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EXPERT REVIEW

Current and Emerging Therapies in T-cell Acute Lymphoblastic Leukemia

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Abstract: Current studies of T-cell acute lymphoblastic leukemia (T-ALL) show promise for improving the treatment for this previously difficult to cure neoplasm. This has been facilitated by the increased understanding of the molecular basis of leukemogenesis in T-cells as well as advanced analytical technologies in modern molecular biology. Combined with intensive conventional therapies, novel drugs as well as improved diagnostic protocols have been developed for the rational therapy of T-ALL, resulting in a cure rate up to 80%. An understanding of the detailed molecular mechanism of action for T-ALL specific alterations in gene expression has led to the design and development of targeted molecular therapies of this aggressive cancer. Several novel, target-specific drugs are now available, including mitotic inhibitors with more specificity and potency for growth inhibition, γ-secretase inhibitors (GSIs) for leukemic NOTCHI signaling blockage in T-ALL as well as growth inhibition, tyrosine kinase inhibitors for correction of uncontrolled proliferation caused by certain genetic lesions, and inhibitors of BCL2 proteins leading to sensitization of leukemic cells to apoptosis induction. Some of these drugs are under development in the different phase of clinic trials, but others are currently included in successful therapeutic protocols, and, as hoped, they cause the remission of patients that suffered from certain types of T-ALLs, and who previously were poor responders using conventional treatment protocols. However, these new approaches still often need to be combined with highly toxic conventional treatment to obtain satisfactory overall outcome. The encouraging achievements in targeted molecular therapy challenge researchers to achieve no-event complete remission in T-ALL patient by developing novel therapies with even more specific targeting and efficacy to minimize complications. Finally, with the development of targeted molecular therapy, rational approaches for individually tailored treatment of T-ALL patients in the near future now may be an achievable goal.

Keywords: T-acute lymphoblastic leukemia, chemotherapy, apoptosis

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Introduction

Leukemia is a fairly common cancer, with an incidence of 30–40 per million. It is estimated that 43,050 new cases of leukemia were diagnosed in the United States in 2010. The major types of leukemia include acute lymphoblastic (or lymphoid) leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, chronic myelogenous (or myeloid) leukemia, and other, rarer forms of leukemia. Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, with over 70% of diagnosed cases occurring in children and adolescents less than 20 years old.[1–4] ALL can progress quickly if untreated, and it is responsible for about 1,400 deaths a year in the U.S. Approximately, 2,900 new ALLs are diagnosed each year in the United States, and in the past several years, there has been a gradual increase in the incidence of ALL.[5–7] Acute lymphoblastic leukemia is a heterogeneous disease. It originates as a single B- or T-lymphocyte progenitor, and it is further characterized as pre-B, B, or T-cell ALL. T cell ALL (T-ALL) is diagnosed in 15%–20% of children and adults with ALL, while about 80%–85% of ALL cases are of the B-cell lineage. Current treatment for T- and B-ALL mainly depends on multi-agent combination chemotherapy, and over the past six decades, overall cure rates for pediatric ALL have significantly improved to long term (5 years event-free) survival rates of nearly 80%–90%.[2,8–12]

T-ALL is a malignancy of thymocytes (T-cell progenitor) that develops mainly in children and adolescents, which is much less common or rare in adults. Upon spreading throughout the body, rapid progression of this aggressive tumour leads to high peripheral blood cell counts, increased numbers of blast cells, CNS dissemination and, frequently, to large mediastinal masses that cause tracheal compression and respiratory distress at diagnosis, and which is fatal without treatment. Comparing to B-cell ALL, T-cell precursor acute lymphoblastic leukemia is clinically regarded as a high risk disease with a high frequency of treatment failure and a relapse rate of about 30%–40%.[4,13–16] T-ALL is now treated the same way as high-risk B-progenitor ALL. With appropriately intensive therapy, children with T-ALL have an estimated 5-year event-free survival rate at 75%–80%.[1,14,17,18] Nevertheless, T-ALL patients have increased risk for remission induction failure, early relapse (2 years, >50%), and, especially, isolated CNS relapse.[19–21] Treatment outcome is poor among those patients who relapse on current frontline chemo-regimens and over the past two decades, survival rates after relapse have been consistently low. Furthermore, much less success has been achieved in adult T-ALL patients, with a long term survival rate at only about 30% to 40% (<60 years of age) or 10% (>60 years of age), at most.[16,20–28] Moreover, during or after intensive treatment, many T-ALL patients develop serious acute and late complications because of the side effects of the highly toxic chemotherapeutic reagents. These realities have challenged investigators to develop novel approaches that incorporate salvage regimens and frontline therapeutic strategies for these high-risk patients.[12,21,25,28–30] This is accomplished by treatment protocols that more efficiently and specifically target the leukemic cells to improve the rate of complete remission (relapse free) as well as the quality of life of patients.

