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Differences among young adults, adults and elderly chronic myeloid leukemia patients

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Background: The incidence of chronic myeloid leukemia (CML) increases with age, but it is unclear how the characteristics of the disease vary with age. In children, where CML is very rare, it presents with more aggressive features, including huge splenomegaly, higher cell count and higher blast cell percentage.

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Patients and methods: To investigate if after childhood the disease maintains or loses these characteristics of aggressiveness, we analyzed 2784 adult patients, at least 18 years old, registered by GIMEMA CML WP over a 40-year period.

Results: Young adults (YAs: 18–29 years old) significantly differed from adults (30–59 years old) and elderly patients (at least 60 years old) particularly for the frequency of splenomegaly (71%, 63% and 55%, $P < 0.001$), and the greater spleen size (median value: 4.5, 3.0 and 1.0 cm, $P < 0.001$). According to the EUTOS score, that is age-independent, high-risk patients were more frequent among YAs, than among adult and elderly patients (18%, 9% and 6%, $P < 0.001$). In tyrosine kinase inhibitors-treated patients, the rates of complete cytogenetic and major molecular response were lower in YAs, and the probability of transformation was higher (16%, 5% and 7%, $P = 0.011$).

Conclusions: The characteristics of CML or the host response to leukemia differ with age. The knowledge of these differences and of their causes may help to refine the treatment and to improve the outcome.

Clinical trial numbers: NCT00510926, NCT00514488, NCT00769327, NCT00481052.

Key words: chronic myeloid leukemia, BCR-ABL, prognosis, young adults, tyrosine kinase inhibitors

introduction

Chronic myeloid leukemia (CML) is characterized by a specific genomic abnormality, the BCR-ABL1 gene, coding for a tyrosine kinase protein (PTK) and causing the leukemic transformation of hemopoietic stem cells [1]. In absence of treatment, the outcome is fatal and the course varies from few months to many years. Also with very effective treatments, as tyrosine kinase inhibitors (TKIs), about 20% of patients are still at risk of dying of leukemia [1–5]. The prognosis of CML is still based on three

scoring systems including clinical and hematologic variables, such as spleen size, platelet count, and the percentage of blast cells, eosinophils and basophils in the peripheral blood. The Sokal [6] and EURO [7] scoring systems, based on the overall survival (OS) of CML patients treated with conventional chemotherapy and with recombinant interferon- α (rIFN- α), respectively, also include the age: some patients are classified in the high Sokal and EURO risk category mainly because of old age, and some patients are not classified in the high Sokal and

Table 1. Baseline demographic and hematologic characteristics, according to the frontline treatment

| | CHT | rIFN- α | TKIs | Total |
|--|-----------------|-----------------|-----------------|-----------------|
| Patient number, N (%) | 948 (34) | 1062 (38) | 774 (28) | 2784 |
| Gender male, N (%) | 510 (54) | 630 (59) | 450 (58) | 1590 (57) |
| Age, years, median (range) | 52 (18–87) | 46 (18–74) | 52 (18–86) | 50 (18–87) |
| Spleen, cm ^a , median (range) | 4.0 (0–30.0) | 3.5 (0–25.0) | 1 (0–24.0) | 3 (0–30.0) |
| Palpable spleen, N (%) | 601 (63) | 687 (65) | 436 (56) | 1724 (62) |
| Blasts ^b , %, median (range) | 1.0 (0–14.5) | 1.0 (0–12.0) | 1.0 (0–10.0) | 1.0 (0–14.5) |
| Basophils ^b , %, median (range) | 2.0 (0–19.5) | 2.0 (0–19.5) | 2.0 (0–19.0) | 2.0 (0–19.5) |
| Eosinophils ^b , %, median (range) | 1.0 (0–37.0) | 2.0 (0–24.0) | 2.0 (0–19.0) | 2.0 (0–37.0) |
| PLT count, 10 ³ /ml; median (range) | 350 (100–3412) | 355 (100–3018) | 353 (101–4920) | 352 (100–4920) |
| Hemoglobin, g/dl, median (range) | 12.0 (4.0–17.8) | 12.0 (5.3–18.4) | 12.4 (6.4–17.5) | 12.1 (4.0–18.4) |
| WBC count, 10 ³ /ml; median (range) | 94 (14–880) | 52 (13–780) | 47 (12–544) | 58 (12–880) |
| Sokal score, N (%) | | | | |
| Low | 328 (35) | 489 (46) | 301 (39) | 1118 (40) |
| Intermediate | 350 (37) | 352 (33) | 310 (40) | 1012 (36) |
| High | 270 (28) | 216 (20) | 163 (21) | 649 (23) |
| NE | 0 | 5 (1) | 0 | 5 (1) |
| EURO score, N (%) | | | | |
| Low | 354 (37) | 539 (51) | 327 (42) | 1220 (44) |
| Intermediate | 441 (47) | 422 (40) | 398 (51) | 1261 (45) |
| High | 110 (12) | 91 (9) | 49 (6) | 250 (9) |
| NE | 43 (5) | 10 (1) | 0 | 53 (2) |
| EUTOS score, N (%) | | | | |
| Low | 807 (85) | 938 (88) | 725 (94) | 2470 (89) |
| High | 98 (10) | 114 (11) | 49 (6) | 261 (9) |
| NE | 43 (5) | 10 (1) | 0 | 53 (2) |

