly affected by the Sokal score (Table 2). The cumulative incidence of MMR was 66% (95% CI: 62–70%) by 12 months and 85% (95% CI 82–88%) by 6 years, with a significant difference between the low- and intermediate-risk patients, and the high-risk ones. The median time to MMR was 7 months in low- and intermediate-risk patients, significantly shorter compared with that in high-risk ones, where the median time to MMR was 12 months ($P < 0.001$) (Table 2). The cumulative incidence of $MR^{4.0}$ was 25% (95% CI: 22–29%) by 24 months and 61% (95% CI: 57–65%) by 6 years. For $MR^{4.0}$, the Sokal score was not

Table 2. Response and outcome by Sokal score

	All patients	*Sokal score*			P-*values*
		Low	*Intermediate*	*High*	
Early molecular response					
$< 10\%$ at 3 months (%)	82	83	79	84	0.488
$< 1\%$ at 6 months (%)	76	77	80	67	0.021
Major molecular response ($MR^{3.0}$)					
Median time to $MR^{3.0}$ (months)	8	7	7	12	< 0.001
$MR^{3.0}$ by 12 months (%)	66	72	68	52	0.001
$MR^{3.0}$ by 6 years (%)	85	90	89	69	< 0.001
Deep molecular response ($MR^{4.0}$)					
Median time to $MR^{4.0}$ (months)	42	42	42	NR	0.007
$MR^{4.0}$ by 24 months (%)	25	25	25	25	0.913
$MR^{4.0}$ by 6 years (%)	61	68	63	44	< 0.001
Complete cytogenetic response (CCyR)					
Median time to CCyR (months)	6	6	6	12	0.012
CCyR by 12 months (%)	79	83	81	69	0.006
CCyR by 6 years (%)	88	92	91	75	< 0.001
Outcome					
Event-free survival (6y) (%)	58	66	59	44	< 0.001
Progression-free survival (6y) (%)	87	93	84	82	0.003
Overall survival (6y) (%)	89	94	87	83	0.002
Leukemia-related death (6y) (%)	5	3	5	12	0.002
Patients, *N* (%)	559	219 (39)	216 (39)	124 (22)	—

Abbreviations: $MR^{3.0}$, BCR-ABL1^{IS} ratio $\leqslant 0.1\%$; $MR^{4.0}$, BCR-ABL1^{IS} ratio $\leqslant 0.01\%$ or undetectable disease with $\geqslant 10\,000$ ABL1 transcripts in all the replicates from the same sample; CCyR, absence of Philadelphia-positive metaphases over at least 20 metaphases analyzed by conventional banding analysis; 6y: 6-year outcome; NR, not yet reached.

