Prognostic relevance of genetic variations in T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma

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Abstract: T-cell acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are highly aggressive malignant tumors. With the current intensive treatment regimens, event-free survival (EFS) rates of up to 60–90% can be achieved, but the survival rate of relapsed patients remains poor—only approximately 3–12%. Therefore, precise and effective prognostic parameters are highly needed to further improve survival rates along with reduced acute and long-term toxicities, including the rate of secondary malignancies. In addition, gene mutations can be used as therapeutic targets. This review highlights several gene mutations with a high frequency or a strong influence associated with favorable or unfavorable aspects of prognosis—*NOTCH1*, *FBXW*7, *PTEN*, LOH6q, *CASP8AP2*, *c-MYC*, *IL-*7, *CALM-AF10*, and *CDKN2A/B*—and indicates that the actual incidence of mutations in T-ALL/LBL is much higher than currently recognized. The development of multicenter clinical trials and molecular genetics research aimed at understanding the biology of these diseases offers promise for targeted and more effective therapy.

Keywords: Molecular genetics; prognostic factor; T acute lymphoblastic leukemia/lymphoma

Introduction

Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are highly aggressive malignant tumors that originate from precursor T-cells, B-cells or lymphoblasts (1-3). LBL is the second most common subtype of non-Hodgkin's lymphoma (NHL) in children and adolescents, accounting for approximately 2% of all NHL cases (4). T-cell LBL (T-LBL) accounts for nearly 90% of all LBL cases and tends to occur in children and adolescents, predominantly in males (3). In contrast with T-LBL, T-ALL is not as common as B-cell ALL (B-ALL) and accounts for nearly 15% of all childhood ALL cases. T-ALL and T-LBL have similar morphological,

immunophenotypic, and clinical features; therefore, the World Health Organization (WHO) classification has unified these entities as precursor T-cell lymphoblastic leukemia/lymphoma (pre-T-ALL/LBL). In this review, we use the term T-ALL/LBL to refer to both T-ALL and T-LBL.

With the current intensive combinations of chemotherapy with or without local radiotherapy, a 5-year EFS of approximately 60–90% can be achieved (5-7). Despite these acceptable EFS rates, the 5-year overall survival (OS) rate of relapsed patients remains poor—only approximately 3–12% (8-11). Therefore, precise and effective prognostic parameters are highly needed. Although many clinical parameters are currently used

to predict the prognosis of T-LBL, the validity of these parameters is insufficient, unreliable and nonspecific. Understanding the significance of gene mutations in the prognosis of disease can help to stratify the risk of disease, identify individualized treatment for patients with different risks, and improve the prognosis of patients. For example, preventing relapse is important in patients identified to have a high risk of relapse; in contrast, for low-risk patients, significant acute and long-term toxicity caused by current treatment regimens should be avoidable if the treatment intensity can be reduced without affecting the outcome. Future studies focusing on these aspects and novel prognostic indicators will undoubtedly contribute to this understanding. Risk groups are stratified and given appropriate treatment options accordingly, bringing unanticipated results. Gene expression profiling has identified several potential prognostic indicators of inherited T-LBL, such as *NOTCH1*, F-box and WD repeat domain-containing 7 (*FBXW7*), phosphatase and tensin homolog (*PTEN*), loss of heterozygosity at chromosome 6q (LOH6q), CASP8-associated protein 2 (*CASP8AP2*), *c-MYC*, interleukin-7 (*IL-7*), *CALM-AF10*, and cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*). Although most of these are controversial, they help to distinguish disease severity in patients, guide therapy in the clinic, and predict prognosis.

NOTCH1

Over 50% of T-LBL patients carry activating mutations of the gene *NOTCH1* (12,13), and the frequency of *NOTCH1* activating mutations between pediatric and adult patients with T-LBL is not significantly different (14). Activating mutations of *NOTCH1* mainly result from the t(7;9) (q34;q34.3) translocation, the most common genetic abnormality found in T-LBL (15).

