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ORIGINAL RESEARCH

Characteristics and mutation analysis of Ph-positive leukemia patients with T315I mutation receiving tyrosine kinase inhibitors

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Background: TKIs are the first-line treatment for patients with Ph-positive (Ph+) leukemia. However, drug resistance is frequently observed, mainly due to mutations within the breakpoint cluster region-Abelson leukemia virus (BCR-ABL) kinase domain. The T315I substitution confers complete resistance to TKIs. The aim of this study was to analyze the clinical characteristics of 17 patients with T315I mutation after TKI treatment and provide a basis for prognosis.

Patients and methods: The clinical data of 17 TKI-resistant Ph+ leukemia patients who were found to have a ABL kinase domain mutation from September 2008 to January 2017 were collected. Karyotypes and *BCR-ABL* fusion gene were analyzed by R-banding and fluorescence in situ hybridization, respectively. Total RNA was extracted by TRIzol reagent, and the ABL kinase domain mutation was detected by direct sequencing.

Results: A total of 17 patients reached effective remission including major molecular response and complete cytogenetic response. However, all the patients subsequently developed a T315I mutation after treatment with TKIs. The rate of the BCR-ABL fusion gene in most of the patients who developed the T315I mutation was significantly higher than that before the mutation. At initial diagnosis, patients average platelet count was 149.7×10^9/L, whereas the average platelet count was only 53.88×10^9/L after the T315I mutation ($P<0.01$). The results also showed that the survival time of patients with a high proportion of blast cells or a high number of white blood cells was obviously shortened.

Conclusion: Patients platelet count decreased when detected with the T315I mutation compared with the initial diagnosis. Combined use of different TKIs and complex chromosomal karyotypes may promote the development of the T315I mutation. When the ratio of blast cells was >50% and the number of white blood cells was $>20\times10^9$/L, poor survival prognosis was observed.

Keywords: acute lymphoblastic leukemia, chronic myeloid leukemia, BCR-ABL positive, T315I mutation

Introduction

For adult patients with acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML), the Philadelphia chromosome (Ph) resulting from t(9;22) (q34;q11) translocation between the Abelson leukemia virus (*ABL*) oncogene on chromosome 9 and the breakpoint cluster region (*BCR*) gene on chromosome 22 is the most common cytogenetic abnormality.[1] The *BCR-ABL* fusion oncogene encoded by Ph can activate tyrosine kinase activity, which causes the proliferation of tumor cells by multiple signaling pathways, such as MAPK/ERK cascades, PI3K/AKT/mTOR, and STAT pathway.[2–4]

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Therefore, the *BCR-ABL* fusion oncogene plays an essential role in the pathogenesis of Ph-positive (Ph+) leukemia and is considered the underlying mechanism of treatment.

Imatinib, the first tyrosine kinase inhibitor (TKI) approved by the Food and Drug Administration in 2001 is currently the first-line therapy for Ph+ leukemia. However, some patients still have primary or acquired drug resistance, of whom the BCR-ABL kinase domain point mutation is the most common reason for acquired resistance. Second-generation drugs, such as nilotinib and dasatinib, were developed to benefit patients who are unable to achieve effective remission with imatinib or who have BCR-ABL kinase domain mutations other than the T315I mutation.[5] Third-generation TKIs, such as ponatinib, are designed to overcome all BCR-ABL kinase domain mutations, including the T315I mutation.[6] However, recent research revealed that the T315I mutation still occurs to patients even when second- and third-generation TKIs are used. For example, the T315I gatekeeper mutation appeared in 5 of 12 patients receiving dasatinib.[7] These molecular mutations have driven the development and standardization of sophisticated molecular monitoring methods to identify therapeutic failures.[8]

So far, no consensus about the reasons for mutations has been achieved. Thus, we collected the clinical data of 17 Ph+ ALL and CML cases treated with TKIs in Nanjing Drum Tower Hospital. We analyzed the possible reasons of the T315I mutation to provide a theoretical basis for timely prediction of prognosis and improve therapeutic regimen.

Patients and methods

Patient selection

Among 17 patients with T315I mutation, 10 and 7 cases had ALL and CML, respectively. All 17 patients were diagnosed by means of clinical manifestations, laboratory tests, cell morphology, and immunology. They were followed up at intervals of 2–3 months. Patients with the primary T315I mutation who detected through direct sequencing were excluded from the observation group. Each patient was treated with TKIs, and the ABL kinase domain mutation was detected by direct sequencing when TKI resistance was observed during treatment. We used a coding system to ensure the privacy of patients participating in our study. All the patients provided informed consent for genetic analysis based on the Declaration of Helsinki. They were informed of the existence of other treatment options according to the ethics committee of the Affiliated Drum Tower Hospital, School of Medicine, Nanjing University. The ethics committee of the Affiliated Drum Tower Hospital, School of Medicine, Nanjing University approved this study.

