Review Article
Adult Ph-positive acute lymphoblastic leukemia-current concepts in cytogenetic abnormalities and outcomes

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Abstract: Recurrent chromosomal and molecular abnormalities characterize acute lymphoblastic leukemia (ALL) subtypes in both adult and pediatric patients and are of great value for diagnosis, risk stratification, disease monitoring and treatment selection. The Philadelphia (Ph) chromosome, which creates a novel hybrid gene called BCR-ABL1, is the most common cytomegolocytic abnormality in adult ALL patients. As the understanding of the genetic characteristics of Ph-positive ALL continues to improve, the prognostic value of cytogenetic abnormalities is becoming increasingly recognized. It is likely that the clinical guidelines and recommendations will also evolve. Accordingly, it will be very important to effectively and economically utilize current knowledge to guide treatment decisions within the clinical context of each patient. In this review, we will summarize the advances in the understanding of cytogenetic abnormalities in adult patients with Ph+ ALL, with an emphasis on the incidence, characteristics and prognosis of different types of abnormalities, to provide a basis for the clinical prognostic stratification and precise individualized treatment of these patients.

Keywords: Acute lymphoblastic leukemia, cytogenetic, BCR-ABL, philadelphia chromosome

Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease, and the understanding of the underlying genetics is continuously evolving, which will likely influence treatment decisions. Both B-cell ALL and T-cell ALL exhibit cytogenetic abnormalities that can be detected by conventional G-binding and interphase fluorescence in situ hybridization (IP-FISH) methods, including numeric or structural abnormalities, which are associated with characteristic and recurrent cytogenetic changes [1]. The Philadelphia (Ph) chromosome, which creates a novel hybrid gene called BCR-ABL1, accounts for 25-30% of all cytogenetic abnormalities in adult ALL patients and in patients with the hallmark chronic myeloid leukemia (CML). Before the advent of tyrosine kinase inhibitors (TKIs) targeting BCR-ABL1, the prognosis of adult Ph+ ALL patients was poor, and the 3-year overall survival (OS) rate of patients undergoing traditional chemotherapy was usually lower than 20% [2, 3]. In recent years, the incorporation of TKIs into chemotherapy regimens has significantly improved the prognosis of these patients. The study conducted by Daver N et al. showed that intensive chemotherapy combined with imatinib, a first-generation TKI, can improve the complete remission (CR) rate of adult Ph+/BCR-ABL1+ ALL patients to more than 90%, and the associated 5-year OS rate and relapse-free survival (RFS) rate were found to be 43% [4]. Nonetheless, the guidelines formulated by the 2019 National Comprehensive Cancer Network (NCCN) still recommend allogeneic hematopoietic stem cell transplantation (allo-HSCT) as the first choice for adult Ph+ ALL patients after remission due to a lack of long-term data on patients treated with combination chemotherapy and TKIs without allo-HSCT [5].

Cytogenetic analysis and molecular screening at the time of diagnosis show that the outcomes among these patients were quite heterogeneous. Some patients had the Ph chromosome
as the sole abnormality, some patients had additional cytogenetic abnormalities (ACAs), some patients had a complex-/variant-Ph chromosome and some patients had a cryptic Ph chromosome with the BCR-ABL1 rearrangement (Ph-/BCR-ABL1+) [6-9]. With a deep understanding of the spectrum of cytogenetic abnormalities in adult Ph+ ALL patients, the prognostic value of abnormal cytogenetics has become increasingly clear. In this review, we summarize the progress in research on cytogenetic abnormalities in adult patients with Ph+ ALL in terms of the incidence, clinical characteristics, and prognostic significance of different types of abnormalities to provide a reference that can be used to assist the clinical prognostic stratification and precise individualized treatment of these patients.

