Adult Acute Lymphoblastic Leukemia: A Genetic Overview and Application to Clinical Practice

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Background: Cytogenetic and molecular features of diseases, such as B-cell precursor acute lymphoblastic leukemia (BCP-ALL), are increasingly used for diagnostic, prognostic, and treatment decisions in healthcare.

Objectives: This review provides information on the current recommendations for evaluating genetic aberrations in patients with BCP-ALL and details how the results are incorporated to determine risk stratification. It also offers a brief overview of developing research on newly found genetic features that may play a role in prognostic and treatment decisions.

Methods: Databases were reviewed using search terms relevant to BCP-ALL genetics, as well as to the prognostic significance of genetic changes commonly seen in BCP-ALL. Because of the scope of this review, studies identified as having outcomes with implications for clinical practice were included.

Findings: Cytogenetic and molecular aberrations in BCP-ALL are important not only for risk stratification but also for treatment decisions. To provide efficient and effective care for patients with BCP-ALL, clinical practitioners need to be aware of current recommendations and the state of prevailing research.

According to the National Comprehensive Cancer Network (NCCN, 2016), 6,590 new cases of acute lymphoblastic leukemia (ALL) were estimated to occur in 2016, along with 1,430 deaths. ALL is the most common cancer seen in children (Mullighan, 2012). Among ALL classifications, lymphoblasts derived from B-cell lineages (B-cell precursor ALL [BCP-ALL]) represent the majority of these instances, with 88% of childhood ALL and 75% of adult ALL cases identified as B cell (NCCN, 2016). Risk factors for the development of ALL can be found in Figure 1. Childhood ALL has relatively good outcomes associated with diagnosis; about 80% of those diagnosed in childhood achieve long-term event-free survival (EFS), whereas adults with ALL typically have much poorer outcomes (National Cancer Institute [NCI], 2016b).

In addition to clinical factors, such as age and white blood cell count, cytogenetic and molecular techniques have been used to provide prognostic information regarding risk stratification and treatment response in patients with BCP-ALL. In addition, the NCCN (2016) has made treatment recommendations, including whether a patient should proceed with hematopoietic stem cell transplantation (HSCT) based on these cytogenetic and molecular risk classifications.

Various cytogenetic techniques (e.g., karyotyping, fluorescence in situ hybridization [FISH]) have identified several recurrent genetic aberrations in this population shown to correspond with poor outcome. These poor risk aberrations include BCR-ABL translocation (chromosome abnormality in which parts of separate chromosomes become rearranged), MLL rearrangements, hypodiploidy, and a complex karyotype (greater than five genetic abnormalities) (Moorman, 2012). Patients harboring one or more of these alterations are identified as being in a high-risk group (NCCN, 2016). In contrast, patients with BCP-ALL found to have hyperdiploidy...
or an ETV6-RUNX1 translocation have been shown to have better EFS and overall survival (OS) (Burmeister et al., 2008; Forestier et al., 2008; Gandemer et al., 2012). Many other common chromosomal or molecular aberrations have been identified through the techniques mentioned, as well as by methods like single-nucleotide polymorphism analysis, comparative genomic hybridization arrays, and genomewide association studies (Migliorini et al., 2013; Rand et al., 2011). This review will primarily focus on literature regarding clinically relevant genetic abnormalities that are used in risk stratification of patients with BCP-ALL. In addition, examples of other common genetic aberrations that may have future clinical significance will be discussed. Figure 2 lists key terminology related to genetics and methods of genetic testing.

Literature Review

A review of current literature was performed using PubMed, MEDLINE® and CINAHL Plus as search engines. Search terms consisted of the following: genetic markers of B-cell ALL, genetics and B-cell ALL, BCR-ABL and B cell ALL, ETV6-RUNX1, CRLF2 and B-cell ALL, TCF3-PBX1 and B-cell ALL, hyperdiploidy and B-cell ALL, and prognostic markers for B-cell ALL. An overview of the literature review findings is depicted in Table 1.

