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Research Article

ACA Rearrangement is Associated with the Prognosis of CML in the Era of TKI

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Abstract

Approximately 9-13% of CML patients Acquire Additional Chromosomal Aberrations (ACAs) in chronic phase and blast crisis. Major route ACAs emergence indicates an increased risk of progression and shorter survival. We analyzed the chromosome data of 280 CML patients from Department of Hematology, Union Hospital, Tongji Medical College, affiliated to Huazhong University of Science and Technology, and ACA were detected in 19 patients of them. Bone Marrow (BM) morphology, molecular biology and cytogenetics of 19 CML patients with ACA were monitored. Our data displayed that no significant difference in Complete Cytogenetic Remission (CCR) or Major Molecular Remission (MMR) was existed between CML patients with minor route ACA or major route ACA (P>0.05), which may be due to the small sample size in our study. However, we found that patients with well-responsive chromosomes to Imatinib had a higher probability of acquiring CCyR or MMR. Our data implied that chromosomes could be used for prognosis stratification of CML, which may be critical for formulations of treatment strategies during CML therapy.

Keywords: Chronic myelogenous leukemia; Major route; Minor route

Abbreviations

IM: Imatinib Mesylate; ACAs: Additional Chromosomal Abnormalities

Introduction

Chronic Myelogenous Leukemia (CML) is characterized by the Philadelphia chromosome (Ph), which originated by reciprocal translocation t(9;22) (q34;q11.2) [1]. Current evidence indicates that acquired genetic instability was a consequence of the Philadelphia (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/or Blast Crisis (BC) of CML [2]. Cytogenetic clonal evolution occurred in approximately 50-80% of patients with BC of CML and was associated with poor prognosis [1,2]. However, CAs (chromosomal abnormalities) other than the standard Ph are described in less than 10% of cases with Chronic Phase (CP) CML at diagnosis [3,4]. The study of Lee et al reflected the relevance of cytogenetic evolution to CML course [3]. In the era of IM (Imatinib Mesylate) therapy, the prognostic implications of ACAs in CP CML still remain to be found. Several studies have indicated that ACAs occurring in CP patients treated with IM were associated with poor prognosis, especially with poor OS and Poor PFS [3-6]. However, other studies have indicated that in CP, ACAs could be transient [4], presence of ACAs are not associated with the possibility of achieving MCyR (Major Cytogenetic Remission) and CCyR (Complete Cytogenetic Remission), even with the long term of cytogenetic and molecular remission or OS [7-9]. Johansson et al has suggested that aberrations occurring in >5% of CML with secondary changes, which include +8(34% of cases with additional changes), +Ph(30%), i(17q)(20%), +19(13%), -Y(8% of males), +21(7%), +17(5%) and monosomy 7(5%), should be denoted major route ACAs [4], while the other ACAs belong to minor route ACAs such as -17, +13, +4, t(5;13), t(3;21) and so on. Alice Fabarius et al., has indicated that in patients with major-route ACAs, times to achieve CCyR and MMR (Major Molecular Remission) were longer and PFS and OS were shorter (P< .001) than in patients with standard Ph [2]. In addition, major route ACAs at diagnosis have a negative impact on survival and signify progression to the AP or BC, no difference in the cumulative incidence of CCyR or MMR was seen among patients with standard Ph, variant translocation, -Y (not shown), and minor route ACAs [2]. Additionally, according to the treatment recommendations of European Leukemia Net (ELN) for CML, the expert panel has brought the emergence of major route, not minor route, cytogenetic changes into the criterion for AP [10]. Although major route ACAs in CP has been considered as not only negative factors for achieving CCyR or MMR but also association with poor prognosis, significance of minor route ACAs in CP is not clear yet. To testify the importance of minor route ACAs, we investigated the effects of additional chromosomal abnormalities besides the standard Ph in CP on the clinical outcome of CML. Here, we detected the occurrence of ACAs, especially minor route ACAs in 19 patients with CP-CML before or during IM treatment, and then analyzed their characteristics and effects on treatment responses to TKI and their prognosis.

Materials and Methods

Patients and response analyses

From July 2003 to April 2013, 280 newly-diagnosed CML patients were analyzed, 147 of them were only treated with IM, while 133 of them were administrated with interferon before the initiation of IM treatment. ACAs were detected in 19 of 280 patients with CML, their Bone Marrow (BM) morphology, molecular biology and cytogenetics were monitored every 3 months during the therapy.

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Table 1: Patient demographic and clinical characteristics.

