Novel Therapies for Relapsed Acute Lymphoblastic Leukemia

Amber Fullmer, PharmD, Susan O’Brien, MD, Hagop Kantarjian, MD, and Elias Jabbour, MD

The outcome of salvage therapy for relapsed acute lymphoblastic leukemia (ALL) remains poor. Salvage therapy mimics regimens with activity in newly diagnosed ALL. Novel strategies under investigation as monotherapy or in combination with chemotherapy improve the treatment of relapsed disease. For some ALL subsets, specific therapies are indicated. The addition of targeted therapy in Philadelphia chromosome–positive ALL has improved responses in relapsed patients without resistance to available tyrosine kinase inhibitors. Nellarbene demonstrates activity as monotherapy in T-cell ALL and is approved by the US Food and Drug Administration. Clofarabine, a second-generation purine analogue approved in pediatric leukemia, has shown activity in adult acute leukemias including ALL and acute myeloid leukemia. The role of pegasparagase in adult ALL requires further investigation. The benefit of matched related-donor allogeneic stem cell transplantation is significant for standard-risk ALL but not for high-risk ALL. Development of new drugs and agents tailored to subset-specific cytogenetic-molecular characteristics remains vital to success in treating adult ALL.

Etiology

The etiology of ALL remains unknown. Chromosomal translocations occurring in utero during fetal hematopoiesis have been suggested as the primary cause of pediatric ALL, and postnatal genetic events are suggested as secondary contributors. A higher incidence of ALL is noted among monozygotic and dizygotic twins of patients with ALL, reflecting possible genetic predisposition. Patients with trisomy 21, Klinefelter’s syndrome, and inherited diseases with excessive chromosomal fragility (eg, Fanconi’s anemia, Bloom syndrome, and ataxia-telangiectasia) have a higher risk of developing ALL [2]. Implications have also hinted at infectious etiologies. Associations between human T-cell lymphotrophic virus type 1 and adult T-cell leukemia/lymphoma, as well as HIV and lymphoproliferative disorders, have been established. In addition, associations with varicella and influenza viruses have been suggested.

Classification

The French-American-British (FAB) Cooperative Group distinguishes three ALL groups (L1 to L3) based on...
morphologic criteria (cell size, cytoplasm, nucleoli, basophilia, vacuolation) [3]. The morphologic distinction between L1 and L2 has lost its prognostic significance. L3 morphology is associated with mature B-cell ALL (Burkitt’s leukemia). The World Health Organization (WHO) proposed new guidelines for the diagnosis of neoplastic diseases of hematopoietic and lymphoid tissues [4,5]. In addition to lowering the blast count to greater than or equal to 20% as sufficient for an ALL diagnosis, the morphologic distinction of L1, L2, and L3 morphologies is abandoned as no longer relevant. Both the FAB and WHO classification systems continue to rely heavily on morphologic assessment. Identification of the immunophenotype has become a major part of ALL diagnosis. Three broad groups can be distinguished: precursor B-cell ALL, mature B-cell ALL, and T-cell ALL.

Prognostic Factors
Several factors are considered when determining prognosis for adult patients with ALL. The presence of these risk factors increases the risk of relapse. Older age, high leukocyte count, immunophenotype other than T-cell, Philadelphia chromosome (Ph) positivity, and longer time to achieve initial complete response (CR) have all been associated with poor prognosis [6]. Other predictors of poor prognosis that have been suggested include poor performance status, presence of organomegaly, low platelet counts, low albumin levels, and elevated serum lactate dehydrogenase levels. In relapsed ALL, the presence of circulating peripheral blasts at the initiation of salvage treatment correlates with lower likelihood of response to chemotherapy and shorter survival [6]. In addition, short duration of complete response, increased bone marrow blasts, thrombocytopenia, and hypoalbuminemia adversely affect survival in relapsed patients [7••].

Chemotherapy
The treatment of ALL remains among the most complex therapies of anticancer programs. Multiple drugs are molded into regimen-specific sequences of dose intensity and time intensity, with the goal of reconstituting normal hematopoiesis, preventing the emergence of resistant subclones, providing adequate prophylaxis of sanctuary sites (eg, central nervous system [CNS], testicles), and eliminating minimal residual disease (MRD) through postremission consolidation and maintenance [2]. Three distinct phases (induction, intensified consolidation, and maintenance) are distinguished, with four components including CNS prophylaxis, which accompanies induction and consolidation.

The combination of vincristine, corticosteroids, and anthracyclines represents the backbone of ALL induction regimens. This combination achieves remission rates of 72% to 92%, with a median remission duration of about 18 months [8]. Dexamethasone is often substituted for prednisone because of better in vitro antileukemic activity and achievement of higher drug levels in the cerebrospinal fluid (CSF) [9,10]. Although L-asparaginase is an important agent in the treatment of pediatric ALL, its role in adult ALL is not well defined. Hematopoietic growth factors during induction accelerate recovery from myelosuppression and allow timely administration of dose-intense treatment regimens [11].

Consolidation represents a repetition of a modified induction schedule, rotational consolidation programs, or stem cell transplantation. Novel strategies try to emphasize subtype-oriented or risk-oriented approaches of consolidation programs.

The mainstays of maintenance therapy are daily 6-mercaptopurine, weekly methotrexate, and monthly pulses of vincristine and prednisone, given over 2 to 3 years. Extension of maintenance beyond 3 years is not beneficial, nor is the omission or shortening of therapy [2]. No maintenance therapy is given in mature B-cell ALL, as these patients have a high cure rate with short-term, dose-intense regimens, and relapses beyond the first year in remission are rare. The best maintenance for patients with Ph-positive ALL remains disputed but should incorporate effective BCR-ABL tyrosine kinase inhibitors.

Although CNS disease is found in less than 10% of patients at diagnosis, the rate can increase to as high as 50% to 75% at 1 year without CNS-directed therapy [12–14]. Standard prophylaxis for CNS malignancy can involve radiation therapy, systemic chemotherapy, intrathecal (IT) chemotherapy, or a combination of these. Cranial irradiation is associated with adverse effects such as secondary neoplasms, endocrinopathy, neurocognitive dysfunction, and neurotoxicity [15–17]. Combining early intensive systemic and IT chemotherapy can lower the CNS relapse rate in patients with ALL and may provide the opportunity to omit prophylactic cranial irradiation [18]. High-dose cytarabine (1–7.5 mg/m²) and methotrexate (5–8 g/m²) have the ability to penetrate the blood–brain barrier and can serve as CNS prophylaxis [19–22]. However, it is difficult to maintain prolonged therapeutic concentrations of drug in the CSF using only systemic chemotherapy. Furthermore, systemic therapy is associated with widespread toxicities. High-dose cytarabine is associated with liver dysfunction, cerebellar dysfunction, mucositis, diarrhea, rash, and fever [23]. High-dose methotrexate is associated with renal dysfunction, transient hepatitis, mucositis, and (rarely) neurotoxicity [24]. The inclusion of IT chemotherapy in CNS prophylaxis protocols aims to improve the efficacy of systemic therapy while circumventing its limitations. IT chemotherapy allows direct intra-CSF treatment and potentially sustained therapeutic drug concentration in the CSF [13]. Commonly used IT therapies include methotrexate, cytarabine, liposomal cytarabine, and thiopeta. In the absence of IT therapy, isolated CNS recurrence can account for 10% to 16% of relapses, warranting the inclusion of IT chemotherapy in CNS prophylactic regimens [24]. The efficacy of high-