Detection method

All the patients underwent bone marrow puncture, chromosome examination, immunofluorescence in situ hybridization, and nested polymerase chain reaction (PCR) for surveillance of disease. Karyotypes and BCR-ABL fusion gene were analyzed by R-banding and fluorescence in situ hybridization, respectively. Identification and description of anomalous karyotypes were according to the International System of Human Cytogenetic Nomenclature (2009). The specific method and Ph+ cell standard were presented in the literature.[9] Total RNA was extracted by TRIzol reagent and reverse transcribed into cDNA via reverse transcriptase. After amplification and electrophoresis, the PCR products were sequenced by Sanger sequencing to detect ABL kinase mutation.[10] The patients were divided into two groups to draw the survival curve, and it depended on whether the ratio of blast cells is $>50\%$ and whether the number of white blood cells in the mutation is $>20\times10^9$/L. Meanwhile, we collected the platelet count at relapse in patients with T315I mutation and patients without T315I mutation to observe the differences between them.

Follow-up

The median follow-up time was 10 months (range: 4–84 months) from the time of diagnosis to death or the end of follow-up, as of January 30, 2017.

Statistical analysis

SPSS 22.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Paired-samples *t*-test and independent-samples *t*-test were used to compare the platelet count. $P<0.05$ was considered statistically significant. Survival function was analyzed by life tables.

Results

Patient characteristics and treatment

The study population consisted of 17 patients (10 ALL and seven CML; 10 males and 7 females), and the median age was 41 years (20–74 years). A total of 12 patients presented with splenomegaly and lymphadenopathy at diagnosis, suggesting that the disease was in the terminal stage. Karyotype analysis showed that 6 patients had complex karyotypes (patients 5, 7, 8, 11, 15, and 17), and the remaining 11 patients had t(9;22) at initial diagnosis. However, 8 patients had complex karyotypes (patients 5, 7, 8, 11, 12, 14, 15, and 17) at relapse because the karyotype of 2 patients changed from t(9;22) to complex karyotype (Table 1).

Treatment adherence and resistance of these patients were also assessed. Only six (35.3%) patients showed

Table 1 Karyotypes at initial diagnosis and at relapse

Patient	Karyotype (initial diagnosis)	Karyotype (relapse)
1	t(9;22)	t(9;22)
2	t(9;22)	t(9;22)
3	t(9;22)	t(9;22)
4	t(9;22)	t(9;22)
5	Complex karyotype	Complex karyotype
6	t(9;22)	t(9;22)
7	Complex karyotype	Complex karyotype
8	Complex karyotype	Complex karyotype
9	t(9;22)	t(9;22)
10	t(9;22)	t(9;22)
11	Complex karyotype	Complex karyotype
12	t(9;22)	Complex karyotype
13	t(9;22)	t(9;22)
14	t(9;22)	Complex karyotype
15	Complex karyotype	Complex karyotype
16	t(9;22)	t(9;22)
17	Complex karyotype	Complex karyotype

adequate treatment adherence to first- and second-generation TKI therapy, and the rest (64.7%) showed poor treatment adherence. The duration of TKI therapy per patient demonstrated that the minimum duration of TKI therapy before the T315I mutation was 3 months (patient 6), and the maximum duration was 2 years (patient 11), showing high variability in the duration of TKI therapy. Seven patients treated with dasatinib were given a maximum dose of 140 mg/day (patients 1, 2, 5, 6, 7, 12, and 14), and patient 11 who used nilotinib was given a maximum dose of 800 mg/day. Patient 15 received first-generation TKI (imatinib) with a maximum dose of 600 mg/day and did not receive any second-generation TKI thereafter. However, eight patients were treated with two kinds of TKIs (patients 3, 4, 8, 9, 10, 13, 16, and 17), seven of whom were administered imatinib at the beginning and given a second-generation TKI (dasatinib) after they had the Y253H, E255k, Q252H, F317L, M351T, and D276G mutations. Patient 8 developed the T315I mutation after taking dasatinib for 6 months and then switched to ponatinib (Table 2).

