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ORIGINAL ARTICLE

Impact of Additional Chromosomal Aberrations Present at Diagnosis on Outcome of Adolescent and Young Adult Chronic Myeloid Leukemia Patients: A Single Center Experience

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Abstract Studying the influence of additional chromosomal aberrations (ACAs) present at diagnosis on the outcome of adolescent and young adult (AYA) chronic myeloid leukemia (CML) patients as it has not been addressed previously. Eighty-six AYA CML patients have been analyzed for occurrence of ACAs at diagnosis through performing bone marrow karyotyping. All patients received imatinib mesylate upon diagnosis of CML. Overall response, molecular response, survival status, progression and occurrence of events were monitored during the follow up period. There was a statistically significant difference between patients with and without ACAs regarding overall response ($P = 0.049$). There was insignificant difference between the two groups regarding achievement of major molecular response (MMR) ($P = 0.594$), MR^4 ($P = 0.282$) and $MR^{4.5}$ ($P = 0.704$). There was a significant difference between patients with and without ACAs regarding time to MMR ($P = 0.042$) and time to MR^4 ($P = 0.048$) but not regarding time to $MR^{4.5}$ ($P = 0.065$). There was insignificant impact of ACAs at diagnosis on overall survival ($P = 0.152$), progression free survival ($P = 0.112$), failure free survival ($P = 0.114$), event free survival ($P = 0.194$) and alternative treatment free survival ($P = 0.731$). The presence of ACAs at diagnosis does not signal worse prognosis in AYA CML patients but it may delay molecular response to imatinib mesylate.

Keywords Chronic myeloid leukemia · Adolescents and young adults · Additional chromosomal aberrations at diagnosis · Treatment response · Prognosis

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm, characterized by the unrestrained expansion of pluripotent bone marrow (BM) stem cells [1]. The hallmark of the disease is the presence of a reciprocal t(9;22)(q34;q11.2), known as the Philadelphia (Ph) chromosome, resulting in a BCR-ABL fusion gene and production of a BCR-ABL fusion protein with constitutive tyrosine kinase activity [2]. Although most CML patients harbor unique features, they demonstrate heterogeneous characteristics in clinical presentations and outcomes. This heterogeneity might be attributed to the diversity at the molecular and cytogenetic levels [3].

Evidence indicates that acquired genetic instability as a consequence of the Ph translocation and the resulting BCR-ABL fusion causes the continuous acquisition of additional chromosomal aberrations (ACAs) and mutations, and

thereby progression to the accelerated phase (AP) and blast crisis (BC) of CML [4]. ACAs in Ph + ve cells may appear in < 10% of cases at diagnosis [5]. The most common ACAs in CML include trisomy 8, an extra copy of Ph chromosome, i(17)(q10), and trisomy 19. These are so-called "major route" changes, as described in literature [6]. Other less common ACAs are "minor route" changes [6]. The presence of major route ACAs in Ph + clones at diagnosis has been regarded as a "warning" feature, requiring careful monitoring of the patient by the European LeukemiaNet (ELN) [7].

Adolescent and young adult (AYA) cancer patients are different from pediatric and adult cancer populations in the perspective of cancer biology, long-term health and treatment-related complications and psychosocial aspects [8]. CML is a disease of the elderly most commonly presenting in sixth decade [9]. Despite the great advancements that have been realized for patients with CML, the AYA group has seldom been the focus of specific reports and studies, and the outcome appears to be worse than older patients [10–12]. Additionally, few studies addressing the survival outcome of CML patients harboring ACAs at diagnosis in the tyrosine kinase inhibitor (TKI) era have been published previously. For these reasons, we will study the impact of ACAs present at diagnosis on outcome of AYA CML patients.

