European Review for Medical and Pharmacological Sciences 2018; 22: 6015-6019

# Central nervous disease in pediatric patients during acute lymphoblastic leukemia (ALL): a review

M.-W. JIN, S.-M. XU, Q. AN

Department of Pediatrics, Xuzhou Children's Hospital, Xuzhou, Jiangsu, P.R. China

**Abstract. – Acute lymphoblastic leukemia (ALL) is one of the frequently reported malignancies of childhood age. Earlier it was thought to be a fatal pathological state with no cure, but with advancements in medicine and science, new therapeutic approaches have resulted in better management and cure. However, one of the major hurdles in achieving a complete cure is the relapse of ALL at extra-medullary sites like the central nervous system (CNS). The present review article is focused on recent diagnostic avenues available for the detection of CNS disease during acute lymphoblastic leukemia (ALL) in young patients.**

*Key Words:*
Leukemia, Central nervous disease (CNS), Diagnosis, Pediatric.

## Introduction

The acute lymphoblastic leukemia (ALL) is the commonest childhood malignancy accounting for 75-80% cases of leukemia and 25% of all malignancies in children[1]. The prevalence of ALL in under-developed countries, and in poor socioeconomic groups is lower than developed countries. Small differences in prognosis are observed between different races, but the exact mechanisms working behind are still not clear. In the United Kingdom (UK), approximately 300 children are diagnosed with ALL on a yearly basis. The prominent pediatric age of incidence is between 2 and 3 years and is more common in males in comparison to females. Fortunately, recent decades have observed a decrease in mortality from ALL as 5-year overall survival is now above 90%[2]. However, prognosis in relapsed cases is still poor and the majority of children with relapse die due to treatment failure or therapy-related complications[3]. Overall, leukemia is responsible for 30% of cancer-related deaths in children[4]. The exact causes of leukemia are still unknown. However, there are few pre-disposing inherited conditions and acquired risk factors associated with a higher incidence of ALL. Disorders associated with chromosomal aneuploidy or instability, such as down syndrome, ataxia telangiectasia, and bloom syndrome are frequently associated with ALL. Similarly, exposure to mutagens such as ionizing radiation, benzene or chemotherapy also contributed towards the spread of this deadly pathological state. However, the majority of cases occur sporadically[5]. Epidemiologic data point to infections as causal exposure for the development of ALL[6]. Germline single nucleotide polymorphisms (SNPs) in patients with ALL and control populations have implicated ARID5B, IKZF1, and IL-15 genes in leukemia[7]. The mechanistic link between these SNPs and ALL is still unclear.

### Central Nervous System (CNS) and Leukemia

With improving success rates in control of leukemia, central nervous system involvement in ALL emerged as a new phenomenon. The longer the patients lived, the greater the chances of developing CNS disease. Between 1948 and 1960, the incidence of CNS leukemia increased from 3% to 40% as the median survival of patients increased from 4 to 12 months[8]. In a series of 126 autopsies on children who died of leukemia, almost 60% of the autopsies showed evidence of leukemia in the CNS, predominantly the meninges[9]. The increasing incidence of CNS disease was attributed to poor penetration of anti-leukemic agents into the CNS. Further, the realization of any improvement in survival rates could only be possible with an effective clearance of CNS disease. Over the past few decades, survival from ALL has improved dramatically. Yet, CNS disease continues to pose challenges.

CNS disease is diagnosed and monitored by microscopic analysis of CSF. Broadly, there are three

*Corresponding Author:* Qi An, MD; e-mail: aiqiangel@yeah.net

main sub classes of CNS disease viz. CNS 3, CNS 2, and traumatic lumbar puncture (TLP) with blood contamination[10,11]. The majority of children with CNS 3 disease are asymptomatic. However, some might present clinical or radiological signs without leukemic cells in the CSF. Nowadays, a large number of researchers are involved in testing novel methods to improve the diagnostic accuracy of CNS disease.

### Experimental Methods for Detection of CNS Disease

Several alternative methods to detect sub-clinical levels of leukemia in the CSF have been tried and only three main approaches have been widely accepted. The first one is the increasing sensitivity of detecting blasts in the cerebrospinal fluid samples. The second method involves the indirect estimation of CNS leukemia by detecting soluble biomarkers of leukemia in the CSF, and the third method involves the use of radiological diagnostic methods.

