

Younger patients with chronic myeloid leukemia do well in spite of poor prognostic indicators: results from the randomized CML study IV

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Abstract Since the advent of tyrosine kinase inhibitors, the impact of age on outcome of chronic myeloid leukemia (CML) patients has changed. We therefore analyzed patients from the randomized CML study IV to investigate disease

manifestations and outcome in different age groups. One thousand five hundred twenty-four patients with BCR-ABL-positive chronic phase CML were divided into four age groups: (1) 16–29 years, $n=120$; (2) 30–44 years, $n=383$;

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(3) 45–59 years, $n=495$; and (4) ≥ 60 years, $n=526$. Group 1 (adolescents and young adults (AYAs)) presented with more aggressive disease features (larger spleen size, more frequent symptoms of organomegaly, higher white blood count, higher percentage of peripheral blasts and lower hemoglobin levels) than the other age groups. In addition, a higher rate of patients with BCR-ABL transcript levels $>10\%$ on the international scale (IS) at 3 months was observed. After a median observation time of 67.5 months, no inferior survival and no differences in cytogenetic and molecular remissions or progression rates were observed. We conclude that AYAs show more aggressive features and poor prognostic indicators possibly indicating differences in disease biology. This, however, does not affect outcome.

Keywords Chronic myeloid leukemia · Accelerated phase · Blast crisis · Young adults and adolescents

Introduction

Chronic myeloid leukemia (CML) appears in all age groups. The incidence increases with age. In western countries, median age at diagnosis is 64 years [1, 2] and around 54 years [3] in clinical studies. Before the introduction of imatinib, older age was a negative prognostic factor, as reflected by the risk stratification scores, Sokal and Euro [4, 5]. After the introduction of imatinib, the outcome of patients with CML has improved, and older age seems to have lost its negative impact [6, 7].

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A recent analysis that compares patients less than 65 years with patients older than 65 years treated with frontline imatinib reports no difference in an outcome between these two age groups [8]. Another analysis that compares 15–29-year-old adolescents and young adults (AYAs) with patients older than 29 years with newly diagnosed chronic phase (CP) CML treated with first-line tyrosine kinase inhibitors (TKIs) reports inferior response rates in the younger group [9]. AYAs have been of particular interest in oncology because differences compared to older age have been observed in various neoplasias: In acute lymphoblastic leukemia, different disease features and a better outcome are reported in AYAs in comparison to older patients [10, 11]. A worse prognosis has been reported in breast cancer [12, 13], colorectal cancer [14], and soft tissue sarcomas [15], pointing to different biological features of these cancers in younger age [16].

Few data exist on presentation and outcome of AYAs with CML possibly due to the low incidence of CML in this age group.

The aim of this study was to analyze the impact of age on outcome of CML using patients from the German CML study IV with particular attention to the group of patients younger than 29 years.