Materials and Methods

Patients

This study was performed on 86 AYA CML patients (aged 15–39 years) diagnosed during the period 6/2013–9/2017. Patients performed at diagnosis complete blood count (CBC), blood film examination emphasizing on absolute counts of peripheral blood (PB) blasts, BM aspiration and examination for the disease phase and BM karyotyping for detection of ACAs at diagnosis. WHO criteria (2016) were used to define the phase of the disease: chronic phase (CP), AP and BC [13].

Treatment Plan and Evaluation of Response

All patients received upon confirmation of CML diagnosis first line TKI, i.e. imatinib mesylate 400 mg/day. Patients were monitored monthly for achievement of complete hematological response (CHR) by clinical examination, CBC and blood film. A follow up BM aspiration was performed after 3 months in selected patients who presented in AP. The molecular response was assessed at the recommended timelines by ELN (3, 6 and 12 months) and at 6 months intervals thereafter by measuring the percentage of *BCR-ABL* transcript relative to *c-ABL* as an internal reference gene [7]. ELN recommendations published in 2013 were used to define optimal, warning, and failure of response to first line TKI [7]. A follow up BM karyotyping was performed in patients harboring ACAs at diagnosis 1 year after start of TKI therapy and/or progression whichever came first. Patients who could not tolerate first line TKI because of side effects and patients with progressive disease to AP on follow up were shifted to second line TKI (nilotinib or dasatinib) and those who got pregnant during the study period were shifted to interferon alpha. Patients with progressive disease to BC were shifted to systemic chemotherapy in addition to second line TKI.

Definitions and Survival Endpoints

Molecular responses were defined according to ELN recommendations in 2013 [7]. These included major molecular response (MMR): $\leq 0.1\%$ BCR-ABL International Scale (IS); MR^4: $\leq 0.01\%$ BCR-ABL IS; and $MR^{4.5}$: $\leq 0.0032\%$ BCR-ABL IS. Survival end points were defined according to the proposal published by the ELN in 2012 [14]. Overall survival (OS) was defined as time from initiation of first line TKI therapy to death from any cause. Progression free survival (PFS) was defined as time from initiation of first line TKI therapy to progression to AP/BC or death from any cause whichever came first. Failure free survival (FFS) was defined as time from initiation of first line TKI therapy to time of lack of response at recommended timelines by ELN, loss of responses, progression to AP/BC at any time or death whichever came first. Event free survival (EFS) was defined as time from initiation of first line TKI therapy to time of an event. Events for EFS were the same as those for FFS in addition to drug discontinuation because of adverse events. Alternative treatment free survival (ATFS) was defined as time from initiation of first line TKI to switching to second line TKI or other treatment or death from any cause whichever came first. Times to MMR, MR^4 and $MR^{4.5}$ were calculated from the date of start of treatment until the achievement of the first response.

Statistical Methods

Descriptive statistical analysis of variables was done (mean, standard deviation, range, number, and percentage), and they were compared using independent samples *t* test (for continuous variables) and Chi square test (for categorical variables). Patients with no reported event at the time of analysis were censored at the most recent assessment date. Survival probabilities were calculated using the Kaplan–Meier method and were compared using log rank test. Statistical significance was determined at the 0.05

level. All *P* values were two sided. Standard computer program SPSS for Windows, release 17.0 (SPSS Inc, USA) was used for data entry and analysis.

Results

Patient Characteristics

The baseline patient characteristics are summarized in Table 1. Seven patients (8.1%) had ACAs at diagnosis; 2 had major route abnormalities whereas 5 had minor route abnormalities (Table 2). There were no statistically significant differences between patients with and without ACAs at diagnosis regarding baseline characteristics (Table 3).