### Immunological Markers of CNS Leukemia

The immunological markers allowed diagnosis of CNS disease with high accuracy. The initial studies used terminal deoxynucleotidyl transferase (TdT) and TdT/CD10 for the staining of CSF cytospin preparation[12]. It resulted in identification of approximately 25% CNS disease-positive patients. Moreover, TdT staining at diagnosis was predictive of a CNS relapse too. Recently, multi-color flow cytometry has added to the accuracy of diagnosing CNS disease[13]. Moreover, the appearance of leukemic phenotype during the treatment period was predictive of CNS relapse[14].

### Detections of CNS Disease by PCR

PCR for clonal Ig/TCR gene rearrangements could be used to determine the clonality of leukemic cells in the CNS[15]. Studies utilizing PCR have demonstrated not only a higher incidence of CNS disease, but also poor prognosis in CSF PCR positive patients. For example, using PCR, in a series of 37 pediatric ALL patients, 46% were positive for CNS disease, while morphology could only determine 5.4% CNS 3 cases. Moreover, the 4-year EFS in qPCR positive patients were significantly worse than qPCR negative patients[16]. qPCR studies could also be useful in cases suspected of CNS leukemia. Further improvisation has been reported by utilization of flow cytometry along with qPCR for detection of CNS diseases[17]. So, it is clear that when flow cytometry or PCR are used, CNS disease detection rate is quite higher as compared to microscopy.

### Soluble Biomarkers of CNS Disease

The malignant cells might release leukemia-associated soluble factors into the extracellular compartment and their levels in the CSF could be an indirect measure of disease burden in the CNS. Not all soluble biomarkers associated with CNS disease are of use in clinical setting, but are able in providing clues on disease biology –soluble L-selectin (sL-selectin) is one such biomarker (18). The levels of CSF sL-selectin have shown to rise before clinical CNS-relapse, peaking at overt CNS relapse and declining post-treatment. Soluble Interleukin-2 Receptor-α (sIL2-Rα) was tested in 19 patients with CNS disease and 134 controls patients[19]. The chemokine CXCL13 has also been investigated in various CNS malignancies expressed on the tumor, host tissue or secreted in the CSF[20]. CXCL13 and IL-10 combined have a diagnostic specificity of > 99% in primary CNS lymphoma[20]. Several groups have also tested CCL2 and vascular endothelial growth factor 1 and 2 (VEGF 1 and 2) in the CSF from leukemia and lymphoma patients with inconclusive results[21]. In a study[22], sCD19 positivity was associated with poor EFS; however, no CNS relapse was seen on follow-up. Significantly higher CSF osteopontin levels were found in a cohort of pediatric patients with CNS relapse compared to CNS-negative controls[23]. Soluble biomarkers of disease in the CNS are limited by high false negative and false positive results.

### ALL Treatment

Understanding of prognostic risk factors and adaptation of risk-adapted therapeutic regimen along with improved management of toxicities resulted in an excellent survival of pediatric ALL patients. The current treatment of ALL typically involves chemotherapy given for 2-3 years and is intended to achieve cure in patients; therefore, children at a higher risk of treatment failure receive more intense and prolonged chemotherapy. The majority of patients are treated at specialized centers with risk-stratified treatment protocols. The core chemotherapeutic drugs have principally remained unchanged over the last decades. The main classes of drugs used in pediatric ALL include corticosteroids (prednisolone, dexamethasone), anthracyclines (Daunorubicin) and purine analogs (6-Mercaptopurine). The treatment is distributed into different phases spanning over 2 years for girls and 3 years for boys.

### Remission Induction

Remission induction includes intensive chemotherapy for a short period (typically 4 weeks)

and is intended to eradicate the bulk of disease. Commonly used drugs include a glucocorticoid (prednisolone or dexamethasone), vincristine, and asparaginase. This drug combination allows to targeting of multiple key pathways in leukemic cells. High-risk patients might receive additional daunorubicin. BCR-ABL1 ALL patients might also receive a tyrosine kinase inhibitor (Imatinib or Dasatinib)[24]. Following induction chemotherapy, the majority of patients achieve clinical and morphological remission (<5% BM blasts, no circulating and CSF blasts, no cerebral mass). MRD studies performed at the end of induction period are used to assess patient response to treatment and re-assign risk.