Patients and methods

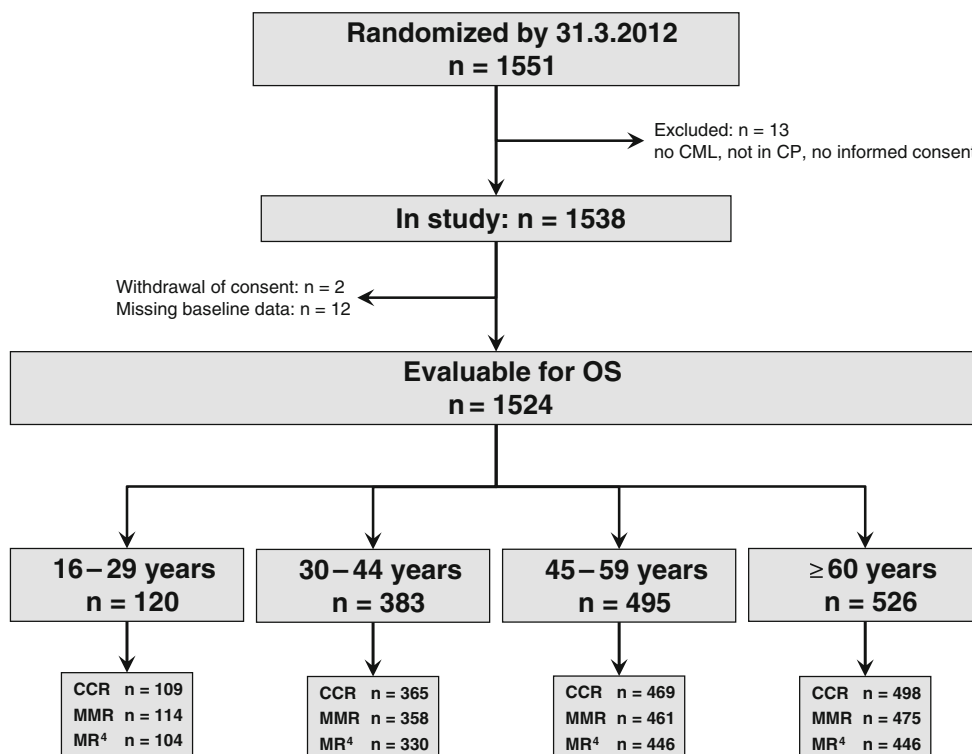
The German CML study IV is a five-arm randomized study which compares 400 mg imatinib, 800 mg imatinib, 400 mg imatinib in combination with interferon alpha (IFN- α), 400 mg imatinib in combination with low-dose cytarabine, and 400 mg imatinib after failure to IFN- α [17].

Newly diagnosed BCR-ABL-positive CP-CML patients diagnosed in participating centers were included. There was no upper age limit. Patients with comorbidities that would preclude study participation or study drug treatment were excluded as well as pregnant or nursing women and patients with secondary malignancy causing reduced life expectancy or requiring therapy.

Patients, 16 years and older, were included. Twenty-nine years was defined as upper cutoff age for AYAs [9, 18–21]. For older patients, the lower cut off at age 60 years was chosen [6, 22]. Age groups, 30–59, were evenly divided into two groups (30–44 and 45–59).

Gender, performance status, risk scores, clinical manifestations, blood count, type of transcripts, and presence of additional chromosomal aberrations (ACAs) [23] were analyzed at the time of diagnosis. Cytogenetic and molecular responses, rates of progression to accelerated phase (AP) and blast crisis (BC), and overall survival (OS) were analyzed throughout the observation time of the study. Patients were analyzed for achieving complete cytogenetic remission (CCR), major molecular remission (MMR), and molecular

Fig. 1 Overview of evaluable patients according to age groups. *n* Number of patients, *CML* chronic myeloid leukemia, *CP* chronic phase, *OS* overall survival, *CCR* complete cytogenetic remission, *MMR* major molecular remission, *MR⁴* molecular remission $\leq 0.01\%$ on the international scale



remission $\leq 0.01\%$ on the international scale (*MR⁴*), if at least one sample of sufficient quality was available.

For follow-up analyses of *CCR*, at least 20 marrow cell metaphases were evaluated. Measurements of *BCR-ABL* and total *ABL* transcripts were determined by quantitative reverse transcriptase polymerase chain reactions from peripheral blood samples [24–26] and were performed in standardized laboratories [27]. The analysis of molecular endpoints was restricted to patients expressing *b2a2* and/or *b3a2* transcripts only.

Response definitions, *AP*, and *BC* were defined according to *ELN* criteria and the recent standardized definitions of molecular response [28–30]. All living patients were censored at the time of their last visit. In estimating the cumulative incidences of molecular or cytogenetic remissions, patients were censored at the time they received a second-generation *TKI* or were transplanted.

OS was calculated from date of diagnosis to death from any cause (whether on or off *TKI*) or to the latest follow-up date.

