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TREATMENT METHODS FOR PATIENTS SUFFERING FROM ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) - A BRIEF REVIEW

Authors' names

1. Zuzanna Czudy MD, ORCID: 0000-0002-1619-4343, University Hospital, Collegium Medicum University of Zielona Gora, Zyty 28, 65-046 Zielona Gora, Poland, zuzanna.czudy@o2.pl
2. Wojciech Paweśka MD, ORCID: 0009-0007-0836-4983, District Hospital, Krakowska 3, 32-700, Bochnia, Poland, wojciech.paweska@gmail.com
3. Jan Radwański MD, ORCID: 0009-0009-1441-8057, Provincial Specialist Hospital No. 4, Legionow 10, 41-902 Bytom, Poland, jan.radwanski97@gmail.com
4. Hanna Dominik MD, ORCID: 0000-0003-0371-2276, University Hospital, Zyty 26, 65-046 Zielona Gora, Poland, hania.dominik31@gmail.com
5. Marika Polatowska, 5th year medical student, ORCID: 0009-0007-8191-4566, Collegium Medicum University of Zielona Gora, Zyty 28, Zielona Gora 65-046, Poland, marika85588@gmail.com
6. Anna Gadomska MD, ORCID: 0009-0004-4029-3925, University Hospital, Zyty 26, 65-046 Zielona Gora, Poland, anna.gadomska@hotmail.com
7. Justyna Kurek MD, ORCID: 0009-0000-3828-9303, Clinical Hospital No. 2, Lwowska 60, 35-301 Rzeszow, Poland, jotkurek@gmail.com
8. Rafał Gorzyński MD, ORCID: 009-0001-0815-1247, Clinical Hospital, Collegium Medicum University of Poznan, Długa ½, 61-848 Poznan, Poland, rafal.gorzynski2@gmail.com
9. Michał Garstka MD, ORCID: 0009-0007-6152-9388, Medical Center HCP, 28 Czerwca 1956 r. 194, 61-485 Poznan, Poland, lek.garstka@gmail.com

10. Justyna Molczyk-Sieńczak DMD, ORCID: 0009-0007-8037-6305,
NZOZ Alicja Ulanecka, Moscickiego 14, 33-100 Tarnow, Poland, justymolz@gmail.com

Corresponding author

Zuzanna Czudy MD,

+48-600 735 524, zuzanna.czudy@o2.pl

University Hospital, Zyty 2, 65-046 Zielona Gora

ABSTRACT

Introduction and purpose: Acute lymphoblastic leukemia is a medical condition with underlying abnormal proliferation of cells of the lymphoid system which are blocked at an early stage of differentiation. As a result of impaired lymphocyte maturation, the proliferation and accumulation of immature blastic cells, derived from tumor-transformed bone marrow precursor cells, develop in the bone marrow. The infiltration of the bone marrow by leukemic cells results in failure of normal hematopoiesis, with subsequent anemia, thrombocytopenia and neutropenia. Acute lymphoblastic leukemia is among the most aggressive proliferative diseases, and survival time is a few to several weeks without appropriate treatment.

Materials and methods: The literature available on PubMed was reviewed using the words “acute lymphoblastic leukemia”, “ALL”, “acute lymphoblastic leukemia treatment”.

Summary: Acute lymphoblastic leukemia was managed with a chemotherapeutic drug combination for several years, with median overall survival of approximately 80% for all newly diagnosed cases. Patients with higher-risk relapses receive more intensive treatment, while patients with more favorable outcomes can avoid more toxic effects. Multicenter randomized controlled trials conducted by international collaborative efforts are helping to advance overall survival by exploring novel treatments. Hope for the future of leukemia therapy is defining the underlying molecular trails in the pathogenesis of the disease and clarifying host pharmacogenetic factors further. If successful, these efforts will allow the identification of new genes with candidate proteins for targeted therapies.

Keywords: acute lymphoblastic leukemia, CAR-T, aggressive proliferative disease, chemotherapy, bone marrow

