REVIEW ARTICLE

New and emerging prognostic and predictive genetic biomarkers in B-cell precursor acute lymphoblastic leukemia

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease at the genetic level. Chromosomal abnormalities are used as diagnostic, prognostic and predictive biomarkers to provide subtype, outcome and drug response information. t(12;21)/*ETV6-RUNX1* and high hyperdiploidy are good-risk prognostic biomarkers whereas *KMT2A* (*MLL*) translocations, t(17;19)/*TCF3-HLF*, haploidy or low hypodiploidy are high-risk biomarkers. t(9;22)/*BCR-ABL1* patients require targeted treatment (imatinib/dasatinib), whereas iAMP21 patients achieve better outcomes when treated intensively. High-risk genetic biomarkers are four times more prevalent in adults compared to children. The application of genomic technologies to cases without an established abnormality (B-other) reveals copy number alterations which can be used either individually or in combination as prognostic biomarkers. Transcriptome sequencing studies have identified a network of fusion genes involving kinase genes - *ABL1*, *ABL2*, *PDGFRB*, *CSF1R*, *CRLF2*, *JAK2* and *EPOR*. *In vitro* and *in vivo* studies along with emerging clinical observations indicate that patients with a kinase-activating aberration may respond to treatment with small molecular inhibitors like imatinib/dasatinib and ruxolitinib. Further work is required to determine the true frequency of these abnormalities across the age spectrum and the optimal way to incorporate such inhibitors into protocols. In conclusion, genetic biomarkers are playing an increasingly important role in the management of patients with ALL.

Clinical epidemiology of acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease at the demographic, clinical and genetic levels. Although ALL can occur at any age, it is more prevalent among children, particularly those aged 3-6 years old. More than 50% of the 600 patients diagnosed annually in England and Wales will be aged 0-14 years old, and fewer than 20% will be over 60 years old (A Moorman, unpublished observations, 2016). Males are diagnosed with ALL more frequently than females, resulting in a sex ratio of 1.4:1, respectively. Survival rates from ALL have improved dramatically over the past four decades but vary significantly with age. Children treated on modern protocols have survival rates exceeding 90%.[1,2] In contrast, survival from adult ALL is approximately 40% for those patients aged between 25 and 59 years old and is significantly lower (<20%) for older adults.[3-5] Improvements in outcome have resulted from optimizing the use of a relatively small number of anti-leukemic drugs, better supportive care, and the introduction of treatment stratification based on risk factors. Traditional risk factors include sex, age, white cell count (WCC) and immunophenotype (B-cell/T-cell) with males, older patients and those with higher white cell count or T-cell ALL having a greater risk of relapse and death. More recently, treatment response (reduction in leukemic burden) has been used to direct treatment.[1,2,6] Measuring treatment response or minimal residual disease is performed either by tracking the leukemic clone in serial samples by PCR or flow cytometry looking for specific Ig/TCR rearrangements or immunopheno-

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typic profiles. Minimal residual disease (MRD) is a useful tool for treatment stratification and has been adopted by many clinical study groups in order to risk-stratify patients. One of the major advantages of MRD is that it is applicable to the majority of patients (>90%). However, as MRD measures treatment response, it is protocol dependent, and MRD time points and thresholds need to be carefully assessed for each type of protocol. There is ongoing debate about how to best integrate genetic risk factors and MRD into a cohesive clinical strategy for improving outcome in ALL and different models are emerging (see below). However, one important advantage of genetic risk factors is that they can also act as useful therapeutic targets; for example, the recently identified network of gene fusions which are sensitive to tyrosine kinase inhibitors.[7]

Genetic landscape of acute lymphoblastic leukemia

Like all cancers, ALL is characterized by the sequential acquisition of genetic aberrations which drive the initiation and maintenance of the leukemic clone.[8,9] Broadly speaking, genetic abnormalities can be considered as primary or secondary events. Primary abnormalities are responsible for the initiation of a pre-leukemic clone which, upon the acquisition of additional secondary or co-operating genetic changes, converts into overt ALL. Elegant studies have demonstrated that the pre-leukemic clone can lie dormant for several years prior to activation.[10] Primary abnormalities in ALL are often chromosomal translocations, resulting in chimeric fusion genes, or gross aneuploidy (gain or loss of multiple whole chromosomes); whereas secondary abnormalities are usually copy number alterations (CNA) (frequently micro-deletions) and point mutations. Primary abnormalities are, by definition, present in all the cells comprising the leukemic clone and define the key features of the leukemia. In contrast, secondary abnormalities are present only in a subset of the leukemic cells and give rise to a complex branching subclonal architecture.[11] In ALL, there is a strong correlation between the primary chromosomal abnormality and the spectrum of secondary or co-operating mutations observed in that subtype (Figure 1).[12] The vast majority of aberrations act either as primary or secondary abnormali-