After TKI treatment, 17 patients had effective remission, of whom 11 patients achieved major molecular response and 6 patients achieved complete cytogenetic response. However, all the patients subsequently developed the T315I mutation; even patients 7 and 9 had allogeneic hematopoietic stem cell transplantation (allo-HSCT). The median time of T315I mutation was 10 months.

A total of 12 patients discontinued TKIs and switched to high-intensity chemotherapy regimens, such as hyper-CVAD (cyclophosphamide, vincristine, adriamycin and dexamethasone), VDCP (vincristine, daunorubicin, cyclophosphamide, and dexamethasone), HAG (homoharringtonine, cytarabine and G-CSF), and HD-MTX (high-dose mitoxantrone) with VP (vincristine and dexamethasone). However, they did not achieve good clinical results, and four of them died due to complications, such as respiratory failure (one), heart failure (one), and sepsis (two), whereas others chose to discharge automatically. Patients 8 and 11 underwent allo-HSCT involving haploid sibling donors, and the conditioning regimen contained modified Bu/Cy. However, the second T315I mutation still occurred (patient 8), and subsequent lymphocyte infusion failed to improve the disease state. Finally, patient 8 died due to viremia. Fortunately, patient 11 did not undergo any mutations until the end of follow-up.

Mutation analysis

We used immunofluorescence in situ hybridization to dynamically monitor the BCR-ABL fusion rate in 17 patients. The fusion rate of BCR-ABL decreased in all the patients after taking TKIs, indicating that the disease status is improved. However, the rate of the BCR-ABL fusion gene in most patients was obviously higher than that before they had the T315I mutation (Figure 1). When the T315I mutation occurred, most of the patients discontinued TKIs and switched to other chemotherapy regimens, but the disease was not effectively alleviated.

We analyzed the platelet count of patients at initial diagnosis and after developing the T315I mutation. At initial diagnosis, the average platelet count of 17 patients was 149.7×10^9/L, which was still within the normal range. In the T315I mutation, the average platelet count of patients was only 53.88×10^9/L, which was a statistically significant difference compared with the former ($P<0.01$). A notable linear change was observed between the platelet count in the mutation and at initial diagnosis ($P=0.028$; Table 3 and Figure 2). The platelet count at relapse in patients with T315I mutation and patients without the T315I mutation was compared, but there was no significant difference ($P>0.05$; Table 4).

We divided the patients into two groups to draw the survival curve depending on whether the bone marrow aspirate contains >50% blast cells. We concluded that the median survival time of patients was 43 months when the rate of blast cells was <50% (group 1). However, it reduced to only 11 months when the rate of blast cells was >50% (group 2; Figure 3).

We also dynamically tested the blood routine of patients and found that the median survival time was 43 months for patients whose white blood cells were $<20\times10^9$/L in the T315I mutation (group 1), whereas it was only 11 months for