NOTCH1 is a transmembrane receptor that can bind to ligands and lead to a series of protein cleavages. After the notch intracellular domain (NICD) is released, it binds to the transcribed regions of genes such as *c-MYC*, *HES1*, and *NF-κB* and plays its role. Mutation of *NOTCH1* mainly affects two domains, the extracellular heterodimerization domain (HD) and proline-glutamic acid-serine-threonine (PEST) domain, which can lead to non-ligand-dependent activation of transmembrane receptors and abnormal activation of downstream genes (15-18). The Notch signaling pathway plays a key role in regulating development and differentiation via diverse cellular processes, such as differentiation, proliferation, apoptosis, adhesion, cell cycle progression, spatial development, and stem cell maintenance and self-renewal, as well as in the normal development of many tissues and organs. In addition, NOTCH1 is necessary and sufficient for the development of T-cells (19,20). Accumulating evidence supports *NOTCH1* as a tumor suppressor. *NOTCH1* plays a role in suppressing cancer mainly by promoting cell cycle exit and cell differentiation, thereby reducing the potential of cancer stem cells and tumor-initiating cells (21).

Numerous studies indicate a good prognosis and an improved treatment response in T-ALL/LBL patients, especially children, with *NOTCH1* activating mutations (22-24), even though these mutations can reverse the effects of other adverse prognostic factors, such as *PTEN* and *RAS* mutations (13). Another study indicated more favorable survival for *NOTCH1* mutation-positive patients than for *NOTCH1* mutation-negative patients (15). Bandapalli *et al.* previously analyzed the effects of *PTEN* and *NOTCH1* mutations on prognosis in 301 ALL-BFM treated children with T-ALL and found that *NOTCH1* mutation was the most important favorable prognostic factor. Regardless of the *PTEN* mutation status, T-ALL patients with *NOTCH1* mutation showed favorable induction sensitivity and prognosis (25). The absence of *NOTCH1* mutation and the presence of other adverse prognostic factors may lead to poor outcome, and children have a better prognosis than adult patients (15).

γ-secretase inhibitors (GSIs) can block the proteolytic cleavage of NOTCH1 receptors as well as suppress the release of activated NOTCH1 (the NICD) from the membrane, and have been proposed as a potential therapeutic strategy in T-ALL (15,26). However, GSIs are clinically effective only for a small proportion of patients with *NOTCH1* activating mutations. Other concurrent factors, such as the PI3K-AKT-mTOR signaling pathway and cycling protein kinase D downstream of *NOTCH*, may influence the effectiveness (13). Moreover, the study of activating mutations of *NOTCH1* provides a strong basis for targeted therapies interfering with the NOTCH signaling pathway (12). However, due to our poor knowledge of T-ALL pathogenesis, further investigation is needed, and novel approaches for diagnosis as well as treatment are urgently needed.

FBXW7

*FBXW*7, a component of the Notch signaling pathway, is

also involved in cell proliferation, apoptosis, the cell cycle and differentiation. FBXW7 is a member of the F-box protein family and a component of the E3 ubiquitin ligase complex that recognizes the PEST domain in the NICD and accelerates the termination of NOTCH1 signaling in the nucleus (27). *FBXW*7 encodes a protease that degrades the NICD in the NOTCH1 signaling pathway. Mutation of *FBXW*7 can lead to the loss of recognition of NOTCH1 and reduce NICD degradation, subsequently leading to abnormal activation of the NOTCH1 pathway (13,18). Dysregulation of NOTCH1 signaling can lead to hyperactivation and confer a proliferative advantage on tumor cells in several cancers, ultimately resulting in developmental defects. In addition, *FBXW*7 is strongly correlated with *NOTCH1* mutations, and they commonly occur concurrently (13,28).

Although the mutation frequency of *FBXW*7 is less than 15% in T-ALL patients (16), *FBXW*7 has been considered a candidate prognostic marker in association with *NOTCH1* mutation (18,29). Numerous studies have been conducted and found that the prognosis of T-ALL patients with *FBXW*7 mutation is more favorable than that of patients without *FBXW*7 mutation (13,29,30). However, in one meta-analysis, *FBXW*7 mutation did not significantly affect the prognosis of children or adults with T-ALL (15).

Regarding the concurrent mutation of *FBXW*7 and *NOTCH1*, more than 83% of T-ALL patients with *FBXW*7 mutation also harbor *NOTCH1* mutation (30). T-ALL patients with concurrent *NOTCH1/FBXW*7 mutation had better prognoses (22,31-33) and a 5-year relapse-free survival (RFS) rate of greater than 85%. *NOTCH1/FBXW*7 mutation also had the same favorable prognostic effect in children with T-ALL (13). A study analyzing *NOTCH1* and *FBXW*7 mutations in 50 South Indian T-ALL patients treated with a regimen modified from the ALL/NHL-Berlin-Frankfurt-Münster (BFM) 95 trial showed that T-ALL patients with *NOTCH1/FBXW*7 mutation had better RFS than patients without *NOTCH1/FBXW*7 mutation in Kaplan-Meier survival analysis of 50 patients with T-ALL (18). However, a few studies have reported no significant difference (34-36) or poor prognosis in *NOTCH1/FBXW*7-mutated patients compared with that in patients without *NOTCH1/FBXW*7 mutation (37,38). Perhaps the outcome is also influenced by the treatment protocol used at the same time or at other times. Therefore, the significance of the double mutation of *NOTCH1/FBXW*7 remains to be further studied.