Good Risk Stratification

One of the most common chromosomal rearrangements in childhood BCP-ALL is the reciprocal translocation t(12;21)(p13;q22), resulting in the fusion product ETV6-RUNX1 (also known as TEL-AML1) (Linka et al., 2013) (see Table 2). This translocation is hidden on a karyotype and requires FISH or molecular techniques for identification, and this fusion results in the impairment of B-cell differentiation while enhancing self-renewal of precursor B cells. Twin studies have identified that this alteration occurs prenatally and is a first hit in leukemogenesis (the development of leukemia in the bone marrow) (Bateman et al., 2010; Ford et al., 1998; Knudson, 1996). Results from a research trial showed that those with the highest rates of relapse-free survival (RFS) and five-year OS were carriers of the ETV6-RUNX1 fusion (Shurtleff et al., 1995). Many studies have confirmed the good prognosis for carriers of this translocation (Bhojwani et al., 2012; Moorman et al., 2014; Uckun et al., 2001). Conversely, other studies have suggested that patients with ETV6-RUNX1 may have a high incidence of relapse (Forestier et al., 2008; Seeger et al., 1999). Another study that focused on the prognosis of relapse in ETV6-RUNX1–positive patients with ALL found no significant difference between the incidence of relapse and presence of ETV6-RUNX1 fusion (Gandemer et al., 2012). Also noted was a significant increase in three-year OS after relapse for ETV6-RUNX1–positive individuals compared to patients without the translocation (p = 0.007). In particular, ETV6-RUNX1–positive patients were found to have a significantly higher five-year OS when relapse occurred at least 36 months after diagnosis rather than before (p = 0.0008) (Gandemer et al., 2012). More research is needed to fully understand the impact of ETV6-RUNX1 translocations on relapse survival measures. Despite the overall good prognosis reported for carriers of the ETV6-RUNX1 translocation, NCCN (2016) guidelines do not suggest any treatment differences based on the presence of this genomic aberration.

High hyperdiploidy is recognized as the nonrandom gain of chromosomes, resulting in increased genetic material (51–67 chromosomes) (Paulsson & Johansson, 2009). The presence of chromosomal gains was one of the first genetic abnormalities in ALL to be identified and researched for prognostic significance (Moorman, 2012; Seeker-Walker, Lawler, & Hardisty, 1978). Like the ETV6-RUNX1 genetic aberration, high hyperdiploidy is more commonly seen in...
pediatric patients with BCP-ALL (20%–30%) and is associated with favorable prognosis (Forestier et al., 2000; Moorman, 2012). Chromosomes X, 4, 5, 6, 8, 10, 14, 17, 18, and 21 are most commonly found duplicated in instances of high hyperdiploidy ALL. Presence of a triple trisomy, characterized by a gain of chromosomes 4, 10, and 17, has been shown to be associated with increased EFS in two separate pediatric ALL cohorts (Sutcliffe et al., 2005).

A study by Paulsson et al. (2013) determined that the most commonly seen extra chromosomes were 21, X, 6, 14, 18, 4, 17, 10, and 8, in order of decreasing frequency. Individuals found to have trisomies or tetrasomies (the presence of three or four chromosomes, respectively, instead of the usual two) of chromosomes 4, 6, 17, 18, and 22 were associated with having a higher probability of EFS; no correlation was found with OS. In addition, patients having triple trisomies or a modal number (most common chromosome number in a patient sample) above 53 were found to have a higher probability of EFS (Paulsson et al., 2013). In contrast, in a retrospective study looking at the prognostic impact of different combinations of chromosomal gains on disease outcomes, Kato et al. (2014) found that patients with high hyperdiploidy had no significant difference in six-year EFS and OS compared to patients without hyperdiploidy. The absence of trisomies in chromosomes 11 and 17 was associated with poorer outcomes (Kato et al., 2014). EFS for patients with high hyperdiploidy without gains in chromosome 11 or 17 was reported to be 71%, compared to 83% for patients with a gain of either 11 or 17 (p = 0.027) (Kato et al., 2014).

