ACUTE LEUKEMIA

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roll no. 16

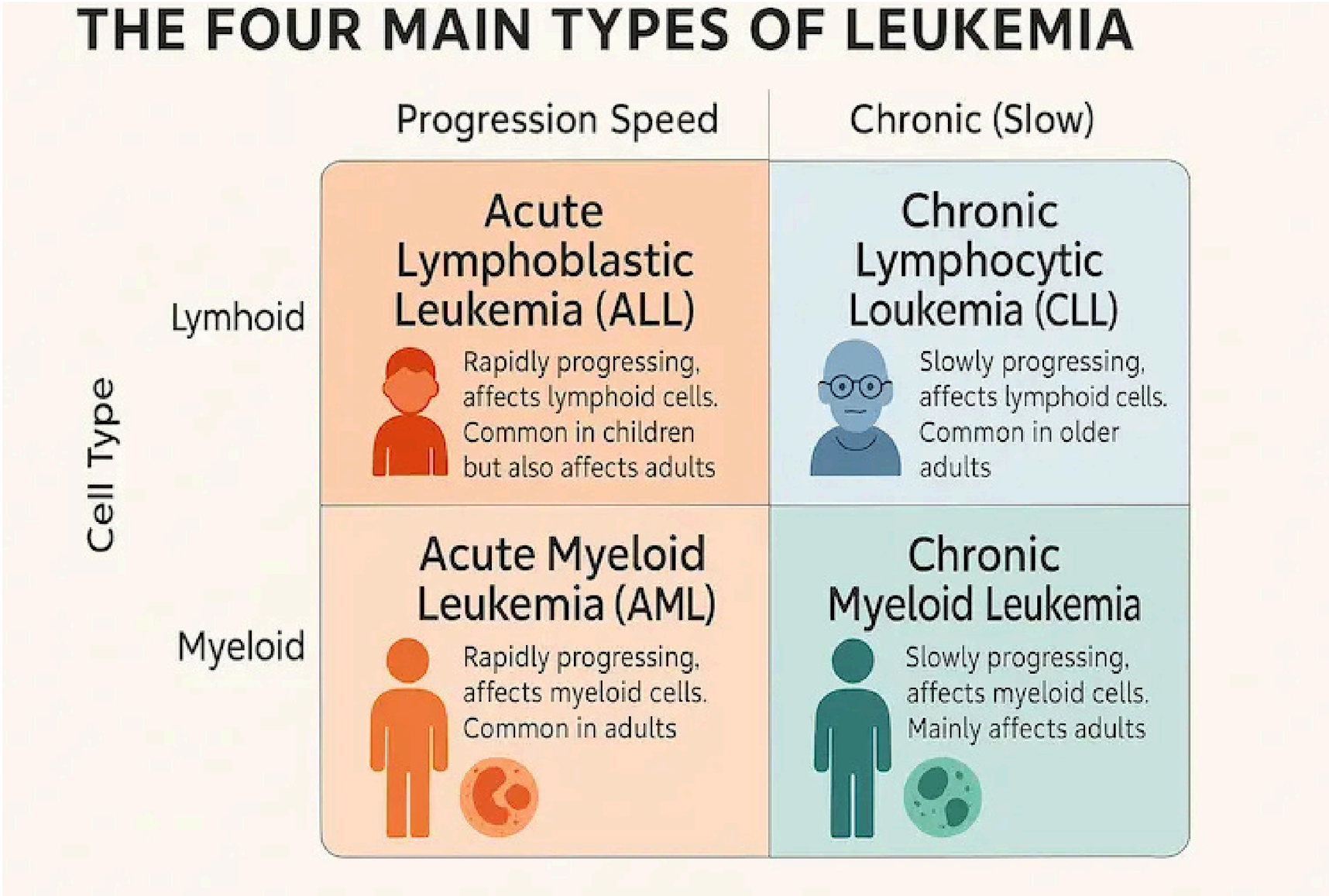
Leukemia

Leukaemias are malignant disorders of the white cell compartment, characteristically associated with increased numbers of white cells in the bone marrow and/or peripheral blood.