Baseline characteristics and hematological parameters were compared with the chi-squared or the *Kruskal–Wallis* tests. Cumulative incidences were calculated under consideration of competing risks [31, 32] defined by *AP*, *BC*, and death. Probabilities of *OS* were calculated by the *Kaplan–Meier* method and compared by log-rank test. Comparisons between cumulative incidences were performed by the *Gray* test [33]. Relative overall survival was calculated dividing the observed survival probabilities by the expected survival probability of the general German population matching age and sex. Level of significance was 0.05. Due to the exploratory character of this work, no adjustment of *p* values was done. All calculations were performed with the *SAS* software Version 9.1.3.

The protocol followed the Declaration of Helsinki and was approved by the ethics committee of the Medizinische

Table 1 Patients and treatment arms

Age groups, years	16–29	30–44	45–59	At least 60
All patients, <i>n</i>	120	383	495	526
Imatinib (400 mg), <i>n</i> (%)	25 (21)	93 (24)	131 (26)	147 (28)
Imatinib (400 mg + <i>IFN-α</i>), <i>n</i> (%)	39 (32)	102 (27)	139 (28)	145 (27)
Imatinib (400 mg + cytarabine), <i>n</i> (%)	13 (11)	39 (10)	53 (11)	53 (10)
Imatinib (400 mg after <i>IFN-α</i> failure), <i>n</i> (%)	8 (7)	35 (9)	37 (7)	48 (9)
Imatinib (800 mg), <i>n</i> (%)	35 (29)	114 (29)	135 (27)	133 (25)

N number of patients, *IFN-α* interferon

Table 2 Patient's characteristics

Age groups, years	16–29	30–44	45–59	At least 60
Number of patients, <i>n</i> (%)	120 (8)	383 (25)	495 (32)	526 (35)
Male	80 (67)	255 (67)	301 (61)	283 (54)
Female	40 (33)	128 (33)	194 (39)	243 (46)
<i>p</i>				0.011 ^a
Karnofsky index, <i>n</i> (%)				
50–80	13 (12)	31 (9)	42 (9)	74 (16)
>80–<100	32 (29)	86 (25)	144 (32)	166 (35)
100	65 (59)	226 (66)	271 (59)	234 (49)
<i>p</i>		<0.001 ^a	<0.001 ^a	<0.001 ^a
Missing	10	40	38	52
EUTOS score, <i>n</i> (%)				
Low	97 (82)	320 (84)	436 (89)	473 (92)
High	22 (18)	63 (16)	54 (11)	41 (8)
<i>p</i>			0.031 ^a	0.002 ^a
Missing	1	0	5	12
Sokal score ^b , <i>n</i> (%)				
Low	64 (54)	190 (50)	226 (46)	90 (17)
Intermediate	23 (19)	100 (26)	155 (32)	300 (58)
High	31 (26)	92 (24)	110 (22)	125 (24)
<i>p</i>			0.035 ^a	<0.001 ^a
Missing	2	1	4	11
Euro score ^b , <i>n</i> (%)				
Low	70 (59)	267 (70)	144 (29)	69 (13)
Intermediate	29 (24)	84 (22)	286 (58)	391 (75)
High	20 (17)	31 (8)	65 (13)	61 (12)
<i>p</i>		0.013 ^a	<0.001 ^a	<0.001 ^a
Missing	1	1	0	5
Presence of organomegaly-related symptoms, <i>n</i> (%)	33 (29)	86 (24)	84 (18)	37 (7)
<i>p</i>			0.009 ^a	<0.001 ^a
Missing	5	19	18	23
Spleen size, below costal margin				
Median (range), cm	5 (0–38)	3 (0–28)	1 (0–25)	0 (0–23)
<i>p</i>		0.014 ^a	<0.001 ^a	<0.001 ^a
Missing, <i>n</i>	1	0	2	6
Blasts in blood				
Median (range), %	2 (0–19) ^c	1 (0–17) ^c	1 (0–30) ^c	0 (0–15)
<i>p</i>			0.010 ^a	<0.001 ^a
Missing, <i>n</i>	1	1	4	6
WBC				
Median (range), 10 ⁹ /L	144 (9–571)	106 (3–539)	74 (3–630)	57 (3–582)
<i>p</i>		0.044 ^a	<0.001 ^a	<0.001 ^a
Missing, <i>n</i>	1	2	2	3
Hemoglobin				
Median (range), g/dL	11.1 (6.9–16.2)	11.8 (5.2–17.5)	12.6 (4.9–19.1)	12.5 (4.7–17.6)
<i>p</i>		0.041 ^a	<0.001 ^a	<0.001 ^a
Missing, <i>n</i>	2	3	3	5
Eosinophils				
Median (range), (%)	2.5 (0–12)	2 (0–13)	2 (0–14)	2 (0–28)
Missing, <i>n</i>	0	2	4	3