### Intensification (Consolidation) Therapy

The aim of consolidation therapy is to eradicate any residual disease using a combination of chemotherapeutic agents. The combination and intensity are dependent upon clinical risk-status and MRD results. The drug combinations vary in different protocols, but include methotrexate, mercaptopurine, asparaginase along with frequent pulses of vincristine and corticosteroids. Intensification is typically administered for 10-12 weeks[25]. CNS directed therapy is given to eliminate CNS disease. Many protocols include a delayed intensification phase consisting of a 3-week re-induction and re-consolidation towards the end of intensification phase[26].

### Maintenance Therapy

Maintenance therapy is typically given over a period of 2-3 years of continuous remission – three years for boys while two years for girls[25]. The maintenance therapy includes oral 6-mercaptopurine or parenteral methotrexate and targets residual slow-cycling leukemic cells. Therefore, careful monitoring of drug toxicities and compliance to drugs is essential for the whole duration of maintenance therapy. Non-compliance to 6-mercaptopurine is shown to be associated with significant increase in relapse risk[27] whereas toxicities might arise in patients with deficiency of S-methyltransferase – an enzyme that inactivates mercaptopurine.

### Bone Marrow Transplant

A bone marrow transplant is a procedure to replace damaged or destroyed bone marrow with healthy bone marrow stem cells and is one of the often-used methods in ALL patients[28]. Bone marrow is the soft, fatty tissue inside our bones[29]. A bone marrow transplant is a procedure to replace damaged or destroyed bone marrow with healthy bone marrow stem cells. The risk factors associated with bone marrow transplant included granulocytopenia, impairment of barrier defenses, impairment of cell-mediated immunity (CMI), and humoral immunity. This impairment leads to an immunocompromised state, allowing microorganisms to cause infection more easily, even those with limited pathogenicity. Patients undergoing BMT experience a sequential suppression of host defenses, allowing for various infectious processes at different phases of the transplantation process. Further, the renal dysfunction is the recently reported risk factors of bone marrow transplant[30].

### Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) is a treatment strategy for patients with hematopoietic malignancies and inborn errors of metabolism or immune-deficiencies. A successful clinical outcome depends on many factors, such as underlying disease, the patients' status, treatment protocol, donor, graft source, and occurrence and severity of complications such as graft *vs*. host disease (GVHD) and infections. When a patient needs of an allogeneic HSCT, a search for a suitable donor begins. The patient and his/her siblings are analyzed about their human leukocyte antigen type (HLA), the human version of MHC. If no suitable related donor is available a search for an HLA-matched unrelated donor is performed in the international donor registries. The hematopoietic stem cells (HSC) from the donor (hereafter called the graft) are collected and transported to the patient (recipient). The graft is analyzed, sometimes processed, and then administered to the patient as an infusion. Early after the transplantation, the patient is isolated until the leukocytes recover. The patient can be treated in reversed isolation in the HSCT ward or be given conditioning treatment at the hospital followed by a monitored treatment period at home according to the home care program[31,32].

The risk of complications after allogeneic HSCT depends largely on the patient's immunological status at a particular time point after HSCT. The main complications after HSCT are infections, GVHD, relapse of the underlying disease, and graft failure/rejection. The rate of the immunological reconstitution after HSCT is slow and dependent on several factors including age, GVHD, conditioning regimen, graft source, donor, etc.[33]. For different cell types, this period

varies considerably, thus making the patient susceptible to different infectious agents at different times during the post-HSCT period[34].

## Conclusions

It could be concluded that great improvisations are being made for a better management of young patients affected by ALL disease. It is clear that CNS disease is the major hurdle in the therapeutic approaches against ALL and the best technological advancements are being made to overcome this hurdle. However, still several challenges are remaining. These challenges include better understandings of the etiological factors that cause leukemia, the study of the gene polymorphisms affecting the development of leukemia, and possible solutions for the associated deadly toxicity, that is resulting in a major cause of mortality in ALL patients.

### Conflict of Interest

The Authors declare that they have no conflict of interest.