**Variant Ph chromosome**

Compared to the classic Ph chromosome, variant Ph rearrangements involving 3 or more chromosomes (all chromosomes can be involved) generate the BCR-ABL1 fusion gene, and the breakpoints involved in variant Ph chromosomes have a certain degree of randomness, which implies the involvement of the same chromosome with different breakpoints [10, 11]. In the normal course of events, the fusion gene BCR-ABL1 is formed from the translocation of the C-ABL1 proto-oncogene on the long arm of chromosome 9 (9q34) to the breakpoint clustering region (BCR) of the long arm of chromosome 22 (22q11). As a result, they present as 22q- and 9q+ under the light microscope, and the former is the hallmark of the Ph chromosome. In the variant Ph chromosome, 22q- is often present, but the missing part can translocate to a chromosome distinct from chromosome 9, or a complex genetic material exchange involving chromosome 9, 22, and others can occur. According to the results of conventional karyotype analysis, the variant Ph chromosome has two different forms: the simple pattern, which involves 22q11 or 9q34 and another chromosome aside from chromosome 9, and the complex pattern, which involves at least 1 other chromosome in addition to 22q11 and 9q34. The latter is the most common type of complex/variant rearrangement [12]. These simple patterns are masked as complex ones and are undetectable by conventional karyotyping analysis. At present, there are two main mechanisms underlying the generation of variant Ph chromosomes: ① the “1-step” mechanism, in which chromosomes 9 and 22 and at least one additional chromosome break and merge at the same time and ② the “2-step” mechanism, in which the classic translocation between chromosomes 9 and 22 occurs first, followed by a second translocation of der (9) to additional chromosomes [10]. This suggests that additional genes may be implicated in BCR-ABL1 rearrangement and may eventually lead to heterogeneity in clinical characteristics and survival prognosis.

Among newly diagnosed adult Ph+/BCR-ABL+ ALL patients, the incidence of variant Ph chromosomes varies from 2.0-5.6% [6, 9, 13-15], which is approximately half (4.0-11.7%) of the reported incidence in CML patients in the chronic phase [10-12]. In the chronic phase of CML, the characteristics of patients with classic Ph and variant Ph chromosomes were found to be identical [10, 12], and the prognoses in both groups were similar when they were treated with TKIs [10-12]. The European Leukemia Net (ELN) panel recommends that variant translocations do not constitute a “warning” category in the imatinib era. The characteristics and implications of the variant Ph chromosome at diagnosis remain unclear, owing to the rarity of the variant Ph chromosome in adult Ph+ ALL patients. For the first time, Sandberg et al. reported variant Ph chromosome translocations in two young adult patients with ALL; one was a 26-year-old man with a simple pattern, t(14:22), and the other was a 36-year-old man with a complex pattern, t(9;15;22). CR was achieved rapidly in both patients with routine chemotherapy, but their long-term prognoses were not described in the report [16]. It was reported that a 25-year-old man who had a complex variant Ph translocation, t(9:22;12), had an OS of 28.2 months after chemotherapy [17]. By reviewing the Mitelman database and the literature, Cho et al. found 22 complex Ph variant translocations in adult ALL patients, and the male-to-female ratio was 1.44, showing a slight but nonsignificant male predominance [18]. There were only 7 patients whose OS was described, and the longest and the shortest were 16 months and a few weeks, respectively. In the era of TKIs, Jain et al. assessed 144 consecutive adults with Ph+ ALL to examine the impact of cytogenetic heteroge-
neity. They found inferior RFS and OS in patients with either a variant (n=8, 5.6%) or a complex-t(9;22) (n=10, 6.9%) compared to all other patients, and multivariate analysis confirmed that variant/complex-t(9;22) was an independent risk factor [9]. However, this conclusion might be confounded by several factors. First, the study was performed with a relatively small number of cases. Second, patients with variant/complex translocations were analyzed as one group, and ACAs were found in 11 cases in this group, including one with hypodiploidy and two with hyperdiploidy. Therefore, the clinical significance of variant Ph chromosomes in ALL patients needs to be further explored, particularly with regard to TKI therapy.

Additional chromosomal abnormalities

ACAs are defined as any numerical or structural abnormality in a Ph chromosome-positive cell. ACAs at diagnosis were observed in 16.3-78% of patients with Ph+ adult ALL [6-9, 13-15, 19-24]. The study conducted by Bacher et al. found that the frequency of ACAs in Ph+ ALL is dependent on disease status and increases from 53.1% at diagnosis to 95.8% at relapse (P < 0.0001), and the median number of ACAs per patient increases from 1 at diagnosis to 5 at relapse (P < 0.0001) [27]. The most frequent abnormalities included +der(22), -9/9p-, -7/7p-, +8, +21 and +X, whereas in CML, the most frequent abnormalities were “major route” ACAs [+der(22), +8, +19, -7/7p, i(17q), 11q23, or 3q26.2 abnormalities and complex aberrant karyotypes], which predict a poorer response to TKIs and a higher risk of progression [25, 26]. Similar results in terms of the main demographic and biological data were observed in patients with isolated Ph+ and those with ACAs in most studies [15, 20-22]. A consistent conclusion has not been reached regarding the prognostic significance of ACAs in Ph+ ALL either before or after the introduction of TKIs, which may be related to the heterogeneity of treatment and the relatively small sample sizes.