Table 2 Clinical information of patients with T315I mutation

Patient	Gender/ age (years)	Disease	Clinical manifestation	Radiographic features	BCR/ ABL	Treatment before mutation	Time of TKIs (month)	Maximum dose (mg)	Best response	Treatment after mutation	Other mutations
1	F/48	ALL Ph+	Weight loss, fatigue	No	P190	DAS+VP; DAS+VDP	DAS: 6	100	MMR	VDP; hyper-CVAD-A	No
2	F/23	ALL Ph+	Fatigue	Lymphadenectasis	P190	VP+DAS	DAS: 4	100	MMR	Hyper-CVAD Vumon+CTX+prednisone MTX+Ara-C; HAG	No
3	M/23	ALL Ph+	Thrombocytopenia	Splenomegaly	P210	VDCP+asparaginase; VDCP; VP+IM; VP+DAS	IM: 12 DAS: 11	400	MMR	VDCP	Y253H
4	M/21	ALL Ph+	Fatigue, fever	Lymphadenectasis, splenomegaly, bone destruction of right humeral head	P190	IM+VP; DAS+VP	IM: 2 DAS: 3	600	MMR	Hyper-CVAD-B	E255k
5	M/61	ALL Ph+	Edema of lower extremities	Lymphadenectasis, splenomegaly	P190	Hyper-CVAD; DAS+VP	DAS: 4	100	MMR	DAVP+daunorubicin	No
6	M/20	ALL Ph+	Fatigue	Splenomegaly	P210	VP+DAS	DAS: 3	100	CCyR	HD-MTX+VP; hyper-CVAD	No
7	F/42	ALL Ph+	Thrombocytopenia	No	P210	VDP+DAS; VP+DAS; VDP+DAS; VP+DAS; HSCT	DAS: 12	100	MMR	VP	No
8	M/21	ALL Ph+	Splenomegaly	Lymphadenectasis, splenomegaly	P190	DAS+VP; VDCP+DAS; PON+VP	DAS: 6 PON: 1	100	MMR	VDCP; HSCT; PON+VP; VP; lymphocyte infusion	No
9	F/41	ALL Ph+	Dizziness and weakness	No	P210	IM+VDLP; IM+VDP; DAS+prednisone; HSCT	IM: 3 DAS: 1	800	MMR	PON+VDP	F317L
10	F/68	ALL Ph+	Fatigue, anorexia, weight loss	Splenomegaly	P210	IM+VP; DAS	IM: 8 DAS: 2	600	CCyR	VDLP	M351T
11	M/50	CML Ph+	Abdominal distention with emaciation	Splenomegaly	P210	NIL	NIL: 24	800	CCyR	HSCT	No
12	M/55	CML Ph+	Weight loss	No	P210	DAS+VP; DAS+VDP; DAS+hormone	DAS: 7	140	MMR	Hyper-CVAD-A	No
13	M/60	CML Ph+	Abdominal distention, fever	Splenomegaly, splenic vein dilatation	P210	IM; DAS	IM: 2 DAS: 1	800	CCyR	No	E255K
14	M/29	CML Ph+	Edema of lower extremities	Lymphadenectasis, splenomegaly	P210	DAS+VP; DAS+VDCP	DAS: 10	100	MMR	Hyper-CVAD	No
15	F/23	CML Ph+	Fatigue	Splenomegaly	P190	Hydroxyurea; IM	IM: 6	600	CCyR	No	No
16	M/31	CML Ph+	Fever	Splenomegaly	P210	IM; DAS	IM: 10 DAS: 2	600	CCyR	No	Q252H
17	F/74	CML Ph+	Fatigue	Splenomegaly	P210	Hydroxyurea; IM; DAS	IM: 14 DAS: 1	600	MMR	VDCP	D276G

Note: Patients' basic information regarding gender, age, clinical manifestation, radiographic features, BCR/ABL, karyotype, treatment before mutation and after mutation, time and maximum dose of TKIs, best response, and other mutations.

Abbreviations: ALL, acute lymphoblastic leukemia; BCR-ABL, breakpoint cluster region-Abelson leukemia virus; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; DAS, dasatinib; F, female; HSCT, hematopoietic stem cell transplantation; IM, imatinib; M, male; MMR, major molecular response; NIL, nilotinib; Ph, Philadelphia chromosome; PON, ponatinib; TKIs, tyrosine kinase inhibitors; IM, imatinib; DAS, dasatinib; VP, vincristine and dexamethasone; VDP, vincristine, daunorubicin, dexamethasone; Hyper-CVAD, cyclophosphamide, vincristine, adriamycin and dexamethasone; Hyper-CVAD-A, cyclophosphamide, pirarubicin, vincristine, and dexamethasone; Hyper-CVAD-B, mitoxantrone, cytarabine; CTX, cyclophosphamide; MTX, mitoxantrone; HD-MTX, high-dose mitoxantrone; HAG, homoharringtonine, cytarabine and G-CSF; VDCP, vincristine, daunorubicin, cyclophosphamide, and dexamethasone; VDLP, vincristine, daunorubicin, L-asparaginase and dexamethasone; DAVP, daunorubicin, cytarabine and vepeside; HSCT, hematopoietic stem cell transplantation.

patients whose white blood cells were more than 20×10^9/L (group 2; Figure 4).

Discussion

The BCR-ABL fusion gene is an oncogene of CML and 30%–50% cases of adult ALL.[11] The BCR-ABL kinase domain has three parts, namely P-loop (P), catalytic domain (C), and activation loop (A). More than 70 types of mutations, involving more than 50 amino acid changes, can occur in the P-ring, A-ring, catalytic region or contact points of the two parts (such as T315 and F317). Point mutations cause changes in the ABL kinase amino acid by interfering directly with the binding of the TKI to the ABL kinase or by inhibiting inactivation of ABL kinase, thereby interfering with the binding of the drug to the target site and eventually leading to drug resistance.[12] The most frequent detectable mutation in Ph+ ALL is T315I (detected in 37% of all patients positive for mutations), followed by E255K and Y253H.[1]