Table 1 Baseline patient characteristics

Variables	Mean (range)
Age (years)	31.6 (18–39)
TLC (cells × 10^9/L)	166.8 (30–416)
Hemoglobin (gm/dL)	9.8 (6–14)
Platelets (cells × 10^9/L)	397.4 (108–1800)
Eosinophil percent (%)	3.3 (0–17)
Basophil percent (%)	3 (0–20)
PB absolute blast count (blasts × 10^9/L)	5.1 (0–35.6)
LDH (unit)	1693.9 (700–5534)
ESR (mm/h)	46.8 (10–125)
Splenic size (cm below left costal margin)	18.8 (12–35)
BM blasts (%)	3 (1–18)
	N (%)
Sex	
Male	27 (31.4%)
Female	59 (68.6%)
Phase	
Chronic	75 (87.2%)
Accelerated	11 (12.8%)
Blastic	0 (0%)
Sokal score	
Low	0 (0%)
Intermediate	38 (44.2%)
High	48 (55.8%)
Hasford score	
Low	8 (9.3%)
Intermediate	61 (70.9%)
High	17 (19.8%)
EUTOS score	
Low	33 (38.4%)
High	53 (61.6%)

TLC total leukocytic count, *PB* peripheral blood, *LDH* lactate dehydrogenase, *ESR* erythrocyte sedimentation rate, *BM* bone marrow, *EUTOS* European Treatment and Outcome Study, *N* number

Outcome of Studied Patients

Fifty-four patients (62.8%) were strictly adherent to treatment. In general, 43 (50%) patients had failure of response to first line TKI (39 had lack of response at recommended timelines by ELN, 2 had loss of MMR and 2 had progressive disease). Three patients (3.5%) progressed from CP at end of study (one to AP and 2 to BC) and 2 patients (2.3%) died. The cause of death was disease progression to BC in the 2 patients. Eight patients (9.3%) had alternative treatment (3 were shifted to interferon alpha because of gestation, 3 to second generation TKI with or without systemic chemotherapy because of disease progression and 2 to second generation TKI because of intolerable side effects of imatinib mesylate). Fifty-seven (66.3%), 28 (32.6%) and 17 (19.8%) patients achieved MMR, MR^4 and $MR^{4.5}$ respectively during the study period.

Impact of ACAs at Diagnosis on Overall Response

Six (85.7%) of the patients harboring ACAs at diagnosis had response failure to first line TKI whereas one (14.3%) achieved optimal/warning response. There was a statistically significant difference between the two groups ($P = 0.049$). Upon stratification according to state of compliance to treatment, all patients harboring ACAs at diagnosis (number = 4) in the non-compliant group had response failure ($P = 0.492$). On the other hand, 2 patients harboring ACAs at diagnosis in the compliant group had response failure (66.7%) whereas one (33.3%) had optimal/warning response ($P = 0.098$). The follow up BM karyotyping revealed the same clonal abnormality in patients 6, 8, 28, 47 and 71. Patient 35 had optimal/warning response to first line TKI and his follow up BM karyotyping revealed disappearance of the baseline ACA. Patient 50 progressed to BC and gained new ACA on progression, i.e. 47, XY, + 8, der(9) t(9;22)(q34,q11), del (16)(q22), i(17)(q10).

Impact of ACAs at Diagnosis on Molecular Response

Four patients (57.1%) with ACAs achieved MMR whereas 3 (42.9%) did not. There was not significant difference between the two groups ($P = 0.594$). Regarding MR^4, one patient (14.3%) with ACAs achieved it whereas 6 (85.7%) did not without significant difference between the two groups ($P = 0.282$). One patient (14.3%) with ACA achieved $MR^{4.5}$ whereas 6 (85.7%) did not without significant difference between the two groups ($P = 0.704$).