PTEN

The tumor suppressor *PTEN*, located on chromosome band 10q23, can negatively regulate phosphatidylinositol 3-kinase (PI3K)-AKT signaling, which plays a key role in cellular metabolism, proliferation and survival (39,40). Expressed *PTEN* has a dephosphorylation function; it can remove the phosphoric acid moiety from phosphatidylinositol 3,4,5-trisphosphate (PIP3) to form phosphatidylinositol 4,5-bisphosphate (PIP2), resulting in PI3K-AKT signaling pathway blockade (41). Inactivation of *PTEN* may lead to overactivation of the PI3K-AKT signaling pathway, uncontrolled cell proliferation, and even to malignant tumors (42). Deletion or mutation of *PTEN* in T-LBL/ALL was initially found in cell lines (43,44), and restoring *PTEN* expression can suppress the PI3K-AKT signaling pathway, which in turn promotes apoptosis (45).

PTEN deletion or mutation is one of the most common oncogenic mutations in T-ALL/LBL. Deletion or mutation of *PTEN* is reported to be found in over 20% of patients with T-ALL, and deletion or mutation of *PTEN* usually does not occur along with *NOTCH1* and *FBXW*7 mutations (13). Clinical observation showed that the disease-free survival (DFS) rate of patients with *PTEN* mutation in T-LBL (0.59±0.12) was significantly lower than that of T-LBL patients with wild-type *PTEN* (0.82±0.04, P=0.014) (46). T-LBL patients with *PTEN* mutation seem more insensitive to hormone therapy and exhibit a poorer response than T-LBL patients with wild-type *PTEN* (25). Some studies have found that deletion or mutation of *PTEN* is associated with poor prognosis and that *NOTCH1* mutations can overcome the negative effects of *PTEN* mutation (25,46), but the mechanisms remain unclear. However, deletion or mutation of *PTEN* cannot reverse the favorable prognostic effect of *NOTCH1/FBXW*7 mutation, with only a nonsignificant decrease in OS (13,47). Some centers have identified *PTEN* as a significant, independent risk factor for relapse in T-ALL patients treated with various protocols (25,48-50). Moreover, T-ALL patients with *RAS* and/or *PTEN* mutations showed notably unfavorable survival compared to that of T-ALL patients without mutations in the French Group for Adult T-ALL Research (51).

PTEN deletion has been proposed to be associated with GSI resistance in T-ALL patients in a manner dependent on *NOTCH1* (48,52,53), but some issues remain to be investigated further (42). However, this finding provides a

new clinical therapeutic target.

LOH6q

LOH6q is not uncommon in various hematological malignancies, especially T-LBL/ALL (54,55). LOH6q is reported to be the first molecular parameter described to be related to the prognosis of pediatric patients with T-LBL (56).

Burkhardt *et al.* analyzed the 108 T-LBL patients and 127 T-ALL-patients, and reported that the frequency of LOH6q is detectable at similar frequencies about 20% in both T-ALL and T-LBL (54,57). However, the commonly deleted regions are different in terms of the prognostic relevance of LOH6q (54). Numerous studies found that LOH6q is associated with an increased risk of relapse in T-LBL patients but not in T-ALL patients, although both are considered to be different presentations of different stages of the same disease (54,57-59). Another study from Burkhardt *et al.* confirmed that LOH6q was highly significantly correlated with poor outcome and increased risk of relapse in a retrospective analysis of T-LBL patients treated with NHL-BFM protocols (55).

In addition, the clinical features of LOH^pos T-ALL/LBL patients were not significantly different from those of LOH^neg patients, except for a trend towards younger age in LOH^pos patients than in LOH^neg patients (54,58). In addition, some centers claimed that *NOTCH1* mutations were observed only in patients with LOH6q mutations (58). Further knowledge of the genetic landscape of pediatric T-ALL/LBL is hampered by the rarity of patient material for molecular biological research. Therefore, sufficient availability of material is needed for future studies.