^aMaximum distance below the costal margin, assessed by manual palpation.

^bPercentage in peripheral blood.

CHT, chemotherapy; rIFN- α , recombinant interferon- α ; TKIs, tyrosine kinase inhibitors; PLT, platelets; WBC, white blood cells; NE, not evaluable.

EURO risk category mainly because of young age. The more recent EUTOS scoring system, designed to predict the complete cytogenetic response (CCyR) probability at 18 months in TKIs-treated CML patients, did not account for age [8, 9]. It is known since many years that, in children Ph+, BCR-ABL-positive, CML have more aggressive clinical and hematologic features, particularly huge splenomegaly, high white blood cell (WBC) count and higher blast cell percentage [10–13]. It is unclear if and how much these characteristics of aggressiveness are still present after childhood and, if so, how long. For this purpose, we reviewed all the GIMEMA CML databases, spanning over 40 years, to investigate if in adults the characteristics of the disease and the risk score distribution differ according to the age.

methods

The GIMEMA CML Working Party, previously Italian Cooperative Study Group on CML, promoted several multicentric prospective clinical studies since 1972 to today. A total number of 2784 adult, ≥ 18 years old, chronic phase (CP) CML patients were enrolled: 948 (34%) treated frontline with chemotherapy between 1972 and 1988, 1062 (38%) treated frontline with rIFN- α -based regimes between 1986 and 2002, 774 (28%) treated frontline with TKIs, mainly imatinib and nilotinib, between 2003 and 2010. An allogeneic stem-cell transplantation (alloSCT) was carried out in 83/948 patients

(9%) in the chemotherapy cohort, in 292/1062 patients (27%) in the rIFN- α cohort, and in 22/774 patients (3%) in the TKIs cohort, respectively.

The diagnosis of CML was based on the identification of the Ph chromosome by chromosome banding analysis of marrow cell metaphases, or on interphase fluorescence *in situ* hybridization in case of masked Ph, and after 2001 also on the demonstration of the BCR-ABL transcript by polymerase chain reaction, as recommended [5]. The European LeukemiaNet (ELN) criteria for distinguishing CP from accelerated and blastic phase (AP and BP) were used [4, 5]. The hematologic, cytogenetic and molecular responses were defined as recently recommended by ELN [5]. Baseline data were obtained before any treatment. The spleen size was always reported as maximum distance in centimeters below the costal margin, as assessed by manual palpation. Risk scores were calculated according to the original reports [6–8]. All patients provided written informed consent before the enrollment. All studies were approved by the Institutional Review Board of all participating institutions and carried out in accordance with the Declaration of Helsinki, but only the most recent studies could be preregistered at NCT.

Baseline characteristics and hematological data were compared by the χ^2 or the Kruskal–Wallis tests, as appropriate. The survival times were calculated from the date of treatment start until death for any cause (OS) or leukemia-related death (leukemia-related survival). The death was attributed to leukemia in all the patients who died after progression to AP or BP or with hematologic evidence of leukemia, who died after alloSCT, or who died due to unknown reasons. The cumulative incidence of progression was calculated from the date of start of treatment until the date of transformation to AP or BP. The patients who underwent alloSCT were not censored at transplant.