Table 2 Summary of ACAs at diagnosis (Cytogenetic analyses were made and interpreted according to the International System for Human Cytogenetic Nomenclature 2009) [15]

Case number	Karyotyping of cases with ACAs at diagnosis [no. of analyzed metaphases]
6	46, XX, t(3;14)(q25;p13), t(9;22)(q34;q11) [20]
8	46, XX, t(1;21)(q21;q22), t(9;22)(q34;q11) [19]
28	46, XY, t(6;10)(p21;q22), t(9;22)(q34;q11) [25]
35	45, X, − Y, t(2;9;22)(p13;q34;q11) [20]
47	47, XX, t(9;22)(q34;q11), + 19, del (16)(q22) [22]
50	47, XY, + 8, t(9;22)(q34,q11), i(17)(q10) [10]
71	46, XX, t(2;7)(p13;p21), t(9;22)(q34;q11) [16]

ACAs additional chromosomal abberations

Table 3 Comparison of characteristics of patients with and without ACAs at diagnosis

Variables	ACAs at diagnosis		*P*
	+ ve (N = 7)	− ve (N = 79)	
Age (years)	30.9 ± 5.6	31.6 ± 5.9	0.738
TLC (cells × 10^9/L)	205.4 ± 119.4	163.4 ± 90.5	0.255
Hemoglobin (gm/dL)	10.8 ± 1.7	9.7 ± 1.7	0.089
Platelets (cells × 10^9/L)	481 ± 197.3	390 ± 269.1	0.385
Eosinophil percent (%)	2.7 ± 2.1	3.4 ± 3	0.574
Basophil percent (%)	4 ± 1.3	2.9 ± 3	0.349
PB absolute blast count (blasts × 109/L)	6.2 ± 5.4	5 ± 5.5	0.589
LDH (unit)	1914.4 ± 860	1674.4 ± 743.8	0.421
ESR (mm/h)	57.1 ± 20.6	45.9 ± 23.5	0.224
Splenic size (cm below left costal margin)	20.6 ± 6.9	18.6 ± 5.1	0.352
BM blasts (%)	3.4 ± 3.2	3 ± 2.6	0.678
Sex			
Male	3 (42.9%)	24 (30.4%)	0.495
Female	4 (57.1%)	55 (69.6%)	
Phase			
Chronic	6 (85.7%)	69 (87.3%)	0.902
Accelerated	1 (14.3%)	10 (12.7%)	
Sokal score			
Intermediate	1 (14.3%)	30 (38%)	0.385
High	6 (85.7%)	49 (62%)	
Hasford score			
Low	0 (0%)	8 (10.1%)	0.702
Intermediate	5 (71.4%)	54 (68.4%)	
High	2 (28.6%)	17 (21.5%)	
EUTOS score			
Low	2 (28.6%)	33 (41.8%)	0.578
High	5 (71.4%)	46 (58.2%)	

TLC total leukocytic count, *PB* peripheral blood, *LDH* lactate dehydrogenase, *ESR* erythrocyte sedimentation rate, *BM* bone marrow, *EUTOS* European Treatment and Outcome Study, *ACAs* additional chromosomal abberations, *N* number

After a median duration of follow up of 24 months (range 9–48 months), there was a significant difference between patients with and without ACAs regarding time to MMR (MMR = 57.1% vs. 67.1%, median = 36 months vs. 21 months respectively, $P = 0.042$) (Fig. 1a). There was a significant difference between patients with and without ACAs regarding time to MR^4 (MR^4 = 14.3% vs. 34.2%, median = 30 months vs. 24 months respectively, $P = 0.048$; Fig. 1b). There was insignificant difference between patients with and without ACAs regarding time to $MR^{4.5}$ ($MR^{4.5}$ = 14.3% vs. 20.3%, median = 30 months vs. 24 months respectively, $P = 0.065$; Fig. 1c).