CASP8AP2 (FLASH) deletion

The CASP8AP2 protein is encoded by the *CASP8AP2* gene, located at chromosome region 6q15 in humans (60). *CASP8AP2*, also known as FLICE or FLASH, was initially identified as a proapoptotic protein transmitting apoptosis signals via involvement in the glucocorticoid signaling pathway (22,61). More recently, various functions have been found, including TNF-induced activation of NF-kappa B, mediation of S-phase cell cycle progression and cell proliferation, and regulation of the transcription and maturation of the 3' end of histone mRNAs (60,62,63). It is possible that more functions remain to be investigated.

The clinical significance of *CASP8AP2* in childhood ALL was first reported by Flotho *et al.*, who associated the expression of different genes with the *in vitro* response to chemotherapy in ALL patients, demonstrating that decreased expression of *CASP8AP2* was associated with dramatically increased rates of minimal residual disease (MRD) and hematological relapse (60,64,65). In addition, this result was verified in another study showing that *CASP8AP2* expression in patients with newly diagnosed ALL is a valuable marker for predicting relapse (66). *CASP8AP2* deletion is particularly frequent (50%) and adult ALL patients with *CASP8AP2* deletion had a lower 18 months event-free survival (EFS) (31% *vs.* 41%) and a higher relapse rate (70% *vs.* 37%, P=0.02) compared with patients without *CASP8AP2* deletion. Furthermore, other possibilities for *CASP8AP2* silencing should also be considered (60,67).

Although both miR-210 and *CASP8AP2* expression act as prognostic indicators in pediatric ALL, and *CASP8AP2* is a target of miR-210 in bone marrow stem cells, there is no evidence revealing any association between *CASP8AP2* and miR-210 expression in ALL patients (66). In addition, one study showed that the combined expression of these molecules predicted relapse in ALL patients. Among patients with high expression of both genes, none relapsed, while the group of ALL patients with low expression of both genes exhibited the poorest outcomes for 3-year RFS, EFS and OS, and no statistically significant difference was observed in any of the 3 prognostic indexes for low expression of either gene alone (66). Therefore, combining the expression of miR-210 and *CASP8AP2* may more precisely predict whether patients are at increased risk of relapse.

The expression of *CASP8AP2* can also be influenced by *E2F3a*. *E2F3a* can enhance the transcriptional activity of *CASP8AP2* directly. Moreover, overexpression of *E2F3a* promotes the sensitivity of leukemic cells to chemotherapeutic drugs by increasing the proportion of leukemic cells in S and G2/M phases and accelerating proliferation (61,64). Additionally, downregulation of *CASP8AP2* reverses the promotive effect of *E2F3a* on chemotherapeutic sensitivity (61). Thus, in childhood ALL, the prognostic significance of *CASP8AP2* expression may be actualized by *E2F3a*.

While the biological basis of the variation in *CASP8AP2* expression should be considered, the occurrence of a deletion at the chromosome 6q15-16.1 region (22), corresponding to the gene's location, in some patients with T-ALL could lead to downregulation of *CASP8AP2* and

poor response to early treatment (61). In addition, this deletion can lead to a decrease in *CASP8AP2* expression, and these effects may be associated with the presence of MRD (60). In addition, combining *CASP8AP2* expression with the presence of MRD can contribute to distinguishing patients with an increased risk of bone marrow relapse.

A previous study reported that low expression of *CASP8AP2* was related to high rates of MRD and relapse (61,68). However, the mechanisms of *CASP8AP2* downregulation in childhood ALL remain unclear.

c-MYC

The *c-MYC* gene is a protooncogene coding for a transcription factor that plays a major role in many processes, including the cell cycle, apoptosis and cellular transformation (69). Mutation of *c-MYC* may lead to dysregulated expression of many genes involved in cell proliferation and may even ultimately result in the formation of cancer.

The correlation of *BCL-2* and *c-MYC* translocation with poor prognosis in B-cell lymphomas was first indicated by Kanungo *et al.* (70), and the correlation of *BCL-2* and *c-MYC* gene rearrangement was later found in adults with lymphoblastic leukemia/lymphoma (71). In addition, *BCL-2* and *c-MYC* may play a vital cooperative role in the pathogenesis of ALL/LBL (69).

