

Review Article

Diagnosis and management of Acute Lymphoblastic Leukemia in children in India

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Abstract: The cure rates of cancers in children have increased during the past few years. Children have better prognosis compared to adult patients particularly in cases of Acute Lymphoblastic Leukemia. To achieve this high cure rate it is essential to diagnose the disease early and institute appropriate protocol based treatment on time. It is possible to achieve event free survival and give normal life to the patient. For this it is important to sensitize and educate the medical and paramedical persons. To make them understand this subject easily, this article has been written in a simple style.**Keywords:** ALL, cure, diagnosis, treatment

INTRODUCTION

Most of the cancers in children are curable with modern management. One third of the cancers in children are blood cancers (ALL, AML, CML) of which ALL (Acute Lymphoblastic Leukemia) is the most easily curable malignancy, with a overall survival rate of about 90%. Unfortunately in India though we have advanced reasonably well most of the cancers particularly the easily curable ones are not diagnosed early and they don't receive appropriate treatment also. The reason for this is lack of awareness among the public and sometimes among the medical and paramedical people that childhood cancers are easily curable and also because the number of pediatricians trained to treat children with cancer are not adequate to handle the patient load. Hence we do not have many centers to treat children with cancer. As a result children with cancer are either not diagnosed or under diagnosed or inadequately and inappropriately treated. As a result the morbidity and mortality due to cancer is very high. On seeing this high mortality and morbidity and the stress that is involved in treating these children many young Pediatricians do not come forward to take up this field for specialization in India. This situation will improve only when we educate the public about cancers in children and also train the Para medical and medical people in the early diagnosis of these cancers

and teach & train Pediatricians about the current management and treatment of Pediatric cancers. When we do this the mortality and morbidity will significantly come down in children with cancer. On seeing this many young doctors and nurses will come forward to take up this specialty. Then we will be able to develop many more centers dealing with children with cancer. This understanding has prompted us to write this article on the diagnosis and management of ALL in children. Among the blood cancers in children (ALL, AML, CML) ALL is the easily curable malignancy. Hence it is appropriate to discuss the diagnosis and management of ALL.

Evolution of symptoms and signs of leukemia

In acute lymphoblastic leukemia there is an abnormal production of lymphoblasts in the bonemarrow. Other cell lines are suppressed e.g. red cell precursors, white cell precursors and platelet precursors. As a result hemoglobin goes down, neutrophil count goes down and platelet count goes down. Thus there is bone marrow failure. The enormous numbers of lymphoblasts that have proliferated in the bone marrow come out of the bone marrow and circulate to all parts of the body. They may settle down anywhere in the body during the circulation particularly in the lymphnodes, spleen, liver, joints, periosteum and

nervous system. As a result the patient may have symptoms caused by anemia e.g easy fatigability, pallor and effort intolerance, fever due to infection, and bleeding usually in skin and mucous membranes, joint pains and swelling over bones. Sometimes they may present with cranial nerve paralysis and convulsions due to CNS involvement. When the child is brought to the hospital on examination we may find pallor, CCF, fever, purpuric spots, significant lymphadenopathy, splenomegaly, hepatomegaly, joint swellings and tenderness, bony tenderness, testicular enlargement etc. Superior mediastinal nodes are significantly enlarged in T cell ALL. They may be present with superior mediastinal syndrome (engorged veins over the chest, dyspnea, flushed face, sweating, anxiety, cyanosis etc). If the blood cell count in the blood is so high the patient may have slowing of the microcirculation in the brain and lungs resulting in hyperviscosity syndrome/hyperleucocytosis syndrome. Patient may also present with symptoms and signs of meningitis and increased ICT.

Diseases which can closely mimic ALL are a) juvenile idiopathic arthritis b) aplastic anemia c) scrub typhus d) infectious mononucleosis e) neuroblastoma and f) ITP. Having these differential diagnoses in mind we have to do a complete blood count with peripheral smear study. In ALL we usually find low Hb, low platelet count, neutropenia and increase in total count, and blast cells in the peripheral smear. If we do not see blast cells in the peripheral smear we have to do a bone marrow aspiration to confirm a diagnosis of leukemia (more than 25% of the nucleated cells are lymphoblasts.) With these blast cells we have to do further studies like cytochemistry (PAS/Sudan black/MPO etc), Immunophenotyping with monoclonal antibodies (Marker study) and cytogenetic studies.