## References


1) National Cancer Institute. 2014. SEER Cancer Statistics Review (CSR) 1975-2011.
2) Zhang J, Ding L, Holmfeldt L, Wu G, Heatley S, Mullighan CG. The genetic basis of early T-cell precursor acute lymphoblastic leukemia. Nature 2012; 481: 157-163.
3) Roy A, Cargill A, Love S, Moorman AV, Stoneham S, Lim A, Saha V. Outcome after first relapse in childhood acute lymphoblastic leukemia - lessons from the United Kingdom R2 trial. Br J Haematol 2005; 130: 67-75.
4) Cancer research Uk. 2014. Childhood cancer mortality statistics [Online]. London. Available: http://www.cancerresearchuk.org/.
5) Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in pediatric leukemia. Lancet Oncol 2008; 9: 257-268.
6) Greaves M. Infection, immune responses and the etiology of childhood leukemia. Nat Rev Cancer 2006; 6: 193-203.
7) Lin D, Liu C, Xue M, Liu R, Jiang L, Yu X, Bao G, Deng F, Yu M, Ao J, Liu H. The role of interleukin-15 polymorphisms in adult acute lymphoblastic leukemia. PLoS One 2010; 5: e13626.
8) Evans AE, Craig M. Central nervous system involvement in children with acute leukemia - study of 921 patients. Cancer 1964; 17: 256-258.
9) Price RA, Johnson WW. The central nervous system in childhood leukemia. I. The arachnoid. Cancer 1973; 31: 520-533.
10) Burger B, Zimmermann M, Mann G, Kuhl J, Loning L, Riehm H, Reiter A, Schrappe M. Diagnostic cerebrospinal fluid examination in children with acute lymphoblastic leukemia: significance of low leukocyte counts with blasts or traumatic lumbar puncture. J Clin Oncol 2003; 21: 184-188.
11) Gajjar A, Harrison PL, Sandlund JT, Rivera GK, Ribeiro RC, Rubnitz JE, Pui, CH. Traumatic lumbar puncture at diagnosis adversely affects outcome in childhood acute lymphoblastic leukemia. Blood 2000; 96: 3381-3384.
12) Omans AC, Barker BE, Forman EN, Cornell CJ, Dickerman JD, Truman JT. Immunophenotypic characteristics of cerebrospinal fluid cells in children with acute lymphoblastic leukemia at diagnosis. Blood 1990; 76: 1807-1811.
13) Cancela CSP, Murao M, Barcelos JM, Furtado VM, Oliveira BMD. Central nervous system involvement in acute lymphoblastic leukemia: diagnosis by immunophenotyping. Jornal Brasileiro de Patologia e Medicina Laboratorial 2013; 49: 260-263.
14) Martinez-Laperche C, Gomez-Garcia AM, Lassaletta A, Moscardo C, Vivanco JL, Ramirez, M. Detection of occult cerebrospinal fluid involvement during maintenance therapy identifies a group of children with acute lymphoblastic leukemia at high risk for relapse. Am J Hematol 2013; 88: 359-364.
15) Biojone E, Queiróz Rde P, Valera ET, Odashima NS, Takayanagui OM, Viana MB, Tone LG, Scrideli CA. Minimal residual disease in cerebrospinal fluid at diagnosis: a more intensive treatment protocol was able to eliminate the adverse prognosis in children with acute lymphoblastic leukemia. Leuk Lymphoma 2012; 53: 89-95.
16) Scrideli CA, Queiroz RP, Takayanagui OM, Bernardes JE, Melo EV, Tone, LG. Molecular diagnosis of leukemic cerebrospinal fluid cells in children with newly diagnosed acute lymphoblastic leukemia. Haematologica 2004; 89: 1013-1015.
17) Del Principe MI, Buccisano F, Cefalo M, Maurillo L, Di Caprio L, Di Piazza F, Sarlo C, De Angelis G, Irno Consalvo M, Fraboni D, De Santis G, Ditto C, Postorino M, Sconocchia G, Del Poeta G, Amadori S, Venditti A. High sensitivity of flow cytometry improves detection of occult leptomeningeal disease in acute lymphoblastic leukemia and lymphoblastic lymphoma. Ann Hematol 2014; 93: 1509-1513.
18) Stucki A, Cordey AS, Monai N, Deflaugergues JC, Schapira H, Spertini O. Cleaved L-selectin concentrations in meningeal leukemia. Lancet 1995; 345: 286-289.
19) Lee W, Kim SJ, Lee S, Kim J, Kim M, Lim J, Kim Y, Cho B, Lee EJ, Han K. Significance of cerebrospinal fluid sIL-2R level as a marker of CNS involvement in acute lymphoblastic leukemia. Ann Clin Lab Sci 2005; 35: 407-412.
20) Rubenstein JL, Wong VS, Kadoch C, Gao HX, Barajas R, Chen L, Josephson SA, Lowell, C. Cxcl13 plus in-

terleukin 10 is highly specific for the diagnosis of CNS lymphoma. Blood 2013; 12: 4740-4748.