Despite the early classification of high hyperdiploidy as a favorable risk marker, the mechanisms leading to leukemogenic transformation are still poorly understood (Moorman, 2012). The chromosomal gains are suspected to occur early in B-cell development during a single event while in utero. Similar to ETV6-RUNX1, this is suggested to be the first hit needed in the process of leukemogenesis (Knudson, 1996). Continued research is needed to delineate the addition of driver genes from passenger genes in this genotype.

### Poor Risk Stratification

**BCR-ABL** positivity (Philadelphia chromosome) is the most common chromosomal aberration found in adults with ALL. It is reported to be present in about 25% of adult patients with ALL and in 3%–5% of pediatric patients with ALL.

### TABLE 1. Clinically Relevant Genetic Abnormalities in B-Cell Precursor Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Genetic Aberration</th>
<th>Gene or Chromosome</th>
<th>Clinical Relevance</th>
<th>NCCN Recommendation</th>
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<tbody>
<tr>
<td>11q23 (MLL) rearrangements</td>
<td>MLL-AFF1 (AF4), MLL-MLLT3 (AF9)</td>
<td>Poor response to therapy, with shorter RFS</td>
<td>High risk</td>
</tr>
<tr>
<td>High hyperdiploidy</td>
<td>21, X, 6, 14, 18, 4, 17, 10, 8</td>
<td>Favorable prognosis; however, differences are seen depending on the chromosomes gained.</td>
<td>N/A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>t(1;19) (q23;p13)</td>
<td>TCF3-PBX1</td>
<td>Previously shown to be associated with poor prognosis; newer studies have brought this into question. Alternative data from recent research have led to unclear prognostic significance.</td>
<td>N/A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>t(9;22) (q34;q11.2)</td>
<td>BCR-ABL1</td>
<td>Poor prognosis with lower OS and lower rates of complete remission; TKI treatment is recognized as the standard of care.</td>
<td>High risk</td>
</tr>
<tr>
<td>t(12;21) (p13;q22)</td>
<td>ETV6-RUNX1</td>
<td>Good prognosis, with high OS even in relapse populations</td>
<td>N/A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Xp22.33 (CRLF2) rearrangements</td>
<td>CRLF2-P2RY8, CRLF2-IGH@</td>
<td>Differing results, with some showing lower OS and EFS; others show only intermediate risk.</td>
<td>N/A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Although evidence for clinical significance of these genomic alterations has been identified, they are not included in NCCN’s risk assessment recommendations.

**EFS**—event-free survival; **N/A**—not available; NCCN—National Comprehensive Cancer Network; OS—overall survival; RFS—relapse-free survival; TKI—tyrosine kinase inhibitor

**Note.** Based on information from NCCN, 2016.

### TABLE 2. Prevalence of Genetic Aberrations in Childhood and Adult Adult Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Genetic Aberration</th>
<th>Prevalence in Children (%)</th>
<th>Prevalence in Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR-ABL1</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>CRLF2</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>ETV6-RUNX1</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>High hyperdiploidy</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>MLL rearrangements</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>TCF3-PBX1</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

**Note.** Based on information from Harrison, 2013; National Comprehensive Cancer Network, 2016.

**Note.** The prevalence of poor prognostic genetic aberrations is more common in adults, whereas good prognostic aberrations are more widespread among children. This may lend some understanding to the more favorable outcomes for children with B-cell precursor acute lymphoblastic leukemia compared to adults.
The Philadelphia chromosome was initially described in 1960 (Mullighan, 2012). The Philadelphia chromosome occurs as a result of a translocation between the ABL gene on chromosome 9 and the BCR gene on chromosome 22 (see Figure 3). This translocation produces a chimeric (containing two or more genetically distinct populations) BCR-ABL gene and is associated with lower complete remission rates and inferior OS (Couban et al., 2014). Because of data indicating worse outcomes in these patients, the NCCN (2016) has recommended that patients with the Philadelphia chromosome abnormality be considered for HSCT, the only option for potential curative treatment.