In the olden days diagnosis and treatment of ALL was based on morphology and cytochemistry only. Now for about 3 decades monoclonal antibodies markers) are used for immunophenotyping. This technique became simple with the availability of flow cytometer for the past 20 years. In the present day karyotyping technique has also become easier and 24 colour karyotyping (spectral karyotyping) is also available for use. This can help us to identify the number of chromosomes, structural changes like deletions and translocations. Advanced molecular studies are also available to detect specific genetic mutations.

Treatment

Treatment depends upon the type of ALL (Pre B, B cell ALL), prognostic factors and the presenting white cell count, age and cytogenetic abnormalities. The most important prognostic factor is the treatment. Without proper treatment the disease is fatal. Poor prognostic factors are age below 1 year and above 10 years, presenting white cell count more than 50,000/cu. Mm, Cytogenetic abnormalities like hypodiploidy and pseudodiploidy. If the prognostic factors are poor we should consider the possibility of hemopoietic stem cell transplantation and advise accordingly.

The treatment for the case in the beginning should start with supportive care. If the presenting white cell count is so high e.g. more than 100,000/cu.mm an exchange transfusion with fresh whole blood is useful. It will remove a lot of blast cells, potassium phosphate and uric acid from the blood and provide fresh platelets, thus correcting biochemical abnormalities as well & preventing bleeding and reducing the viscosity. If this is not possible leucopheresis with apheresis machine may be useful.

If there is superior mediastinal syndrome it is an emergency. The child needs reassurance and minimum invasive procedures like CBC with peripheral smear and if it is not conclusive a bone marrow aspiration by the most experienced person in the sitting position of the child. Child may be given dexamethasone or mediastinal radiotherapy to shrink the mediastinal nodes to relieve the obstruction.

Blood may be taken for biochemistry and culture & sensitivity and antibiotics should be given if patient is febrile. Nephrotoxic drugs like aminoglycosides should be avoided during the first week of treatment. Foods containing high potassium should be avoided during the first week of treatment. Antihyperuricemic drugs like allopurinol should be started to reduce the formation of uric acid. If the initial white cell count is more than 100,000 then urate oxidase should be given instead of allopurinol. Hyperhydration should be started with 5% Dextrose in 1/5 Normal Saline. Potassium containing IVF should not be given. Allopurinol/ urate oxidase and hyperhydration should start at least 24 hours prior to starting specific treatment.

If the patient has very low level of platelets, platelet concentrates should be given. If the hemoglobin is very low packed RBCs should be given (avoid old

blood) to raise the hemoglobin up to 7 or 8 gm% and not more than that to avoid hyperviscosity.

Specific treatment is given under 4 categories. They are 1) Induction of remission 2) consolidation / intensification treatment 3) CNS treatment and 4) Maintenance treatment. Maintenance treatment is usually given for 2 years in female children and 3 years in male children. If for 5 years after the diagnosis the disease has not come back it is unlikely to come back and the patient is cured of leukemia.

Induction of remission is usually given for 4 weeks. During this time the tumour cell load comes down from 10 power 10 to 10 power 12 (99%). At this time (after 4 weeks) the patient is symptom free – he has no bleeding, no fever, and he has no organomegaly. Blood counts are normal. Bone marrow aspirate is also normal (blast cell count is < 5%). CSF is normal. This stage is called as remission.

To achieve this state of remission some drugs are given. If the prognostic factors are poor 4 drugs are given i.e weekly once vincristine and anthrocyline, 9 doses of Leunase (E.Coli Asparaginase)3 days a week for 3 weeks, and steroid (dexamethasone/ prednisolone) for 4 weeks [3]. All other cases will receive only 3 drugs excluding anthrocyclines.