Commonly Used Chemotherapies for T-ALL

Using standard intensive chemotherapy, the current cure rate of T-ALL has risen to about 70%–80% in children and 40%–50% in adults, with the expectation of better overall outcome in the near future. This significant progress in outcome largely depends on the selective use and combination of the anti-leukemia regimens together with stringent applications of risk-directed therapy (by prognostic factors) in clinical trials. And in general, a combined modality (directed by different phases of treatment), intensive chemotherapy is currently used to treat T-ALL in a manner that is essentially the same as high risk ALLs.[4,16,18,21,22,26–28,30–35] Various protocols based on different combinations of drugs have been developed for T-ALL treatment at various phases.

1. Induction therapy: Initially, different combinations of various cytoctoxic drugs are used to elimanate the leukemic cells by inducing cell lysis and growth inhibition. There are over 10 different drugs currently available and generally used in combinations for intensive treatment. The cytoxicity of these drugs can be grouped according to the manner in which they interfere with the biological functions of leukemic cells, for example, as a

metabolic inhibitor for an essential metabolistic pathway or as signaling molecules that promote apoptosis or lysis of the cancer cells. Table 1 lists the commonly used chemotherapeutic drugs for the current treatment of ALL and their biological effects on leukemic cells. These drugs include DNA damaging agents (anthracyclines,[36] alkylating agents,[37] and epipodophyllotoxins[38,39]), anti-metabolites (nucleotides analogues such as 6-mercaptopurine[40] and methotrexate[41,42]), mitotic inhibitors (vincristine[43,44]), protein synthesis inhibitors (specifically, asparaginase and its more potent derivatives, PEG-asparaginase or Oncaspar®,[45–49] etc.) and corticosteroids (glucocorticoid analogues, prednisone and dexamethasone).[47,50–55]

2. Consolidation: Treatment is directed at leukemic cells in the central nervous system (CNS). High dose systemic methotrexate or cranial irradiation with continued systemic chemotherapy (mercaptopurine and vincristine) is adopted to prevent CNS relapses. The treatment may last for 4 weeks.
3. Interim maintenance and delayed intensification: At this stage, the phase of interim maintenance followed by delayed intensification is repeated. Interim maintenance is designed to adopt less intense therapies after the induction therapy and between the courses of delayed intensification, which allow for normal cell recovery. Delayed intensification is a repeat of more intense induction therapy, in attempts to destroy any trace of leukemic cells surviving the induction therapy. Multiple drugs are administered in an intensive schedule to intensify the remission. This phase is usually two months long and consists of primarily oral medications given at home.
4. Maintenance: A 1–2 year maintenance phase of treatment is required. The treatment in this phase is important because it aims at eliminating any remaining, slow dividing leukemia initiating cells, thus prevent relapse. Maintenance treatment consists of oral administration of 6-mercaptopurine and methotrexate, monthly visits for pulses of vincristine and corticosteroids (dexamethasone) and intrathecal methotrexate every 12 weeks.
5. Prognosis and risk-directed therapy: Early treatment response is the most important prognostic factor to stratify risk-directed therapy. This strategy

Table 1. Mechanism of commonly used chemotherapy for ALLs.

Agent	Mechanism of action
Prednisone Dexamethasone	Small signaling molecular to activate glucoccorticoid signaling pathway; Binds to and activates glucocorticoid receptor, a member of nuclear steroid receptor and transcription factor, to regulate gene expression; Induces sensitive apoptosis of ALL leukemic cells in vitro and in vivo.
Vincristine	Binds to tubulin protein and inhibits formation of mitotic spindle, leading to growth arrest and cell death.
Daunorubicin Doxorubicin Idarubicin	Binds to DNA and inhibits the progression of the enzyme topoisomerase II by stabilizing the topoisomerase II complex after it has broken the DNA chain for replication, leading to double-stranded DNA breaks and stop of DNA replication, which causes DNA damage and apoptosis.
Etoposide Teniposide	Forms a ternary complex with DNA and the topoisomerase II enzyme and prevents re-ligation of the DNA strands, leading to DNA damage and apoptosis.
Asparaginase	catalyzes the hydrolysis of asparagine to aspartic acid, inhibits protein synthesis in ALL leukemic cells by depriving the circulating asparagine since ALL leukemic cells are unable to synthesize the non-essential amino acid asparagine.
Methotrexate	Inhibits the synthesis of DNA, RNA, thymidylates, and proteins by inhibiting dihydrofolate reductase (DHFR) involved in the de novo synthesis of the nucleoside thymidine and purine; leading to growth inhibition and cell death.
6-Thioguanine 6-Mercaptopurine Azathioprine	Interferes with purine nucleotides synthesis; incorporates into RNA and DNA, leading to genotoxic stress (growth inhibition and cell death).
Cytarabine	Inhibits the synthesis of DNA by incorporating into DNA, leading to DNA damage, growth inhibition (cell cycle arrest) and cell death.
Cyclophosphamide	Forms DNA crosslinks (irreversible) between and within DNA strands at guanine N-7 positions, leading to cell death.