Parameters	Totals (n=19)	major route ACAs (n=7)	minor route ACAs (n=12)
Age, y, median (range)	44 (19-56)	49 (19-55)	35 (20-56)
Sex, n (%)			
Male	13 (68.4%)	5 (38.5%)	8 (61.5%)
Female	6 (31.6%)	2 (33.3%)	4 (66.7%)
Previous-IFN treatment, n	9	2	7
Presence of ACAs[a]			
Before IM treatment	14	5	9
During IM treatment	7	3	4

a: There are 2 patients, one with major route ACAs and the other with minor route ACAs before IM treatment, then new ACAs were emerged during IM treatment, respectively.

Table 2: Clinical Response of patients with major route or minor route.

				At 12 month IM therapy		At 24 month IM therapy		
Patient	Age	Sex	ACAs before or during IM treatment	Cytogenetic responses	Molecular responses	Cytogenetic responses	Molecular responses	cause of event
			The patients with major route					
1	53	M	45, X, -Y, t(9;22)(q34;q11)	NA	NO MMR	NA	NA	lost after 18 mons
2	19	M	45, X, -Y, del(7)(q31), t(9;22)(q34;q11)[7] /45, X, -Y[3]	NA	NA	NA	NA	lost after 9 mons
3	49	M	Before IM treatment: 47, XY, +C, inc, t(9;22)(q34;q11) IM treatment for 24 months:47, XY, +8, +C (Ph-)	NA	NO MMR	complete	CMR	loss of MMR
4	50	M	IM treatment for 24 months:48, XY, +8, +9[90%]/46, XY[10%]	NA	NO MMR	complete	NO MMR	none
5	40	M	47, XY, t(9;22)(q34;q11), +der(22)t(9;22)(q34, q11)	minimal	NO MMR	NA	NO MMR	progression at 42 mons/ death/E255V at 12 mons, M244V at 42 mons
6	55	F	IM treatment for 18 months:47, xx, t(7;7) (p10;q10), t(9;22)(q34;q11), i(7)(q10), +der(22)	NA	NO MMR	NA	NO MMR	progression at 24 mons
7	47	F	47, XX, double Ph	NA	NO MMR	NA	NO MMR	death
			The patients with minor route					
8	32	M	47, XY, del(22)(q11), +del(22)(q11)	minimal	NO MMR	NA	NO MMR	loss of MMR
9	31	F	46, XY, del(22)(q11), +(22)(q13)	NA	NA	NA	NA	intolerance, rash
10	56	M	IM treatment for 12 months:46, XY, del(22)(q11)[40%] /46XY[60%]	complete	CMR	NA	NO MMR	loss of MMR
11	49	M	43-45, XY, polyploid[20%]	complete	CMR	complete	CMR	none
12	34	M	polyploid[30%]	complete	CMR	complete	CMR	none
13	36	F	IM treatment for 9 months: hypodiploid, hyperdiploid	NA	NO MMR	complete	CMR	none
14	20	M	Before IM treatment: 46, XY, t(9;22)(q34;q11)[9]/46, idem, t(3;21)(p23;q22)[11] IM treatment for 2 months: 46, XY, inv(3)(p26;q25), t(9;22)(q34;q11), +(21)(q22)[20]	NA	NA	NA	NA	progression at 2 mons , death
15	44	M	IM treatment for 9 months: 47-48, XY, +c[6], +G[4], Ph-	complete	CMR	NA	NA	lost after 12 mons
16	55	M	47, XY, t(9;22)(q34;q11), +22	complete	CMR	complete	CMR	none
17	23	F	46, XX, +4, t(9;22)(q34;q11)[40%] /46, XX, t(9;22)(q34;q11)[60%]	NA	NA	NA	NA	progression at 5 mons, death
18	45	F	46, XX, der(1)t(1;22)(p21, q11), der(9), t(1;9)(p21;34), der(22), del(22)(q11)	NA	NO MMR	complete	NO MMR	BCR-ABL1>1% at 36 mons
19	25	M	variant Ph	complete	CMR	NA	NA	lost after 12 mons

Abbreviations: NA, not available

Definitions

Clinical phase and clinical outcome were defined according to recent criteria [11]. Cytogenetic alterations and clonality were defined according to the International System for Human Cytogenetic Nomenclature [12]. ACAs were displayed as additional or variant cytogenetic alterations in Ph positive cells. The patients with major-route were referred to those with the karyotypes of major route ACAs (with or without minor route ACAs). The patients with minor route ACAs were referred to those only with the karyotypes of minor route (without major route ACAs).