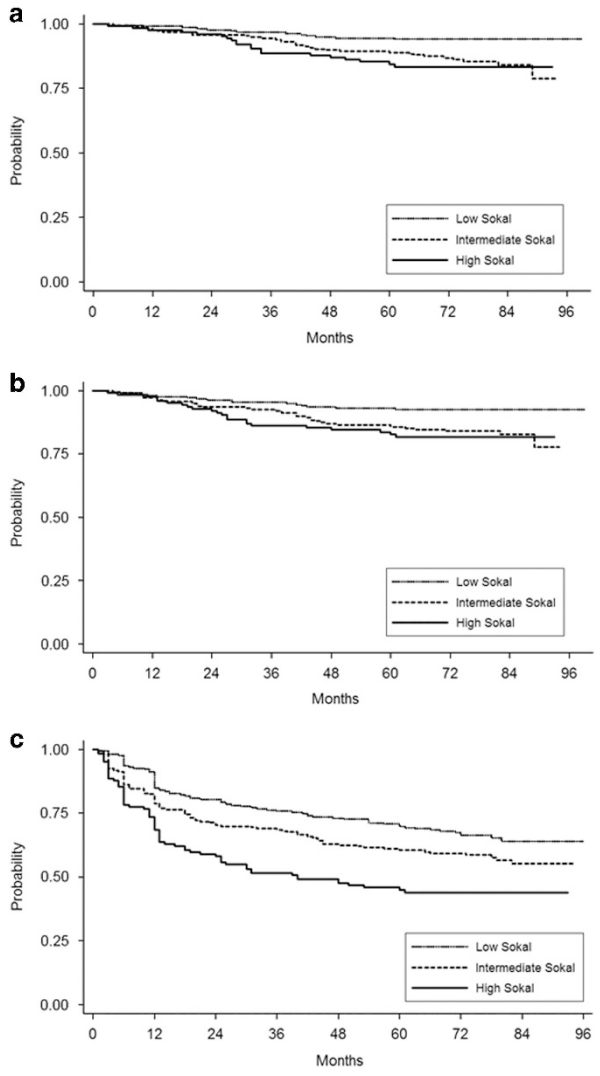

Figure 2. Outcome by Sokal score. (**a**) OS: the 6-year estimated OS was 94% (95% CI, 90–96%) in low-risk patients, 87% (95% CI, 82–91%) in intermediate-risk patients and 83% (95% CI, 75–89%) in high-risk patients ($P = 0.002$). (**b**) PFS: the 6-year estimated PFS was 93% (95% CI, 88–95%) in low-risk patients, 84% (95% CI, 78–88%) in intermediate-risk patients and 82% (95% CI, 73–88%) in high-risk patients ($P = 0.003$). (**c**) EFS: the estimated 6-year EFS was 66% (95% CI, 60–72%) in low-risk patients, 59% (95% CI, 52–65%) in intermediate-risk patients and 44% (95% CI, 35–52%) in high-risk patients ($P < 0.001$).

significant by 24 months, but it became significant by 6 years. The median time to $MR^{4.0}$ was not yet reached in high-risk patients, whereas it was 42 months in low- and intermediate-risk patients ($P = 0.007$) (Table 2). The cumulative incidence of CCyR was 79% (95% CI: 76–83%) by 12 months and 88% (95% CI: 86–91%) by 6 years; the incidence of CCyR was higher in low- and intermediate-risk patients compared with that in high-risk ones. The median time to CCyR was 6 months in low and intermediate Sokal score patients, but 12 months in high-risk ones ($P = 0.012$) (Table 2).

Outcome by response at milestones

OS and cumulative incidence of LRD according to response at milestones are shown in Table 3, in Figure 4 and in Supplementary Figure 4. The prognostic impact of an early reduction of BCR-ABL1 transcript levels on OS was significant for both the EMR at 3 months ($P = 0.015$) and at 6 months ($P < 0.001$). The achievement of an MMR at 12 months was significantly related with both

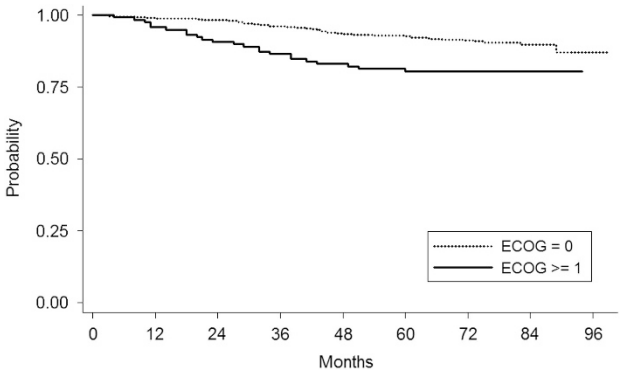

Figure 3. OS by performance status (ECOG) at baseline. The 6-year estimated OS was 91% (95% CI, 88–94%) in patients with ECOG 0 and 80% (95% CI, 72–86%) in patients with ECOG 1 or higher ($P < 0.001$).

higher OS (94% vs 84%, $P < 0.001$) and lower probability of LRD (1% vs 11%, $P < 0.001$). Interestingly, the achievement of $MR^{4.0}$ at 24 months predicted for a significantly lower probability of LRD (0% vs 7%, $P = 0.004$). The achievement of CCyR at 12 months was significantly associated with both better OS (93% vs 79%, $P < 0.001$) and inferior LRD (2% vs 18%, $P < 0.001$).