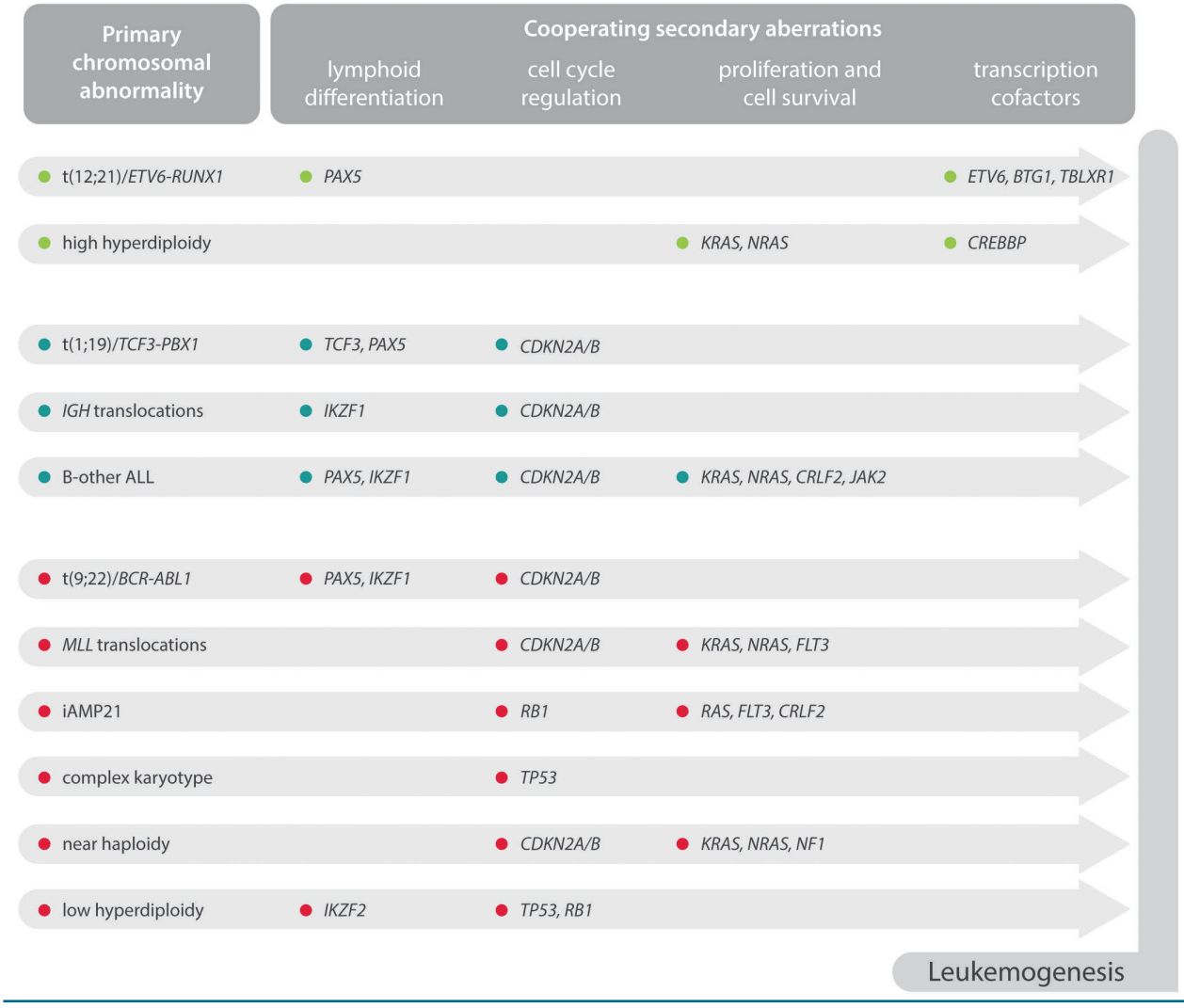


Figure 1. Overview of key co-operating mutations in relation to distinct genetic subtypes of B-cell precursor acute lympholastic leukemia.

ties; however, a few have been reported as both types in different contexts. The comprehensive genetic testing of patients suspected of having ALL can confirm the diagnosis of ALL and identify important prognostic and predictive biomarkers which can be used to tailor therapy. Primary genetic abnormalities are more reliable prognostic markers than secondary aberrations, probably due to the fact that they define the key features of the clone and are ubiquitous. Therefore, the focus of most screening algorithms in ALL is on the reliable detection of key primary chromosomal abnormalities used to stratify patients into different risk groups. This can be achieved using a combination of cytogenetics, FISH (fluorescence *in situ* hybridization) and RT-PCR (reverse transcription polymerase chain reaction) but more modern techniques such as multiplex ligation-dependent probe amplification (MLPA), DNA copy number arrays and targeted gene resequencing are increasingly being used to screen for new and emerging genetic biomarkers. In this article, I will describe and discuss established, new, and emerging diagnostic, prognostic and predictive genetic biomarkers in the major subtype of B-cell precursor ALL.