introduces a stringent assessment of the risk of relapse for subgroups of patients, which is critical in selecting therapy that will avoid excessive toxicity but maintain a high cure rate, as well as efficiently designing experimental therapy for very high risk patients. Currently, risk classification is based on apparent clinical features of patients and characteristics of leukemia subtypes; interestingly, the response to a single week of mono-treatment with steroids strongly predicts outcome of treatment. In fact, steroid analogues have been a mainstay in all protocols developed to treat ALL including T-ALL.[53–55]

Nevertheless, for rare cases of adult T-ALL, even with the most intensified protocol, the outcome is much less favourable,[56] and in childhood T-ALL, about 20% of patients are still uncured.[2,4,21,35] Currently there are no effective ways to treat these patients; very high doses of cytoxic drug combinations must be used for treatment, which exerts severe side-effects on patients during or after the treatment. These serious short and long-term complications that result from the toxicity of these therapies must be considered. Thus, there remains a need for more effective agents to be incorporated into T-ALL treatment regimens, and novel reagents/strategies are needed to obtain cures for patients when commonly used therapies fail.

An important trend in anti-cancer drug development is to understand the molecular basis of leukemogenesis (e.g., genetic and epigenetic changes, alterations to the proteome) and therapeutic resistance in leukemia. These studies have led to the development of new agents against relevant molecular targets, and fostered the concept of "molecular targeted therapy" for the highly specific treatment of T-ALL.[56–59] An excellent example of this is the development of imatinib for chemotherapeutic regimens now widely used to treat Philadelphia chromosome-positive (Ph+) ALL (B-ALLs and a rare portion of T-ALLs) and chronic myelogenous leukemia (CML).[59,60] Based on the presentation of molecular abnormalities of a patient's leukemic subtype, more effective, and potentially less toxic, individually tailored treatment protocols for T-ALL are under development.

The Biology of T-ALL

The biological knowledge of T-ALL has been greatly expanded in the past several years. T-ALL originates from immature, stem-cell-like thymocytes. In normal T-cell development, lymphoid progenitor cells migrate from the bone marrow towards the thymus, where CD4 CD8 double-negative progenitor cells developed into mature T-cell receptor (TCR) β or δ positive T-cells. Neoplastic transformation of the lymphoblast during this process leads to leukemogenesis of these progenitor cells as T-ALL.[61–63] Recent studies have revealed that this requires multi-step mutagenesis and genetic/genomic alterations. These changes cause the deregulation of certain genes involved in the critical events of normal T-cell development, e.g., cell-cycle control, differentiation, cell survival and proliferation, which ultimately result in developmental arrest at nearly all stages of T-cell maturation.[63,64] Clarification of the molecular bases and cytogenetic changes specifically associated with T-ALL has provided novel opportunities for developing highly efficient, targeted therapy of this cancer.

T-ALL is characterized by various chromosomal translocations and aneuploidy.[61] Using animal models together with advanced detection techniques in molecular biology, the molecular-genetic abnormalities in T-ALL, including chromosomal translocations, deletions, amplifications, duplications and point mutations, have been intensively investigated. T-ALLs may be grouped into distinct subgroups, TAL/LOM, LYL1, TLX1 (HOX11), TLX3 (HOX11L2), MYB, HOXA, or other defects (e.g., PICALM-MLLT10 and SET-NUP214), which are characterized by ectopic expression of certain genes. This may represent an alternative to conventional karyotyping for diagnostic classification and therapy selection. Gene expression analysis in specific T-cell ALLs has revealed that 70% of these genetic alterations involve altered expression of transcription factors. In childhood T-ALL, deregulation of MYB, TAL/SCL or the homebox gene TLX3 (HOX11L2) is observed in over 50% of patients, while in adults the expression of TLX1 (HOX11) or SCL is found in two major groups.[65–74] It is notable that these transcription factors are "master" transcription factors that regulate the development, differentiation, and proliferation of T-lymphoblast cells, which determines the gene signature and the characteristic T-ALL subsets.[75] In addition, homozygous deletions of tumour suppressor genes, e.g., genes coded by the CDKN2A/2B loci (p16INK4A, p15INK4B and p14ARF), occur in 90%

of the cases of leukemic T-lineage lymphoblasts.[61] These subsets of different genetic alterations possibly are of clinical relevance. For example, expression of TLX1 (HOX11) in T-ALLs is associated with favourable treatment outcomes, while unfavourable results have been observed with TAL1 and LYL1 expression.[69,72] Potentially, based on the genetic markers associated with the clinical presentations, these studies may provide a means of T-ALL classification for rational treatment.