In the pre-TKI era, a study reported by Wetzler et al. showed that there were no differences in prognostic indicators such as the CR rate, cumulative incidence of relapse (CIR) and OS according to the presence or absence of ACAs [13]. In a small sample (n=115) of adult Ph+ ALL patients who received chemotherapy with or without imatinib, patients with ACAs had shorter disease-free survival (DFS) times (median: 7 vs. >13 months; P = 0.02) and OS (median: 13 vs. >17 months; P = 0.043) in the chemotherapy combined with the imatinib group and shorter DFS (median: 4 vs. 7 months; P = 0.037) times in the chemotherapy group [23]. Similarly, in a series of 80 adult patients with Ph+ ALL who were treated with chemotherapy including imatinib, Yanada et al. found that the presence of ACAs was the only independent prognostic factor for RFS and was associated with a 2.8-fold increased risk of treatment failure (P = 0.027) [8]. Additionally, Aldoss et al. identified 78 consecutive adults with Ph+ ALL who had received pretransplant TKI-based therapy from the City of Hope Medical Center between 01/2003 and 04/2014, including 41 patients (53%) with ACAs and 37 with isolated Ph+. They found that although patients with ACAs had a lower rate of minimal residual disease (MRD) positivity prior to allo-HSCT, the long-term survival rate of patients in this group was still lower than that in the isolated Ph+ group. In the two groups, the leukemia-free survival (LFS) rates were 39.5% and 79.8% (P = 0.01), respectively, and the 3-year OS rates were 45.6% and 83%, respectively (P = 0.02) [15]. Unfortunately, they did not perform multivariate analysis due to the limited sample size. In a larger retrospective study of adult patients with Ph+ ALL treated with chemotherapy plus either imatinib (63.4%) or dasatinib (35.6%) before allo-HSCT (n=224), Yu et al. found that patients with ACAs tended to have a higher CIR rate than patients without ACAs, and the CIR rates in these patients at 4 years were 28.9% and 21.9%, respectively (P = 0.051). However, the presence of ACAs was not associated with a higher CIR rate or higher overall mortality in multivariate analysis [19]. Seol et al. also investigated the prognostic significance of ACAs in a group of 122 adult Ph+ ALL patients in the TKI era. Among the patients (n=74) who received allo-HSCT, they found that the 5-year OS rate of the ACA group was significantly lower than that of the isolated Ph+ group (40.5±7.7% vs. 76.5±10.3%, P = 0.024), and the DFS rate also tended to be lower (45.9±8.5% vs. 61.1±12.6%, P = 0.195). In patients receiving only chemotherapy, including TKIs (n=34), the median OS (11.5±3.1 months vs. 25.3±15.8 months, P = 0.663) and DFS (17.6±10.0 months vs. 22.8±1.5 months,
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$P=0.985$) of patients in the ACA group were not significantly lower than those in the isolated Ph+ group [22].

Unlike in the above reports, several studies showed that patients with ACAs and those with isolated Ph+ ALL had no differences in prognosis. Jaso et al. retrospectively studied a cohort of 65 adult patients with Ph+ ALL who received treatment with TKI-based therapy to assess the clinical implications of cytogenetic heterogeneity. Their results showed that there was no difference in disease-specific survival (DSS) between patients with and without ACAs [7]. Short et al. evaluated the impact of ACAs in 152 adult patients with Ph+ ALL receiving the hyper-CVAD regimen plus imatinib (n=36), dasatinib (n=74) or ponatinib (n=42). In their study, the proportions of TKIs of each generation were similar between patients with and without ACAs. The 5-year RFS and OS rates did not differ significantly between patients with isolated Ph+ and patients with ACAs (RFS: 59% and 53%, respectively, $P=0.42$; OS: 57% and 56%, respectively, $P=0.51$) [20]. In the ALL-Ph-08 trial of adult patients with Ph+ ALL, Motlló et al. [21] also did not find any significant differences in the CR rate, CR duration, OS or event-free survival (EFS) between patients with and without ACAs.