Good-risk prognostic genetic biomarkers

t(12;21)/*ETV6-RUNX1* and high hyperdiploidy (51-65 chromosomes) are well recognized diagnostic and prognostic biomarkers in both pediatric and adult ALL. *ETV6-RUNX1* results from the chromosomal translocation, t(12;21)(p13;q22) which is cytogenetically cryptic and therefore FISH or RT-PCR is required for its accurate detection. High hyperdiploidy (51-65 chromosomes) is readily detectable by cytogenetics but also by the application of locus specific and centromeric FISH probes as the pattern of chromosomal gain is non-random with eight chromosomes accounting for more than 75% gains; namely chromosomes X, 4, 6, 10, 14, 17, 18 and 21.[13-17] These two biomarkers account for approximately 60% of pediatric and adolescent ALL but less than 15% of adult ALL (Figure 2) with *ETV6-RUNX1* being virtually non-existent among adults over 30 years of age.[18] Patients with either of these abnormalities have a very good outcome compared to their age-matched counterparts, and overall survival (OS) rates at five years is over 90% in pediatric ALL and 55% in adult ALL (Figure 3A).[19,20] Although many studies have examined the prognostic relevance of secondary abnormalities (including *IKZF1* deletion, *ETV6* deletions, RAS pathway mutations) within these two subgroups, no reliable additional biomarkers have emerged.[21-25] In addition, within high hyperdiploidy, many studies have assessed specific trisomies, modal chromosome number and structural abnormalities as additional prognostic markers. Although specific trisomies (+4, +10, +17 and +18) have emerged as clinically relevant biomarkers within particular treatment protocols, they have not proved to