Recently, expression of *c-MYC* has been found to play an important role in the occurrence and development of T-LBL/ALL and is strongly associated with poor prognosis. In addition, *c-MYC* expression can be an independent prognostic factor for T-LBL/ALL (72). This result was also observed in a later study. The study further presented the association between the expression of *c-MYC* and the prognosis of patients via analysis of 90 patients with T-LBL/ALL (the positive group) and 30 patients with lymph node reactive hyperplasia (the control group). The rate of positive *c-MYC* protein expression was positively correlated with Ki-67 expression and was significantly higher in the positive group than in the control group, while the inverse correlation was seen between positive *c-MYC* protein expression and OS, suggesting that patients with *c-MYC* protein expression may have worse prognoses (73). Thus, *c-MYC* can be used as a parameter to predict the clinical outcome of patients with T-ALL/LBL.

IL-7R

The interleukin-7 receptor (IL-7R) is a cell surface protein that plays a critical role in the development of T-cells and is important for the immune system (74-77). Loss-of-function mutations in this receptor can lead to severe combined immunodeficiency (SCID), which is an intractable disease (75,77,78).

Approximately 10% of patients with T-ALL have activating mutations of *IL-7R* (79). Recently, studies showed that *IL-7* and *IL-7R* may contribute to T-cell leukemia progression and that 9% of patients with T-ALL display somatic gain-of-function *IL-7R* exon 6 mutations (74,77). Additionally, considerable evidence indicates that *IL-7* and *IL-7R* are involved in T-cell leukemogenesis in humans (77,80). The involvement of mutational activation of *IL-7R* in human T-cell leukemogenesis lays the foundation for therapeutic targeting in T-ALL mediated by *IL-7R* (77). However, some obstacles remain to be addressed.

Steroids are the basis of current chemotherapy regimens for the treatment of T-ALL/LBL. However, recent studies have found that steroid resistance is not uncommon in patients with ALL, is associated with poor prognosis and increases the risk of recurrence (81,82). Steroid resistance is mainly caused by activation of the main IL7R signaling pathway components, MEK-ERK and AKT, which are located downstream of the IL7R signaling pathway. This activation induces a strong antiapoptotic response mainly by upregulating the expression of *BCL-XL*. In addition, IL-7R inhibitors can enhance the effect of steroids (83,84), but other related toxicities may remain to be further explored. Moreover, the *IL-7R* gene expression levels in blood may reflect the rate of aging and the health status of elderly individuals (85).

CALM-AF10

CALM-AF10, also known as *PICALM-MLLT10*, is a classical oncogene marker in various malignant tumors (86) and is considered to be the most common fusion protein resulting from the t(10;11) (p12;q14) translocation (86), which is found in immature acute myeloid leukemia (AML), ALL and malignant lymphoma (87,88). CALM-AF10 was originally found in a patient with diffuse histiocytic lymphoma and later became the most common fusion protein in T-ALL (89,90). CRM1 was found to recruit CALM-AF10 into the *HOXA* cluster, resulting in increased expression of the *HOXA* gene and eventual cell transformation. Thus, CALM-AF10 causes the occurrence of leukemia mainly by upregulating the expression of *Hox* homeobox genes, including *HOXA5*, *HOXA7*, *HOXA9* and

HOXA10 (89,91,92).

The incidence of *CALM-AF10* in patients with T-ALL, including both adults and children, is reported to be greater than 10% (93). Patients with *CALM-AF10+* acute leukemia were previously found to typically have poor prognoses (86,90,93), but this finding was mainly based on sporadic reports and had not been evaluated in prospective clinical trials of ALL or AML (86,94,95). Indeed, subsequent studies found no difference in the 3-year EFS and OS between the *CALM-AF10+* and *CALM-AF10–* groups (93).

Based on the pathogenic mechanism of leukemia induced by *CALM-AF10* (92), it is proposed that nuclear export inhibitors be included in the treatment of *CALM-AF10+* leukemia (89,92). However, no relevant studies have been conducted, and the potential side effects need further exploration. In addition, *CALM-AF10+* leukemia cells are more sensitive to iron-restricted growth inhibition than normal hematopoietic cells, and the tumor burden in the spleen appears to be reduced by dietary iron restriction (96,97). However, whether the iron depletion strategy improves the prognosis of *CALM-AF10+* leukemia patients has not been verified. Considering the side effects, this treatment modality remains to be investigated further.