Table 2. Baseline demographic and hematologic characteristics, according to age, at diagnosis

| | <30 years | 30–39 years | 40–49 years | 50–59 years | 60–69 years | ≥ 70 years |
|--|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patient number, N (%) | 329 (12) | 444 (16) | 613 (21) | 693 (25) | 473 (17) | 232 (8) |
| Gender male, N (%) | 201 (61) | 279 (63) | 335 (55) | 401 (58) | 260 (55) | 114 (49) |
| Spleen, cm ^a , median (range) | 4.5 (0–28.0) | 5.0 (0–27.0) | 3.0 (0–25.0) | 2.0 (0–28.0) | 1.8 (0–30.0) | 1.0 (0–20.0) |
| Palpable spleen, N (%) | 234 (71) | 312 (70) | 379 (62) | 414 (60) | 266 (56) | 119 (51) |
| Blasts ^b , %, median (range) | 1.0 (0–14.5) | 1.0 (0–12.0) | 1.0 (0–10.0) | 1.0 (0–14.0) | 1.0 (0–14.5) | 0.7 (0–14.0) |
| Basophils ^b , %, median (range) | 2.0 (0–19.5) | 2.0 (0–19.0) | 2.0 (0–19.5) | 2.0 (0–19.5) | 2.0 (0–16.0) | 2.0 (0–16.0) |
| Eosinophils ^b , %, median (range) | 2.0 (0–16.0) | 2.0 (0–10.0) | 2.0 (0–23.0) | 2.0 (0–37.0) | 1.3 (0–12.0) | 2.0 (0–11.0) |
| PLT count, 10 ³ /ml; median (range) | 370 (100–3018) | 355 (100–4920) | 380 (100–4553) | 350 (100–3594) | 333 (100–1750) | 345 (100–2208) |
| Hemoglobin, g/dl, median (range) | 11.8 (6.0–17.0) | 12.1 (5.3–16.7) | 12.0 (4.0–17.8) | 12.2 (5.6–18.4) | 12.3 (4.5–17.0) | 12.1 (5.3–16.2) |
| WBC count, 10 ³ /ml; median (range) | 62 (15–880) | 66 (16–516) | 54 (14–780) | 57 (13–600) | 54 (12–544) | 71 (12–481) |
| Sokal score, N (%) | | | | | | |
| Low | 199 (60) | 243 (55) | 302 (49) | 258 (37) | 115 (24) | 1 (1) |
| Intermediate | 64 (19) | 134 (30) | 182 (30) | 259 (37) | 225 (48) | 148 (64) |
| High | 66 (20) | 67 (15) | 127 (21) | 173 (25) | 133 (28) | 83 (36) |
| NE | 0 | 0 | 2 (1) | 3 (1) | 0 | 0 |
| EURO score, N (%) | | | | | | |
| Low | 228 (69) | 325 (73) | 457 (75) | 99 (14) | 79 (17) | 32 (14) |
| Intermediate | 82 (25) | 99 (22) | 125 (20) | 453 (65) | 332 (70) | 170 (73) |
| High | 15 (5) | 7 (2) | 14 (2) | 131 (19) | 54 (11) | 29 (12) |
| NE | 4 (1) | 13 (3) | 17 (3) | 10 (1) | 8 (2) | 1 (1) |
| EUTOS score, N (%) | | | | | | |
| Low | 267 (81) | 392 (88) | 539 (88) | 615 (89) | 438 (93) | 219 (94) |
| High | 58 (18) | 39 (9) | 57 (9) | 68 (10) | 27 (6) | 12 (5) |
| NE | 4 (1) | 13 (3) | 17 (3) | 10 (1) | 8 (2) | 1 (1) |

^aMaximum distance below the costal margin, assessed by manual palpation.

^bPercentage in peripheral blood.

PLT, platelets; WBC, white blood cells; NE, not evaluable.

The survival probabilities and the cumulative incidences were estimated using the Kaplan–Meier method. Survival times and times to event were compared by the log-rank test.

results

baseline characteristics

The baseline demographic and hematologic characteristics are shown in Table 1. The frequency of high-risk patients decreased over the years: from 28% to 21% by Sokal score; from 12% to 6% by EURO score and from 10% to 6% by EUTOS score.