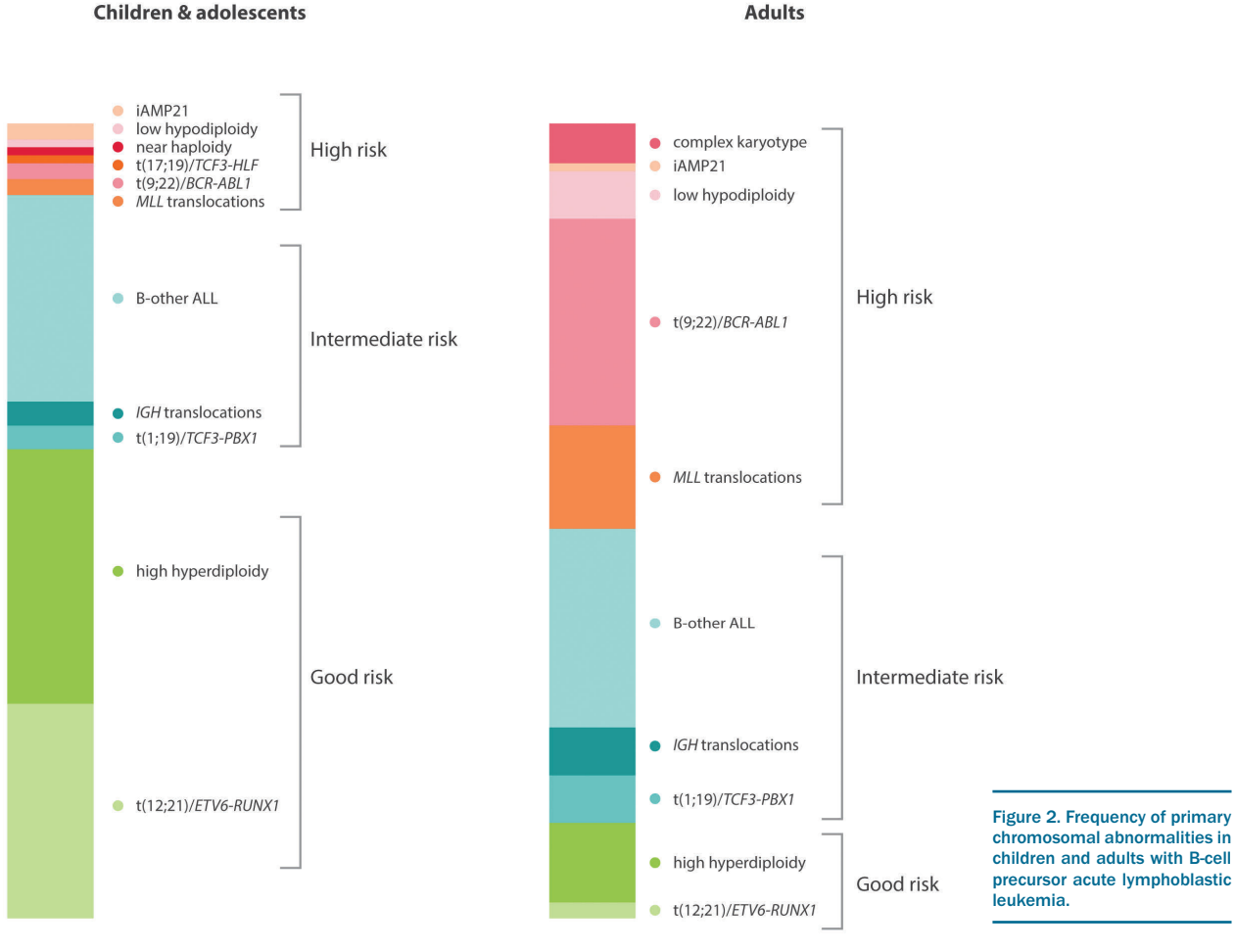


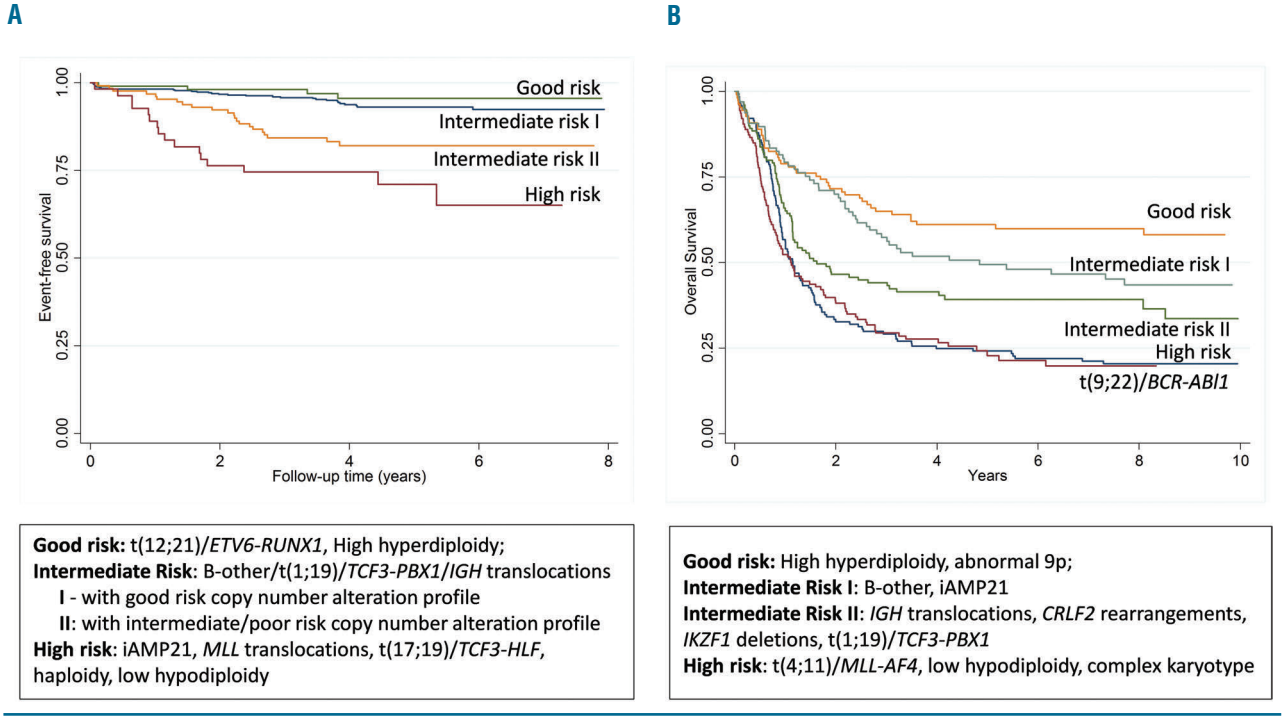
Figure 2. Frequency of primary chromosomal abnormalities in children and adults with B-cell precursor acute lymphoblastic leukemia.

be universally applicable.[13-17] Given the excellent outcome of patients with *ETV6-RUNX1* and high hyper-diploidy in pediatric ALL, it is difficult to envisage further clinically actionable biomarkers emerging from within this risk group.

High-risk prognostic genetic biomarkers

Five chromosomal abnormalities [*KMT2A* (*MLL*) translocations, t(9;22)/*BCR-ABL1*, t(17;19)/*TCF3-HLF*, near haploidy and low hypodiploidy] are well recognized prognostic biomarkers of high-risk disease at all ages.[8] The *KMT2A* (*MLL*) gene located at 11q23 undergoes rearrangements, usually translocations, with a plethora of partner genes; with *AFF1* (*AF4*), *MLLT1* (*ENL*), *MLLT4* (*AF6*), *MLLT3* (*AF9*) and *MLLT10* (*AF10*) accounting for more than 85% ALL cases.[26] Near haploidy and low hypodiploidy are defined by massive chromosomal loss resulting in a modal number of less than 30 chromosomes and 30-39 chromosomes, respectively.[27] Recent studies have identified the *RAS* gene and *TP53* mutations, respectively, as key additional drivers of these distinct ploidy subgroups.[28] Both subgroups display a propensity to undergo chromosome doubling which can create a diagnostic dilemma if only the doubled-up subclone is dividing and hence masquerades as high hyperdiploidy.[27] However, the pattern of chromosomal loss/gain is distinctive, and these two subgroups are usually distinguishable from one another. All *MLL* translocations, as well as *BCR-ABL1* and *TCF3-HLF*, are readily detectable by cytogenetics, FISH and RT-PCR. Given the promiscuity of the *MLL* gene, FISH with a dual-color break-apart directed to the 11q23 locus is the most convenient method of detection. The frequency of these five high-risk genetic aberrations is four times higher in adults compared to children and adolescents (Figure 2), explaining, in part, the strong correlation between age and outcome (Figure 3A and B). *KMT2A* (*MLL*) translocations are also highly prevalent in infant ALL (<1 year) where they account for approximately 80% of patients.[29] Patients with one of these five abnormalities are classified as high risk in UK protocols and treated with the most intensive regimens.[19] If treated as standard risk, patients with one of these aberrations have an approximately 3-fold increased risk of relapse and/or death compared to intermediate-risk patients.[19] *BCR-ABL1* is a predictive biomarker for targeted therapy with a tyrosine kinase inhibitor, such as imatinib or dasatinib.[30] Tyrosine kinase inhibitors directly inhibit the leukemogenic effect of the BCR-ABL1 oncoprotein and, in combination with standard chemotherapy, produce significantly superior outcomes in patients of all ages.[31,32] Recent studies of *MLL*-rearranged ALL have highlighted the importance of epigenetic dysregulation in this sub-group and, in particular, the requirement for the histone methyltransferase, DOT1L.[33] These studies raise the possibility of developing a targeted therapy for these high-risk patients using DOT1L inhibitors such as EPZ004777.[34]