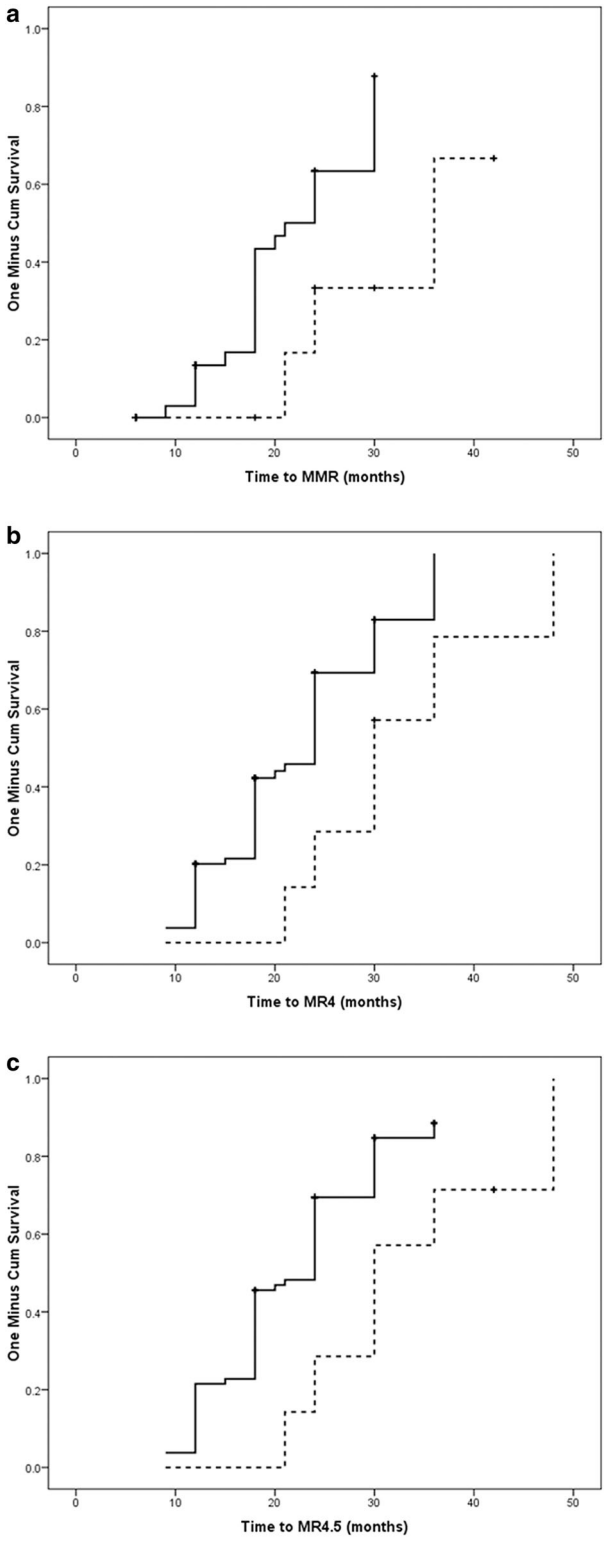

Fig. 1 Kaplan Meier curves of patients with (dashed line) and without (continuous line) ACAs at diagnosis regarding: **a** Time to MMR (MMR = 57.1% vs. 67.1%, median = 36 months vs. 21 months respectively, $P = 0.042$); **b** Time to MR^4 (MR^4 = 14.3% vs. 34.2%, median = 30 months vs. 24 months respectively, $P = 0.048$); **c** Time to $MR^{4.5}$ ($MR^{4.5}$ = 14.3% vs. 20.3%, median = 30 months vs. 24 months respectively, $P = 0.065$)

Impact of ACAs at Diagnosis on OS, PFS, FFS, EFS and ATFS

After a median duration of follow up of 24 months (range 9–48 months), OS did not differ in patients with ACAs at diagnosis than those without them (OS = 85.7% vs. 98.7% respectively; median survival = not reached (NR) in both groups; $P = 0.152$). There was a non-significant difference between patients with and without ACAs at diagnosis regarding PFS (PFS = 85.7% vs. 97.5% respectively; median survival = NR in both groups; $P = 0.112$) (Fig. 2a). There was a non-significant difference between patients with and without ACAs at diagnosis regarding FFS (FFS = 14.3% vs. 53.2%; median survival = 12 months vs. 33 months respectively; $P = 0.114$; Fig. 2b). There was insignificant difference between patients with and without ACAs at diagnosis regarding EFS (EFS = 14.3% vs. 48.1%; median survival = 12 months vs. 18 months respectively; $P = 0.194$; Fig. 2c). ATFS did not differ in in patients with ACAs at diagnosis than those without them (ATFS = 85.7% vs. 91.1% respectively; median survival = NR in both groups; $P = 0.731$) (Fig. 2d).