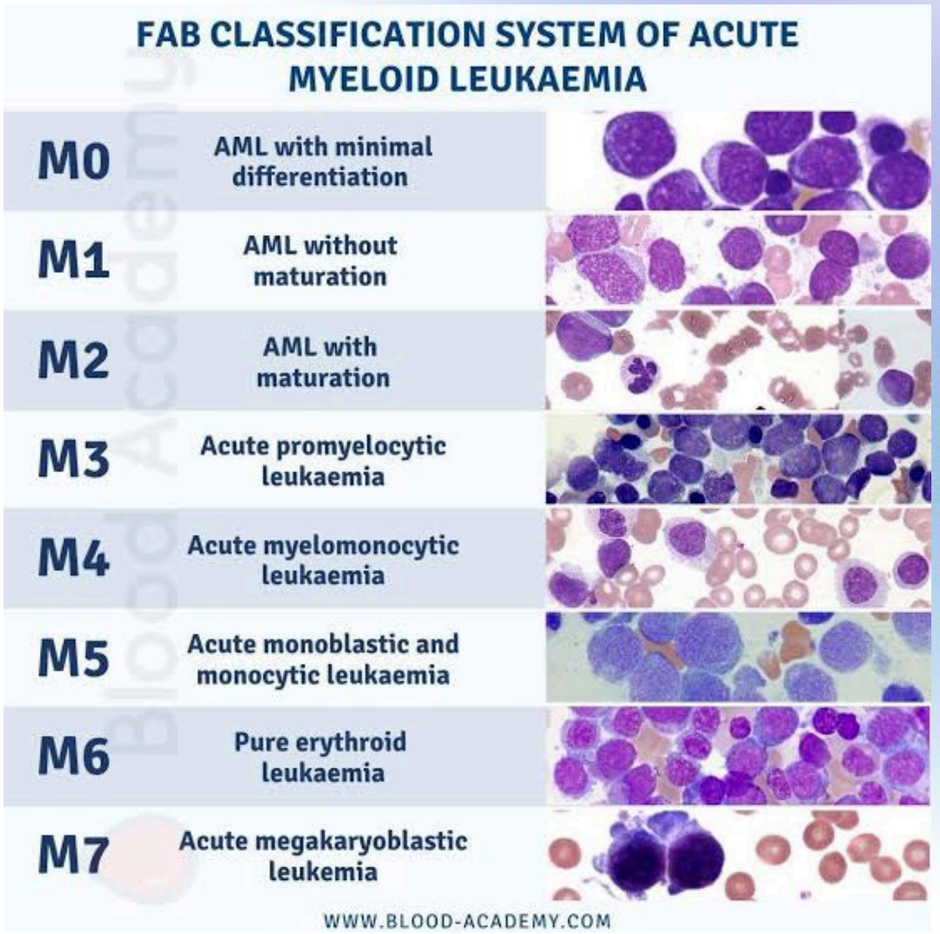
CLASSIFICATION

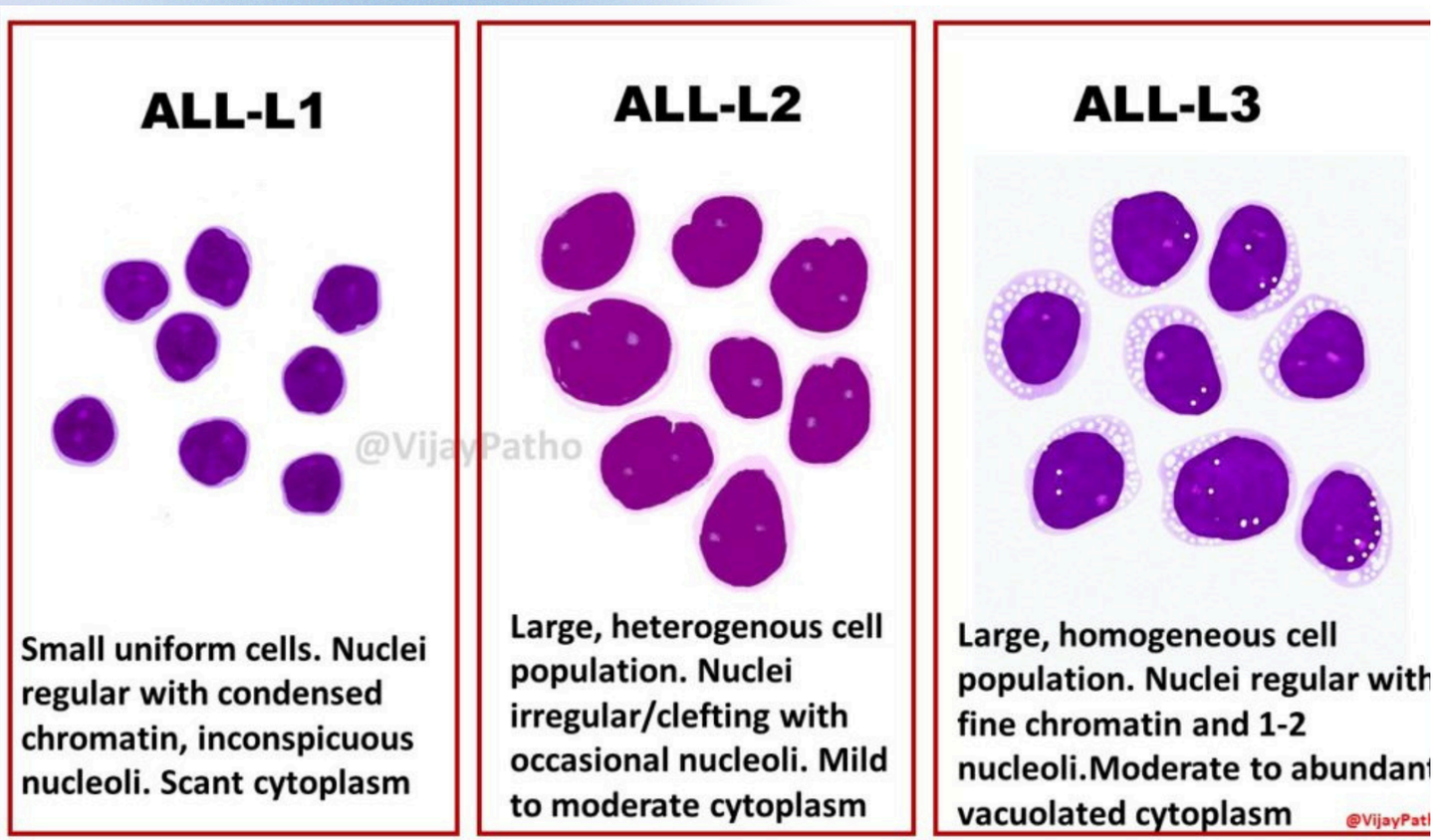
- Traditional classification
- Revised French- American-British classification of acute leukemia
- WHO classification

CLASSIFICATION



FAB Classification





25.44 WHO classification of acute leukaemia

Acute myeloid leukaemia (AML) with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22.1), gene product *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1;q22), gene product *CBFB-MYHL1*
- Acute promyelocytic leukaemia t(15;17), gene product *PML-RARA*
- AML with t(9;11)(p21.3;q23.3), gene product *MLLT3-KMT2A*
- AML with t(6;9)(p23;q34), gene product *DEK-NUP214*
- AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2), gene products *GATA2, MECOM*
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.3), gene product *RBM15-MKL1*
- AML with mutated *NPM1*
- AML with biallelic mutations of *CEBPA*

Acute myeloid leukaemia with myelodysplasia-related changes

- e.g. Following a myelodysplastic syndrome

Therapy-related myeloid neoplasms

- e.g. Alkylating agent or topoisomerase II inhibitor

Myeloid sarcoma

Myeloid proliferations related to Down syndrome

Acute myeloid leukaemia not otherwise specified

- e.g. AML with or without differentiation, acute myelomonocytic leukaemia, erythroleukaemia, megakaryoblastic leukaemia

Acute lymphoblastic leukaemia (ALL)

- B-lymphoblastic leukaemia/lymphoma
- T-lymphoblastic leukaemia/lymphoma

Acute leukemia

- Proliferation of mutated hemopoietic stem and progenitor cells, with limited accompanying differentiation , leading to and accumulation of blasts, predominantly in the bone marrow, which causes bone marrow failure

Risk factors

- Ionising radiation, X- rays
- Drugs eg: chemotherapy drugs
- Chemical : Benzene used in paint industries, plastic glues
- Retroviruses : HTLV-1 association with T cell leukemia
- Immunological
- Acquired stem cell disorders like aplastic anemia
- Myelodysplastic syndrome