The patient characteristics according to the age are shown in Table 2. Only the spleen size showed an impressive variability, ranging from a median value of 4.5 cm in the youngest group (18–29 years old) to a median value of 1.0 cm in the oldest one (≥ 70 years old), with a progressive decrease, starting at the age of 40. As expected, the proportion of high Sokal and high EURO score patients increased with age, rising from 20% and 5%, respectively, in the youngest patients, to 36% and

12%, respectively, in the oldest patients. Conversely, the proportion of high EUTOS score patients was highest (18%) in the youngest age group (18–29 years), intermediate (9–10%) in patients 30–59 years old, and lowest (5–6%) in patients ≥ 60 years old. Based on the EUTOS score distribution, in all subsequent calculations, the patients were divided into three age groups, 18–29 years old, 30–59 years old and ≥ 60 years old; high-risk patients, were 18%, 9% and 6%, respectively, $P < 0.001$. An analysis of baseline characteristics within the three age groups has been carried out (Table 3 and supplementary Table S1, available at *Annals of Oncology* online). The main difference among the three age groups was the proportion of patients with a palpable spleen (71%, 63% and 55%, respectively, $P < 0.001$) and the spleen size (median, 4.5, 3.0 and 1.0 cm below costal margin respectively, $P < 0.001$). Moreover, the patients < 30 years old were more frequently males, had a higher blast cell percentage in the peripheral blood, a lower hemoglobin concentration and a slightly higher platelet count (Table 3).

Table 3. Comparison of baseline demographic and hematologic characteristics among young adults, adults and elderly (18–29 years, 30–59 years, ≥ 60 years)

| | <30 years | years | ≥ 60 years | P |
|--|-----------------|-----------------|-----------------|--------|
| Patient number, N (%) | 329 (12) | 1750 (63) | 705 (25) | - |
| Gender male, N (%) | 201 (61) | 1015 (58) | 374 (53) | 0.024 |
| Spleen, cm ^a , median (range) | 4.5 (0–28.0) | 3.0 (0–28.0) | 1.0 (0–30.0) | <0.001 |
| Palpable spleen, N (%) | 234 (71) | 1105 (63) | 385 (55) | <0.001 |
| Blasts ^b , %, median (range) | 1.0 (0–14.5) | 1.0 (0–14.0) | 1.0 (0–14.5) | 0.003 |
| Basophils ^b , %, median (range) | 2.0 (0–19.5) | 2.0 (0–19.5) | 2.0 (0–16.0) | 0.485 |
| Eosinophils ^b , %, median (range) | 2.0 (0–16.0) | 2.0 (0–37.0) | 2.0 (0–12.0) | 0.410 |
| PLT count, 10 ³ /ml, median (range) | 370 (100–3018) | 358 (100–4920) | 336 (102–2208) | 0.041 |
| Hemoglobin, g/dl, median (range) | 11.8 (6.0–17.0) | 12.1 (4.0–18.4) | 12.2 (4.5–17.0) | 0.019 |
| WBC count, 10 ³ /ml, median (range) | 61 (15–880) | 57 (13–780) | 59 (12–544) | 0.627 |
| e13a2 transcript present ^c , N (%) ^d | 30 (54) | 202 (44) | 122 (47) | 0.382 |
| CCA Ph+, N (%) ^d | 2 (4) | 22 (5) | 8 (3) | 0.514 |
| Variant translocation, N (%) ^d | 0 | 27 (6) | 21 (8) | 0.071 |
| Sokal score, N (%) | | | | |
| Low | 199 (60) | 803 (46) | 116 (16) | <0.001 |
| Intermediate | 64 (19) | 575 (33) | 373 (53) | |
| High | 66 (20) | 367 (21) | 216 (31) | |
| NE | 0 | 5 (1) | 0 | |
| EURO score, N (%) | | | | |
| Low | 228 (69) | 881 (50) | 111 (16) | <0.001 |
| Intermediate | 82 (25) | 677 (39) | 502 (71) | |
| High | 15 (5) | 152 (9) | 83 (12) | |
| NE | 4 (1) | 40 (2) | 9 (1) | |
| EUTOS score, N (%) | | | | |
| Low | 267 (81) | 1546 (88) | 657 (93) | <0.001 |
| High | 58 (18) | 164 (9) | 39 (6) | |
| NE | 4 (1) | 40 (2) | 9 (1) | |

^aMaximum distance below the costal margin, assessed by manual palpation.