To better clarify the prognostic role of ACAs, researchers further divided the population of patients with ACAs into different groups according to numeric or structural abnormalities, and the prognostic value of high hyperdiploid (HeH), hypodiploid, complex karyotypes and specific types of ACAs were defined. HeH is defined as the presence of more than 50 chromosomes and occurs in approximately 4.1-16.7% of adult patients with Ph- ALL [6, 13-15, 20-23, 32]. In the pre-TKI era, Rieder et al. observed a 100% (n=11) CR rate in the HeH group, whereas in other cytogenetic groups (n=51), including groups of patients with -7, 9p abnormalities, other ACAs and without ACAs, the CR rate was only 55-67%. With respect to prognosis, OS was also found to be superior in that HeH group compared with all other patients, including those without ACAs [14]. Data from the study by Fielding et al. also showed that HeH was related to a significantly better RFS [OR: 0.55 (0.33-0.91), $P=0.01$] [32]. Tauro et al. reported a HeH karyotype plus double Ph+ at diagnosis in five adult patients with ALL. Of the four patients who achieved cytogenetic remission after induction and subsequently received allo-HSCT, only one patient relapsed; that patient subsequently achieved durable remission through donor lymphocyte infusions [28]. Contrasting results have been obtained from studies exploring the nature and prognostic implications of ACAs in adults with Ph+ ALL by the Cancer and Leukaemia Group B (CALGB): in a cohort of 111 newly diagnosed adults with Ph+ ALL, the outlook for patients with HeH did not differ from that of those without HeH (CR rate: 88% vs. 71%, $P=0.23$; 3-year CIR: 0.74 vs. 0.6, $P=0.38$; median survival: 18 months vs. 13 months, $P=0.28$) [13]. Treatment details were, however, not available, and therefore, it is unclear how many patients with the HeH karyotype underwent allo-HSCT. In the TKI era, data from Short et al. showed that the HeH karyotype in patients with high-risk ACAs (“+der(22)t(9;22)” and “-9p”) was still associated with superior outcomes, with 5-year RFS and OS rates of 64% and 66%, respectively ($P=0.08$ and $P=0.06$) [20]. Additionally, in the analysis of a group of patients treated with allo-HSCT after receiving TKI-containing chemotherapy, Seol et al. found that the HeH karyotype was still correlated with slightly longer OS and DFS than other ploidy levels. In addition, worse OS and DFS were observed in patients carrying pseudodiploids than in patients with isolated Ph+ (median OS: 51.8 vs. 122.9 months, $P=0.025$; median DFS: 47.5 vs. 111.9 months, $P=0.057$) [22], indicating that HeH is a unique clinical entity not only in patients with Ph- ALL but also in those with Ph+ ALL.

In the literature, the incidence of complex karyotypes (CKs) varies according to the number of abnormalities included in the definition. The frequency of CKs (≥5 abnormalities) identified by Motlló et al. was 24%. In their analysis, no differences were observed in outcomes when comparing patients with or without CKs who were included in the ALL-Ph-08 study [21]. In patients treated with imatinib combined with chemotherapy followed by HSCT, Seol et al. compared prognoses between patients with isolated Ph+ and CKs (≥4 abnormalities). The OS and DFS of patients with CKs were similar between patients with and without CKs (≥4 abnormalities). The 5-year RFS and OS rates did not differ significantly between patients with isolated Ph+ and CKs (≥4 abnormalities). The 5-year RFS and OS rates did not differ significantly between patients with isolated Ph+ and CKs (≥4 abnormalities).
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series, CK was defined as more than three and five aberrations, including the Ph chromosome, which occurred in approximately 11.9% and 7.2% of patients, respectively [19]. The researchers speculated that there are two potential explanations: the implementation of intensive pediatric-like regimens in both Ph+ and Ph-negative ALL patients and the use of TKIs in Ph+ ALL patients, which could affect the prognostic impact of CKs. In the literature, the incidence of CKs (≥5 abnormalities) among adult patients with Ph+ ALL ranges from 30% to 44% [11, 13, 23, 24, 26, 27]. Additionally, in the above literature, the prognostic significance of some specific ACAs, such as +der(22), -9/9p-, -7, and +8, has been well established.