Second-line treatment

With a minimum follow-up of 66 months, 366 of the 559 enrolled patients (65%) were still on imatinib. Ninety-eight patients (18%) discontinued imatinib because of treatment failure, including progression to AP or BP, 24 patients (4%) because of toxicity, 30 patients (5%) died while on imatinib treatment, 29 patients (5%) because of other or non-identified reasons and 12 patients (2%) because of treatment-free remission. Overall, 151 patients (27%) received at least another treatment after imatinib (Table 4): nilotinib or dasatinib in 82/151 patients (54%), two or more second-generation tyrosine kinase inhibitors (TKIs) in 12 patients (8%), α-interferon in 2 patients (1%), allogeneic stem cell transplantation in 14 patients (9%) and conventional chemotherapy, including hydroxyurea, in 18 patients (12%), respectively. The second-line treatment was unknown in 23/151 patients (15%).

Causes of death

The number and the causes of death are shown in Table 5. Deaths were classified as leukemia-related when they occurred after progression to AP or BP and 'leukemia-unrelated' when the patient was in cytogenetic and/or molecular remission and the cause of death was identified. Overall, 33 deaths (51% of deaths, 6% of all patients) were classified as 'leukemia-unrelated' and 32 deaths (49% of deaths, 6% of all patients) as 'leukemia-related', respectively. The causes of 'leukemia-unrelated' deaths were mainly other tumors (17 out of 65 deaths, 3% of all patients). Overall, other tumors were recorded in other 18 patients, leading the total number of other tumors to 35 (6% of all patients) (Supplementary Table 3). Other tumors occurred rarely in patients < 60 years old (3 cases out of 179 patients, 2%), whereas they were more frequent in patients > 60 years old (32 cases out of 380 patients, 8%).

DISCUSSION

This is the final comprehensive report of an intention-to-treat analysis of three consecutive, prospective, national, multicentric, investigator-initiated studies, designed 10 years ago and enrolling 559 newly diagnosed, chronic-phase Ph+ and/or BCR-ABL1+ adult CML patients. These data can provide a solid information on the

Table 3. Overall survival and leukemia-related deaths by response at different milestones

	Responders	*Overall survival*			*Leukemia-related death*		
	N *(%)*	*Yes*	*No*	P-*value*	*Yes*	*No*	P-*value*
Early molecular response (3 months)	456 (82%)	90% (87–93%)	82% (74–89%)	0.015	4% (3–7%)	10% (5–16%)	0.019
Early molecular response (6 months)	425 (76%)	92% (89–94%)	81% (73–86%)	< 0.001	3% (1–5%)	14% (9–21%)	< 0.001
Major molecular response (12 months)	330 (59%)	94% (91–96%)	84% (78–88%)	< 0.001	1% (0–3%)	11% (8–16%)	< 0.001
Deep molecular response (24 months)	100 (18%)	95% (88–98%)	91% (88–94%)	0.344	0	7% (5–9%)	0.004
Complete cytogenetic response (12 months)	434 (78%)	93% (90–95%)	79% (70–86%)	< 0.001	2% (1–4%)	18% (12–25%)	< 0.001

The estimated 6-year overall survival and the estimated 6-year cumulative incidence of leukemia-related death probabilities with the 95% confidence interval, according to the presence or absence of response at milestones, are presented. Early molecular response (3 months): BCR-ABL1 ratio < 10% IS at 3 months; early molecular response (6 months): BCR-ABL1 ratio < 1% IS at 6 months; major molecular response (12 months): BCR-ABL1 ratio < 0.10% IS at 12 months; deep molecular response (24 months): BCR-ABL1 ratio < 0.01% IS or undetectable disease with ⩾ 10 000 ABL1 transcripts in all the replicates from the same sample at 24 months; CCyR (12 m): absence of Ph+ metaphases over at least 20 metaphases by conventional banding analysis or < 1% BCR-ABL1-positive nuclei over at least 200 nuclei by fluorescence *in situ* hybridization analysis at 12 months. Abbreviations: IS, International Scale.