^bPercentage in peripheral blood.

^cPatients with e13a2 transcript or with both e13a2/e14a2 transcripts were included.

^dAvailable data in 774 patients: age < 30 years, 56 patients; age 30–59 years, 457 patients; age > 60 years, 261 patients.

PLT, platelets; WBC, white blood cells; e13 a2 transcript, b2a2 BCR-ABL transcript; CCA Ph+, clonal chromosomal abnormalities in Philadelphia positive cells; NE, not evaluable.

response to therapy and outcome

The response to the therapy was fully evaluable only in the TKIs cohort. In this cohort, the cumulative incidence of CCyR by 5 years was lower in the young adult (YA) group (80%) than in the remaining two age groups (90% in both groups) ($P = 0.041$, YA compared with all others). Also the cumulative incidence of major molecular response (MMR) by 5 years was lower in the YA group (71%) than in the two other age groups (86% and 88%) ($P = 0.004$, YA compared with all others).

The OS according to the frontline treatment and by age group is shown in Figure 1. In the chemotherapy and in the rIFN- α cohorts, the OS was better in YA than in adult patients, and it

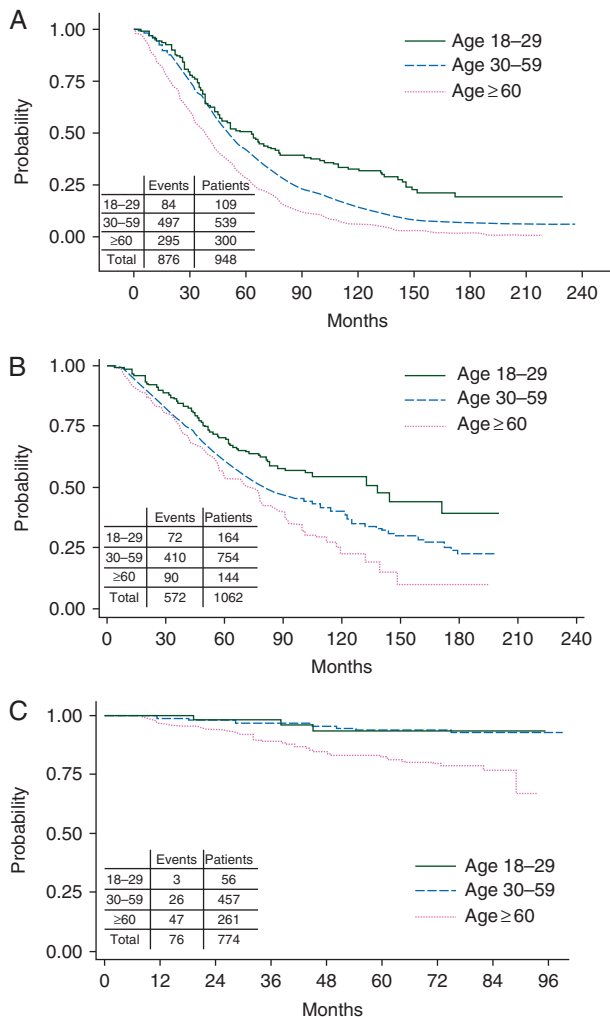


Figure 1. Overall survival (OS) by age groups (<30, 30–50, >60 years) in the chemotherapy cohort (A), the rIFN- α cohort (B) and the TKIs cohort (C). In the chemotherapy cohort, the 15-year survival was 20% [95% confidence interval (CI) 12% to 28%] in young adults, 7% (95% CI 5% to 9%) in adults and 2% (95% CI 0 to 4%) in the elderly ($P < 0.001$). In the rIFN- α cohort, the 15-year survival was 39% in young adults (95% CI 25% to 53%), 22% in adults (95% CI 16% to 30%) and 10% (95% CI 3% to 24%) in the elderly ($P < 0.001$). In the TKIs cohort, the 8-year survival was 93% (95% CI 80% to 98%) in young adults, 93% (95% CI 90% to 95%) in adults, and 77% (95% CI 69% to 83%) in the elderly ($P < 0.001$). These survival calculations were made counting all deaths, for any reason and without any censoring.