Table 3: Response of patients with ACAs in Ph- cells during IM treatment.

Patient	Age	Sex	ACAs in Ph- cells	response
2	19	M	45, X, -Y, del(7)(q31), t(9;22)(q34;q11) [7]/45, X, -Y[3]	Never o MMR at 9 months
3	49	M	Before IM 47, XY, +C, inc, t(9;22)(q34;q11) /During IM 24 months 47, XY, +8, +C, Ph-	CMR at 84 months
4	50	M	During IM 24 months 48, XY, +8, +9[90%]/46, XY[10%]	CMR at a point after 24 months
15	44	M	During IM 9 months 47-48, XY, +c[6], +G[4], Ph-	CMR at a point after 24 months

Comparison of responses in CML-CP patients with and without ACA

Table 4: The characteristics and clinical response in Alleviated patients with ACAs in Ph+ cells or ph-cells.

Patients	*Age*	SEX	ACAs before or during IM treatment
3	49	M	Before IM 47, XY, +C, inc, t(9;22)(q34;q11) /During IM 24 months 47, XY, +8, +C, Ph-
4	50	M	IM treatment for 24 months:48, XY, +8, +9[90%]/46, XY[10%]
10	56	M	IM treatment for 12 months:46, XY, del(22)(q11)[40%] /46XY[60%]
11	49	M	43-45, XY, polyploid[20%]
12	34	M	polyploid[3
13	*36*	F	IM treatment for 9 months: hypodiploid, hyperdiploid
15	44	M	IM treatment for 9 months: 47-48, XY, +c[6], +G[4], Ph-
16	55	M	47, XY, t(9;22)(q34;q11), +22
18	45	F	46, XX, der(1)t(1;22)(p21, q11), der(9), t(1;9)(p21;34), der(22), del(22)(q11)
19	25	M	variant Ph

Results

The characteristics of ACAs in 280 patients.

ACAs were detected in 19 CML patients with a median age of 44 years (range 19-56y), 7 of 19 patients had major route ACAs [13-20], other 12 patients had minor route ACAs, the rare atypical transcript type of bcr-abl1 gene was detected in one patient with minor route ACAs. No significant differences were found between two groups with major route or minor route ACAs in terms of Age, Sex, and the presence of ACAs (Table 1). The commonest ACAs were shown on chromosome 22(n=6), 7(n=2), 8(n=2), C(n=2), Y(n=2). The partial polyploidy were detected in two patients and complex karyotype in five patients. Complex karyotype was also detected in one patient with variant Ph [21-26].

There are 2 patients, one with major route ACAs and the other with minor route ACAs before IM treatment, then new ACAs were emerged during IM treatment, respectively.

The clinical response for patients with major route or minor route ACAs

Response in patients with major route or minor route ACAs was shown in (Table 2). Of 7 patients with major route ACAs, two patients achieved CCyR and CMR during IM treatment, and 5 patients never achieved MMR during the follow-up. Patient 3, with the karyotypes of +C, inc and Ph achieved CCyR and CMR with gain of the trisomy 8 when he has been treated with IM for 24 months. But unfortunately, this patient got molecular biology relapse after IM treatment for 72 months, and then he achieved CMR again after treatment with 600mg IM per day for 12 months. Patients 4, with the karyotypes of XY, +8, +9[90%]/46, XY[10%] achieved CCyR after he has been treated with IM for 24 months and didn't achieve CMR. CMR was identified after 24 months with 600mg IM daily. Patient 5, with the karyotypes of Ph, +der(22)t(9;22)(q34, q11) experienced the mutation of E255V after treatment with IM for 12 months. This patient was progressed to AP with the detection of M244V mutation when he was treated with IM for 42 months and then died. Patient 6, with the karyotypes of t(7;7)(p10;q10), Ph+, i(7)(q10), +der(22), was progressed to AP after IM treatment for 24 months, then IM was discontinued and nilotinib was administrated. Patient 7, with double Ph, never achieved MMR during 24 months of IM treatment and then died. Patient 1, with 45, X, -Y, Ph+, and Patient 2, with 45, X, -Y, del(7)(q31), Ph+[7]/45, X, -Y[3] were lost to follow-up after IM treatment for 18 months and 9 months, respectively, they never achieved MMR during the follow-up.