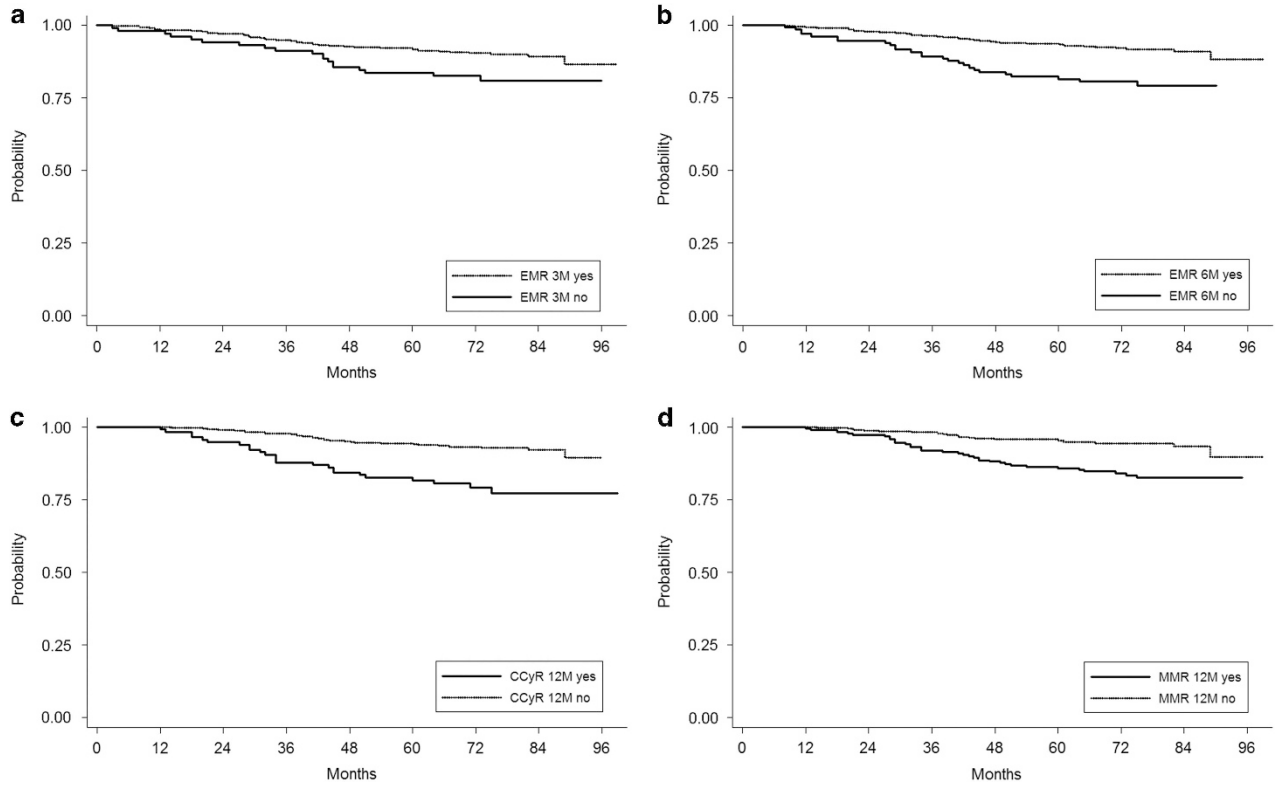

Figure 4. OS by response at milestones. (**a**) OS according to the presence or absence of an EMR, defined as a BCR-ABL1 ratio ⩽10% IS at 3 months (EMR 3): the estimated 6-year OS was 90% (95% CI, 87–93%) in patients with an EMR 3 and 82% (95% CI, 74–89%) in patients without an EMR 3 ($P = 0.015$). (**b**) OS according to the presence or absence of an EMR, defined as a BCR-ABL1 ratio ⩽1% IS at 6 months (EMR 6): the estimated 6-year OS was 92% (95% CI, 89–94%) in patients with an EMR 6 and 81% (95% CI, 73–86%) in patients without an EMR 6 ($P < 0.001$). (**c**) OS according to the presence or absence of a CCyR at 12 months (CCyR 12): the estimated 6-year OS was 93% (95% CI, 90–95%) in patients with a CCyR 12 and 79% (95% CI, 70–86%) in patients without a CCyR 12 ($P < 0.001$). (**d**) OS according to the presence or absence of a major molecular response at 12 months (MMR 12): the estimated 6-year OS was 94% (95% CI, 91–96%) in patients with an MMR 12 and 84% (95% CI, 78–88%) in patients without an MMR 12 ($P < 0.001$).

response and the outcome of imatinib-treated CML patients outside the setting of company-sponsored and academic studies designed to investigate differences in treatment. Similar studies were reported from other sources, but with less patients or with shorter follow-up[4,12,17–19,21–24] with few exceptions,[36] mainly because the long-term observation of patients enrolled within prospective trials is laborious and expensive. The evolution of CML therapy has also been influenced by the results of retrospective analyses of phase 3 comparative studies, not always planned in the original study design.[24–34] The results and the meaning of such analysis are sometimes difficult to interpret because many observed differences are small and many potentially confounding variables may jeopardize the results.