At the end of 4 weeks the patient is reassessed. The presence of leukemic cell load (minimal residual disease) is assessed with the help of special flow cytometry or PCR with the Bone Marrow aspirate. If the minimal residual disease is high ie. > 0.01% the patient should be subjected to hemopoeitic stem cell transplantation. If that is not possible the patient can be given high dose intensive chemotherapy which may be very toxic.

Consolidation treatment

At the end of induction treatment almost all patients will come under remission. But if we stop treatment at this time almost all patients will relapse. The reason is that though most of the cancer cells have been destroyed some cells still remain in the body sites like CNS, testis and ovary. Because of the barriers drugs are not able to penetrate and reach these sites. (sanctuary sites). Or they may be resistant clones of cancer cells which cannot be destroyed by the drugs which were given already, and they will require more and different drugs (multi pronged attack) to be destroyed. The drugs like Etoposide, 6 Thioguanine, anthracyclines, vincristine, steroid, Cyclophosphamide

etc are used in different combinations and at high doses. Depending upon the prognostic factors they may be given 2 intensification (consolidation) treatment or 3 intensification treatment.

CNS treatment

In the olden days all the children were given craniospinal irradiation which may cause long term sequelae like short stature and brain dysfunction [5]. In the present day the practice is to achieve not only disease free survival but also event free survival aiming for a high quality of life. Hence there are 3 types of CNS treatment available depending upon the prognostic factors [4]. 1) low dose cranial radiotherapy 2) Intrathecal methotrexate 3) High dose intravenous methotrexate [2]. These are given in different combinations. When we are giving high dose I.V. methotrexate we should assess the GFR and also estimate the level of methotrexate in the blood and to administer folinic acid (calcium leukovorin or citrovorum factor) as a rescue [1].

Maintenance treatment

It is given with weekly once oral methotrexate and daily 6 mercaptopurine for 2 to 3 years.

During the period of 2-3 years of treatment, particularly during intensive treatment the neutrophil count can go down to very low levels when the patient can pick up infections mainly endogenous infections and get fever and sometimes from indwelling catheters. (febrile neutropenia). Because their total immunity is low they can pick up infections with more than one organism at the same time and develop poly microbial sepsis. This requires a special protocol of treatment. After taking the blood and swab from the suspected infected sites for cultures empirical antibiotic treatment is started with ceftriaxone and amikacin. If the temperature does not settle down within 48 hours the patient should receive meropenem and an aminoglycoside. Soon the culture report will be available and appropriate antibiotics can be given. If the patient continues to be febrile after 5 days of appropriate antibiotic treatment it should be considered as fungal infection and be treated with liposomal amphotericin B.

Also during treatment patient may develop oral mucositis which requires warm saline mouth wash, or monilial infection which requires oral Nystatin. Counseling of the parents is important regarding the prognosis and treatment and care of the child. The child should be able to take all types of food which is

clean. Rough food items like sugarcane, bones etc should be avoided as they can traumatize the buccal mucosa and result in the entry of commensals and produce septicemia because these patients who are receiving chemotherapy are severely immunocompromised. They should be able to take bath like normal children. They should be able to go to school like other normal children except during their treatments, fever and when the blood counts are very low.

They should not be given live vaccines. If they come in contact with measles during the period of infectivity they should be administered Measles Hyperimmunoglobulin within 48 to 72 hours of contact. If they come in close contact with chickenpox they should be started on Acyclovir and zoster immunoglobulin within 48-72 hours of contact.

CONCLUSION

This article deals with the diagnosis and management of Acute Lymphoblastic Leukemia in children. Early diagnosis and protocol based treatment improves the chances of survival in ALL. The aim of the authors in writing this article is to educate the general practioners and paramedical people in the diagnosis and treatment of ALL thereby reducing the morbidity and mortality due to ALL. The clinical signs and symptoms, diagnosis, Differential diagnosis and treatment of complications of ALL have been briefly described in this article. It is hoped that this article will inspire young doctors and prompt them to take up this field of specialization which will ultimately help thousands of poor children to see the light of life and lead a normal life.

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