+der(22)t(9;22)

+der(22)t(9;22), also known as the double Ph chromosome, occurs at an overall frequency of 4.1-22.5% in adult Ph+ ALL patients when detected by conventional cytogenetics analysis [6, 8, 9, 13, 15, 19, 21, 23, 32], whereas its frequency increases to 30.4-36.5% when detected by FISH [7, 29]. The possible mechanism of +der(22)t(9;22) is believed to be nondisjunction occurring during mitosis in the Ph+ B-ALL clone [30]. In an investigation of the distributions of ACAs by age group, Seol et al. found that +der(22)t(9;22) was more frequently observed in the 19-30 age group (54%) than in all other age groups (P=0.008) [22]. Primo et al. observed an association between +der(22)t(9;22) and higher expression levels of CD19 (P=0.02) and CD22 (P=0.006) in a group of 46 adult BCR-ABL+ B-cell precursor ALL patients [29], while Jaso et al. found that the CD20 expression level was relatively higher in patients with +der(22)t(9;22) (P<0.001) [7]. Some studies on the cytogenetic heterogeneity of Ph+ ALL have shown that the presence of +der(22)t(9;22) is associated with an adverse prognosis, whereas several studies did not find that +der(22)t(9;22) had a negative impact. Tang et al. [30] reported an elderly patient diagnosed with +der(22)t(9;22) B-ALL. Although remission was achieved after intensive chemotherapy combined with TKIs, he still died within 13 months after diagnosis. In an earlier study conducted with 111 newly diagnosed adults with Ph+ ALL treated with front-line CALGB clinical protocols, patients with +der(22)t(9;22) had a higher CIR than patients with isolated Ph+ and all other ACAs with the exception of those with only -7 (P=0.02) [13]. Similarly, Wassmann et al. found that in 64 patients with relapsed or refractory Ph+ ALL treated with imatinib, the incidence of +der(22)t(9;22) was reported to be as high as 36%. When compared to the outcomes of patients with a single Ph chromosome, patients with a double Ph chromosome had a lower complete hematological response rate (13% vs. 39%, P=0.04), shorter progression time (1.6 months vs. 3.2 months, P=0.006), and shorter OS (5.2 months vs. 9.6 months; P=0.01) [31]. In further analysis by Yanada et al., the results indicated that ACAs, especially +der(22)t(9;22) and abn(9p), had a significant negative effect on RFS in Ph+ ALL patients who received chemotherapy plus imatinib [8]. In the setting of treatment with TKIs and allo-HSCT, Seol et al. [27] found that patients with extra Ph chromosomes had a lower DFS rate (5-year DFS: 34.1±14.9% vs. 61.1±12.6%, P=0.072) and OS rate (5-year OS: 31.6±13.2% vs. 76.5±10.3%, P=0.014) than patients with isolated Ph+. As mentioned above, Short et al. [20] suggested that patients with +der(22) and -9/9p in the absence of HeH constituted a high-risk ACA group. After receiving TKIs combined with chemotherapy, the 5-year RFS rate and OS rate in the high-risk ACA group were significantly lower than those in the isolated Ph+ group and the non-high-risk ACA group combined (RFS rate: 33% vs. 59%, P=0.01; OS rate: 24% vs. 63%, P=0.003), and the adverse impact of high-risk ACAs could be offset by administering third-generation TKIs. However, the study by Motlló et al. did not identify a particularly inferior outcome in a cohort of patients with +der(22)t(9;22) and/or -9/9p in the absence of HeH [26]. Furthermore, multicenter prospective trials (MRC UKALLXII/ECOG2993 study) conducted by Fielding et al. demonstrated that the presence of +der(22)t(9;22) was associated with a lower risk of recurrence, which conflicts with the findings of the above studies [32]. It is worth mentioning that there is a clear overlap between HeH and +der(22)t(9;22) in this article, which may have impacted the results.