The molecular basis or mechanisms of genetic alterations in T-ALL have been intensively explored. Gene expression profiling, as well as several genome-wide approaches, have shown that tyrosine kinases (e.g., BCR-ABL1, EML1-ABL1, ETV6-ABL1 and ETV6-JAK2), and certain important signaling pathways, including NOTCH1, PTEN, and (pre)TCR signaling, are specifically associated with development of thymocytes and are deregulated in T-ALL. Activating NOTCH1 mutations have now been identified in more than 50% of T-ALL, resulting in constitutive NOTCH signaling in these cells.[76–82] In one study, the presence of activating NOTCH1 mutations was associated with a favourable early treatment response. Targeting the signaling pathway of NOTCH1 has been suggested to be a potential therapeutic strategy in T-ALL.[83–86] Furthermore, multiple components of the (pre)TCR signaling pathway are targeted by either mutations or chromosomal rearrangements in T-ALL.[61] The RAS protein is involved in the transmission of TCR signaling from membrane receptors to the ERK protein, which is commonly mutated in a wide variety of malignancies. In T-ALL, activating RAS mutations have been identified in 4%–10% of cases.[64] These patients would potentially benefit from additional treatment with RAS inhibitors.

Recent studies in T-ALL also have focused on understanding apoptosis in lymphoblast cells. Apoptosis plays important roles in the normal development and homeostasis of lymphoid lineages.[87,88] The cytotoxicity of the most chemotherapeutic agents currently in use largely depends on their ability to induce a killing response in leukemic cells at different phases of the cell cycle.[89,90] Chemotherapeutic drugs stimulate an apoptosis response in leukemic cells using different upstream mechanisms. Methotrexate, cytosine arabinoside, camptothecin, etoposide and adriamycin preferentially induce apoptosis in S phase. Prednisone (or dexamethasone) and 6-mercaptopurine effectively induce apoptosis in the G1 phase and G1 + S phases, respectively. Another cytotoxic agent used to treat leukemia, cyclophosphamide, induces apoptosis with no cell cycle phase specificity.[91] However, these agents eventually induce apoptosis through a common, mitochondrial dependent (intrinsic pathway) downstream death machinery mechanism, involving a cascade of caspase activation that is conserved in eukaryotic cells across species. This downstream process is fundamentally regulated by BCL-2 family members.[92–94] The BCL-2 family of proteins consists of three subgroups, anti-apoptotic proteins (e.g., Bcl-2, Bcl-xL, Mcl-1) that promote cell survival, pro-apoptotic proteins (BH3 only proteins, e.g., Bid, Bim, PUMA) that trigger cell death, and pro-apoptotic effector proteins (Bax, Bak and Bok, having intrinsic pore-forming activity) that act downstream of BH3-only and pro-survival Bcl-2 members to induce mitochondrial outer membrane permeabilization (MOMP). This ultimately leads to the activation of caspase effectors. The balance of anti-apoptotic and pro-apoptotic BCL-2 family members determines the survival of lymphoblast cells during development of the normal lymphoid lineage and, in T-ALL, the ratio of BCL-2/BIM affects apoptosis in response to multiple chemotherapeutic reagents. In fact, possibly due to downregulation of antiapoptotic genes, TLX1 (HOX11)+ in adult T-ALL is associated with a favourable outcome of treatment. Conversely, the poor prognosis found in T-ALL subtypes expressing TAL1 or LYL1 is thought to be caused by the concomitant upregulation of antiapoptotic genes that confer resistance to chemotherapy.[65,72] It has been shown that, frequently, overexpression of pro-survival BCL-2 proteins may contribute to the profound resistance to chemotherapy in T-ALL poor responders.[95,96] These studies have highlighted the clinical relevance of the BCL-2 family members as potential targets for novel molecular targeting therapy in T-ALL.

