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Acute Lymphoblastic Leukemia

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Leukemias are most common malignancies
41% of all malignancies in < 15 yr
4.5 cases per 100,000

ALL	77%
AML	11%
CML	2-3%
JCML	1-2%
Others	8-9%

* Genetic abnormalities in hematopoietic cells

* Unregulated clonal proliferation

* Increased rate of proliferation

* Decreased rate of spontaneous apoptosis

* Disruption of normal bone marrow

* Marrow failure

Epidemiology

* First curable disseminated Cancer
* Peak age 2-6
* More frequently in boys
* More common in chromosomal abnormalities:
    - Down syndrome
    - Bloom syndrome
    - Ataxia – telangiectasia
    - Fanconi syndrome
* Risk to 2nd twin greater if one develops leukemia
* Risk is > 70% if first diagnosed during first yr
* Risk twice that of general population if one develops ALL by 5-7 yr

Etiology

* Unknown

* Genetic and environmental factors

* B-cell ALL and Epstein – Barr virus

Predisposing Factors

Genetic Conditions

* Down syndrome
* Fanconi syndrome
* Bloom syndrome
* Diamond – Blackfan anemia
* Schwachman syndrome
* Klinefelter syndrome
* Turner syndrome
* Neurofibromatosis syndrome
* Ataxia - telangiectasia
* Severe combine immune deficiency

Environmental

* Ionizing radiation
* Drugs
* Alkylating agents
* Nitrosurea
* Epidophyllotoxin
* Benzene exposure

Clinical Manifestation

* Anorexia, fatigue, irritability
* Fever
* Bone and joint pain
* Pallor
* Bruising, bleeding diathesis
* Purpuric, petechial spots
* Lymphadenopathy
* Hepatosplenomegaly
* Sign of raised intracranial pressure
* Respiratory distress
* Mediastinal mass

* Early pre – B-cell ALL is the most common immunophenotype

* Median leukocyte count is 33,000

* 75% of patients have counts < 20,000

* 75% patients have thrombocytopenia

* 30-40% have hepatosplenomegaly

* CNS symptoms in 5%

* Testicular (20%) , ovarian (30%) involvement

Diagnosis

* Suggested by peripheral blood findings

* Indicative of BM failure

* Anemia, thrombocytepenia

* Blast cells in peripheral film

* BM demonstrated > 25% lymphoblast

* CSF for blast cells

Treatment

Supportive Treatment:

* **Blood transfusion** (Packed RBCs) for anemia,
* Platelet concentrates for thrombocytopenia
* Granulocyte concentrates for neutropenia

* **Antibiotics** are needed for control of infections. Co- trimoxazole for prophylaxis against pneumocystis carinii pneumonia

* **Allopurinol** (10 mg/kg/day in 3 dd for 10 days) is given along with induction therapy

* Analgesics

* Adequate fluids (3L/m^2/day) and nutritional support

* Prophylaxis for malaria is recommended

* Live virus vaccine are contra-indicated
  Avoid contact with patients of measles, chicken pox etc.

* Hepatitis B vaccine may be given

* Psychological support of the patient and family, during the prolonged period of illness and its treatment

Specific Treatment

1- Induction of remission (4-6 wk)

* **Vincristine** 1.5 mg/m^2 (max. 2 mg) IV/wk
* **Prednisolone** 40 mg/m^2 (max. 60 mg) po/day
* **L-asparaginase** 10,000 U/m2/day biweekly IV (9 doses given over 21 days starting on the third day of chemotheapy)
* Irradiation for mediastinal mass spinal tumor, and other mass-like lesions
* For resistant cases and for re-inducting give either daunorubicin (25 mg/m^2/wk, 4-6 injections) or cytosine arabinoside) 50 mg/m^2/day IV for 4 days)

A patient is said to be in remission if there are no blast cells in the peripheral smear and the bone marrow is also in remission i.e. < 5% blast cells

2- CNS Prophylaxis

* Intrathecal methotrexate weekly x 6 doses during induction and then every 8 weeks for 2 years, plus cranial irradiation for high risk patients **or**

* Intrathecal methotrexate (12.5 mg at two weekly intervals, total three injections) **or**

* Intrathecal methotrexate, cytarabine, hydrocortisone

3- Consolidation Treatment (2-4 wk)

* It is given after induction therapy.
  Removes residual or resistant leukemic cells

* Asparaginase, (6000 U/m^2 IV on alternate days for 9 doses

* Cyclophosphamide 1200 mg/m^2/day IV in infusion given at 2 weekly intervals, total 3 doses

* Cytosine arabinoside (100g/m^2.dose IV bolus 12 hrly on 4 consecutive days every week of therapy

4- Maintenance Therapy (2-5 yr)

* 6 – mercaptopurine (50 mg/m^2/d oral)

* Methotrexate 20 mg/m^2/wk oral, IV

* With reinforcement:
  - Vincristine 1.5 mg/m^2 (max. 2 mg) IV every 4 weeks
  - Prednisone 40 mg/m^2/day oral x 7 days every 4 weeks

5- Bone Marrow Relapse

* Bone marrow transplant

* Multiple drug re-induction, intensive chemotherapy, CNS irradiation

6- Local Tissue Relapse

* CNS: irradiation, intrathecal methotrexate plus re- induction chemotherapy

* Testis: irradiation plus re-induction chemotherapy

7- Bone marrow transplant

* Bone marrow transplant is rarely used as initial treatment for ALL, as most patients are cured with chemotherapy alone

* Bone marrow transplant is recommended after first remission with acute leukemis

Prognosis

Without treatment disease is fatal.

With adequate treatment > 50% of the patients can achieve a prolonged remission (> 5 years) and can be considered cured

Factors responsible for poor prognosis are:

* Age < 1 yr or > 10 yrs
* A white blood cell count > 100,000 /m^3
* Presence of mediastinal mass on chest x-ray
* CNS or testicular disease at presentation
* Massive hepatosplenomegaly (> 3cm)
* Male
* T or B cell disease
* L2 or L3 morphology
* Deletions, translocations and hypodiploidy
* No remission in 4 weeks
* Philadelphia chromosome
* MLL gene rearrangement
* Translocations [t(1:19) or t(4:11)]

Most favorable chraracteristics

1- Rapid response to therapy

2- Hyperdiploidy

3- Trisomy

4- Rearrangement of TEL/AML 1 genes

Thank you