National Comprehensive Cancer Network Guidelines for Pediatric Acute Lymphoblastic Leukemia

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The National Comprehensive Cancer Network has recently published the first pediatric guidelines for the management of children, adolescent and young adults with acute lymphoblastic leukemia (ALL). The recommendations for diagnosis, work up, genetic evaluation, treatment and follow up of pediatric ALL have been provided. Genetic risk factors and newer therapeutic agents have been discussed. We highlight the major points in the guidelines.

Keywords: *Diagnosis, Management, Recommendations.*

Acute lymphoblastic leukemia (ALL) is the commonest pediatric malignancy representing 75-80% of the pediatric leukemia.The age-adjusted incidence rate in United States is 1.38 per 100,000 population per year [1]. Indian incidence varies with region and age-adjusted rates of up to 101.4 per million and 62.3 per million for boys and girls, respectively have been reported [2,3]. ALL is slightly more common in boys with peak incidence in 2-5 years. T cell ALL constitutes about 15-20% of pediatric ALL; though, in India, a higher proportion of T-ALL (20-50%) has been reported [3].

The survival rate of children with ALL has improved dramatically owing to better understanding of pathogenesis and molecular genetics, adoption of risk-stratified therapy and availability of newer therapeutic agents. Five-year overall survival (OS) rate of children has improved to 89%[4]. In India, OS has been estimated at 45-81% [5].Although the increasing survival rates give confidence, there was an unmet need for recommendations for a standard diagnostic and treatment approach in wake of the latest available evidence.

The National comprehensive cancer network (NCCN) has developed guidelines for pediatric ALLwith the goal of providing recommendations with focus on risk assessment, risk stratified therapy and supportive care [6]. These guidelines are intended to apply for the pediatric (up to 12 years of age) and adolescent and young adults (AYA) patients (up to 30 years of age). All recommendations are category 2A, unless specified.

DIAGNOSIS

Typical clinical features, bone marrow hemato-pathological examination and immunophenotyping are required to confirm the diagnosis and classify pediatric ALL. The NCCN guidelines give a cutoff of >20% blasts in bone marrow to diagnose ALL; although, most treatment guidelines require presence of >25% blasts for diagnosis. If there is significant amount of circulating disease, ≥20% lymphoblasts or 1000 circulating lymphoblasts/mm^3 in blood can establish the diagnosis. Immunophenotyping is essential, not only for diagnosis confirmation, but also to classify ALL into T cell (cCD3 or sCD3 positive) or B cell (CD19, CD22, CD79a positive), characterization of leukemic clones, and assessment of minimal residual disease (MRD) [7]. CD10 negativity correlates with presence of *KMT2A* mutations and portend poor prognosis. ETP ALL (CD1a/CD8 negative, variable CD5 positive and one or more myeloid markers positive) carries poor prognosis. Mixed phenotype acute leukemia (bi-lineage or bi-phenotypic) are defined as per WHO 2008 criteria [8].

Genetic Abnormalities and Molecular Subtypes

Genetic testing [karyotyping, fluorescent in situ hybridization *i.e*. (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR)] has become an essential component of leukemia characterization and is recommended in all patients to help in risk stratification, treatment planning and prognosis. The guidelines mention the seven recurrent genetic abnormalities for B ALL given by WHO in 2016, with two new additions in both B ALL (iAMP21, BCR-ABL like ALL) and T ALL(ETP ALL, NK cell ALL) [8]. The guideline recommends evaluation for the WHO defined recurrent genetic abnormalities, and if negative, for BCR-ABL1 and ETV-RUNX1, and

encourages evaluation for Ph like ALL as they may be responsive to tyrosine kinase inhibitor therapy.