Moleular Targets in T-ALL and Emerging New Therapeutic Compounds

Gowth arrest and inhibition of cell cycle progression

Nelarabine: Nelarabine is an analog of arabinosylguanine and acts as a prodrug of ara-G.[97]

By becoming demethylated and coverted into ara-GTP intracellularly, nelarabine induces rapid cell cycle arrest (G1-S or S phase), elevated expression of FasL and apoptosis of leukemic cells via both the extrinsic and intrinsic pathways. Nelarabine is much more effective in T-cell ALL than B-ALL, probably because of a genetic deficiency of purine nucleoside phosphorylase in T-cells leading to a selective sensitivity of T-ALL to deoxyguanosine.[98] Phase II trials on refractory or relapsed T-cell malignancies were conducted.[99,100] In the pediatric study, an initial nelarabine dose of 1,200 mg/m^2/d was administered for 5 consecutive days was de-escalated due to neurotoxicity, resulting in the final dose of 650 mg/m^2/d, with further de-escalation to 400 mg/m^2/d for patients with CNS complications. A complete remission was achieved in 46% of 39 patients in first relapse, 25% of 40 patients in second relapse, and 21% of 28 with CNS disease.[101] In the adult trial, 26 patients were given nelarabine on an alternate day schedule (days 1, 3, and 5) at 1,500 mg/m^2 per day. 31% of them achieved complete remission.[102–104] Nelarabine had been approved by the US Food and Drug Administration (FDA) for third-line treatment of patients with T-cell leukemia or lymphoma.

Flavopiridol: Flavopiridol (FP) is a flavonoid derived from an indigenous plant from India. FP is a potent inhibitor of cyclin dependent kinases (cdks) 1, 2, 4 and 7 in vitro, which induces transient cell cycle arrest at G1/S and/or G2/M and apoptosis.[105] In ALL cells, FP treatment suppresses the activity of cdks. This decreases the expression of phosphorylated retinoblastoma protein (ser-795/807/811) and effectively leads to cell cycle arrest. Furthermore, FP also reduces the expression of Mcl-1 and phosphorylated forms of the C-terminal domain of RNA polymerase II.[106–108] In primary ALL blasts, FP treatment increases cell death by approximately two-fold over baseline.[106] FP was more potent in vitro than glucocorticoids and thiopurines and at doses that recent phase I experience predicts will translate into clinical efficacy.[109] FP should be widely effective in ALL if sufficient plasma levels can be achieved clinically.

Inhibition of NOTCH1 signaling

NOTCH signaling is deregulated in the majority of T-cell acute lymphoblastic leukemias as a result of activating mutations in NOTCH1.[76–79] NOTCH signalling is activated by a series of proteolytic cleavage events, leading to the release of the intracellular domain (NICD) via ligand-dependent cleavage mediated by the gamma secretase (GS) complex. Upon GS cleavage, NICD translocates to the nucleus, binds to the transcription factor CSL and other protein cofactors, and activates the transcription of NOTCH target genes including HES1, HEY1, MYC, PTCRA, DTX1 and certain protein components in NFkB signaling pathway. Also, activated NOTCH1 can regulate the activity of the mTOR signaling pathway by phosphorylation.[78,83,86] The high frequency of NOTCH1 mutations found in associating to human T-ALLs makes the NOTCH signaling pathway the best available rational target in treatment of this disorder.

Gamma-secretase inhibitors (GSIs): GSIs comprise a class of small molecules that interfere with the proteolytic cleavage of the receptor and inhibit the release of NICD.[86] Potentially, by suppressing the NOTCH signaling pathways, GSIs may induce growth arrest in T-ALL cells and cause prolonged cell cycle arrest and apoptosis.[84,110] The potency of GSIs in T-ALL treatment has been shown by multiple pre-clinical studies. A reversible, noncompetitive, gamma-secretase inhibitor, PF-03084014, has been investigated for the treatment of T-ALL and advanced solid tumours in phase I clinical trials. PF-03084014 selectively inhibits gamma-secretase and reduces endogenous NICD levels, which results in the down-regulation of Notch target genes Hes-1 and c-Myc in T-ALL cell lines in vitro and in vivo. In T-ALL, PF-03084014 treatment also causes cell growth inhibition through cell cycle arrest and induction of apoptosis. Animal models have demonstrated the broad antitumor efficacy of PF-03084014 at well-tolerated dose levels. Treatment of PF-03084014 induces gastrointestinal toxicity, while glucocorticoids abrogate PF-03084014-induced gastrointestinal toxicity.[85,111] These studies show promise for the development of an approach using PF-03084014 and steroid therapy for Notch receptor-dependent T-ALL and other cancers. In another study, GSI developed by Merck (MRK-003) effectively suppresses Notch1 target gene expression and causes apoptosis of T-ALL leukemic cells in vivo, and significantly extended the survival of leukemic cell grafted mice in animal study.[112]