The median time from diagnosis to the T315I mutation in 17 patients was 10 months, suggesting that treatment with TKIs did not postpone disease progression. Ten patients in the course of treatment failed to undergo regular treatment and timely monitoring due to various reasons, which may also be an important reason for the deterioration of the disease. Johansson et al[13] and Pfeifer et al[14] reported that additional cytogenetic and molecular genetic aberrations are likely to promote disease progression because of increased genomic instability. In the current study, eight patients with complex chromosomal karyotypes developed the T315I mutation; such results were similar to a related study. Aggoune et al[15] showed that the combined use of different TKIs may inadvertently promote the development or selection of mutations in the BCR-ABL kinase domain. Seven patients with the T315I mutation in our cohort had combined with Y253H, E255k, and other mutations, because imatinib was used before dasatinib, which may contribute to the T315I mutation.

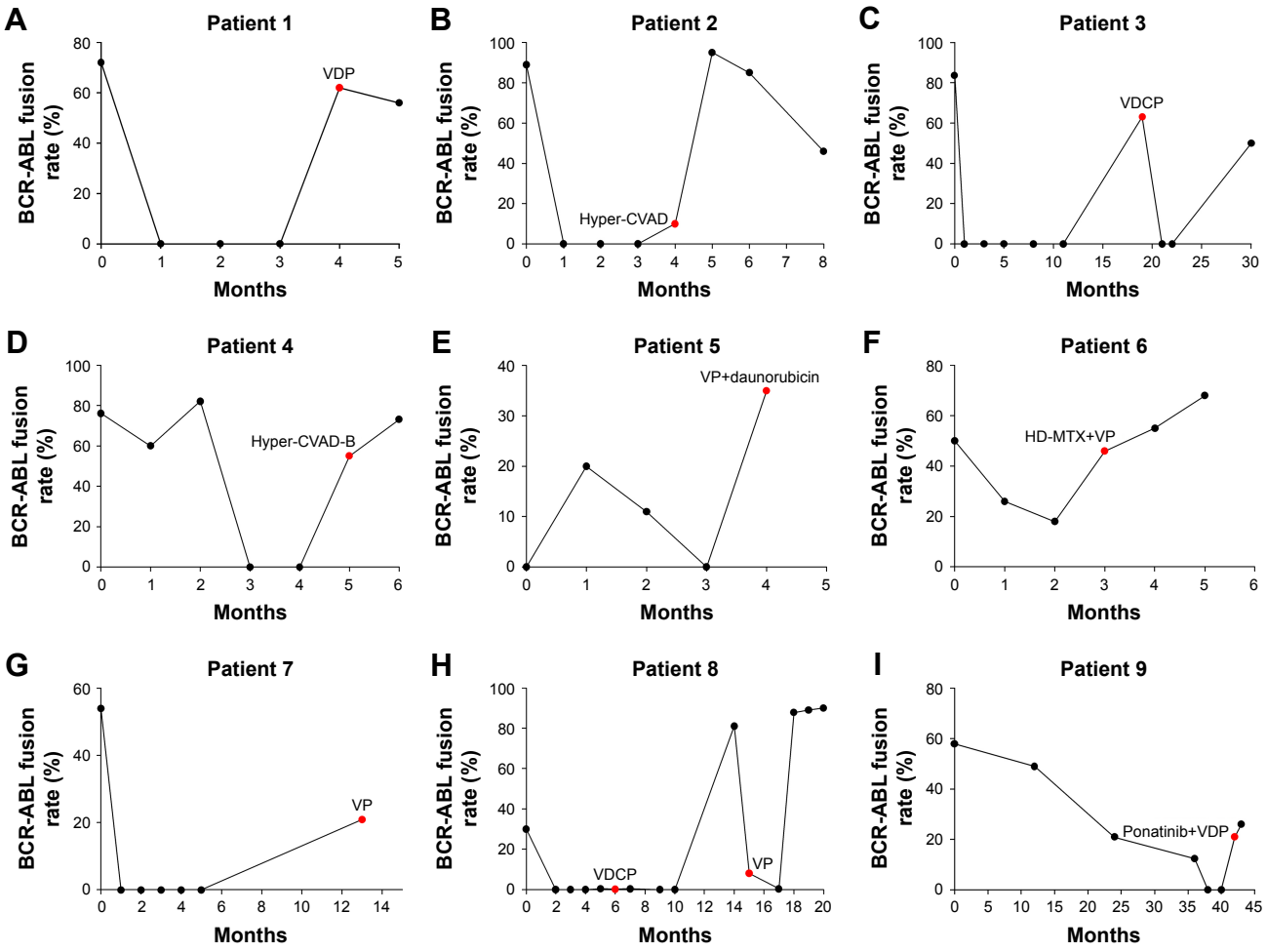

Figure 1 (*Continued*)