Of 12 patients with minor route ACAs, 8 patients achieved CCyR and 7 of 8 patients achieved CMR during IM treatment; 4 patients never achieved MMR during the follow-up. Patient 11 with 20% of polyploidy (43-45, XY) and Patient 12 with 30% of polyploidy, both achieved CCyR and CMR after IM treatment for 12 months and maintained this status up to 24 months. Patient 13, with the karyotypes of hypodiploid and hyperdiploid, achieved CCyR and CMR at 24 months. Patient 16, with the karyotypes of Ph and triple 22, achieved CCyR and CMR at 12 months and maintained to 24 months. Patient 15, with 47-48, XY, +c[6], +G[4] and Ph, achieved CCyR and CMR at 12 months. Patient 14, with the initial karyotypes of 46, XY, Ph+[9]/46, idem, t(3;21)(p23;q22)[11], gained a new karyotype of inv(3)(p26, q25) and progressed to AP after 2 months of IM treatment, and then died soon. Patient 17, with the karyotype of 46, XX, +4, Ph+[40%]/46, XX, Ph+[60%], progressed to BC after IM treatment (400mg daily) for 5 months and then 800 mg of IM daily was administrated, six months later, this patient died. Patient 8, with del(22)(q11)+del(22)(q11), achieved CMR at 40 months and lost CMR at 46 months. Therefore, IM was transferred to nilotinib, but CMR was never obtained during 8 months of follow-up. Patient

Table 5: Therapeutic response and prognosis in Ph postive CML with ACAs.

ACAs	response	Prognosis
t(7;11;9;22;9)(q22;q13;q34;q11.2;q34)	Good, imatinib	Good
inv(3)(q21q26.2)/t(3;3)(q21;q26.2)	Poor to TKIs	Poor
t(3;21)(q26.2;q22)	Poor to TKIs	Poor
Trisomy 8	Good to TKI	good
−Y, extra copy of Ph	**Good to TKIs**	**good**

Table 6: Therapeutic response and prognosis in Ph negative CML with ACAs.

ACAs	Response	Prognosis
Trisomy 8	Poor to interferon-α, intermediate to imatinib	Good
Monosomy 7	**Good to nilotinib**	**N/A**

9, with the karyotype of del(22)(q11), +(22)(q13), transferred IM to nilotinib because of intolerance. Patient 10, with 46, XY, del(22)(q11)[40%]/46, XY, Ph[60%] achieved CCyR and CMR at 12 months and lost CMR at 24 months, he died from renal failure without obtaining MMR until the 70th month. Patient 18, with der(1)t(1;22)(p21, q11), der(9)t(1;9)(p21;q34), der(22)del(22)(q11), only achieved CCyR at 24 months without gain of MMR and maintained this response up to 36 months. Patient 19, with variant Ph, achieved CCyR and CMR at 9 months and was lost at 12 months.

Overall, for a median follow-up of 24 months (range, 2-84 months), 2-year EFS of the patients with major route or minor route ACAs were 28.6% and 33.3%, respectively, their differences were not significant (P>0.05). The patients with the karyotypes of +der(22) t(9;22)(q34;q11), t(7;7)(p10;q10), +Ph, i(7)(q10), or +der(22) were progressed to AP or died. 2 patients with the karyotype of -Y didn't achieve CCyR and CMR at 6 months and 12 months, respectively, one of them with additional ACA, del(7)(q31). Although 2 of 4 patients involved del(22)(q11)achieved CMR, they failed to maintain CMR during the subsequent follow-up, their molecular relapses happened at 36 months and 70 months, respectively. Two patients with t(3;21)(p23;q22), inv(3)(p26;q25) and +4 progressed to AP at 2 months and BC at 5 months, respectively. However, 2 patients involved partial polyploid achieved CCyR and CMR after 12 months of Imatinib treatment and maintained the status up to 24 months. The characteristics and clinical response in patients with ACAs in Ph- cells.

In 5 patients, including three of patients with major route and one patient with minor route, treatment related ACAs were emerged after a median of 24 months (range, 12-84 months) from the initiation of IM therapy. 5 kinds of ACAs in Ph- cells from 5 male patients were identified, involving+8(n=2), +C(n=2), –Y(n=1), +9(n=1), +G(n=1).

Clinical responses for patients with ACAs in Ph negative cells were shown in (Table 3). Patient 2 with the previous karyotype of 45, X, -Y, del(7)(q31), Ph+[7]/45, X, -Y[3], never obtained MMR until the end of our follow-up. Patient 3, with the karyotype of +8, +C and Ph, achieved CCyR and CMR after IM treatment for 24 months but molecular relapse happened at 48 months, he reobtained CCyR and CMR through increasing IM dose from 400mg to 600mg daily. After IM treatment for 24 months, the karyotype of patient 4 was emerged as 48, XY, +8, +9[90%]/46, XY[10%] With the disappearance of Ph chromosome, CMR was obtained after IM treatment for 48 months. Ph chromosome in BM from patient 15 was eliminated and 47-48, XY, +c[6], +G[4] was emerged after 9 months of IM treatment, and then CCyR and CMR were achieved after 12 months of IM treatment.