The response rates and the outcome measures described in different studies cannot be easily compared because of differences in inclusion/criteria, management, monitoring, definitions

Table 4. Reasons of treatment change and subsequent treatment

Patients with treatment change, *N*	151
Reason of treatment change, N *(%)*	
Failure	98 (65)
Toxicity	24 (16)
Other (refusal, consent withdrawal, unknown reason)	29 (19)
Subsequent treatment, N *(%)*	
Nilotinib or dasatinib	82 (54)
Two or more second- and/or third-generation TKIs	12 (8)
Interferon	2 (1)
Allogeneic stem cell transplantation (with or without TKIs)	14 (9)
Conventional chemotherapy	18 (12)
Unknown	23 (15)

Abbreviation: TKI, tyrosine kinase inhibitor. Twelve additional patients with a stable deep molecular response discontinued imatinib and achieved a treatment-free remission.

Table 5. Causes of death

Total number of deaths, *N*	65
Leukemia-related deaths, *N* (%)	32 (49)
Leukemia-unrelated deaths, *N* (%)	33 (51)
Other tumors[a]	17 (26)
Infections[b]	5 (8)
Cardiovascular events[c]	6 (9)
Hemorrhage[d]	2 (3)
Respiratory insufficiency[e]	2 (3)
Starvation[f]	1 (2)

[a]The full list of the observed tumors is reported in the Supplementary Materials (Supplementary Table S3). For each tumor type, there was no evidence of increase over expectancy. [b]Infections: three soft-tissue infections (1 skin, 1 perineum, 1 iliac fossa) and 2 lung infections (pre-existing chronic obstructive pulmonary disease in both patients). [c]Cardiovascular events: three ischemic heart disease (pre-existing risk factors or pre-existing clinical condition in all patients), 1 heart failure (unspecified), 1 dilated cardiomyopathy with subsequent heart transplantation and 1 pulmonary embolism after orthopedic surgery. [d]Hemorrhage: One cerebral hemorrhage while on anticoagulant therapy; 1 gastric hemorrhage. [e]Respiratory insufficiency: One chronic obstructive pulmonary disease, 1 chronic pleuritis. [f]Senile dementia and progressive starvation.

and reporting (i.e., response 'at' or 'by' time points, estimated cumulative incidence probabilities or cumulative response rates, competing risks, composite end points).[49,52] In the German CML-Study IV, which was similar for many aspects (multicentric investigator-sponsored trial with analogous enrollment period), the CCyR and an MMR rate by 12 months were 49% and 31% in patients treated with 400 mg IM and 63% and 55% in patients treated with 800 mg IM, respectively [17] (79 and 66% in our study); the cumulative incidence of $MR^{4.0}$ was 35% by 2 years and 69% by 6 years, respectively [30] (25 and 61% in our study); after a median observation of 7.1 years, the 10-year OS and PFS were 84 and 82%,[36] whereas in our study, with a median observation of 6.3 years and a minimum observation of 5.5 years, the 6-year estimated OS and PFS were 89 and 87%, and the 6-year cumulative incidence of LRD was 5% (corresponding to a yearly rate of about 1%).