Work-up

Clinical evaluation including testicular screening (clinical palpation, ultrasound testes only if clinically indicated) for all males and pregnancy screening for post-menarchal females; baseline hemogram, biochemical evaluation including tumor lysis syndrome panel, chest *X*-ray for mediastinal mass and appropriate imaging depending on symptomatology and signs are recommended. Both cerebrospinal fluid examination at the time of first intrathecal therapy and baseline echocardiogram are recommended. Assessment of the certain gene mutations (*e.g*. TPMT, NUDT 15) may be considered for adjusting the dose of thiopurines. Fertility counselling/preservation options should be presented to all patients. Clinical features of leukemia predisposition syndrome (*e.g*. Down syndrome), if present, should be confirmed by further tests as chemotherapy may need modification.

Risk Stratification

Risk stratification for B-ALL is done using clinical, biologic and response variables including patient age, white blood cell count (WBC), immunophenotypic/cytogenetic/ genetic subtype, presence of central nervous system (CNS) disease, and response to therapy (*i.e.* Day8/day15 peripheral smear and MRD at end of induction). This helps in tailoring therapy. T-ALL is considered high risk and none of above factors except MRD are found to be predictors of outcome. The present NCCN guideline mentions Children's oncology group (COG), St Jude Consortium approach and Dana Farber cancer institute (DFCI) ALL consortium approach for risk stratification.

TREATMENT STRATEGY

Specific treatment regimens (drugs, doses and durations) differ according to age group (pediatric, AYA and infant) and sub-type of ALL; however, basic principles of therapy remain same. Treatment consists of induction (to reduce tumor burden and eliminate maximum blasts from bone marrow), consolidation (further eradication of any residual disease), maintenance therapy (to prevent disease relapse) and extramedullary disease prophylaxis or treatment (to prevent CNS relapse and clear leukemic cells from sites which are not accessible by systemic chemotherapy due to blood brain barrier). The guideline recommends enrolling patients in clinical trials, whenever possible.

Treatment of Specific Groups

Ph negative and Ph – likeB-ALL: NCCN recommends pediatric and AYA patients with Ph negative or Ph – like should be grouped according to risk criteria and multi-agent induction be given.Patients who are MRD negative at end of induction (EOI) continue treatment on same risk arm. Patients, who are MRD positive at EOI are given intensified consolidation. In case of persistent MRD despite intensified chemotherapy, blinatumumab or tisagenlecleucel (Category 2B) can be considered. In all MRD positive cases at EOI, hematopoietic stem cell transplant (HSCT) may be considered as a part of consolidation or maintenance therapy.

Ph positive B-ALL: Pediatric and AYA patients with Ph positive disease should be treated with tyrosine kinase inhibitor containing protocols. Those who achieve MRD negative at EOI may continue the same protocol with tyrosine kinase inhibitor. For those who are MRD positive at EOI, blinatumumab or tisagenlecleucel (Category 2B) can be considered. The panel recommends HSCT for consolidation followed by post-transplant tyrosine kinase inhibitor.

T-ALL: The guideline recommends systemic chemotherapy. Those who have MRD >0.1% at end of consolidation should receive intensified chemotherapy to attain MRD negativity and thenceforth be considered for HSCT as consolidation therapy. Addition of nelrabine should be strongly considered in all patients with T cell ALL who are MRD positive or have CNS disease at diagnosis or those who fail induction.

Infant ALL: Infant ALL is to be treated with Interfant-based regimen that incorporates elements of ALL and AML therapy [9]. Assessment of baseline *KMT2A* status is essential. Infants without KMT2A rearrangement and MRD negative at EOI, continue to receive the Interfant consolidation, those who are MRD positive may receive intensified consolidation and HSCT may be considered. Those with KMT2 rearranged, are treated with intensive Interfant-based consolidation. High-risk patients (<3 months with any WBC, <6 months with WBC >3,00,000, persistent MRD after intensified consolidation) may receive maintenance therapy or may be considered for HSCT, non TBI regimen are preferable. For non-high-risk, KMT2 rearranged patients, usual maintenance therapy is recommended.