However, during phase I clinical trial, MRK-003 failed to induce favourable responses in relapsed/refractory T-ALL patients. One possible explaination might be attributed to the finding that the dysfunction of Notch1 signalling is more likely a secondary (acquired) leukemogenic event in T-ALLs.[113] Several other pre-clinical studies and clinical trials are testing the anti-tumour use of GSIs. These attempts should verify the therapeutic promise of GSIs in treatment of T-ALL and certain other cancers.[114–116]

Resveratrol: Resveratrol (RES), a potential chemopreventive agent is a natural phytoalexin.[117] The cytotoxicity of resveratrol is shown by its ability to inhibit cell proliferation and induce apoptosis in a variety of cancer cell lines. In MOLT-4 acute lymphoblastic leukemia cells, RES inhibits the survival and induces apoptosis by (1) inhibiting Notch signaling pathways and their down stream effectors; (2) increasing the pro-apoptotic protein p53 and its effectors $p21^{waf}$ and Bax; and, (3) inhibiting the PI3K/Akt pathway and activating Gsk-3beta.[118] Thus, future studies may further indicate a role for RES as an inhibitor of the NOTCH signaling pathway and as an apoptosis inducer in the treatment of T-ALL.

Tyrosine kinase inhibitors

The c-ABL proto-oncogene product, ABL1, is a tyosine kinase that regulates key processes including cell growth and survival, differentiation, stress and cell migration. The c-ABL gene is frequently one of the targets of mutations and genetic lesions in various cancers. Chromosome translocation t(9;22)(q34;q11) results in the formation of a Philadelphia chromosome (Ph) and generates an active chimeric BCR-ABL tyrosine kinase.[119] Typically, BCR-ABL is found in chronic myelogenous leukemia (CML) and precursor B-acute lymphoblastic leukemia (pre B-ALL), but it is exceptionally rare in patients with T-ALL (less than 1%). Another active fusion of ABL1 has been identified, ETV6-ABL1. It is caused by an acquired del(6)(q15q23), which is also preferentially associated with CML and B-ALL, and rarely in T-ALL (<1%). Furthermore, a unique T-ALL case had identified an EML1-ABL1 fusion due to a cryptic t(9;14)(q34;q32). However, in T-ALLs, another type of genetic lesion, episomal fusion of NUP214 to ABL1 (NUP214-ABL), resulted by episomal ABL1 gene amplication, and this has been identified in 6% of T-ALL patients.[73,120] Overexpression of the ABL fusion gene activates a number of downstream signaling cascades including the mitogen activated protein kinase (MAPK) and Janus kinase signal transducer and activator of transcription (JAK-STAT) signaling pathways, leading to growth-factor independent proliferation.[121] It also effectively promotes the survival of leukemic cells in the face of apoptosis induction. Until the recent introduction of tyrosine kinase inhibitors (imatinib and its more potent analogues), these genetic lesions had been one of the most unfavourable prognosis subsets among all types of acute lymphoblastic leukemia, with very poor outcome and high rate of refractoriness to treatment.[122,123]

Imatinib mesylate (Imatinib, STI-571): Imatinib is a tyrosine kinase inhibitor that inhibits the ABL, KIT and PDGFR kinases, and which has considerable activity against active BCR-ABL1 fusions in CML and ALL. Imatinib is used in the treatment of Ph+ associated leukemia, and it is a dramatic example of targeted molecular therapy against a specific genetic/molecular lesion.[60,124,125] Several studies have shown that imatinib combined with chemotherapy induces complete remission rates at levels of 90% to 100% and dramatically improves disease-free survival duration in patients with Ph+ ALL. In another study, combined with stem cell transplantation, administration of imatinib improved the treatment outcome of Ph+ ALL patients with a 3 year event-free remission of over 78%.[126] NUP214-ABL1 T-ALL is sensitive to the tyrosine kinase inhibitor imatinib in vitro, which indicates a potential new therapeutic approach to these cases. However, in a clinical study of one NUP214-ABL1 T-ALL case, imatinib failed to induce remission of patient.[127,128] This might suggest a resistance mechanism of NUP214-ABL1 T-ALL to imatinib treatment in vivo.