The Philadelphia chromosome was initially described in patients with chronic myelogenous leukemia (CML), and the development of tyrosine kinase inhibitors (TKIs) to target this mutation was initiated for these patients (Kantarjian & Talpaz, 2001). The use of this drug class has expanded to patients with ALL and is recognized as a standard of treatment for all patients with BCR-ABL positivity, per NCCN (2016) guidelines. Although the addition of TKI therapy to standard treatment regimens for these patients has improved outcomes, a need for additional research exists within this field. Resistance of BCR-ABL to TKIs has been witnessed in many patients and is attributed to point mutations within the ABL kinase domain; more than 100 of these mutations have been identified to date (Egan, Beppu, & Radich, 2015).

Many point mutations within the BCR-ABL kinase domain have been studied and defined for CML, primarily those associated with tyrosine kinase resistance for treatment of disease (Khorashad et al., 2013). Point mutations are being evaluated in ALL for associations with prognosis of disease. Soverini et al. (2011) performed a retrospective analysis of patients’ bone marrow (N = 15) to evaluate for point mutations among patients with Philadelphia-positive ALL. The authors’ review revealed 61 mutations, five of which had previously been reported with resistance to TKIs (V289A, T315I, F317L, E281K, and H396F); the remaining 56 mutations were not previously associated with TKI resistance and were randomly distributed across the kinase domains (Soverini et al., 2011). The NCCN (2016) has recommended specific TKIs depending on point mutations; ponatinib (Iclusig®) has specific activity against T315I mutations and is recommended in combination with standard chemotherapy for patients with ALL found to have this mutation. Additional recommendations regarding TKI therapy for point mutations in BCR-ABL, per the NCCN, can be seen in Table 3.

### Table 3. Recommended TKIs for Point Mutations of BCR-ABL

<table>
<thead>
<tr>
<th>BCR-ABL Point Mutation</th>
<th>Recommended TKI</th>
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<tr>
<td>E255K/V, F317LV/IC, F359V/CI</td>
<td>Bosutinib (Bosulif®)</td>
</tr>
<tr>
<td>F317LV/IC, T315A, V299L</td>
<td>Nilotinib (Tasigna®)</td>
</tr>
<tr>
<td>T315I</td>
<td>Ponatinib (Iclusig®)</td>
</tr>
<tr>
<td>Y253H, E255K/V, F359V/CI</td>
<td>Dasatinib (Sprycel®)</td>
</tr>
</tbody>
</table>

**Note.** Based on information from National Comprehensive Cancer Network, 2016.

(q21;q23)/MLL-AFF1(AF4)], followed by [t(9/11)(p22;q23)/MLL-MLLT3(AF9)] (Mullighan, 2012). A cytogenetic review of patients with BCP-ALL by Gómez-Seguí et al. (2012) confirmed prior study results of shorter RFS. The study had statistically significant results (p = 0.05), with RFS at 4 months in the MLL group compared to 22 months in the group of those without MLL rearrangement (Gómez-Seguí et al., 2012). MLL-rearranged ALL exhibits distinct gene expression profiles, as well as epigenetic profiles. In addition, MLL-rearranged ALL is exemplified by fms-related tyrosine kinase 3 (FLT3) overexpression; some animal models have demonstrated potential benefit in the use of a new class of drugs, FLT3 inhibitors, as treatment (Mullighan, 2012). More studies are needed to determine all possible MLL rearrangements and whether potential treatment options may be developed to target MLL rearrangement in patients with ALL.

Developing Research

Research has suggested that deregulation of cytokine receptor-like factor 2 (CRLF2) could identify a group of individuals who have poor prognosis (Cario et al., 2010; Chen et al., 2012). The two most well-characterized genetic abnormalities responsible for aberrant CRLF2 expression are an interstitial deletion, resulting in the shift of a region in the PAR1 promoter next to CRLF2 (P2RY8-CRLF2), and a translocation of CRLF2 with the immunoglobulin heavy chain locus (IGH@-CRLF2). In addition, overexpression of CRLF2 has been shown to correlate with mutations in the Janus kinase genes (Chen et al., 2012).