Extramedullary Disease Prophylaxis and Treatment

The guideline recommends inclusion of CNS prophylaxis or/and treatment in all regimens.Those who are CNS disease negative receive CNS-directed prophylactic therapy including intrathecal therapy and/or systemic chemotherapy that incorporates high dose methotrexate. CNS disease positive cases may receive cranial irradiation

(total recommended dose of 18 Gray) in addition as per the treatment protocol. Testicular involvement not resolved by the end of induction should be considered for bilateral testicular irradiation (total recommended dose of 24 Gray).

Hematopoietic Stem Cell Transplantation

HSCT has shown improved survival in pediatric ALL with evidence of certain high-risk features and persistent disease. In early relapse of Ph negative B-ALL, HSCT is the only known curative therapy. The benefit of allogenic HSCT is controversial in infants; only the subgroup with KMT2A rearrangement and high risk features showed survival advantage with HSCT over chemotherapy. When possible, HSCT should be done after eradication of MRD. Survival is comparable irrespective of stem cell source.

Use of Targeted Agents

Tyrosine kinase inhibitors are a standard part of treatment in Ph positive ALL. In Ph like ALL with CRLF2 or JAK mutations, Janus kinase inhibitors are being explored. Nelarabine has been approved for use in relapsed/ refractory T-ALL. Monoclonal antibodies to surface agents *e.g.* rituximab, epratuzumab, inotuzumab ozogamicin, blinatumomab; chimeric antigen receptors T cell targeting the CD19 (tisagenlecleucel) may be incorporated as part of induction, consolidation or maintenance therapy, especially in refractory/relapsed B-ALL.

Box I Criteria for Assessing Response at the End of Induction in Acute Lymphoblastic Leukemia

Complete remission (CR)

No circulating blast

No extramedullary disease

Bone marrow with trilineage hematopoiesis and <5% blasts on microscopy and <1% on flowcytometry

ANC >1000/mm^3, platelet counts >1,00,000/mm^3 and no recurrence in last 4 weeks

Complete remission with incomplete blood recovery (CRi): All criterion for CR except for ANC or/and platelet counts.

Refractory disease: Failure to achieve CR at end of induction.

Progressive disease: Increase of at least 25% in peripheral circulating or bone marrow blasts or development of extramedullary disease.

Relapsed disease: Reappearance of blasts in peripheral blood or bone marrow of >5% or >1% with molecular testing or appearance of extramedullary disease after CR.

Modified from reference 1.

Assessment of MRD

MRD has a high prognostic value in identifying patients at risk of relapse and hence needing an intensification of treatment. The optimal sample for the MRD assessment is first pull or early pull of bone marrow aspirate, done after completion of induction phase, with additional assessments at other points during therapy. MRD of greater than 0.01% in bone marrow is considered positive as assessed by flowcytometry method. Patients with MRD positivity at the EOI should receive more intensive chemotherapy and should be evaluated for HSCT.

Response Assessment

Response assessment is done during the therapy and treatment is tailored accordingly. These recommen-dations divide patients based on certain criteria into complete remission, complete remission with incomplete blood recovery, refractory and progressive diseasefor response assessment following therapy (***Box* I**).

Surveillance After Completion of Therapy

After completion of therapy, it is recommended that the patient should be periodically assessed for disease status (complete physical examination including testicular evaluation, complete blood count with differential count, liver function tests); every 1-4 monthly in first year, 3-6 monthly in second year, and 6-12 monthly in the third year. Monitoring for long term side effects of chemotherapy including weight and height monitoring, echocardiography for cardiotoxicity, neuro-psychological function and reproductive health monitoring are recommended, as previously published by COG [10].

Recommendations for Supportive Care

The recommendations for the supportive care are given in ***Box* II**.

Box II Recommendations for Supportive Care of Children and Young Adults with ALL

- Infection control
- Acute tumor lysis syndrome
- Hyperleukocytosis
- Drug toxicity management for methotrexate, vincristine, thiopurine, asparaginase and steroids
- Antiemesis
- Nutritional support
- Treatment of pain
- Transfusion of blood products/cytokine support for severe cytopenias

Modified from reference 6.

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