Nilotinib and dasatinib: Nilotinib and dasatinib were developed as second-generation tyrosine kinase inhibitors, which are significantly more potent than imatinib. While nilotinib is the aminopyrimidine modified analogue of imatinib, dasatinib has no structural similarity to imatinib. Dasatinib is a dual Src/Abl kinase inhibitor that is 300-fold more potent against active ABL1 kinase than imatinib, both in vitro and in vivo. Both nilotinib and dasatinib seem to be well tolerated and show activity against imatinib-resistant Ph+ leukemias, except in resistant leukemias with a

T315I mutation in the ABL1 gene.[129,130] Subsequent clinical studies have shown that dasatinib induces a complete hematological response in 43% of patients and a cytogenetic response in 32% of 23 patients with CML.[131] Patients with initial imatinib intolerance had more favourable responses to dasatinib than did patients with initial imatinib resistance. A combination of imatinib with dasatinib is expected to overcome drug resistance.[132,133] However, the optimal dose schedule of dasatinib in combination with Ph+ ALL regimens remains to be determined.[25,134] Remarkably, in a clinic study, complete hematologic and cytogenetic remission was achieved on a NUP214-ABL1 positive T-ALL patient after 3 weeks of dasatinib monotherapy treatment (70 mg of dasatinib two times daily).[128] These studies have raised the hope of treating these rare deadly cases of T-ALLs with this enhanced tyrosine kinase inhibitor.

Sensitizing apoptosis by targeted activation of pro-apoptotic BCL-2 family proteins

Activation of pro-apoptotic members of BCL-2 family proteins (BH3-only proteins) is a key event that commits cancer cells to apoptosis in response to many apoptosis-inducing chemotherapeutic agents. This is also strongly regulated by pro-survival BCL-2 proteins (e.g., BCL-2, MCL1) that bind to pro-apoptotic proteins and prevent apoptisis in normal conditions. The BH3-only protein, BIM, plays a pivotal role in regulating apoptosis of lymphoblast cells. Overexpression of prosurvival protein BCL-2 or downregulation of BIM effectively results in resistance to apoptosis-inducing agents, including radiation, corticosteroids, and chemotherapy. Therefore, several drugs targeting these proteins may potentially benefit the treatment of T-ALL by sensitizing the leukemic cells to apoptosis.

Rapamycin and mTOR kinase inhibitors: The mammalian target of rapamycin (mTOR) is a serine-threonine protein kinase that belongs to the phosphoinositide3-kinase(PI3K)-relatedkinasefamily. Inhibition of mTOR kinase results in dephosphorylation of its two major downstream signaling components p70 S6 kinase (p70S6K) and eukaryotic initiation factor 4E binding protein 1 (4E-BP1), which in turn inhibits the translation of specific mRNAs involved in cell cycle progression and proliferation and thus leads to G1 growth arrest.[135] A major regulator of the mTOR pathway is the PI3K/AKT kinase cascade, and the activation of PI3K/AKT/mTOR has been observed in lymphoid malignancies.[82] Rapamycin and the second generation of mTOR inhibitors (temsirolimus, everolimus, and deforolimus) have demonstrated activity in preclinical models of ALL, and they form potentially synergistic combinations with doxorubicin and methotrexate.[136–138] Dual inhibition of PI3K and mTOR prevented expansion of human BCR-ABL–positive leukemia cells.[139,140] Significantly in T-ALL model cell lines, gene expression profiling analysis showed that rapamycine treatment causes downregulation of the prosurvival protein MCL1, which increases the activation of pro-apoptotic BH3 only protein BIM and sensitizes leukemic cells to glucocorticoid treatment and apoptosis.[137,141] These studies have suggested the potential utilization of rapamycin in sensitizing T-ALL to apoptosis-induction via chemotherapy.

Obatoclax (GX15–070): The small molecule obatoclax is an antagonist of BCL-2 like proteins. It is an indole bipyrrole compound that is designed to target all BCL-2 family proteins, and it is especially potent against MCL1. Although obatoclax is currently used in developing single-agent therapy or in combination in phase I/II clinical trials directed at leukemia, the molecular mechanisms of cell death induced by obatoclax are not entirely clear. Studies in ALL model cell lines have revealed that obatoclax induces cell death through BAK-dependent apoptosis (by disrupting the MCL1/BAK complex) and via ATG5-dependent (becline-1 independent) autophagy.[142–146] Unlike the other small-molecule BCL-2 inhibitors, e.g., ABT-737 and ABT-263, obatoclax can overcome the resistance conferred by high levels of MCL1.[142,146] Potentially, obatoclax can be developed as a monotherapeutic agent against T-ALL.