Results from the ALL-Berlin-Frankfurt-Münster 2000 trial (N = 1,933) in a childhood BCP-ALL (aged 18 years or younger) population (n = 555) found that patients with high CRLF2 expression had worse six-year EFS compared to those with low CRLF2 expression (61% versus 83%, respectively) (Cario et al., 2010). In addition, another study found high CRLF2 expression to be a significant predictor of RFS (Chen et al., 2012). Other studies have suggested that little to no difference exists in outcomes related to CRLF2 deregulation (Ensor et al., 2011; Krawczyk et al., 2013). Results from these studies suggest that CRLF2 expression be categorized in an intermediate-risk group. Research in larger populations is needed to determine the true prognostic importance of CRLF2 rearrangements in BCP-ALL.

Another common rearrangement observed in BCP-ALL is the TCF3-PBX1 translocation. This translocation, t(1;19) (q23;p13), is seen in about 3%–5% of childhood and adult patients with BCP-ALL (Barber et al., 2007). The TCF3-PBX1 fusion product combines the DNA binding homeodomain (part of the protein that binds to specific sites on a gene) of PBX1 with the transactivating domain (transcription factor domain that has binding sites for other proteins) of TCF3, resulting in increased activation of PBX1 target genes (Diakos et al., 2014; Hunger, 1996). Early studies suggested that the presence of TCF3-PBX1 was associated with a poor prognosis (Crist et al., 1990; Seeker-Walker et al., 1992). However, other studies suggest that, in part because of the intensification of treatment regimens, the rearrangement may not be associated with increased risk (Asai et al., 2014; Burmeister et al., 2010; Felice et al., 2011).

Burmeister et al. (2010) studied a group of adult patients with BCP-ALL (N = 402, with 23 expressing TCF3-PBX1), reporting that individuals with the translocation actually had higher OS and remission duration compared to non–TCF3-PBX1 carriers. A study by Felice et al. (2011) in a pediatric population found a similar result, with TCF3-PBX1 mutation carriers having an EFS rate of 85% compared to 60% for TCF3-PBX1–negative individuals. A study by Asai et al. (2014) found that TCF3-PBX1 was not associated with poor outcomes for measures of OS and EFS. Conversely, newer studies support the poor outcome previously associated with carriers of TCF3-PBX1 (Andersen et al., 2011; ElGendi, Abdelmaksoud, Eissa, & Abusikkien, 2014; Iqbal et al., 2013). In addition, these studies also found that TCF3-PBX1 may be associated with higher instances of central nervous system involvement at presentation and relapse (ElGendi et al., 2014; Iqbal et al., 2013). These conflicting results necessitate more research in the areas of survival analysis and the potential for CNS involvement in patients with BCP-ALL with the TCF3-PBX1 rearrangement to provide accurate, clinically relevant prognostic information for this subgroup.

Many other cytogenetic and molecular aberrations in patients with ALL are being identified and studied, such as IKZF1 gene alterations (Tokunaga et al., 2013). The incidence and clinical impact of these alterations have yet to be determined, and how IKZF1 alterations contribute to leukemogenesis is still unknown (Mullighan, 2012). Continued research is needed on IKZF1, as well as other genomic aberrations, to provide a clearer picture of disease development and progression. This increased understanding will result in better treatment strategies and patient outcomes.

Conclusion

Cytogenetic and molecular features of diseases, such as BCP-ALL, are increasingly incorporated into prognostic classification and treatment decisions. The NCCN (2016) and American Society for Hematology (Arber, 2016) have incorporated many of these findings into their recommendations for stratification of patients, including additional guidance on how to treat patients with high-risk BCP-ALL.
The role of nurses and other healthcare providers should be to remain knowledgeable about current recommendations that are considered to be best practice to obtain optimal outcomes for patients with ALL. Appropriate stratification of patients is imperative for proper diagnosis and treatment and early referral for HSCT in high-risk patients (NCCN, 2016). Many genetic alterations that are being studied are not defined as being the standard of care by national guidelines. As more data on whether these alterations have clinical significance in terms of prognosis and treatment outcomes become available, healthcare providers should be prepared to incorporate them into practice. To provide safe and quality care to patients, providers should be current on how these cytogenetic and molecular features are tested for and how to interpret results.

References