In adult ALL, patients without an established chromosomal translocation or ploidy sugroups are classified as having a complex karyotype if their karyotype harbors five or more chromosomal abnormalities.[35] This definition identified approximately 5% patients which have a higher risk of relapse or death in some, but not all, treatment protocols (Figure 3B).[35-37] Given the subjective nature of chromosomal analysis and the vagaries of cytogenetic nomencla-



Good risk: t(12;21)/*ETV6-RUNX1*, High hyperdiploidy;
Intermediate Risk: B-other/t(1;19)/*TCF3-PBX1*/*IGH* translocations
I - with good risk copy number alteration profile
II: with intermediate/poor risk copy number alteration profile
High risk: iAMP21, *MLL* translocations, t(17;19)/*TCF3-HLF*, haploidy, low hypodiploidy

Good risk: High hyperdiploidy, abnormal 9p;
Intermediate Risk I: B-other, iAMP21
Intermediate Risk II: *IGH* translocations, *CRLF2* rearrangements, *IKZF1* deletions, t(1;19)/*TCF3-PBX1*
High risk: t(4;11)/*MLL-AF4*, low hypodiploidy, complex karyotype

Figure 3. Outcome of patients with acute lymphoblastic leukemia (ALL) by genetic risk group. (A) Event-free survival of children and adolescents with B-cell precursor ALL treated on ALL2003 and stratified by cytogenetics and copy number alterations profile. (B) Survival of adults treated on UKALLXII stratified by genetic risk group.

ture, complex karyotype is not an ideal biomarker for the reliable identification of high-risk patients. The intensive research described below aimed at unraveling the genetics of B-other ALL. This will, in time, provide a more reliable biomarker for this subset of patients.

t(1;19)(q23;p13)/*TCF3-PBX1*

Approximately 3% of children/adolescents and 6% of adults harbor the translocation t(1;19) which in more than 95% cases results in *TCF3-PBX1* fusion.[38] It is an intriguing biomarker in ALL: as a diagnostic biomarker it correlates tightly with a pre-B immunophenotype with the leukemic cells expressing cytoplasmic μ. It is readily and reliably identified by cytogenetics, FISH and RT-PCR, making it an ideal prognostic biomarker in practical terms. However, outcome studies have produced variable results and there is a stark contrast between pediatric and adult ALL regarding how these patients are viewed in terms of risk. In pediatric cohorts, early studies reported *TCF3-PBX1* as a biomarker of poor prognosis, but most recent studies from protocols delivering more intensive chemotherapy have reported considerably improved outcome (OS >80%).[19,39-41] Interestingly, some studies have reported an association with central nervous system (CNS) relapse and a poor outcome after first relapse, indicating substantial clinical heterogeneity, which may point to the presence of additional prognostic biomarkers in this subgroup.[40] There is a similar story in adult ALL, with the larger and more recent studies showing *TCF3-PBX1* to be associated with intermediate risk.[35,42,43] However, some clinical study groups classify adult patients with *TCF3-PBX1* as high risk and treat these patients more aggressively.[44]

Intrachromosomal amplification of chromosome 21 (iAMP21)

In the past few years, iAMP21 has become an important prognostic and predictive biomarker in childhood ALL. iAMP21 is a grossly abnormal chromosome generated *via* breakage-fusion-bridge cycles and chromothripsis.[45] The result of these rearrangements is the amplification and loss of multiple regions along the length of chromosome 21. The consistent feature of all iAMP21 cases is the amplification of the *RUNX1* locus located at 21q22.12, which provides the basis for a convenient and reliable detection assay: FISH using locus-specific probes.[46] The internationally accepted definition of iAMP21 is three or more extra copies of the *RUNX1* gene on a single abnormal chromosome 21, equating to more than 5 signals per cell.[46] Patients with iAMP21 are older than other children with ALL (median age 9 years) but a lower median WCC.[47,48] Studies by the UK and the Children's Oncology Group (COG) have reported that iAMP21 patients treated as standard risk have a very high rate of relapse (>80%) but that this is significantly reduced (<20%) when the pa-tients are treated intensively, notably on the most intensive arm of UKALL2003 (regimen C).[49,50] Thus, iAMP21 can be considered both a prognostic and predictive biomarker in pediatric ALL. However, the Associazione Italiana di Ematologia ed Oncologia Pediatrica (AEIOP) and Berlin-Frankfurt-Munster (BFM) study groups have reported that MRD can also be used to identify iAMP21 patients at risk of relapse.[51,52] As iAMP21 is extremely rare among adult patients (≥25 years), its prognostic effect in this age group is unclear.