More recently, a prognostically informative risk stratification system was proposed by Wang and colleagues to account for these heterogeneities. With the occurrence of ACA in CML, the 6 commonest ACAs were divided into 2 groups: group 1 with a relatively good prognosis including trisomy 8, -Y, and an extra copy of Philadelphia chromosome; and group 2 with a relatively poor prognosis including i(17)(q10), -7/del7q, and 3q26.2 rearrangements. We synthesized the reported chromosomal abnormalities and their various responses to TKI (5, 6). In our study, patients with chromosomes that responded better to TKI showed higher CCyR or MMR (4).

Discussion

While inferior survival was always associated with the presence of ACA at the time of diagnosis in CML patients treated with interferon alpha and other therapies, Disputations were always existed within the prognostic relevance of ACAs in CML patients with ACA treated with imatinib.

Metaphase karyotyping may reveal additional clonal chromosomal abnormalities in Ph+ cells (ACA/Ph+), which was referred to as clonal cytogenetic evolution. The commonest ACAs are +8, +Ph, +19, i(17q). [4, 6, 22, 23] The impact of ACAs on therapeutic effect and prognosis of CML is not clear now, there are some controversial views on this issue. ACAs emergences during treatment should be considered as progression to Accelerated Phase (AP) or Blast Crisis (BC) and imatinib treatment failure [10, 18-20]. Bozkurt et al., has reported that all patients (0/5) carrying ACAs in their Ph-negative metaphases didn't progress to AP or BP and obtained major or complete CyR, but patients (7/12, 58 %) with ACAs in their Ph-positive metaphases developed AP/BC at diagnosis or follow-up (p=0.03) and most didn't have a CyR [18]. However, another study including 72 CML patients (21 in AP, 50 in CP with previous interferon treatment, and one was relapsed after stem cell transplant), including 49 patients only with Ph chromosome and 23 patients with one or more ACAs at the initial of IM treatment, showed that there was no difference in OS between patients with or without ACAs (log-rank test, P=0.391) [9]. And Cortes et al., thought that cytogenetic clonal evolution was not an independent significant factor for achieving a major or complete cytogenetic response, but it remained an independent prognostic factor for poorer survival in the setting of different clinical phases of CML [8]. ACAs were classified as major route ACAs and minor route ACAs. In Wang's study(608 patients had ACAs), the most common ACAs are +8, +Ph, -Y, 3q26.2, i(17)(q10) and -7/del(7q), which were stratified as 2 groups: group 1 with better prognosis including +8, -Y, +Ph and group 2 with a poorer prognosis including i(17), -7/del(7q), and 3q26.2 rearrangements [6]. They also found that patients with single ACA had the similar survival to those with better prognosis, whereas patients with 2 or more ACAs (complex karyotypes) had the similar survival to those with poorer prognosis. ACAs were emerged prior to therapy, or during treatment, but most of them were detected in newly-diagnosed patients [3, 8, 19, 22, 24]. Mohamed's et al., study showed that patients (6 of CP, 6 of AP, 3 of BP) obtained CyR with detected ACAs prior to Imatinib treatment, 11 of 15 patients had only one kind of ACAs, other 4 patients had 2 kinds of abnormalities

[22]. During the nilotinib therapy, 3 patients were reported to be with newly-developed ACAs, one was in BC and another was progressed from CP to BC. In addition, the presence of ACAs prior to nilotinib therapy can be used to predict worse prognosis [23]. For a median follow-up of 78.6 months (range, 1.4-126.1 months), OS, EFS, and FFS were 100%, 66.3%, and 52.1%, respectively, for patients with ACAs; 96.0%, 91.3%, and 83.7%, respectively, for patients with a standard Ph [3]. Patients with the presence of ACA prior to treatment had lower EFS (P=0.015) and FFS (P=0.016) than those with standard Ph. Marin et al analyzed 224 CP CML patients who received IM as first-line therapy and showed that the presence of ACA in Ph-positive (Ph+) cells, either at diagnosis or emerging during therapy, was associated with poor outcomes [25]. So, the current mainstream view on the ACAs is that ACAs have a poor effect on CML treatment.