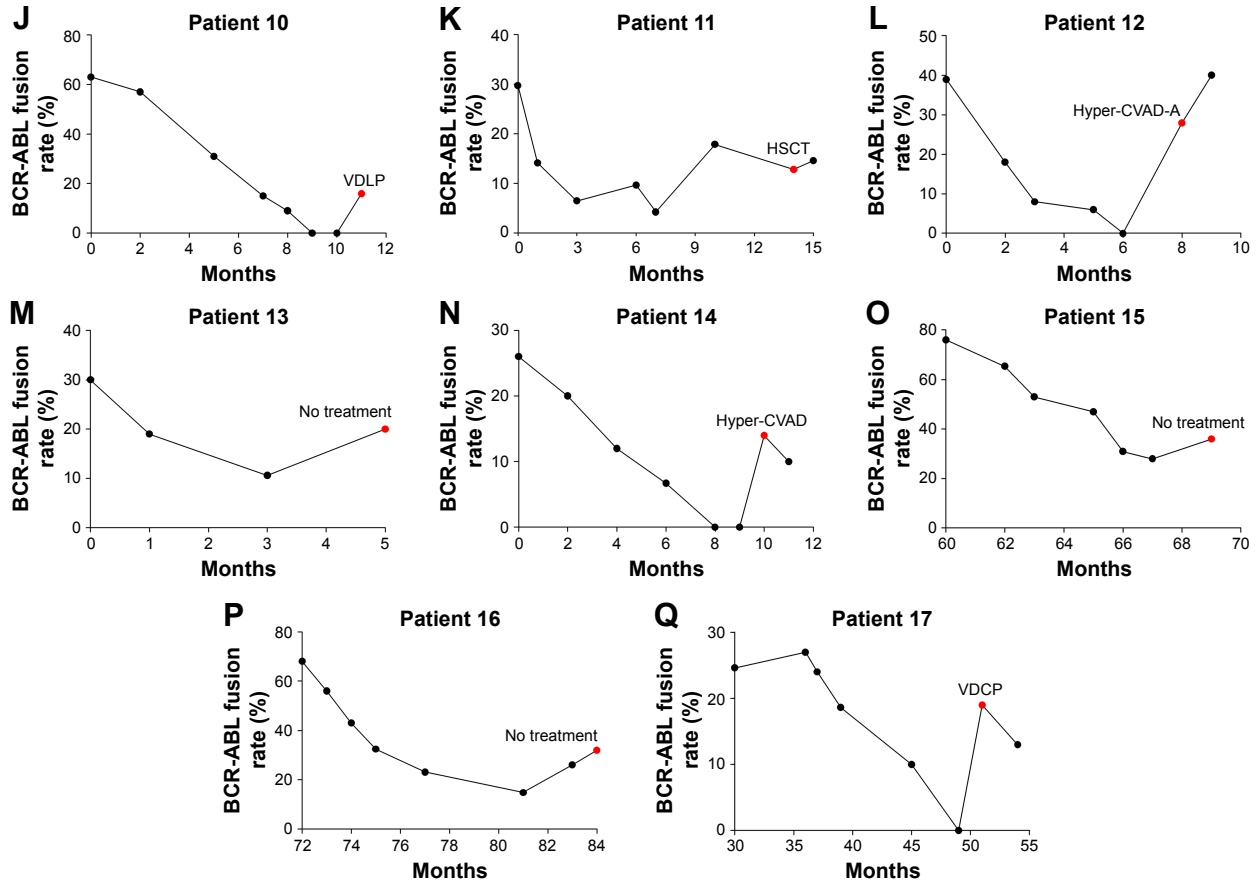

Figure 1 BCR-ABL fusion rate of 17 patients.

Notes: The x-axis shows the time from diagnosis expressed in months, and the y-axis represents the rate of BCR-ABL fusion gene. The x-axis value of the red dot indicates the time of mutation. The y-axis value of the red dot indicates the rate of BCR-ABL fusion gene in the mutation. Drugs around the red dot refer to the chemotherapy regimen after the T315I mutation occurred.