Table 2 (continued)

Age groups, years	16–29	30–44	45–59	At least 60
Basophils				
Median (range), (%)	3 (0–19)	3 (0–22)	4 (0–26)	3 (0–66)
Missing, <i>n</i>	0	2	5	6
Platelets				
Median (range), × 10 ⁹ /L	430 (59–2,590)	369 (39–2,799)	364 (49–3,020)	381 (34–2,716)
Missing, <i>n</i>	0	1	1	2
BCR-ABL transcript type, <i>n</i> (%)				
b2a2	55 (48)	146 (39)	200 (42)	186 (38)
b3a2	42 (36)	166 (45)	210 (44)	233 (47)
Either	18 (16)	61 (16)	65 (14)	72 (15)
Missing	5	10	20	35
ACAs, <i>n</i> (%)				
Yes	6 (6)	13 (4)	22 (5)	12 (3)
No	98 (94)	321 (96)	421 (95)	452 (97)
Missing	16	49	52	62
>10 % BCR-ABL^{IS} at 3 months				
<i>n</i> , (%)	25 (42)	74 (42)	60 (26)	53 (25)
<i>p</i>			0.026 ^a	0.018 ^a
Missing, <i>n</i>	60	204	263	313
>10 % BCR-ABL^{IS} at 6 months				
<i>n</i> , (%)	6 (13)	30 (19)	28 (13)	29 (15)
Missing, <i>n</i>	72	224	272	320

BCR-ABL^{IS} BCR-ABL transcript levels on international scale ACAs: additional cytogenetic aberrations except –Y

^a *p* value refers to test between group 1 and the respective groups. Values not shown were above 0.05

^b In Sokal and Euro score age is included for risk stratification

^c Eight patients with blasts in blood > 15 % were included as chronic phase patients after judged so by the treating physicians. All had bone marrow blasts ≤ 10 %

Fakultät Mannheim der Universität Heidelberg and by local ethics committees of participating centers. Written informed consent was obtained from all patients before they entered the study.

Results

One thousand five hundred fifty-one patients with newly diagnosed BCR-ABL-positive CML in CP were randomized from July 2002 through March 2012. Data entry was closed on May 24, 2012.

One thousand five hundred twenty-four patients at the age of 16 years and older were evaluable for follow-up (Fig. 1). The median age at diagnosis was 52 years. The median observation time was 67.5 (0.1–123.8) months.

Patients were divided into four age groups according to age at diagnosis: group 1, 16–29 years (*n*=120, 8 %); group 2, 30–44 years (*n*=383, 25 %); group 3, 45–59 years (*n*=495, 32 %); and group 4, ≥60 years (*n*=526, 35 %). All patients

received imatinib as first or second-line treatment in the study except for ten patients who only received IFN. Recruitment to this arm was terminated in 2005 [17]. More patients in group 1 were transplanted (19 %) compared to 12, 7, and 1 % in groups 2, 3, and 4, respectively. The number of patients according to age groups and therapy arm are shown in Table 1.

There was a predominance of male gender in all age groups, but group 1 showed a significantly higher percentage of male patients in comparison to group 4 (67 % for groups 1 and 2 each, 61 % for group 3, and 54 % for group 4, *p*=0.011).

Most patients had a Karnofsky index >80 %, but 12 % of patients in group 1 had a Karnofsky index between 50–80 % compared to 9 % in groups 2 and 3 and 16 % in group 4 (Table 2).