Translocation involving the IGH locus

IGH translocations are well recognized in lymphoid malignancies where the juxtaposition of an oncogene to the *IGH* enhancer drives its overexpression.[53] *IGH* translocations are frequent in lymphomas and mature leukemias. However, recent studies have revealed an extensive network of *IGH* translocations specific to BCP-ALL, which drive the expression of a variety of oncogenes.[54] The most common *IGH* translocation involves *CRLF2*, accounting for approximately 25% of cases. Other recurrent translocation partners include five members of the *CEBP* gene family and *ID4*, accounting for approximately 10% and 7% of cases, respectively. Although numerous partner genes have yet to be identified, there does not appear to be any functional link between the partner genes of *IGH* translocations. Given the wide spectrum of these partners and the finding that several, including *IGH-CRLF2*, are cytogenetically cryptic, FISH using a break-apart probe directed to the *IGH* locus provides a reliable detection method. The most notable clinical feature of patients with *IGH* translocations is their age profile. Their frequency is low among children under ten years of age (<3%) but considerably higher (10%) among adolescents and young adults (15-24 years).[54] Patients with *IGH* translocations have been shown to have an inferior outcome compared to other patients in both the adolescent and young adult setting.[54]

Dissecting B-other acute lymphoblastic leukemia

Approximately 70% of pediatric and 60% of adult patients with ALL harbor a genetic abnormality regarded as an established diagnostic and/or prognostic biomarker (Figure 2). Patients without one of these abnormalities are collectively referred to as B-other ALL. Unraveling the genetic landscape of B-other ALL has been the main focus of research efforts over the past ten years. A wide variety of techniques, ranging from cytogenetics to whole genome sequencing, have been applied in order to define and assess biomarkers in this subgroup. Two main approaches have shaped the current research strategy. Firstly, a plethora of micro-deletions affecting genes in key pathways, including lymphoid differentiation, cell-cycle differentiation and proliferation were discovered using SNP arrays in both childhood and adult ALL.[55-58] Numerous studies have assessed the role of individual lesions and copy number alteration (CNA) profiles as prognostic biomarkers. Almost all of these CNA are secondary aberrations which are sub-clonal and can be acquired, lost or enriched for between diagnosis and relapse.[59-61] Secondly, gene expression profiling has been used to define cytogenetic subgroups and at the same time identify novel subgroups of patients.[62,63]

IKZF1 and *ERG* deletions

IKZF1 deletions occur in 15% of pediatric and 30% of adult ALL, but are more prevalent among patients with

BCR-ABL1 (>60%).[14,64-66] In addition, they are associated with other high-risk features such as older age, high WCC, persistent MRD, and Down syndrome.[12,67] Initial reports suggested that patients harboring an *IKZF1* deletion had a significantly inferior outcome, implying that it was a reliable prognostic marker.[68] However, more recent studies based on larger and more representative cohorts have suggested that its effect is pleiotropic.[69-73] In particular, a COG study found that *IKZF1* deletions were prognostic among National Cancer Institute (NCI) high-risk (age >10 years or WCC >50x10^9/L) patients but not NCI standard-risk patients.[74] In addition, studies have found that the presence of an *IKZF1* deletion does not abrogate the prognosis associated with other good risk genetic abnormalities such as *ETV6-RUNX1* and *ERG* deletions (see below).[21,72,73,75] These results correlate with those from studies that have examined the interaction of *IKZF1* deletions and MRD. Several studies have now reported that *IKZF1* deletions are not prognostic among patients who clear their disease rapidly. Instead the prognostic effect is restricted to, or at least strongest in, patients with higher levels of disease burden after initial chemotherapy.[69,70,76] Furthermore, *IKZF1* deletions were not associated with a greater risk of second relapse or death after a first marrow relapse.[77] However, within the context of *BCR-ABL1* ALL, it appears that *IKZF1* deletions are strongly prognostic even when these patients are treated with imatinib-containing regimens.[66] Therefore, it is likely that *IKZF1* deletions, which are secondary abnormalities, are also a "secondary" marker of poor outcome rather than being a key independent prognostic biomarker.

Three studies have now identified a distinct subgroup of pediatric B-other ALL patients characterized by a monoallelic deletion of the *ERG* gene.[63,72,73] The frequency is 10%-15% of B-other ALL which equates to 3%-5% of BCP-ALL overall. Interestingly, these patients have an excellent outcome of over 90% at five years despite having a very high incidence of *IKZF1* deletions (approx. 40%).[63,72,73] Even though the presence of an *ERG* deletion appears to define a distinct subgroup of B-other ALL, there is evidence that it is a sub-clonal event which can be lost or gained between diagnosis and relapse. Its role as a robust prognostic marker requires urgent further investigation, particularly within adult ALL.

CRLF2 deregulation

The interstitial deletion in the PAR1 region of chromosome X and Y gives rise to dysregulation of *CRLF2 via* juxtaposition of this gene to the *P2RY8* promoter.[78,79] Overexpression of *CRLF2* can also arise from an IGH translocation and, more rarely, an activating mutation.[80] In addition, high *CRLF2* expression can occur in patients who lack a clear genetic alteration at this locus. *CRLF2* rearrangements have been associated with activation of the JAK-STAT, ERK and mTOR/PI3K pathways and it is noteworthy that approximately 50% of cases also harbor a *JAK2* mutation.[7,78,79,81] The overall frequency of *CRLF2* rearrangements in BCP-ALL is 5% but is higher in B-other (30%) and patients with Down syndrome (>50%).[67,78] Studies investigating the prognostic relevance of *CRLF2* have varied in the method used to identify cases. Some studies have focused on genetic rearrangements whilst others have measured CRLF2 mRNA expression. Perhaps unsurprisingly the results of these studies have been conflicting with some studies concluding that it was a prognostic marker of poor outcome[82,83] while others concluded that it was not relevant in the context of other risk factors.[52,67,75,84] Interestingly, three studies found discordant results depending on whether *CRLF2* involvement was determined by genetics or expression,[74,82,85] thereby emphasizing the requirement for standardized definitions. In addition, *P2RY8-CRLF2* is a secondary abnormality and often present only within low level subclones which do not drive relapse.[86] Although *CRLF2* does not appear to be a robust prognostic marker, it is an attractive therapeutic target particularly within the context of Down syndrome patients who are prone to the toxic side-effects of chemotherapy. Therefore, inhibition of the JAK and PI3K pathways represent potential therapeutic strategies in these cases.[7,87]