Discussion

Recent interest in ACAs in CML patients is going on. ACAs have been more frequently observed among young CML patients in Egypt [16]. This can be explained by the relatively younger age at presentation of CML patients in Egypt (median age = 43 years) [16]. It has been observed that the average age at presentation segregates with geographical location. For example, in Africa and Latin America, CML patients are diagnosed at least 15 years younger compared to Australia, Europe and the USA [17]. In our study group (AYA), 7 patients (8.1%) had ACAs at diagnosis which is similar to the frequency reported in CML patients in the literature (less than 10%) [5]. ACAs at diagnosis had no impact of on demographic, clinical and laboratory characteristics of CML patients. This is consistent with a study performed in University of Texas MD Anderson Cancer Center [18]. Also, ACAs at diagnosis did not correlate with risk scores of patients which is in agreement with a study performed by the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Working Party on CML [19]. It should be noted that Sokal and Hasford risk scores were developed in the chemotherapy and interferon era and the predictive value of EUTOS score has not been universally confirmed which necessitates developing a new risk scoring system for CML in the TKI era [20, 21].

ACAs at diagnosis were associated with higher rate of response failure to first-line TKI in our study. However,

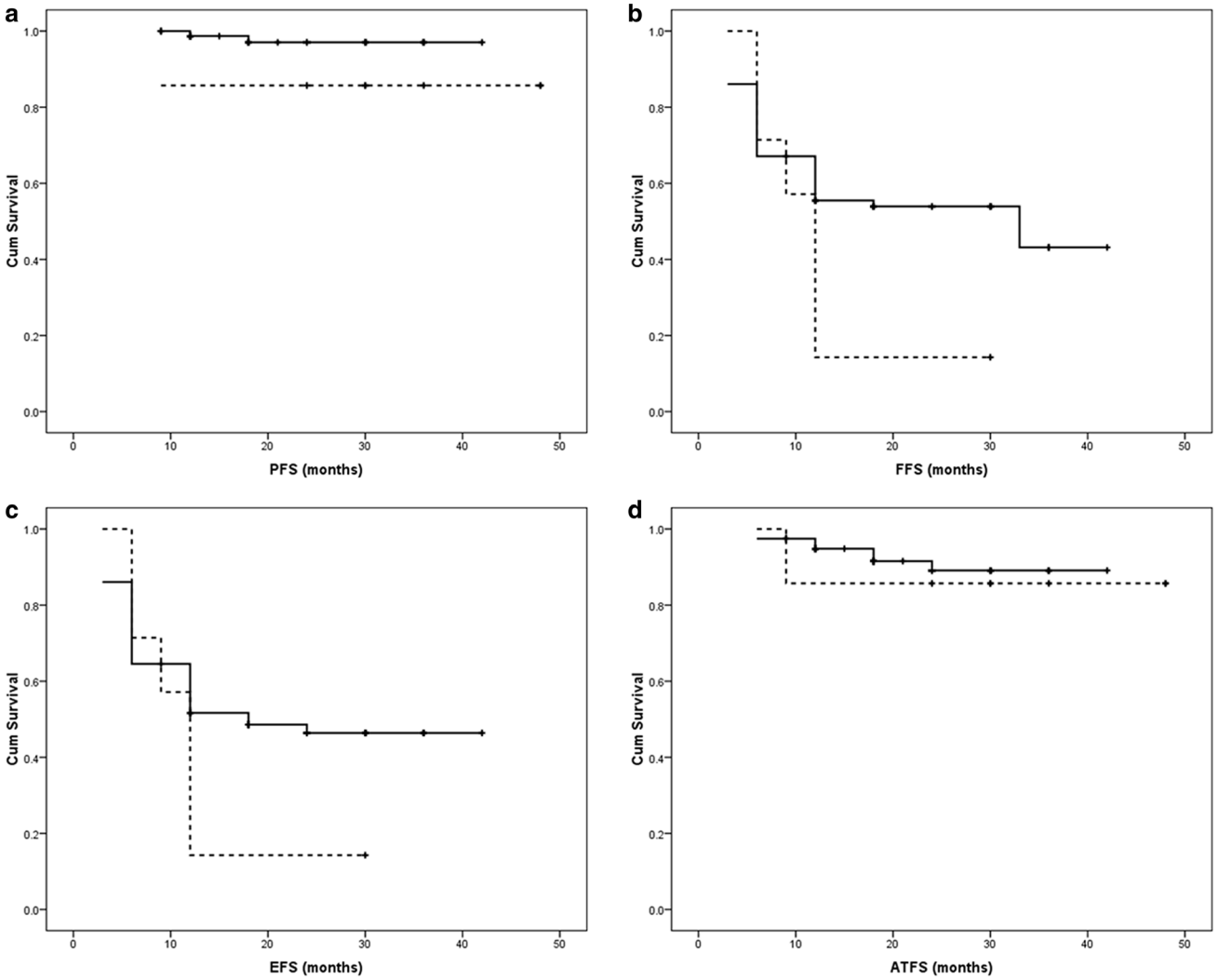