Recently, it has been reported that patients with criteria for AP at the time of diagnosis had a favorable outcome mimicking that of patients with CP criteria when treated with TKI, particularly if using second generation agents. This is much in contrast with the emergence of AP during the course of therapy, whether by hematologic or cytogenetic parameters, which is indeed associated with an inferior response to therapy and long-term survival endpoint.

Cortes JE Study suggest that higher doses of imatinib induce earlier and deeper cytogenetic and molecular responses compared with imatinib 400 mg daily. CML-ACA patients treated with 800mg IM per day .In Ahmad Alhuraiji study higher dose of IM had swift responses to achieve a major cytogenetic response interestingly, Here, it is noteworthy patient 3 of our series with CML-major ACA, with the karyotypes of +C, inc and Ph achieved CCyR and CMR with the gain of the trisomy 8 when he has been treated with IM for 24 months. But unfortunately, this patient got molecular biology relapse after IM treatment for 72 months, and then he achieved CMR again after treatment with 600mg IM per day for 12 months. It particularly indicates once chromosomal abnormalities are diagnosed, high-dose IM therapy should be considered.

With the development of Tyrosine Kinase Inhibitor (TKI) and its approval in chronic myelogenous leukemia, CML seems like one kind of chronic diseasesmore than a fatal disease [13]. Currently, there are three commercially available TKIs for the treatment of CML including imatinib, dasatinib, and nilotinib in China. The responses to imatinib were also durable, as shown in an 8-year follow up of the IRIS study, as well as EFS (estimated event free survival) rate was 81%, and OS rate was 93% when only CML-related deaths were considered [10, 15-17]. Imatinib has been the first-line therapy of CML for better therapeutic effects and less adverse effects, but with the approval of dasatinib and nilotinib as the first-line therapy, there are more possibilities to use different strategies for CML patients [16].

Metaphase karyotyping may reveal additional clonal chromosomal abnormalities in Ph+ cells (ACA/Ph+), which was referred to as clonal cytogenetic evolution. The commonest ACAs are +8, +Ph, +19, i(17q) [4, 6, 22, 23]. The impact of ACAs on therapeutic effect and prognosis of CML is not clear now, there are some controversial views on this issue. ACAs emerged during treatment should be considered as progression to Accelerated Phase (AP) or Blast Crisis (BC) and imatinib treatment failure [10, 18-20]. Bozkurt et al., has reported that all patients (0/5) carrying ACAs in their Ph-negative metaphases didn't progress to AP or BP and obtained major or complete CyR, but patients (7/12, 58%) with ACAs in their Ph-positive metaphases developed AP/BC at diagnosis or follow-up (p=0.03) and most didn't have a CyR [18]. However, another study including 72 CML patients (21 in AP, 50 in CP with previous interferon treatment, and one was relapsed after stem cell transplant) (Table 4), including 49 patients only with Ph chromosome and 23 patients with one or more ACAs at the initial of IM treatment, showed that there was no difference in OS between patients with or without ACAs (log-rank test, P=0.391) [9]. And Cortes et al., thought that cytogenetic clonal evolution was not an independent significant factor for achieving a major or complete cytogenetic response, but it remained an independent prognostic factor for poorer survival in the setting of different clinical phases of CML [8]. ACAs were classified as major route ACAs and minor route ACAs. In Wang's study(608 patients had ACAs), the most common ACAs are +8, +Ph, -Y, 3q26.2, i(17)(q10) and -7/del(7q), which were stratified as 2 groups: group 1 with better prognosis including +8, -Y, +Ph and group 2 with a poorer prognosis including i(17), -7/del(7q), and3q26.2 rearrangements [6]. They also found that patients with single ACA had the similar survival to those with better prognosis, whereas patients with 2 or more ACAs (complex karyotypes) (Table 5) had the similar survival to those with poorer prognosis.