REVIEW

Acute lymphoblastic leukemia is a disease with an underlying abnormal proliferation of cells of the lymphoid system blocked at an early stage of differentiation. As a result of impaired lymphocyte maturation, there is proliferation and accumulation in the bone marrow of immature blastic cells, derived from neoplastically transformed myeloid precursor cells. Infiltration of the bone marrow by leukemic cells leads to failure of normal hematopoiesis and consequent anemia, thrombocytopenia and neutropenia. Acute lymphoblastic leukemia is one of the most aggressive proliferative diseases, and the survival time without appropriate treatment ranges from a few to several weeks. The male to female ratio is about 1-2:1,2 and the disease is more common in children. The age-dependent incidence is highest in children aged 1-4, and lowest between the ages of 25 and 45. Beyond this age range, there is only a slight increase in incidence. [1] The reasons for the emergence of ALL are not yet fully understood. Exposure to certain chemicals, such as benzene, previous treatment with cytostatics or exposure to ionizing radiation, increases the risk of leukemia. Other factors that may influence the risk of malignant transformation and the occurrence of ALL include: genetic factors, viral infections, maternal environment of fetal development. [2] The reasons for the emergence of ALL are not yet fully understood. Exposure to certain chemicals, such as benzene, previous treatment with cytostatics or exposure to ionizing radiation, increases the risk of leukemia. Among other factors that may impact the risk of neoplastic transformation and the onset of ALL are: genetic factors, viral infections, the maternal environment of fetal development. The first phase of the diagnostic procedure is cytomorphological assessment of the bone marrow. The presence of 20% lymphoblasts in the bone marrow is the fundamental criteria for the recognition of ALL. It should be mentioned that the morphology of leukemic cells in the blood and in the bone marrow may differ substantially, therefore bone marrow evaluation is crucial to determine a final recognition of ALL. Before treatment, it is advisable to include: biochemical tests to assess liver and kidney function, lactate dehydrogenase activity, glucose, uric acid, electrolytes, coagulation tests and the patient's blood type. It is also necessary to perform tests for the presence of viral infections.

Treatment options for acute lymphoblastic leukemia (ALL)

Prognostic factors determine assignment to a given risk group, and thus the choice of appropriate intensification of therapy. Various treatment protocols for ALL are used in developed countries, each distinguishing risk groups and prognostic factors: minimal residual disease (MRD), response to steroid therapy, immunophenotype, genetic factors, patient age, and white blood cell (WBC) count at diagnosis used to qualify patients. One of the most important prognostic factors in patients with ALL remains MRD status, which is defined as surviving tumor cells resistant to the chemotherapy used. The detection of 1 tumor cell per 10,000 healthy cells (0.01%) is sufficient for a positive MRD result. Minimal residual disease informs about the efficacy of the applied treatment and the chemosensitivity of the patient, which allows the determination of the remaining disease burden and the risk of recurrence. First-line therapy for acute lymphoblastic leukemia typically comprises four phases lasting 2-3 years: induction, consolidation, intensification and long-term supportive management. Induction chemotherapy is aimed at eliminating the burden of illness and re-establishing proper hemopoiesis to reach a complete remission. Consolidation is the second stage of treatment management and consists of multiple short sequential (usually repeated every two weeks) cycles of chemotherapy, containing cytarabine and high-dose methotrexate ($>500 \text{ mg/m}^2$), in addition to vincristine, asparaginase, mercaptopurine and glucocorticoids, administered over 12 weeks. After completing the entire cycle, a late intensification phase should be implemented (this is reinduction therapy), which consists of the combination of drugs used during consolidation. It is essential to supplement the patient with folic acid after high doses of methotrexate. Unfortunately, however, high levels of this substance are associated with an increased risk of relapse, so it should be supplemented slowly. Maintenance therapy, which is the next step in the chemotherapy cycle, includes mercaptopurine, which must be given daily, and methotrexate given weekly with or without vincristine, as well as pulsed corticosteroids given every 1-3 months. This therapeutic step should be implemented for 2-3 years after induction. Although, thioguanine also inhibits de novo purine synthesis, it acts with higher in vitro lymphoblast cytotoxicity than mercaptopurine. Pondato has not proven clinical benefit in randomized trials designed to compare the two drugs. What's more, doses of thioguanine at 40 mg/m^2 per day administered long-term, consequently led to death and significant side effects (sinus obstruction syndrome, thrombocytopenia and portal hypertension). For this reason, mercaptopurine is the standard of maintenance treatment. Besides chemotherapy, radiation therapy is also being used to treat acute lymphoblastic leukemia in targeted groups of patients. According to the old treatment guidelines, craniospinal irradiation has been an essential component of leukemia treatment. At present, eligibility for radiation therapy depends on the