Fig. 2 Kaplan Meier curves of patients with (dashed line) and without (continuous line) ACAs at diagnosis regarding: **a** PFS (PFS = 85.7% vs. 97.5% respectively; median survival = NR in both groups; $P = 0.112$); **b** FFS (FFS = 14.3% vs. 53.2%; median survival = 12 months vs. 33 months respectively; $P = 0.114$); **c** EFS (EFS = 14.3% vs. 48.1%; median survival = 12 months vs. 18 months respectively; $P = 0.194$); **d** ATFS (ATFS = 85.7% vs. 91.1% respectively; median survival = NR in both groups; $P = 0.731$)

this influence was lost when patients were stratified according to their state of compliance to treatment. The impact of ACAs on overall response was not analyzed in other studies. ACAs did not have influence on achievement of MMR, MR^4 or $MR^{4.5}$. We agree with two studies in this aspect. [18, 22] However, higher rates of molecular response rates were reported in the University of Texas MD Anderson Cancer Center study which can be attributed to the high rate of non-compliance to treatment in our study and to the use of high dose imatinib (800 mg), second and third line TKIs in the other study [18]. In contrast, the overall MMR rates were significantly lower in patients with ACAs in the GIMEMA Working Party on CML study ($P = 0.03$) [19]. This difference can be attributed to the exclusion of a large number of patients with < 20 evaluable metaphases from analysis in the other study [19]. Times to MMR and MR^4 were longer in patients with ACAs at diagnosis than those without them in our study which is in agreement with the GIMEMA Working Party on CML study regarding time to MMR [19]. In a study performed by the Schweizerische Arbeitsgemeinschaft fur Klinische Krebsforschung (SAKK)/German CML Study Group, there was no difference regarding time to MMR between patients with standard t(9;22) and minor-route ACAs whereas for the major-route ACAs, the time to MMR was deferred [23].