Analysis of chromosomal translocations contributes to the understanding of the biological characteristics of various hematological malignancies (98) and provides novel ideas for advanced methods of disease diagnosis and classification and even new targets for the treatment of hematological malignancies (90).

CDKN2A/B

The *CDKN2A/B* genes, located at chromosome region 9p21, are tumor suppressor genes frequently involved in various human cancers, such as pediatric ALL, breast cancer, lung cancer, and pancreatic cancer (99-102). The *CDKN2B* gene encodes the cyclin-dependent kinase inhibitors p16^{INK4A} and p15^{INK4B}, while *CDKN2A* encodes the alternative reading frame protein p14^{ARF} (103). These 3 proteins, as components of the RB1 and TP53 pathways, negatively regulate the G1-S transition in the cell cycle during proliferation to maintain normal cell growth (99). Therefore, inactivation of *CDKN2A/B* may lead to growth that is rapid or out of control and even to the subsequent formation of cancer. Deletion is one form of inactivation. Over 60% of childhood T-ALL cases are found to exhibit deletions of the *CDKN2A/2B* genes at first presentation (99,104). Most *CDKN2A/B* deletions can be detected at initial diagnosis or at relapse, suggesting that *CDKN2A/B* deletions are a marker

of poor prognosis (99,105). Studies have found that deletion of the *CDKN2A/B* genes is associated with poor survival outcomes in pediatric ALL (106,107) and that the OS rate of children with ALL is significantly lower in India than in other countries (108). In addition, some studies have found that *CDKN2A/B* deletions are associated with poor outcomes in B-ALL patients (102,109).

CDKN2A/B can be used as a target for the treatment of T-ALL. Currently, cyclin-dependent kinase inhibitors are being tested in clinical trials for various cancers and have been clinically used to treat breast cancer (110). Moreover, whether this treatment approach can be extended to other cancers, such as childhood ALL or colorectal cancer, is being investigated further (111). Future studies should highlight the combined use of CDK4/6 inhibitors with other targeted drugs, which still face enormous challenges, such as clinical efficacy and cytotoxicity (99).

Conclusions

Although current treatment protocols have improved the overall outcome for patients with T-ALL/LBL, challenges remain, including further improvement in survival rates accompanied by reductions in acute and long-term toxicities and decreasing rates of secondary malignancies. A significant number of patients remain at high risk of relapse, and few individuals survive recurrence. Currently, no useful prognostic parameters have been confirmed for appropriate treatment stratification of T-ALL/LBL. Hence, knowledge of molecular genetic abnormalities can help us not only understand the pathogenesis of disease but also establish more complete risk stratification approaches to identify patients with high-risk factors and develop appropriate individualized treatment to reduce recurrence and improve treatment efficacy. Balbach *et al.* analyzed of outcome in pediatric T-LBL and proposed a new genetic classifier defining three risk groups: (I) good-risk group, defined by *NOTCH1* mutation and no RAS or PIK3-AKT pathway mutation. (II) Intermediate-risk group including all non-GR and non-high-risk patients. (III) High-risk group, defined by *NOTCH1* wild type in combination with *PTEN*mut- and LOH6q-positive patients (46). They proposed that for the high-risk group, analogous to treatment of pediatric high-risk T-ALL patients, new drugs and allogeneic stem cell transplantation in first remission should be considered. In contrast, for the low-risk group, treatment de-escalation may be a future option (45). We cannot use this classifier for all the type of T-ALL/LBL patients, because through our review, we learned about the mutated genes between LBL

and ALL, the mutations between adult and children have great differences in the frequency of mutations, mutation sites, and prognosis. The reasons for the inability to analyze are different mutation rates, low incidence, different implementations, and other important factors without detailed stratification.

One of the most important aspects of evaluating patients' prognosis is simply assessing MRD. Combining cancer-associated genes with the MRD status may improve the accuracy of predicting the prognosis of patients and the risk of recurrence and may providing more effective guidance for later clinical use. In addition, gene mutations can be used as therapeutic targets—for example, Notch pathway inhibitors such as γ-secretase antagonists, NF-κB pathway inhibitors such as bortezomib, or epigenetic drugs such as decitabine.

This review highlights several gene mutations with a high frequency or a strong influence in T-ALL/LBL and indicates that the actual incidence of T-ALL/LBL mutations is much higher than currently recognized. The development of multicenter clinical trials and molecular genetics research aimed at understanding the biology of these diseases offers promise for targeted and more effective therapy in the future.

Acknowledgments

Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.10.04). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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