specific central nervous system (CNS) status at the time of diagnosis. Allogeneic hematopoietic cell transplantation targets patients with high-risk disease or those with minimal residual disease present. In adults, the use of this method is much less effective than in children, while 5-year overall survival ranks below 45%. [3] The hyper-CVAD program recommends implementing treatment that is based on alternating two blocks of chemotherapy. Block A, which includes giving the patient large fractionated doses of cyclophosphamide and, importantly, also vincristine, doxorubicin and dexamethasone. Block B, which involves giving the patient large doses of methotrexate and large doses of cytosine arabinoside. The most common complications of this treatment include neutropenic fever due to the strong myelosuppressive effect, as well as infectious complications. Late consequences of treatment include infertility, cardiomyopathy and secondary cancers. Patients at moderate risk are treated for at least two years to sustaining remission. Among this group of patients, autologous hematopoietic stem cell transplantation (auto-HSCT, autologous hematopoietic stem cell transplantation) should also be thought of. Another treatment option concerns the group of patients in whom CD20 expression has been confirmed in at least 20% of blasts. In this case, it should be remembered that in addition to chemotherapy treatment during induction, consolidation and maintenance treatment, another chemotherapeutic agent -rituximab - should also be implemented. Such treatment results in a significant reduction in the risk of relapse, ALL patients with the presence of the Philadelphia chromosome(ALL-Ph+) are a separate group in which a special treatment protocol should be implemented. In this case, it is extremely important to implement a tyrosine kinase inhibitor (TKI, tyrosine kinase inhibitor).[4] The use of TKIs should be combined with reduced-intensity chemotherapy. During disease remission, the patient should undergo allo-HSCT as early as possible. After transplantation, cyclic monitoring of MRD is essential. Conducting intrathecal CNS prophylaxis is necessary for patients who have been tested for CD20 expression, and the result was more than 20% blasts. Allo-HSCT is performed for patients who have an unfavorable prognosis resulting in relapse due to consolidation therapy. The method of allogeneic hematopoietic cell transplantation is recommended as first-line treatment for patients with a positive Philadelphia chromosome. It is also the recommended therapeutic method in adult patients with acute lymphoblastic leukemia, also with a negative Philadelphia chromosome for that with residual disease that persists after induction or consolidation. For the group of patients who receive less intensive chemotherapy, the importance of MDR is much less important, and the decision to transplant should be based on parameters indicating a poor prognosis of the disease. This therapy is particularly important in fit patients whose leukemia is relapsed or refractory to treatment. In patients who have penetrated a second complete remission, allogeneic hematopoietic cell transplantation is the recommended procedure, especially in adults. It is very important to

minimize the patient's risk of residual disease, as it is correlated with relapse after this therapeutic modality. [5]

The role of immunotherapy in the treatment of ALL

In recent years, new opportunities have been provided by the development of immunotherapeutic approaches. These include free monoclonal antibodies, toxin-conjugated antibodies, antibody fragments that engage T cells and genetically modified T cells. Examples of immunotherapeutic preparations include Rituximab and ofatumomab, which are antibodies capable of identifying the CD20 molecule on target cells. Epratuzumab is an example of a humanized monoclonal antibody with anti-CD22 specificity. The implementation of this drug in combination with chemotherapy (clofarabine + cytarabine) was part of a phase II study on a group of 32 patients suffering from a refractory form of ALL. CR was achieved in 45% compared to 17% in a historical group with similar characteristics treated with clofarabine and cytarabine alone. The efficacy of this agent should remain the subject of further studies. Alemtuzumab, on the other hand, identifies the CD52 molecule, but attempts to implement this formulation have been unsuccessful. Its use is associated with profound immunosuppression and may lead to cytomegalovirus activation. Inotuzumab ozogamycin is an anti-CD22 antibody conjugated to the toxin calicheamicin. It is able to bind to the membrane antigen, followed by internalization and the release of calicheamicin, which binds to double-stranded DNA and breaks this acid. In a study on 90 patients with refractory ALL, the CR rate was 50%, what's more, in most of the subjects it was associated with negative results of the MDR. [6] Tyrosine kinase inhibitors have found use in combination with standard chemotherapy, as I discussed in the paragraph above, to improve its efficacy. ABL1 inhibitors (e.g., imatinib, dasatinib, nilotinib and ponatinib) are finding use in treating patients with BCR/ABL-positive variant ALL. Ruxolitinib is in clinical trials in patients with JAK-STAT activating mutations, which accounts for less than today's percentage of ALL cases in the pediatric population. In contrast, a recent study proved that 44.4 percent of pediatric T-ALL samples and 16.7 percent of adult T-ALL samples are sensitive to dasatinib through inhibition of preTCR-LCK signaling.

Proteasome inhibitors have proven efficacy in ALL and work together in synergy with chemotherapeutic drugs such as corticosteroids and doxorubicin. In contrast, a clinical trial involving 22 children with relapsed ALL who were treated with bortezomib in combination with vincristine, dexamethasone, pegaspargase and doxorubicin, achieved a remission rate of 73%. However, in the randomized controlled trial of patients of newly diagnosed T-ALL or T-lymphoblastic lymphoma (T-LLy), the inclusion of bortezomib in the phase of induction and late

consolidation was linked to improved outcomes, as compared to those in patients who did not receive bortezomib. [7]