was better in adult than in elderly patients. In the TKIs cohort, the difference between YA and adults disappeared, and both groups had higher OS than the elderly group ($P < 0.001$). In the chemotherapy and in the rIFN- α cohorts, the leukemia-related deaths were 97% and 96%, respectively. In the TKIs cohort, all deaths in the YA group were leukemia-related, while the leukemia-related deaths occurring in the adult and elderly groups were 69% and 40%, respectively (Table 4). The 5-year estimated probability of progression to AP and BP was 16% in the YA group, 5% in the adult group and 7% in the elderly group ($P = 0.011$) (Figure 2). Therefore, the leukemia-related survival was much less affected by age: 93% in the YA group, 95% in the adult group and 89% in the elderly group, $P = 0.079$ (Figure 3).

discussion

This study of 2784 Ph+ CML patients in early CP, enrolled in multicentric studies over a long period of time, shows that the clinical

Table 4. TKIs cohort

| Age group | Patients, N | Progressions, N (%) | Deaths, N (%) | | |
|-------------|-------------|---------------------|---------------------|--------------------|---------|
| | | | Leukemia-related | Leukemia-unrelated | Total |
| <30 years | 56 | 8 (14) | 3 (5) | 0 | 3 (5) |
| 30–59 years | 457 | 21 (5) | 18 (4) | 8 (2) | 26 (6) |
| >60 years | 261 | 14 (5) | 19 ^a (7) | 28 (11) | 47 (18) |
| Total | 774 | 43 (6) | 40 (5) | 36 (5) | 76 (10) |

Progression to AP and BP, as defined by ELN criteria (6), and death, by age group. All leukemia-related deaths occurred after transformation to AP or BP, with the exception of five elderly patients who did not die in remission, but did not fit the criteria of AP or BP.

^aFive patients died because of leukemia without fitting the criteria of AP and BP.

TKIs, tyrosine kinase inhibitors; AP, accelerated phase; BP, blastic phase; ELN, European LeukemiaNet.

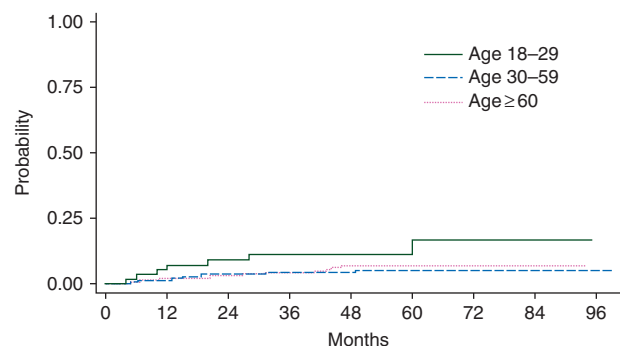


Figure 2. Estimated cumulative probability of progression to AP and BP by age groups (<30, 30–50, >60 years) in the TKIs cohort. At 8 years, it was 16% (95% CI 8% to 31%) in young adults, 5% (95% CI 3% to 8%) in adults and 7% (95% CI 4% to 11%) in the elderly ($P = 0.011$).

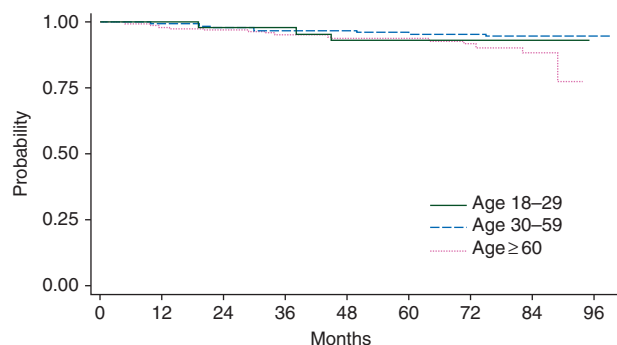


Figure 3. Estimated probability of CML-related survival by age groups in the TKIs cohort. The 8-year survival was 93% (95% CI 80% to 98%) in young adults, 95% (95% CI 92% to 97%) in adults and 89% (95% CI 81% to 93%) in the elderly ($P = 0.079$).