Patients in group 1 had the highest proportion of high-risk patients according to Euro and EUTOS scores. By EUTOS score, 18 % of patients in group 1 were high risk in comparison to 16 % (ns), 11 % (*p*=0.031), and 8 % (*p*< 0.002) in groups 2, 3, and 4, respectively.

Group 1 presented with a larger spleen size (median length of 5 cm below the costal margin), more often with symptoms of organomegaly, higher white blood cell counts (WBC), a higher percentage of blasts in the peripheral blood (median of $144 \times 10^9/L$), and lower hemoglobin levels (median of 11.1 g/dL). There were no differences in fatigue, weight loss, fever, or other symptoms, in the percentage of eosinophils, basophils, platelets, bone marrow blasts, ACAs, and type of BCR-ABL transcripts at diagnosis between the four groups (Table 2).

No significant differences in cumulative incidences of CCR, MMR, and MR⁴ were found between group 1 and the other 3 groups (Fig. 2a–c).

The 5-year OS probability of group 1 was 96.7 %, 93.8 % for group 2, 92.5 % for group 3, and 82.9 % for group 4. OS was lower only in group 4 in comparison to the other three age groups ($p < 0.001$) as observed in the general population [34]. The relative survival (RS) when the general German population was taken into account was 96.9 % in group 1, 94.5, 95.1, and 93.1 % in groups 2–4, respectively [34].

Regarding progression during the observation time, no differences were observed between the age groups. The cumulative incidences of progression at 5 years were 8.7, 7.3, 5.3, and 6.1 % for groups 1 to 4, respectively (Fig. 3).

More patients in group 1 had BCR-ABL^{IS} ≥ 10 % at 3 months (42 %) than patients above 44 years (26 % for group 3, $p = 0.026$ and 25 % for group 4, $p = 0.018$). There was no difference to group 2 (Table 2).

A correlation between a specific cause of death age group and therapy arm was not observed. Causes of death in each group are shown in Table 3.

Discussion

The median age of the 1,524 CML patients of the CML study IV was 52 years with a male preponderance. AYAs represented 8 % of the study population in agreement with reports of CML incidence in AYAs [9, 35].

AYAs in our study presented features of a more aggressive disease, with higher levels of WBC and blasts in the peripheral blood, lower hemoglobin, larger spleen size, and more frequent organomegaly-related symptoms. The larger spleen size is reflected in the EUTOS score in which age is not included as a parameter and is in line with a study of Pemmaraju et al. who report a higher frequency of splenomegaly at diagnosis in 61 AYAs than in 407 older patients [9], and a study of Cortes et al. who report that splenomegaly was more frequent in patients below 60 years than above 60 years [6]. Similar observations have been made in children with CML (increased rates of splenomegaly and