Copy number alteration profiling

The major limitation to assessing the prognostic relevance of individual CNAs is that it does not take into account the fact that many cases will harbor more than one deletion while others may have none. An alternative approach has been to integrate a CNA profile into the existing established cytogenetic risk-group classification. Here a CNA profile based on the presence or absence of the eight most frequently deleted genes segregates patients with intermediate-risk cytogenetics (mostly B-other) into two new genetic risk groups (Figure 4).[88] The prognosis of patients with good- or high-risk cytogenetics was unaffected by their CNA profile. However, intermediate cytogenetic risk patients, separated into two subgroups (good risk *vs.* intermediate-/high-risk CNA profile) with differential OS rates (98% *vs.* 87%).[88] Thus, this approach has identified a group of B-other ALL patients with a good-risk CNA profile and a very low risk of relapse who potentially could be considered for treatment deintensification. The validity of such an approach is supported by observations that the prognostic effect of *IKZF1* deletions depends on the presence/absence of other deletions (e.g. *ERG* and *CDKN2A/B* deletions) and MRD levels.[63,72,73,76]

BCR-ABL1-like

Four independent studies reported a subgroup of B-other ALL patients with a gene expression profile similar to *BCR-ABL1* positive ALL.[68,89-91] Although these patients lacked the fusion gene they shared the same poor outcome. The subgroups were termed *BCR-ABL1*-like or Ph-like and both accounted for approximately 50% of B-other ALL cases. There were significant differences in the genetic make-up of these subgroups; especially with respect to the prevalence of *IKZF1* deletions, *CRLF2* rearrangements and *JAK2* mutations.[68,89] Crucially, the gene expression signatures were not transferable, and when applied to the same cohort of patients, the signatures classified different patients as *BCR-ABL1*-like/Ph-like.[92] Therefore, gene expression signatures do not provide an ideal prognostic biomarker for use between different clinical trials. However, the common features of these subgroups are poor outcome and enrichment of *CRLF2* rearrangements