Monosomy 9 or deletion 9p

The incidence of -9/9p- in adult patients with Ph+ ALL is 13.5-18.2% [21, 23]. Compared to -9, more research has focused on 9p- or 9p...
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abnormalities, which occur in approximately 3.1-22.4% of adult patients with Ph+ ALL [7, 8, 13, 14, 32]. In regard to the correlation with biological characteristics, Rieder et al. indicated that 9p abnormalities usually lack the coexpression of myeloid antigens [14]. Similarly, Primo et al. indicated that del(9p21) was associated with a lack of expression of both CD13 (P=0.04) and CD33 (P=0.03) myeloid-related antigens [29]. In contrast, Wetzler et al. found that half of patients with 9p abnormalities expressed myeloid antigens on the surface of leukemic blasts [13]. Moreover, Rieder et al. found that when compared with -7 patients, patients with 9p abnormalities tended to express p190 transcripts [14]. In terms of prognosis, Rieder et al. showed that patients in the 9p abnormalities group had a worse outcome, with a CR rate of only 58% and an OS shorter than 2 years [14]. Primo et al. [29] found that in 46 adult Ph+ ALL patients, the RFS time of patients with supernumerary Ph chromosomes, trisomy 8 and del(9p21) was significantly shortened, and only the latter had an independent risk effect on RFS. Another finding concerning -9/9p- showed that the 1-year OS rate was 23.1% and 34.3% in the conventional chemotherapy group and chemotherapy combined with imatinib group, respectively, which was significantly shorter than the OS rates of other ACAs (except -7/7p-) [23]. Correspondingly, the report from Seol et al. [22] also showed that patients with -9/9p- had a worse prognosis than those with isolated Ph+ in the setting of chemotherapy combined with imatinib followed by allo-HSCT (5-year OS: 76.5±10.3% vs. 44.0±14.3%, P=0.091; 5-year DFS: 61.1±12.6% vs. 34.3±15.3%, P=0.189). Additionally, Short et al. [20] reported that a high-risk ACA group composed of +der(22) and -9/9p independently increased the risk of recurrence or death in Ph+ ALL patients by 2-fold, and this prognostic effect did not appear to be mediated by differences in rates of CMR or allo-HSCT. However, these above results were not confirmed in the results reported by Motlló et al. [21].

Monosomy 7

Monosomy 7 was identified in 4.1-18.5% of adult Ph+ ALL patients [6-9, 13-15, 19, 21, 23, 29, 32]. Rieder et al. found that patients with -7 had notably higher expression levels of p210 transcripts and CD10 [14]. Similarly, a study reported that patients with -7 had a higher rate of positivity for CD10 (87.5%). It is worth noting that 91% of the study population was positive for CD10 [13]. Interestingly, Primo et al. [29] found that the expression levels of CD19 (P=0.02), CD22 (P=0.01), CD34 (P=0.03), and cCD79a (P=0.004) were lower in patients with -7. In the pre-TKI era, Wetzler et al. performed an analysis in 111 adult Ph+ ALL patients. The results showed that the CR rate in patients with -7 as a sole secondary abnormality was significantly lower than those in patients with +der(22)t(9;22), isolated Ph+ and all other secondary cytogenetic aberrations combined (25% vs. 78%, P=0.004); it was also lower than that in patients with secondary -7 together with at least one other ACA or with a secondary structural aberration classified as the ‘loss of 7p’ (25% vs. 82%, P=0.02) [11]. Rieder et al. found the lowest CR rate (55%) in the -7 group that included 9 adult patients with Ph+ ALL and an OS of no more than 2 years [14]. The subsequent analysis in the report from Li et al. revealed that -7/7p- had a significant impact on patient prognosis, and both were correlated with a poor outcome in both the conventional chemotherapy group and the chemotherapy combined with imatinib group. The 1-year OS of the -7/7p- group was 7.1% in the conventional chemotherapy group and 50.5% in the chemotherapy combined with imatinib group [23]. In the study by Motlló et al., a significantly worse prognosis (CR duration and EFS) was observed in patients with a mononuclear karyotype group (MK) consisting of -7 (n=10) and 9/9p (n=9) who were treated with an intensive imatinib-based protocol [21]. However, the above results were not confirmed in the study by Seol et al. [22]. In contrast, in the study by Aldoss et al., a significant deleterious effect on outcomes after allo-HSCT was observed in patients without -7 when compared to patients with isolated Ph+ and -7 [15]. Likewise, Akahoshi et al. found that the presence of -7 was not associated with a higher cumulative relapse rate or overall mortality compared with the presence of isolated Ph+ [19]. It should be noted that neither article excluded the influence of HeH.