Abbreviations: BCR-ABL, breakpoint cluster region-Abelson leukemia virus; HSCT, hematopoietic stem cell transplantation; VDP, vincristine, daunorubicin, dexamethasone; Hyper-CVAD, cyclophosphamide, vincristine, adriamycin and dexamethasone; VDCP, vincristine, daunorubicin, cyclophosphamide and dexamethasone; Hyper-CVAD-B, mitoxantrone, cytarabine; VP, vincristine and dexamethasone; HD-MTX, high-dose mitoxantrone; VDLP, vincristine, daunorubicin, L-asparaginase and dexamethasone; Hyper-CVAD-A, cyclophosphamide, pirarubicin, vincristine and dexamethasone; VDCP, vincristine, daunorubicin, cyclophosphamide and dexamethasone.

Table 3 Laboratory data of patients with T315I mutation

Patient	PLT $\times 10^9$/L (initial diagnosis)	PLT $\times 10^9$/L (mutation)	WBC $\times 10^9$/L (mutation)	Rate of blast cells (initial diagnosis) (%)
1	100	6	1.5	98
2	139	9	5.5	91.5
3	89	13	5.9	60
4	130	24	35.8	95
5	150	70	30	84.6
6	96	45	32.3	93.5
7	73	24	21	82.5
8	158	21	17	42.5
9	169	136	11.4	40
10	210	93	70	82
11	229	100	49	20
12	150	43	29.6	24.5
13	239	51	5.9	15.5
14	170	49	1.5	21
15	130	78	66	26
16	143	100	29.6	16
17	170	54	18.8	20

Abbreviations: PLT, platelet; WBC, white blood cell.

Our data revealed that platelet count in the T315I mutation was significantly less than that at initial diagnosis. Chui et al[16] found that PDGF/PDGFR plays an important role in promoting differentiation and anti-apoptosis of megakaryocyte.

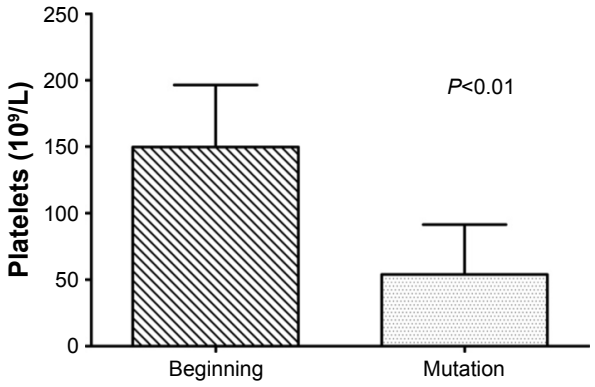

Figure 2 Platelets in different stages ($P<0.01$).

Notes: Data are presented as mean ± SD. Beginning: the average platelet count at initial diagnosis; mutation: the average platelet count in the T315I mutation.

Table 4 Comparison of platelet count at relapse in patients with T315I mutation and patients without T315I mutation

Patient	n	Platelets $\times 10^9$/L (relapse)	*P*-value
Group 1	12	69.50±49.91	0.344
Group 2	17	53.88±37.45	

Notes: Group 1: patients without T315I mutation; group 2: patients with T315I mutation.

TKIs can block the initiation of the PDGF/PDGFR signaling pathway; interrupt several downstream signal cascades, such as PI3K/AKT phosphorylation; and weaken the inhibition of caspase-3 activation, eventually promoting megakaryocyte apoptosis and leading to thrombocytopenia.[17] Therefore, we hypothesized that patients with the T315I mutation were resistant to TKIs, so TKIs acted more on the PDGF/PDGFR signaling pathway and decreased the number of platelets. Whether the decreased platelet count can be used as a marker for predicting the T315I mutation is worthy of further study. Our experience showed that the survival time of patients with a high proportion of blast cells and high number of white blood cells was significantly shortened. The increase in the proportion of blast cells and the number of white blood cells showed a high degree of malignancy, which accelerated the progression of the disease when it was combined with the T315I mutation.