ACAs were emerged prior to therapy, or during treatment, but most of them were detected in newly-diagnosed patients [3, 8, 19, 22, 24]. Mohamed's et al., study showed that patients (6 of CP, 6 of AP, 3 of BP) obtained CyR with detected ACAs prior to Imatinib treatment, 11 patients of these 15 patients had only one kind of ACAs, other 4 patients had 2 kinds of abnormalities [22]. During the nilotinib therapy, 3 patients were reported to be with newly-developed ACAs, one of them was in BC and another one of them was progressed from CP to BC (Table 6). In addition, the presence of ACAs prior to nilotinib therapy can be used to predict the worse prognosis [23]. For a median follow-up of 78.6 months (range, 1.4-126.1 months), the OS, EFS, and FFS for patients with ACAs were 100%, 66.3%, and 52.1%, respectively; while for patients with a standard Ph, those indexes were individually 96.0%, 91.3%, and 83.7% [3]. Patients with the presence of ACA prior to treatment had lower EFS (P=0.015) and FFS (P=0.016) than those with standard Ph. Marin et al analyzed 224 CP-CML patients who received IM as first-line therapy and showed that the presence of ACA in Ph-positive (Ph+) cells, either at diagnosis or emerging during therapy, was associated with poorer outcomes [25]. So, the current mainstream view is that ACAs have a negative effect on CML treatment.

Johansson et al has suggested that major route ACAs should be consisted of +8, +Ph, i(17q), +19, -Y, +21, +17 and -7, the else were minor route ACAs, such as -17, +13, +4, t(5;13), t(3;21) [4]. They considered that the prognostic impact of ACAs in CML is complex, heterogeneous, and likely related to the time of appearance, specific abnormalities and treatment strategies, but they still agreed there is existed a strong association between ACAs and disease transformation. However, Fabarius' study group and ELN 2013 defined major route ACAs as +8, +Ph, i(17)(q10), +19[2, 10]. Fabarius et al., showed that no difference in the cumulative incidence of CCyR or MMR was seen among patients with standard t(9;22) and minor route ACAs [2]. For the major route ACAs group, the number of patients with MMR and CCyR was lower and the time to remission was deferred. Comparing the groups with major and minor route ACAs, 24 of the

25 patients with minor route ACAs were still alive, whereas 8 of 16 patients with major route ACAs died (P<0 .01). High-risk and major route ACA/Ph+ can help identify patients eligible for investigational approaches, and major route ACA/Ph+ developing during treatment were confirmed to be a signal of acceleration.

In conclusion, this study showed that there is no significant difference in minor route ACAs and major route ACAs about the 2-year EFS on CML treated with IM. It still remains to be explored if higher doses of imatinib would be more effective in CML with the presences of ACAs, as compared to the standard dose of 400 mg per day. And more efforts are needed to improve prognostically informative risk stratification system, the study population is not enough. Thus, much more studies and related data were needed to make clear the exact effect of ACAs on prognosis of CML just as that of t(15;17)(q22;q12) on the prognosis of acute myeloid leukemia, and then it may guide the treatment regimens of CML better in the future [27-31]. Our data implied that chromosome assessment should be carried out before the initiate of TKI treatment for patients with ACA, and treatment strategies can be modulated according to different chromosomes, which is very helpful for patients with CML to achieve personal and precise medical treatment.