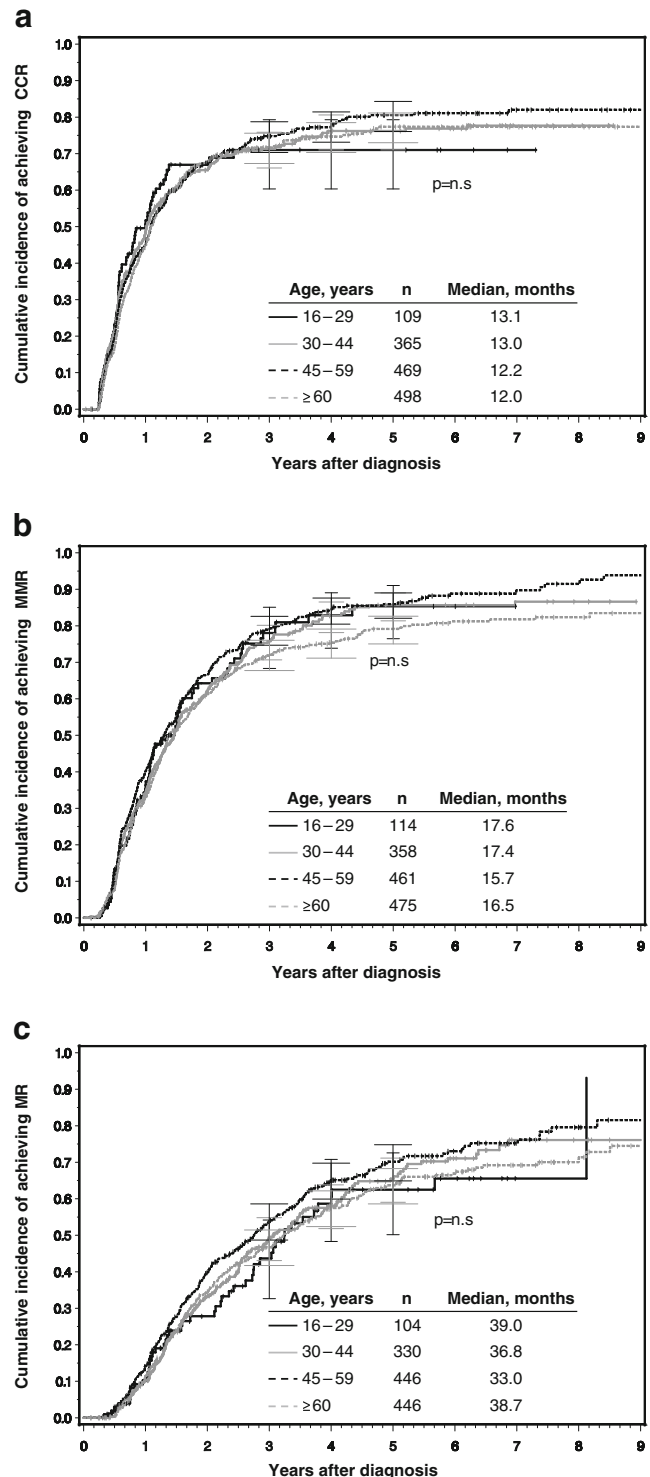
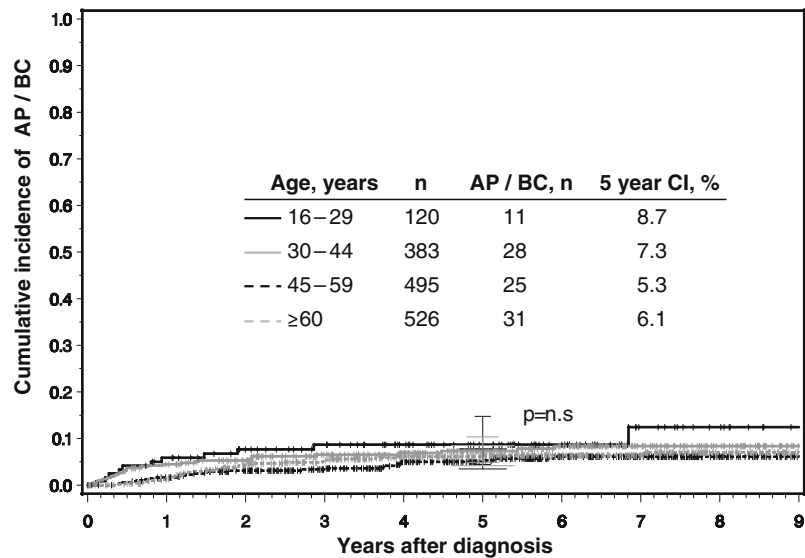


Fig. 2 a–c Cumulative incidences of **a** CCR, **b** MMR, and **c** MR⁴ according to the four age groups determined under consideration of competing risks. *n* Number of patients, CCR complete cytogenetic remission, MMR major molecular remission, MR⁴ molecular remission ≤ 0.01 % on the international scale. *p* refers to level of significance between AYAs and the other three age groups

leucocytosis) [36–38], supporting our findings that aggressive disease features become less apparent as age increases.