Although the reported data are robust, because of the large number of patients, the extended duration of the observation, the small number of patients lost to follow-up and the multicentric characteristics of the study, involving more than 50 hospitals nationwide, it is also acknowledged that these data cannot completely and faithfully represent the real-life and the everyday CML clinical practice, where the age of the patients is higher,[53] and where several patients are not cared by specialists or do not have a regular access to treatment and monitoring facilities.[54]

All patients were treated with first-line imatinib, at an initial dose of 400 mg (76% of patients) or 800 mg (24% of patients). A significant proportion of the patients treated with 800 mg had a high Sokal score, and it was already reported that in these patients the dose of imatinib did not affect significantly the response.[14] Overall, no difference could be detected according to dose, but it is acknowledged that the power of subgroup analysis, by dose and by risk, was low. It is more important to highlight that our results could not be attributed to imatinib alone, as imatinib was followed by second-generation TKIs in 17% of patients, and the subsequent treatment may have influenced, at least in part, the observed differences between OS and EFS. It is also worth noting that the proportion of patients who discontinued the initial imatinib treatment for any cause was 27%; in other contemporary studies, where administrative and regulatory reasons, withdrawal of consent and strict protocol rules were a frequent cause of discontinuation, this proportion ranged between 30 and 50%.[1–11]

The overall survival is the most important and the more precise estimate of treatment outcome, but when treatment is very successful it becomes necessary to analyze separately the causes of death. It is difficult to identify in all patients the response status at death and the causes of death, if leukemia-related or -unrelated, and it is acknowledged that any death could be attributed to leukemia and/or to the treatment, at least theoretically; with these limitations, it is plausible to conclude that about 50% of patients died in remission. Moreover, the OS was significantly influenced by the performance status at baseline. These findings have implications on the evaluation of the treatment efficacy and on the clinical care of CML patients, strongly suggesting that treatment optimization is not only based on progress in drug research, and that monitoring the health state of the patients may be as important as monitoring the molecular response.[55] The second most relevant end point of the CML treatment is the achievement of a deep molecular response because of its impact on survival[30] and because it is a pre-requisite for treatment-free remission:[41] importantly, the 6-year cumulative incidence of $MR^{4.0}$ in our study was 61%.

There are many studies reporting on the results of treatment with imatinib.[1–34] In some of these studies, the prognosis was evaluated mainly using the Sokal score, more rarely using the Euro[7,22,44] or the EUTOS[21,22,45] scores. A relationship between the Sokal score and the CCyR rates, mainly by 12 months, was first shown in the IRIS study[2] and in a GIMEMA study,[56] and subsequently confirmed in at least other four studies.[6,8,12,23] A relationship between the Sokal score and the MMR, mainly by 12 months, has been reported in at least four studies,[2,6,8,23] but was not confirmed in at least two other studies.[5,11] A relationship between the Sokal score and EMR was reported in at least one study, where it was not significant.[30] A relationship between the Sokal risk and the OS and/or PFS was reported in at least three studies,[3,18,22] but it was not significant in other two studies reporting on a small number of high-risk patients.[19,23]

The GIMEMA data presented in this report confirm and strongly support the prognostic value of the Sokal score system in patients treated frontline with imatinib, showing always better responses and outcomes in low-risk patients compared with the high-risk group. The intermediate Sokal risk patients had response rates and outcomes similar to the low-risk ones. We suggest that it is time to conclude that the high Sokal risk patients need specific treatment policies, different from the treatment policies that were so effective in low- and intermediate-risk patients. However, which may be the best treatment for high-risk patients is a matter of investigation. It has been reported that in high-risk patients a high imatinib dose is not more efficacious than the standard dose.[5,14] The first-line treatment with second-generation

TKIs is worth testing, although even with second-generation TKIs, the risk is likely to maintain a prognostic value.[6,7]

With some differences, the prognostic value of baseline disease risk can also be shown for the Euro and EUTOS scores (Supplementary Tables 1 and 2). The calculation of Sokal and Euro scores includes age, not included in EUTOS formulation, because the EUTOS score was based on the 18-month CCyR rate of imatinib-treated patients, and the response to imatinib is only marginally influenced by the old age. The Euro and the EUTOS score segregate much less high-risk patients than the Sokal score: it follows that many high Sokal risk patients respond to therapy and have no events, but several low and intermediate Euro and EUTOS risk patients do not respond and have events. This study was not designed and powered to compare the three risk scores. We have focused on Sokal because so far Euro and EUTOS scores were analyzed and validated in few studies. It is puzzling, and somewhat disturbing, that in the era of molecular hematology and targeted therapy, we must still rely on risk scoring systems that are based on clinical findings (splenomegaly, assessed by manual palpation) and hematologic data. In spite of progress in knowledge of the molecular basis of leukemia, the time to replace these systems has not yet come.