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References

1. Zaccaria A, Testoni N, Valenti AM. Chromosome abnormalities additional to the Philadelphia chromosome at the diagnosis of chronic myelogenous leukemia: pathogenetic and prognostic implications. Cancer Genet Cytogenet. 2010; 199: 76–80.
2. Luatti S, Castagnetti F, Marzocchi G. Additional chromosomal abnormalities in Philadelphia-positive clone: adverse prognostic influence on frontline imatinib therapy: a GIMEMA Working Party on CML analysis. Blood. 2012; 120: 761–767.
3. Verma D. Survival outcomes for clonal evolution in chronic myeloid leukemia patients on second generation tyrosine kinase inhibitor therapy. Cancer. 2010; 116: 2673–2681.
4. Wang W. Chromosomal rearrangement involving 11q23 locus in chronic myelogenous leukemia: a rare phenomenon frequently associated with disease progression and poor prognosis. J Hematol Oncol. 2015; 8: 32.
5. Wang W, Cortes JE, Tang G. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. Blood. 2016; 127: 2742–2750.
6. Baccarani M, Deininger MW, Rosti G. European LeukemiaNet recommendations for the management of chronic myeloid leukemia. Blood. 2013; 122: 872–884.
7. Farag SS. Prognostic significance of additional cytogenetic abnormalities in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia treated with interferon-alpha: a Cancer and Leukemia Group B study. Int J Oncol. 2004; 25: 143–151.
8. Ohanian M. Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. Clin Lymphoma Myeloma Leuk. 2014; 14: 155–162.
9. O'Dwyer ME. Clonal evolution and lack of cytogenetic response are adverse prognostic factors for hematologic relapse of chronic phase CML patients treated with imatinib mesylate. Blood. 2004; 103: 451–455.
10. Radich JP, Dai H, Mao M. Gene expression changes associated with progression and response in chronic myeloid leukemia. Proc Natl Acad Sci USA. 2006; 103: 2794–2799.
11. Apperley JF, Khorashad JS. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention to treat analysis. J Clin Oncol. 2008; 26: 3358–3363.
12. Sokal JE. Prognostic significance of additional cytogenetic abnormalities at diagnosis of Philadelphia chromosome-positive chronic granulocytic leukemia. Blood. 1988; 72: 294–298.
13. Cortes JE, Kantarjian HM, Goldberg SL. High-dose imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: high rates of rapid cytogenetic and molecular responses. J Clin Oncol. 2009; 27: 4754–4759.
14. Deininger MW, Kopecky KJ, Radich JP. Imatinib 800 mg daily induces deeper molecular responses than imatinib 400 mg daily: results of SWOG S0325, an intergroup randomized PHASE II trial in newly diagnosed chronic phase chronic myeloid leukaemia. Br J Haematol. 2014; 164: 223–232.
15. Fabarius A, Leitner A, Hochhaus A. Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: long-term observation of 1151 patients from the randomized CML Study IV. Blood. 2011; 118: 6760-8.
16. Lee SE, Choi SY, Bang JH. The long-term clinical implications of clonal chromosomal abnormalities in newly diagnosed chronic phase chronic myeloid leukemia patients treated with IM mesylate. Cancer Genet. 2012; 205: 563-571.
17. Verma D, Kantarjian H, Shan J. Survival Outcomes for Clonal Evolution in Chronic Myeloid Leukemia Patients on Second Generation Tyrosine Kinase Inhibitor Therapy Cancer. 2010; 116: 2673-2681.
18. Wang W, Cortes JE, Tang G. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. Blood. 2016; 127: 2742-2750.
19. Falchi L, Rege-Cambrin G, Fava C. Sustained molecular remissions are achievable with tyrosine kinase inhibitor therapy inpatients with chronic myeloid leukemia and additional cytogenetic clonal evolution. Cancer Genetics and Cytogenetics. 2010; 199: 139–142.
20. Cortes JE, Talpaz M, Giles F. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemiaonIM mesylate therapy. Blood. 2003; 101: 3794–3800.
21. Holzerová M, Faber E, Veselovská J. IM mesylate efficacy in 72 previously treated Philadelphia-positive chronic myeloid leukemia patients with and without additional chromosomal changes: single-center results. Cancer Genetics and Cytogenetics. 2009; 191: 1-9.
22. Baccarani M, Deininger MW, Rosti G. European Leukemia Net recommendations for the management of chronic myeloid leukemia. Blood. 2013; 122: 872-884.
23. Baccarani M, Cortes J, Pane F. Chronic myeloid leukemia: an update of concepts and management recommendations of European Leukemia Net. J Clin Oncol. 2009; 27: 6041-6051.
24. Shaffer LG, Slovak ML, Campbell LJ. ISCN 2009: an international system for human cytogenetic nomenclature. 2009; 138.
25. Branford S, Rudzki Z, Harper A. Imatinib produces significantly superior molecular responses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. LEUKEMIA. 2003; 17: 2401-2409.
26. Ferrajoli A, Fizzotti M, Liberati AM. Chronic myelogenous leukemia: an update on the biological findings and therapeutic approaches. Crit Rev Oncol Hmatol. 1996; 22: 151-174.
27. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2014 update on diagnosis, monitoring, and management. AM J HEMATOL. 2014; 89: 547-556.
28. Bozkurt S, Uz B, Buyukasik Y, Bektas O, Inanc A, Goker H, et al. Prognostic importance of additional cytogenetic anomalies in chronic myeloid leukemia.

MED ONCOL. 2013; 30: 443.

29. Haaß W, Kleiner H, Weiß C. Clonal evolution and blast crisis correlate with enhanced proteolytic activity of separase in BCR-ABL b3a2 fusion type CML under imatinib therapy. PLOS ONE. 2015; 10: 1-18.

30. Mohamed AN, Pemberton P, Zonder J. The Effect of Imatinib Mesylate on Patients with Philadelphia Chromosome-positive Chronic Myeloid Leukemia with Secondary Chromosomal Aberrations. CLIN CANCER RES. 2003; 9: 1333-1337.

31. Al-Achkar W, Wafa A, Moassass F, Liehr T. A chronic myeloid leukemia case with a unique variant Philadelphia translocation: t(9;22;21)(q34;q11;p12). ONCOL LETT. 2012; 3: 1027-1029.

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