ABT-737: ABT-737 (an orally available derivate ABT-263) ws developed to selectively target BCL-2-like proteins. ABT-737 has effective cytotoxicity against many hematological malignancies including ALL, acute myeloid leukemia (AML), multiple myeloma, lymphoma and chronic lymphocytic leukemia (CLL). It is able to bind BCL-2 family proteins including BCL-2, BCL-XL and BCL-w, but not for

MCL1.[147,148] Potently, its binding activity disrupts the interactions of these pro-survival proteins with their pro-apoptotic counterparts, leading to activation of BH3-only proteins including BIM and BID, which in turn sensitize cells to or trigger apoptosis. This mechanism involves an increase in cleaved fragments of PARP, and caspase-8 and cytochrome C levels shortly after treatment with ABT-737 at low micromolar concentrations.[149] BH3 profiling analysis of ALL cell lines as well as primary samples from ALL patients reveals the BCL-2 dependence of ALL, supporting the potential usefulness of ABT-737, as antagonist of BCL-2, in sensitizing leukemic cells for apoptosis induction.[148,150,151]

Conclusions

Current progress in studies on T-ALL using the technology of modern molecular biology has greatly improved cure rates for this type of cancer. Fundamentally, the goal of modern cancer research is to develop more effective therapies that specifically target the cancer cell with minimal effects on normal cells and tissues. Conventional therapies for T-ALL currently used clinically depend on cytotoxic anticancer drugs that induce apoptosis of malignant cells, but which inevitably cause considerable short or long term side effects and damage to the health of the patient. Furthermore, the non-selective cytotoxicity of anticancer drugs adversely affects the goals of treatment. After intensive chemotherapy, stem cell transplantation has to be performed for some patients, and, in many cases, secondary malignancies occur as the result of the treatment. These situations have prompted the development of novel therapeutic approaches with more specific targeting and efficiency. Based on the elucidation of the molecular basis of T-ALL, a few targets have been identified and drugs and protocols that target these molecules have been developed (summarized in Table 2). However, the specificity and efficiency of these treatments are uncertain, due to the relatively short period that they have been available for clinic applications. Also, it is notable that, in the most cases, these new approaches still have to be combined with conventional treatment to obtain satisfactory outcome. Other novel therapeutic approaches under development include RNA interference to silence leukemic oncogene expression of the T-ALL specific mRNA and immunotherapy that exploits the antitumor activity of cytotoxic T lymphocytes or natural killer cells.[2,152,153] Moreover, protein therapy appears to be another interesting approach. Leukemogenesis is associated with the deregulated expression transcription factors. Specific targeting of transcription factors that are associated with the transformation of certain T-ALLs could potentially lead to strategies for rational antileukemia therapy.

Table 2. Selected new therapies for T-acute lymphoblastic leukemia.

Agent	Mechanism of action	Targeting subtype of leukaemia
Clofarabine	Inhibits DNA polymerase and ribonucleotide reductase; disrupts mitochrondria membrane	All types
Nelarabine	Inhibits ribonucleotide reductase and DNA synthesis	T-cell
Flavopiridol	Serine-threonine cyclin-dependent kinase inhibition	All types
Forodesine	Inhibits purine nucleoside phosphorylase	T-cell
γ-secretase inhibitor (PF-03084014)	Inhibit γ-secretase, an enzyme required for NOTCH1 signaling	T-cell
Resveratrol	Inhibits NOTCH1 signaling; Inhibit PIK3/AKT signaling pathway	T-cell
Imatinib mesilate; Nilotinib	ABL kinase inhibition	BCR-ABL-positive
Dasatinib	BCR-ABL kinase inhibition	BCR-ABL-positive
Rapmycine; Sirolimus; temsirolimus; everolimus; AP-23573	Mammalian target-of-rapamycin (mTOR) inhibition	All types
Obatoclax	Inhibits BCL-2 anti-apoptosis proteins; Disrupt MCL-1/BAK complex	All types
ABT-737 (ABT-263)	Inhibits binding of BCL-2 anti-apoptosis proteins to pro-apoptotic BH3 proteins BIM and BID	All types

Successful techniques of protein transduction mediated by a protein transduction domain (PTD) have made this possible by rendering the cell permeable to any protein molecule. Because of the transient activity of endogenous proteins used for treatment (due to eventual cellular degradation of proteins), very low side effects are expected for this strategy. Using model T-ALL cell lines, a few related studies have been successfully conducted in vitro.[154] More work clearly needs to be done to better exploit this technology. In summary, in the past several years, targeted molecular therapy has emerged as a major focus of interest in T-ALL treatment. Based on an improved future understanding of the molecular mechanism of the leukogenosis, additional treatment targets that are T-ALL specific are expected to be identified. It is hoped that an optimal combination of these target specific drugs will lead to rational treatment of T-ALL patients to obtain complete remission with the lowest possible instances of non-specific side effects.

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