We did not observe a significant impact of ACAs at diagnosis on OS, PFS, FFS and EFS. We agree with the studies of University of Texas MD Anderson Cancer Center and GIMEMA Working Party on CML [18, 19]. In

the study of SAKK/German CML Study Group, there was inferior OS and PFS in patients with major route ACAs in comparison to patients without ACAs and patients with minor route ACAs [23]. We did not compare time to molecular response and survival between patients with major and minor route ACAs because of the small number of patients in both subgroups. A Taiwanese study revealed a significant impact of ACAs at diagnosis on survival in univariate analysis but not in multivariate analysis [3]. This difference can be attributed to the use of cytotoxic agents other than TKIs in the other study. It is well known that the survival of CML patients has improved since the introduction of imatinib therapy as it minimized the impact of known prognostic factors and Sokal risk in CP-CML [24]. Another Chinese study revealed an inferior impact of ACAs at diagnosis on OS, EFS and PFS [22]. This difference can be explained by the larger number and the older age (up to 79 years) of recruited patients in that study [22]. It has been reported that older age is significantly associated with increased probabilities of dying of CML [25]. Up to our knowledge, no study has addressed the impact of ACAs at diagnosis on ATFS. We analyzed it and found that there was insignificant influence of ACAs at diagnosis on ATFS. This denotes that CML patients harboring ACAs at diagnosis should follow the same treatment plan as those not harboring them.

Despite the association between ACAs and disease progression in CML, the role of each individual ACA is largely unknown, and a risk-based classification system that is used in myelodysplastic syndrome and acute myeloid leukemia is currently lacking in CML [26]. Unfortunately, due to the small numbers of patients in our study, subset analysis for these abnormalities in order to determine the impact they may have when present at the time of diagnosis was not performed. A recent study tried to analyze the prognostic impact of ACAs through the stratification of the 6 most common ACAs into 2 groups: group 1 (trisomy 8, − Y, and an extra copy of Philadelphia chromosome); and group 2 (i(17)(q10), − 7/del7q, and 3q26.2 rearrangements) [26]. Patients in group 1 showed much better treatment response and survival than patients in group 2. When compared with cases with no ACAs, ACAs in group 2 conferred a worse survival irrelevant to the emergence phase and time. In contrast, ACAs in group 1 had no adverse impact on survival when they emerged from chronic phase or at the time of CML diagnosis. The concurrent presence of 2 or more ACAs conferred an inferior survival and can be categorized into the poor prognostic group. In our study, only one patient (patient 50) had baseline combination of a group 1 (+ 8) and group 2 (i(17)(q10)) abnormalities which conferred a high risk for progression to BC. Moreover, this patient gained new ACA on progression to BC, i.e. 47, XY, + 8, der(9) t(9;22)(q34,q11), del (16)(q22), i(17)(q10). It is well known that chromosomal abnormalities developing during the course of CML in addition to the Ph chromosome (clonal evolution) indicate a poor prognosis [27, 28]. Notably, none of the patients who had baseline ACAs developed TKI-induced cytopenia during their follow up.

This study holds significance because it is the first study addressing ACAs at diagnosis in a peculiar CML population, i.e. AYA. One limitation of our study is the small number of patients harboring ACAs at diagnosis owing to its single center nature and to its restriction on AYA CML patients. Another limitation is the lack of adherence to treatment in a subset of patients. Moreover, the follow up period in our study was relatively shorter than that in other studies studying ACAs at diagnosis [3, 18, 19, 22, 23]. However, this can be referred to the multi-trial nature of the University of Texas MD Anderson Cancer Center study [18], the multicenter nature of the GIMEMA Working Party on CML and the SAKK/German CML Study Group studies [19, 23], the non-homogenous patient sample in the Taiwanese study [3], and the additional aim of following up evolving ACAs during TKI treatment in the Chinese study [22]. In conclusion, the impact of ACAs on outcome of AYA CML patients is more or less similar to that in the general CML population. Also, the presence of ACAs at diagnosis influences the response to imatinib therapy through deferring MMR and MR^4. Moreover, the presence of ACAs at diagnosis per se does not signal worse prognosis in the TKI era. We recommend further studies addressing the impact of individual ACAs on CML outcome and prognosis. Additionally, we recommend more research to determine other culprits responsible for the diversity in some clinical features and outcome of CML patients.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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