CONFLICT OF INTEREST

FC has acted as a consultant for and received honoraria from Novartis, Bristol-Myers Squibb, Pfizer and ARIAD; GG has acted as a consultant and received honoraria from Novartis and Bristol-Myers Squibb; M Breccia has acted as a consultant for Bristol-Myers Squibb and Novartis, Pfizer, Ariad; EA has acted as a consultant for Novartis and Bristol-Myers Squibb; GM served on the speakers' bureaus of Novartis, Bristol-Myers Squibb and Pfizer; GR has acted as a consultant for and received honoraria from Novartis; FP received research support from Novartis, served as advisor for Novartis, Bristol-Myers Squibb and ARIAD Pharmaceuticals, and received lecture fees from Novartis and Bristol-Myers Squibb; GS has acted as a consultant for and received honoraria from Bristol-Myers Squibb, Novartis, ARIAD Pharmaceuticals and Celgene; G Rosti has acted as a consultant for Novartis, Bristol-Myers Squibb and ARIAD Pharmaceuticals and served on the speakers' bureaus of Novartis, Bristol-Myers Squibb and Roche; M Baccarani received honoraria from Novartis, Bristol-Myers Squibb, Pfizer and ARIAD Pharmaceuticals and served on the speakers' bureaus of Novartis and Bristol-Myers Squibb. The other authors declare no conflict of interest.