Advanced immunotherapeutic methods of leukemia treatment - CAR-T therapy

CAR T cells have been investigated in preclinical and clinical studies. In hematological cancer, effectiveness in fighting cancer extends to the complete and long-lasting durable clinical responses that have been reported in late-stage leukemias and chemotherapy-resistant lymphomas. Chimeric antigen receptors (CAR) consist of modules formed from the ectodomain, hinge, trans-membrane domain (TDM) and intracellular signaling domain. The ectodomain is a signal peptide that binds antigen and is MHC-independent. It was isolated from a monoclonal antibody, a single-chain fragment variant (scFv) formed by variable parts of the heavy and light chains of immunoglobulin. CAR T immunotherapy represents an ideal opportunity. Although it comes with serious challenges, such as cytotoxicity, cytokine release syndrome, neurotoxicity and ICANS. The development in the production of different generations of CAR technology and its combined use in other ways, such as hematopoietic stem cell transplantation, can be used as an effective treatment for ALL after the failure of chemotherapy methods. This technology may be used in the future as an effective and safe treatment method for ALL. A major part of present studies and likely of future studies is focused on identifying new target antigens and new mixtures of the currently available cells. Selecting better pre-clinical tests to identify possible target combinations is one major challenge. Furthermore, exploring mechanisms of antigen losses and identifying overcoming strategies is crucial to achieving the research target. Surmounting inhibitors of T-cell function within the microenvironment of the tumor can advance the progression and development of CAR T-cell adducts. There are currently ~470 clinical trials in the area of CAR T-cell therapy and possibly thousands of drug combinations to explore. [8] CAR-T therapy is developed specifically for each patient and involves reprogramming a patient's immune system cells that can be used to fight cancer. The treatment is highly complex and potentially high-risk, but has been demonstrated in trials to heal some patients, including even those with rather advanced cancers in which all other available therapies have already failed. Although the initial response rate to treatment with CD19-CAR-T cells in B-ALL is high, recurrence has occurred in a substantial number of patients. Present strategies to improve the effectiveness of CAR-T cells focus on enhanced CAR-T cells in vivo, multi-specific CARs to surmount immune leakage and new CAR projects. CAR-T cells can be used to progress to allo-SCT in patients with ALL. Future improvements in CAR-T cell constructs could enable long-term remission without supplemental Allo-SCT. Uncertainties regarding the actual expense of these relatively new therapeutic approaches involve reimbursement questions.[9] The

need for a second treatment with CAR-T in patients with PR or recurrence was unquestionable. In the case of CR, a second CAR-T treatment may eradicate MRDs below the threshold of present assays or concealed in extramedullary locations. Steroids used to treat CRS do not affect the efficacy and kinetics of CAR-T cells in B-ALL. Second treatment with CAR-T cells may enhance the function and prolong the longevity of first CAR-T cells, with the underlying mechanism remaining unknown. One concern about the efficacy of second CD22 CAR-T therapy in CR patients is that patients may lack CD22 antigens to drive CAR-T cell expansion. In conclusion, our sequential combination strategy of CD19 and CD22 CAR-T therapy achieved longer EFS and OS in relapsed B-ALL patients after transplantation, which was also beneficial for patients with EMD at one site.[10]

DISCUSSION:

Acute lymphoblastic leukemia has been treated with a chemotherapeutic drug combination over several years, with a median overall survival of about 80% in total for all patients newly diagnosed. Higher-risk recurrence patients are given more intensive treatment, while more favorable patients may be spared more toxic effects. Therapy is increasingly less aggressive with treatment duration and has to involve therapy targeting the central nervous system (CNS), independently of CNS occupation at the time of diagnosis. Multi-center randomized controlled studies conducted through international cooperation groups are assisting in improving further survivability by investigating new treatment approaches. Indeed, the hope for the future of leukemia therapeutics is in defining the molecular pathways that underlie the pathogenesis of the condition and in further clarifying the host pharmacogenetic agents. These efforts, if they are successful, will allow the identification of novel genes with protein candidates for targeted therapies. The growing number of patients suffering from ALL is forcing the docking of new directions and methods in the treatment of the disease. Due to the multitude of variants of acute myeloid leukemia, it is necessary to constantly improve existing forms of therapeutic treatment and to search for new, effective solutions.

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Author contributions

Conceptualization, Z.C. and H.D.; Methodology M.P.; Validation, W.P. and H.D; Formal Analysis, A.G and Z.C.; Investigation, W.P. and J.M-S; Resources, J.K. and W.R.; Data Curation, M.G., J.R.; Writing – Original Draft Preparation, Z.C., M.P.; Writing – Review & Editing, H.D. and Z.C.; Visualization, R.G.; Supervision, H.D and M.P.; Project Administration, .Z.C.

Conflicts of interest

The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data availability

The data have not been made public, but are kept with the authors, if necessary.

Ethics approval

Written informed consent for publication was obtained from the patient. We complied with the policy of the journal on ethical consent.

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