Trisomy 8

The incidence of +8 in adult Ph+ ALL patients is 1.5-20% [6-9, 13, 19, 21, 23, 29, 32]. Primo et al. found that patients with +8 often had higher
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expression levels of CD19, CD34, CD45 and HLA-DR [29]. Before the TKI era, two studies suggested that +8 was associated with a poor prognosis [29, 32]. The study from Akahoshi et al. is the only report to describe the impact of +8 in the era of TKIs. The results showed that the presence of +8 was associated with a higher recurrence rate in univariate and multivariate analyses but had no impact on overall mortality [19]. A larger sample of patients with +8 may be needed to confirm their results.

Cryptic Ph rearrangement

In a few patients, the Ph chromosome translocation was cryptic owing to some molecular-level insertions or translocations and thus could not be detected by conventional cytogenetic analyses. At this time, RT-PCR can be used to detect the BCR-ABL1 fusion gene, and IP-FISH technology can be used to determine the presence of breakage and rearrangements in the relevant sites on chromosomes 9 and 22 to diagnose the disease. ALL patients with Ph-/BCR-ABL1+ are quite rare and constitute a unique clinical entity. At present, the proposed mechanisms underlying cryptic Ph chromosome formation in BCR-ABL1+ leukemia have mainly been based on CML research. Two major mechanisms have been proposed: ① There is a direct insertion between chromosomes 9 and 22, meaning that proto-oncogene ABL1 is directly inserted into the BCR region and vice versa, although the former is more common; ② there are two sequential translocations: the classic t(9;22), followed by reverse translocation with each other and/or another chromosome, thereby restoring normal chromosome morphology [33, 34]. This suggests that there may be genetic differences between the cryptic and the classic Ph chromosomes, and the particular formation mechanism may lead to heterogeneity in clinical characteristics and survival. Cytogenetic analysis showed that cryptic Ph chromosome translocation was detected at the time of diagnosis in approximately 5.0-10.0% of CML patients, and some of them had a normal karyotype (NK) [35]. The clinical characteristics of Ph-negative, BCR-ABL-positive patients are not different from those of Ph-positive patients [36-39], while a consensus has not been reached with regard to the prognoses in these two groups of patients. Luatti et al. reported 6 patients with of CML who were found to have NKs based on cytogenetic analysis at the time of diagnosis, and all of them received imatinib therapy. Among them, 4 patients with low-risk Sokal scores achieved complete cytogenetic response at a median of 24.5 months after receiving imatinib, 1 patient with a high-risk Sokal score developed imatinib resistance and achieved a major molecular response after switching to nilotinib, and only 1 patient with a moderate-risk Sokal score was transplanted without remission and relapsed [40]. The authors concluded that the clinical benefit of TKIs in patients with NK/BCR-ABL1+ is similar to that in patients with Ph+, and this view is also supported by Bennour et al. [41]. A study published by Hochhaus A et al. also showed that similar to Ph+ patients, CML patients with NKs benefit from nilotinib, as these patients show similar molecular responses [39]. In contrast, 3 CML patients with cryptic Ph chromosomes reported by Haigh et al. failed to achieve a major cytogenetic response after receiving imatinib therapy for at least 3 years, and in 2 of them, cytogenetic analysis at the initial diagnosis indicated the presence of NKs [34]. The authors believed that compared to classic Ph chromosomes, cryptic Ph chromosomes may confer a higher degree of resistance to imatinib. To clarify these controversial results, a large-sample study is needed to further evaluate the prognostic value of cryptic Ph in patients with CML.

Among patients with ALL, it is reported in the literature that approximately 3-11.7% of people are diagnosed with BCR-ABL+ by RT-PCR and/or IP-FISH due to the lack of cytogenetic evidence [6, 7, 15, 19]; the incidence of a NK in BCR-ABL+ ALL patients is 1.8-3.7% [8, 24], and the prognosis of these patients has not been analyzed.

Conclusions

Cytogenetic-molecular abnormalities are well-recognized and powerful independent prognostic factors in ALL patients that can be used to inform risk stratification and treatment decisions. This review systematically summarized the literature on cytogenetic abnormalities in adult Ph+ ALL patients and found that the cytogenetic abnormalities in these patients were quite heterogeneous and that there is a certain correlation between different cytogenetic
abnormalities and prognosis. However, evidence from large-sample studies of the significance of cytogenetic abnormalities in Ph+ ALL patients in regard to clinical treatment and prognosis is still lacking. Further understanding of the cytogenetic changes and their relationship with clinical prognosis will be helpful to supplement the prognostic stratification system and provide a basis for more precise individualized treatment.

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Disclosure of conflict of interest

None.

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