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Antonio e Biagio e Cesare Arrigo', Alessandria); Rupoli S, Scortechini AR (Hematology Department, University of Ancona, Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona, Ancona); Galieni P, Bigazzi C (Hematology Unit, Presidio Ospedaliero 'C e G Mazzoni', Ascoli Piceno); Cantore N, Palmieri F (Hematology Division, Ospedale Civile 'San Giuseppe Moscati', Avellino); Specchia G, Russo Rossi A (Chair of Hematology, University of Bari, Bari); Rambaldi A, Ferrari ML (Hematology Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo); Palandri F, Luatti S, Iacobucci I, Bochicchio MT, Apolinari M, Fogli M, Cervello I (Institute of Hematology 'Seràgnoli', Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna); Capucci A, Giuliani G (Hematology Unit, Azienda Ospedaliera 'Spedali Civili', Brescia); Malpignano A, Girasoli M (Hematology Division, Ospedale 'Perrino', Brindisi); Angelucci E, Usala E (Hematology Unit, Ospedale Oncologico 'A. Businco', Cagliari); De Biasi E (Hematology Unit, Presidio Ospedaliero Camposampiero, Camposampiero, Padova); Tagariello G, Sartori R (Hematology Unit, 'San Giacomo' Hospital, Castelfranco Veneto, Treviso); Di Raimondo F, Vigneri P (Hematology Unit, 'Ferrarotto' Hospital, Catania); Molica S, Lentini M (Hematology Unit, 'Pugliese' Hospital, Catanzaro); Lanza F, Viganò C (Hematology and BMT Unit, 'Istituti Ospitalieri di Cremona' Hospital, Cremona); Grasso M, Rapezzi D (Division of Hematology, 'Santa Croce e Carle' Hospital, Cuneo); Cuneo A, Ciccone M (Chair of Hematology, Dipartimento di Scienze Mediche, 'Arcispedale S Anna' University Hospital, Ferrara); Bosi A, Gozzini A (Chair of Hematology, University of Firenze, Firenze); Gobbi M, Pierri I (Chair of Hematology, IRCCS San Martino, Genova); Chianese R (Hematology Unit, Ospedali Riuniti ASL TO4, Ivrea, Torino); De Blasio A, Ciccone F (Hematology Unit, Ospedale Civile, Latina); Capochiani E, Pelosini M (Oncology and Hematology Unit, Ospedali Civili, Livorno); Musolino C, Russo S (Division of Hematology, University of Messina, Messina); Cortelezzi A (Oncohematology Unit of the Elderly, Oncohematology Division, IRCCS Ca' Granda—Maggiore Policlinico Hospital Foundation, Milano); Luppi M, Marasca R (Chair of Hematology, University of Modena and Reggio Emilia, Modena); Pogliani EM, Gambacorti-Passerini C (Department of Hematology, 'San Gerardo' Hospital, Monza); Luciano L, Izzo B (Department of Biochemistry and Medical Biotechnologies, 'Federico II' University, Napoli); Ferrara F, Annunziata M (Hematology and Bone Marrow Transplantation Unit, 'Cardarelli' Hospital, Napoli); Mettivier V, Sessa U (Hematology Unit, 'Cardarelli' Hospital, Napoli); Latte G, Noli D (Hematology Unit, 'San Francesco' Hospital, Nuoro); Rege-Cambrin G, Fava C (Department of Clinical and Biological Sciences, 'San Luigi Gonzaga' University Hospital, Orbassano, TO); Semenzato G, Binotto G (Department of Internal Medicine, University of Padova, Padova); Fabbiano F, Turri D (Hematology Unit, 'V Cervello' Hospital, Palermo); Siragusa S, Caracciolo C (Chair of Hematology, University of Palermo, Palermo); Musso M, Porretto F (Oncology and Bone Marrow Transplantation Unit, 'La Maddalena' Hospital, Palermo); Cazzola M, Orlandi E (Hematology Unit, 'S Matteo' University Hospital, Pavia); Falini B, Falzetti F (Division of Hematology and Clinical Immunology, Department of Medicine, University of Perugia, Perugia); Visani G, Isidori A (Hematology Unit, 'San Salvatore' Hospital, Pesaro); Di Bartolomeo P, Di Lorenzo R (Hematology Unit, Ospedale Civile dello Spirito Santo, Pescara); Vallisa D, Trabacchi E (Hematology Division, 'Guglielmo da Saliceto' Hospital, Piacenza); Pizzuti M (Hematology Unit, 'San Carlo' Hospital, Potenza); Zuffa E, Salvucci M (Hematology Unit, 'Santa Maria delle Croci' Hospital, Ravenna); Ronco F, Ielo D (Hematology Unit, Ospedali Riuniti, Reggio Calabria); Merli F, Avanzini P (Hematology Unit, Arcispedale Santa Maria Nuova, Reggio Emilia); Tosi P, Merli A (Hematology Unit, Ospedale Infermi Azienda Unità Sanitaria, Rimini); Sica S, Sorà F, (Istituto di Semeiotica Medica, Università Cattolica del Sacro Cuore-Policlinico 'Gemelli', Roma); Latagliata R (Chair of Hematology, 'La Sapienza' University, Roma); De Fabritiis P, Trawiska M (Hematology Unit, 'S. Eugenio' Hospital, Roma); Amadori S, Cantonetti M (Department of Hematology, 'Tor Vergata' University, Roma); Majolino I, Pacilli L (Hematology and Stem Cell Transplantation Unit, Azienda Ospedaliera San Camillo Forlanini, Roma); Ronci B, Cedrone M (Hematology Unit, Ente Ospedaliero San Giovanni Addolorata, Roma); Mengarelli A, Romano A (Hematology Unit, Istituto Regina Elena, Roma); Tafuri A, Montefusco E (Hematology Unit, 'Sant' Andrea' Hospital, Roma); Iuliano F, Infusino S (Hematology Unit, Presidio Ospedaliero 'N Giannettasio', Rossano Calabro); Dore F, Fozza C (Institute of Hematology, University of Sassari, Sassari); Bocchia M, Defina M (Chair of Hematology, University of Siena, Siena); Liberati AM, Luzi D (Hematology and Oncology Unit, Azienda Ospedaliera 'S Maria', Terni); Boccadoro M, Ferrero D (Section of Hematology, Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino) Vitolo U, Nicolosi M (Hematology Unit, Azienda Ospedaliero Universitaria Città della Salute e della Scienza, University of Torino, Torino); Gottardi M, Calistri E (Hematology Unit, 'Ca' Foncello' Hospital, Treviso); Fanin R, Tiribelli M (Chair of Hematology, University of Udine, Udine); Pizzolo G, Bonifacio M (Chair of Hematology, University of Verona, Verona); Rodeghiero F, Di Bona E (Hematology Unit, Ospedale Civile, Vicenza).

AUTHOR CONTRIBUTIONS

FC, MB and GR analyzed the data and wrote the first draft of the manuscript. All the other authors contributed to the design of the study, to the collection of the data and to the final report.

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Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)