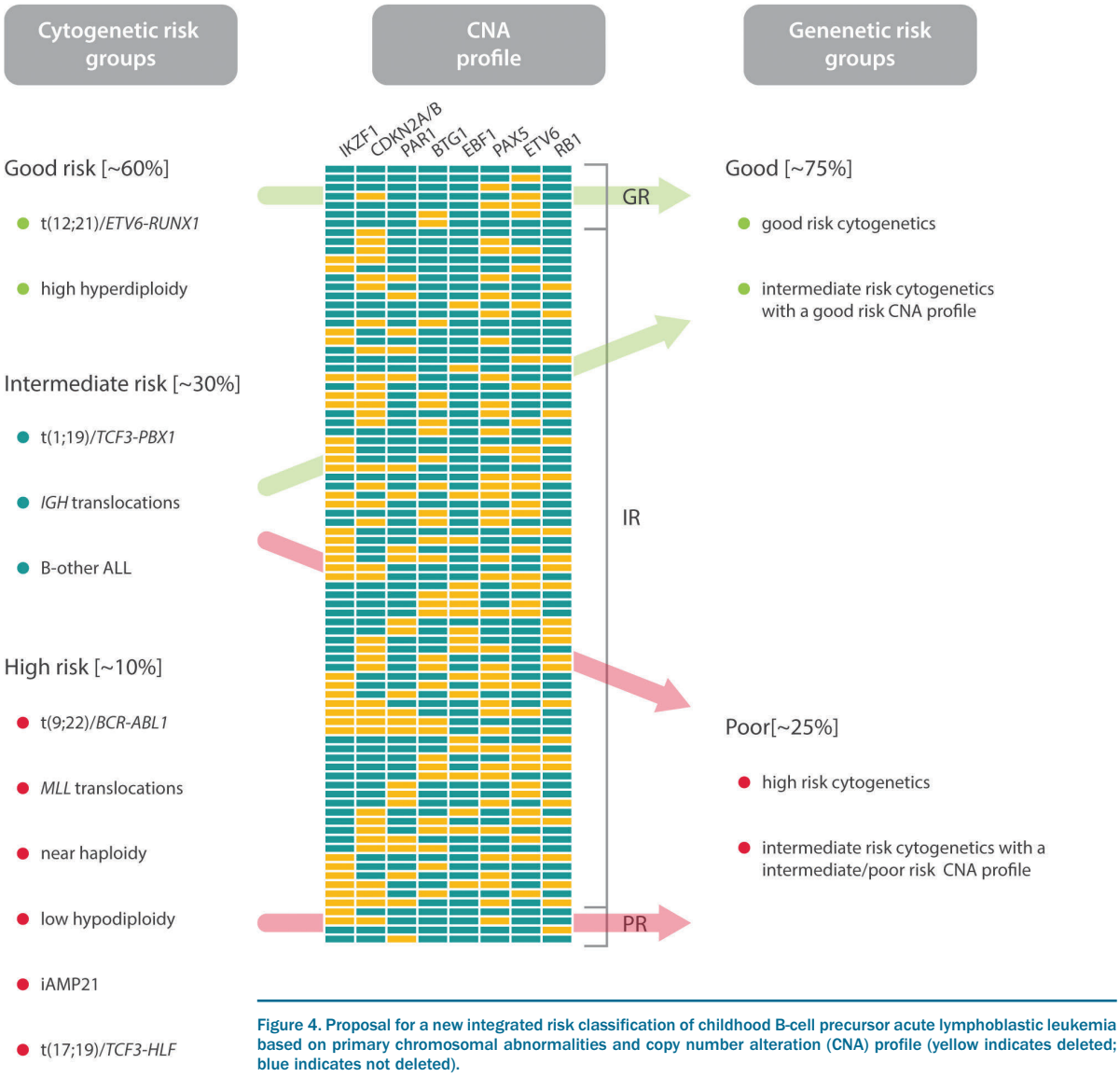


Figure 4. Proposal for a new integrated risk classification of childhood B-cell precursor acute lymphoblastic leukemia based on primary chromosomal abnormalities and copy number alteration (CNA) profile (yellow indicates deleted; blue indicates not deleted).

and *IKZF1* deletion, albeit to varying extents. Although it is unlikely that any gene signature expression will become a robust prognostic biomarker within B-other ALL, there is clearly a subset of patients with B-other ALL who have a poor outcome, and it is now emerging that members of this group can be identified from their distinctive genomic abnormalities.

Kinase activating gene fusions

In 2012, Roberts and colleagues performed RNA sequencing of a small cohort of *BCR-ABL1*-like cases and discovered chimeric fusions involving *PDGFRB*, *ABL1* and *JAK2*.[87] Since this initial study, a complex network of kinase-activating aberrations has been revealed, with many occurring in single patients.[7,93,94] The common feature of these chimeric genes is the fusion of the 3' end of a kinase gene with the 5' portion of so-called activating gene, of which over 30 have now been reported. Theoretically, all these kinase-activating lesions can be targeted with appropriate small molecule inhibitors, and hence become useful predictive biomarkers. For example, *in vitro* and *in vivo* studies have demonstrated that *ABL1, ABL2*, *PDGFRB* and *CSF1R* fusions are sensitive to imatinib and dasatinib, and that *CRLF2*, *JAK2* and *EPOR* are sensitive to JAK inhibitors (e.g. ruxolitinib).[7] Moreover, a small number of children harboring *ABL1*, *ABL2*, *PDGFRB* or *CSF1R* fusions with refractory disease achieved a complete remission following treatment with imatinib or dasatinib.[7,95-98] However, it should be noted that these patients were highly selected and that follow up was extremely limited. Nonetheless, these laboratory and clinical observations provide encouraging evidence that targeted therapies could be offered routinely to patients with one of these predictive biomarkers in the near future. Their prevalence has yet to be firmly established in large representative cohorts. Initial screening of patients in the UK has indicated that *ABL1*, *ABL2*, *PDGFRB* or *CSF1R* fusions collectively occur in 1%-2% of B-cell precursor *ALL* inde-

pendent of age; whereas *CRLF2*, *JAK2* and *EPOR* fusions together occur in 3%-5% of childhood ALL rising to approximately 15% in adolescent and young adult ALL (A Moorman, unpublished observations, 2016). Current published studies have suggested that *IGH-CRLF2*, *PR2Y8-CRLF2* and *EBF1-PDGFRB* are the most prevalent of these gene fusions. The optimal detection method is challenging given the number of genes involved and the complex nature of some of the chromosomal rearrangements which give rise to these fusion genes. FISH using probes to target the kinase gene provides a simple and efficient strategy for detection of many of the fusions, especially *ABL1*, *PDGFRB*, CSF1R, *JAK2* and *CRLF2*, and can readily be incorporated into current screening algorithms. However, assays based on next generation sequencing technology are on the horizon and are likely to provide a more comprehensive approach.

Conclusion and future perspectives

The extensive genetic heterogeneity found within ALL provides a wealth of potential genetic biomarkers that could be used to assist patient management. Prognostic biomarkers such as *ETV6-RUNX1* and high hyperdiploidy can be used to define a cohort of patients with a low risk of relapse on standard therapy whereas patients with high-risk cytogenetics require more intensive or targeted therapy. In the past ten years, genomic analysis has revolutionized the way researchers and clinicians think about the biology of ALL, and new therapeutic strategies and options are beginning to emerge. Additional research is required to assess the clinical utility of some of these discoveries, as a number of questions remain unanswered. For example: 1) what is the optimal way to use copy number alterations as prognostic biomarkers in B-other ALL and within the context of MRD-driven protocols? 2) Which kinase-activating abnormalities are predictive biomarkers for treatment with an appropriate inhibitor? 3) What is the role of these new genetic biomarkers in directing therapy after first relapse? In addition to addressing these translational questions, the large-scale application of whole genome and exome sequencing will undoubtedly identify new genetic biomarkers which may add to or replace our current repertoire of prognostic and predictive biomarkers.

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