Fig. 3 Rates of progression to AP and BC according to age group. No statistical difference was observed between the four age groups. *n* Number of patients, *AP* accelerated phase, *BC* blast crisis, *CI* cumulative incidence. *p* refers to level of significance between AYAs and the other three age groups



Patients at risk	1	2	3	4	5	6	7	8	9
16–29 years	110	99	89	75	60	42	18	11	3
30–44 years	354	326	277	240	193	151	91	55	16
45–59 years	475	442	376	321	269	200	145	80	33
≥60 years	490	430	384	315	252	187	136	78	37

Although a worse outcome was expected in our group of 120 AYAs [9], no differences in cumulative incidence of CCR, MMR, and MR⁴ were observed in comparison to the other three groups. This is different from the results of Pemmaraju et al. [9] who report significantly lower cytogenetic and molecular responses in AYAs. The two studies however did not find difference in OS. No inferior survival after a median observation time of 5.6 years was observed in our study either. We have observed, however, a greater percentage of younger patients with BCR-ABL transcript levels above 10 % at 3 months in comparison to patients 44 years and older. Transcript levels above 10 % are correlated with an

unfavorable prognosis [39, 40] and identify patients that require more frequent monitoring [41].

These findings could suggest different disease biology of CML in younger patients. The identification of distinct age-related genetic and biologic features has been found in various neoplasms: in colon cancer chromosomal instability and a greater tumor invasion is observed in younger patients [42]. In papillary thyroid cancer, different gene expression and advanced disease presentation in AYAs were correlated with better prognosis [43]. In breast cancer, younger women show unique genetic pathways recognized as negative prognostic markers [13]. In acute lymphoblastic leukemia (ALL), distinct

Table 3 Causes of death

Age groups, years	16–29	30–44	45–59	At least 60
All patients, <i>n</i>	120	383	495	526
Total deaths	4	23	38	87
Progression to AP, BC	1	7	13	22
SCT related	2	6	8	1
Infection in CP	0	2	2	8
Secondary malignancy	0	0	2	21
Bleeding	0	2	1	0
Cardiopulmonary	1	0	2	14
Renal insufficiency	0	0	0	3
Thromboembolic/ischemic (not cardiac)	0	1	2	2
Suicide	0	0	0	2
Others	0	1	2	4
Unknown	0	4	6	10

Multiple causes are possible. Autopsy performed only in few cases

n number of patients, *AP* accelerated phase, *BC* blast crisis, *CP* chronic phase, *SCT* stem cell transplantation

biological findings are reported in AYAs, which are generally correlated with poor prognosis: increased incidence of Philadelphia chromosome and intrachromosomal amplification of chromosome 21, increased promoter methylation, and more frequent T cell immunophenotype as well as presence of a mediastinal mass. Due to treatment optimization, ALL outcome is better in AYAs than in adults [10, 11, 44].

In our analysis, we did not detect obvious biological differences. We did not observe differences in transcript type or ACAs nor did others: no differences in transcript type in relation to age were found in 146 pediatric CML patients, including 30 AYAs [36]. Differences in stem cell biology, bone marrow microenvironment, or signaling pathways could exist since many biologic pathways are triggered by BCR-ABL and are successfully inhibited by TKI therapy [45–47] but data to support this in AYAs are still lacking.

Another possible interpretation of the more aggressive features at diagnosis of CML in AYAs could be that younger patients are less frequently transferred to the physician than older ones and only when symptoms are apparent as a consequence of better health and less frequent comorbidities than in older people. As there are no data to support this hypothesis, this remains speculative.

Since the introduction of imatinib, response rates have improved and progression of the disease rarely occurs [48]. Treatment with imatinib explains the high 5-year OS of AYAs in our study (97 %) in comparison to a recently published population-based study in the Netherlands, which started in the pre-imatinib era (1989–2009), in which the 5-year relative survival of AYAs with CML is reported to be 68 % in males and 76 % in females [49].

We conclude that AYAs with CML show features of a more aggressive disease indicating possible biological differences of younger patients that need to be investigated. Also, the higher transcript level at 3 months suggests a worse prognosis of AYAs. Nevertheless, younger patients do well in spite of poorer prognostic indicators.

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