presentation of CML varies consistently and unidirectionally with age, particularly because of differences in spleen enlargement, leading to a relative excess of high-risk patients among YA. It was already well known that the disease is more aggressive in children [10–13]. A recent study on 150 patients younger than 18 years old reported that the spleen was palpable in 78% of children, with a median value of 8 cm below costal margin [13]. For children, a high WBC, a high platelet count, and a high blast cell percentage at the diagnosis have been reported [10–13]. Also a multicentric study, including 120 patients 16–29 years old, reported that, in adolescents and YA, the median value of spleen below costal margin was 5 versus 0 cm in the elderly group [14].

The splenomegaly is almost universally attributed to the expansion of myelopoiesis in the spleen. A classic textbook says: ‘In chronic phase the spleen is enlarged due to infiltration of the red pulp cords by granulocytes in different maturation stages...’ [15]. Spleen is a hematopoietic organ in the fetus. In children, adolescents and YA, the spleen niche may offer a more favorable environment to Ph+ cells, than in older patients; alternatively, it is possible that in younger patients Ph+ stem or progenitor cells could be qualitatively different. There are few, not recent, studies reporting on differences between marrow and spleen hematopoiesis in CML [16–18], but there are not studies investigating the molecular profile of Ph+ cells in different age groups. The spleen enlargement could be not only caused by myeloid metaplasia, but it could also be an expression of host reaction. In a normal spleen, the lymphoid tissue account for about 65% of the whole organ [15]. In CML patients, the exact proportion of myeloid and lymphoid cells in the spleen is not known, apart from an old report regarding 12 CML patients splenectomized at the onset of the disease [16]: based on cytologic evaluation of spleen touches (smears), the median lymphocyte proportion was 40% of all nucleated cells, suggesting that spleen enlargement was due at least in part also to lymphocytes. This may represent an inflammatory reaction, reflecting an age-related difference of the immune-inflammatory response of the host.

The splenomegaly has been always recognized as a negative prognostic factor [6–8, 15]. Also in our series of 2784 patients, enrolled over a long period time, a multivariate analysis confirmed that spleen size was a significant and independent predictor of survival, regardless of age (data not shown). In the pre-TKIs era, the great majority of deaths were preceded by

progression, so that they were attributed to leukemia. In the TKIs era, the deaths not related to leukemia are also uncommon in younger patients, but account for at least 50% of all deaths in the elderly. The concept of leukemia-related survival raises obvious difficulties, suspicions and resistances, because it implies a shared definition, a detailed knowledge of the course of the disease and of the death, and requires other specific biostatistical methods of analysis [19, 20]. However, in the current TKIs era, the problem can no longer be ignored. It is not easy to detect differences in response and outcome according to age, since treatment is so effective and the number of YA patients is small; 12% in our multicentric series of 2784 patients and 8%, 11%, 13% and 8%, respectively, in other reports, where adolescents and YA were frequently grouped in the same age class [14, 21–23]. A difference in the probability of achieving a CCyR and an MMR, according to age, was found in our series and in an independent single-center study [23], but not in another multicentric study on patients from 16 to 29 years old [14]. In all the studies, the OS and the progression-free survival were not affected by age. The more aggressive disease characteristics in YA may explain the lower response rates and the relatively higher probability early disease progression. The impact of a poorer adherence, if any, should be clarified.

In conclusion, we extended to YA the observations already made in children. The most relevant difference was in the spleen size, and a continuous decrease of spleen size by age has been observed. It is acknowledged that the age is a continuous variable, and that cutoffs are artificial. Moreover, selection biases could not be excluded, because patients enrolled in clinical trials may not reflect the characteristics of the whole CML population. We repeated all the calculations reported in this paper, also considering different cutoffs, particularly 18–39, 40–59, 60–69 and ≥ 70 years old: the results did not change. In the current TKI era, multiple treatment choices are available, the differences are small, and the treatment goals may be different according to the age of CML patients [5, 24]. Our data suggest that investigating the differences according to age may be important for understanding the biology of the disease and the response of the host, in order to design age-adapted strategies. A careful monitoring of YA patients should be carried out. It is likely that in YA an extended use of second-generation TKIs may improve the outcome.

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disclosure

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