21) Tang YT, Jiang F, Guo L, Si MY, Jiao XY. The soluble VEGF receptor 1 and 2 expression in cerebral spinal fluid as an indicator for leukemia central nervous system metastasis. J Neurooncol 2013; 112: 329-338.

22) Muniz C, Martín-Martín L, López A, Sánchez-González B, Salar A, Almeida J, Sancho JM, Ribera JM, Heras C, Peñalver FJ, Gómez M, González-Barca E, Alonso N, Navarro B, Olave T, Sala F, Conde E, Márquez JA, Cabezudo E, Cladera A, García-Malo M, Caballero MD, Orfao A; Spanish Group for the Study of Central Nervous System Disease in Non-Hodgkin Lymphoma. Contribution of cerebrospinal fluid sCD19 levels to the detection of CNS lymphoma and its impact on disease outcome. Blood 2014; 123: 1864-1869.

23) Ncesoy-Özdemir S, ŞAhin G, Bozkurt C, Ören AC, Balkaya E, Ertem, U. The relationship between cerebrospinal fluid osteopontin level and central nervous system involvement in childhood acute leukemia. Turk J Pediatr 2013; 55: 42-49.

24) Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, Wang C, Davies SM, Gaynon PS, Trigg M, Rutledge R, Burden L, Jorstad D, Carroll A, Heerema NA, Winick N, Borowitz MJ, Hunger SP, Carroll WL, Camitta B. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009; 2: 5175-5181.

25) Vora A, Goulden N, Wade R, Mitchell C, Hancock J, Hough R, Richards S. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol 2013; 14: 199-209.

26) Schrappe M, Reiter A, Ludwig WD, Harbott J, Zimmermann M, Hiddemann W, Niemeyer C, Henze G, Feldges A, Zintl F, Kornhuber B, Ritter J, Welte K, Gadner H, Riehm H. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German- Austrian-Swiss ALL-BFM Study Group. Blood 2000; 95: 3310-3322.

27) Bhatia S, Landier W, Shangguan M, Hageman L, Schaible AN, Carter AR, Hanby CL, Leisenring W, Yasui Y, Kornegay NM, Mascarenhas L, Ritchey AK, Casillas JN, Dickens DS, Meza J, Carroll WL, Relling MV, Wong FL. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non- Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. J Clin Oncol 2012; 30: 2094-3101.

28) Yang YJ, Li XL, Xue Y, Zhang CX, Wang Y, Hu X, Dai O. Bone marrow cells differentiation into organ cells using stem cell therapy. Eur Rev Med Pharmacol Sci 2016; 20: 2899-2907.

29) http://www.hematologysolutions.com

30) Kemmner S, Verbeek M, Heemann U. Renal dysfunction following bone marrow transplantation. J Nephrol 2017; 30: 201-209.

31) Ringdén O, Remberger M, Holmberg K, Edeskog C, Wikström M, Eriksson B, Finnbogadottir S, Fransson K, Milovsavljevic R, Omazic B, Svenberg P, Mattsson J, Svahn BM. Many days at home during neutropenia after allogeneic hematopoietic stem cell transplantation correlates with low incidence of acute graft-vs-host disease. Biol Blood Marrow Transplant 2013; 19: 314-320.

32) Ringdén O, Remberger M, Törlén J, Engström M, Fjaertoft G, Mattsson J, Svahn BM. Home care during neutropenia after allogeneic hematopoietic stem cell transplantation in children and adolescents is safe and may be more advantageous than isolation in hospital. Pediatric Transplant 2014; 18: 398-404.

33) Seggewiss R, Einsele H. Immune reconstitution after allogeneic transplantation and expanding options for immunomodulation: an update. Blood 2010; 115: 3861-3868.

34) Storek J, Geddes M, Khan F, Huard B, Helg C, Chalandon Y. Reconstitution of the immune system after hematopoietic stem cell transplantation in humans. Semin Immunopathol 2008; 30: 425-437.