After taking TKIs, all the patients achieved effective remission, including complete cytogenetic response and major molecular response. However, the results were unsatisfactory. All the patients had the T315I mutation after a period of remission, indicating that the mutation in the BCR-ABL kinase domain was not related to the remission state. Therefore, the detection rate of gene mutation must be improved, and the therapeutic regimen must be adjusted in time. The mutation in the BCR-ABL kinase domain and chromosomal

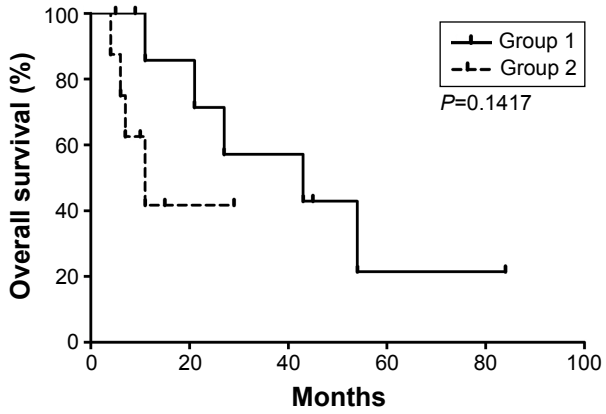

Figure 3 Total survival time demonstrated by life tables.
Notes: Patients were stratified according to the rate of blast cells (group 1 vs group 2; *P*=0.1417). Group 1: patients with the rate of blast cells <50%; group 2: patients with the rate of blast cells >50%.

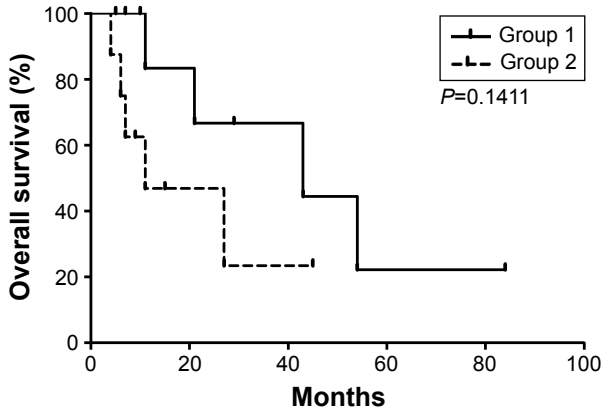

Figure 4 Total survival time demonstrated by life tables.
Notes: Patients were stratified according to the number of white blood cells (group 1 vs group 2; *P*=0.1411). Group 1: patients with white blood cells $<20\times10^9$/L; group 2: patients with white blood cells $>20\times10^9$/L.

abnormalities can be detected in $CD34^+$ leukemic cell subsets, including $CD34^+$ CD38-LSCs.[18] In addition to standard karyotype analysis, real-time PCR and quantitative analysis of BCR-ABL transcripts by sequencing alone or in combination with denaturing high performance liquid chromatography have become tools for monitoring patients undergoing TKI therapy.[7] Baer et al[19] argued that mutation detection by conventional Sanger sequencing requires 10%–20% expansion of the mutated subclone, whereas mutations are detected at loads of 1%–2% by ultra-deep sequencing. Thus, early mutation detection by ultra-deep sequencing might allow treatment to be changed before clonal increase in cells with the T315I mutation.

The broad-spectrum kinase inhibitor, ponatinib, is a clinically available inhibitor that has shown efficacy against the T315I mutation. In a recent Phase III clinical trial with ponatinib, frequent severely adverse vascular effects were observed, leading to termination of the trial and temporary withdrawal from the market.[20] Meanwhile, axitinib shows significant therapeutic effects and relatively few side effects.[21] The most feasible approach to cure leukemia with the T315I mutation is allo-HSCT. However, our research showed that allo-HSCT still failed to achieve the desired results. The feasibility of allo-HSCT is remarkably reduced in clinical practice due to various reasons, such as the source of stem cells, human leukocyte antigen matching, and decreased immunity. Therefore, some scholars searched for other ways to treat Ph+ leukemia. The new MK-0457 is a small-molecule aurora kinase inhibitor with in vitro activity against cells expressing wild-type or mutated BCR-ABL, including the T315I BCR-ABL mutation; three patients with T315I mutation have achieved clinical responses to doses of MK-0457 that are not associated with adverse events.[22]

Peng et al[23] used the mouse model experiment to develop an alternative approach to kinase inhibition, namely, the heat shock protein 90 inhibitor IPI-504, which resulted in BCR-ABL protein degradation and decreased number of leukemia stem cells.

Conclusion

TKIs remain the first-line treatment choice for Ph+ leukemia. However, drug resistance caused by gene mutation must also be considered. Close monitoring of the BCR-ABL fusion gene and researching on novel therapeutic agents are crucial for leukemia patients with the T315I mutation or other mutations.

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Disclosure

The authors report no conflicts of interest in this work.

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