Clinical features

- Patient with ALL and AML present with similar features
- pt presents with non - flu like symptoms due to infiltration of leukemia cells and bone marrow failure
- Shortness of breath , fatigue , weakness (**ANEMIA**)
- Fever , life threatening infections (due to **NEUTROPENIA**)
- Bleeding manifestation like petechiae , epistaxis, etc (**THROMBOCYTOPENIA)**
- Intracranial bleeding is serious and fatal complications
- Disseminated intravascular coagulation seen in AML - M3

- anorexia, weight loss
- bone pain (more common in ALL
- Hepatomegaly
- generalised lymphadenopathy (more in ALL)
- Leukostasis
- Metabolic abnormalities: Hyperuricemia, elevated serum LDH, Serum liver transaminases
- Extra medullary infiltration: gingival hypertrophy, infiltration of skin

Laboratory investigation

AML

1. BLOOD PICTURE:

- Hemoglobin : decreased
- total WBC Count : markedly raised

2. PERIPHERAL SMEAR:

- **RBC:** Normocytic normochromic anemia
- **WBC: Markedly increased, >20% myeloid blasts**
- **MYELOBLASTS:** 3-5 Times larger than small lymphocytes, high NC ratio, more cytoplasm than lymphoblasts
- **AUER RODS :** present
- **PLATELETS:** thrombocytopenia

1. Bone marrow

- Hypercellular
- suppressed erythropiesis
- decreased megakaryopoeisis
- myelopoeisis: suppression of myeloid maturation and myeloblasts >20%

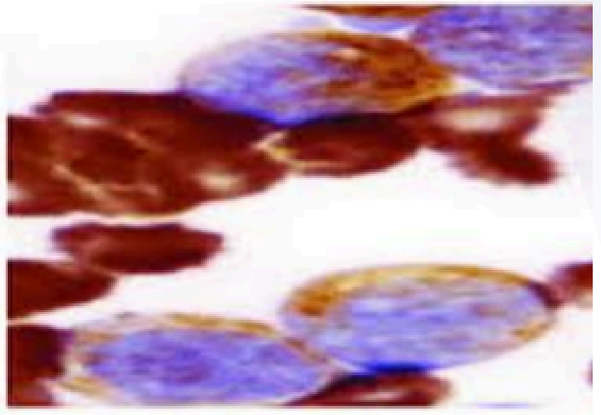
- Cytochemistry

■MPO – positive

■Sudan black B - positive

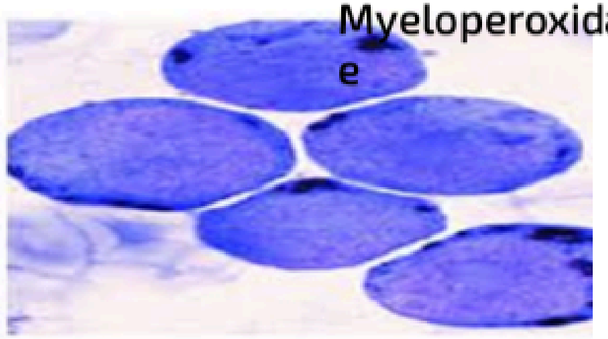
■NSE (Non-Specific Esterase)

■PAS-negative



AML Patient

Myeloperoxidase



AML with Sudan Black B

Sudan black B or myeloperoxidase, can reveal the presence of granules in the leukemic cells, which are characteristic of AML.

ALL

1. Peripheral blood:

- Hb : decreased
- Total WBC: markedly raised
- Platelet: reduced

2. Peripheral smear :

- RBC : Normocytic normochromic anemia
- WBC : Count increased and 20% or more lymphoblasts

(Larger than small lymphocytes, high NC ratio)

- Platelet: Thrombocytopenia

1. Bone marrow

- Hypercellular
- suppressed erythropiesis
- decreased megakaryopoeisis
- myelopoeisis: decreased
- blasts: constitute 20- 100% of marrow cells

Cytochemistry

- Periodic acid-Schiff (PAS): Positive in immature lymphoid cells
- Acid phosphatase: Focal positivity
- MPO and Sudan black- negative

Immunophenotyping

- Pre-B-cell type: Typically positive for pan-B cell markers CD19, CD10, CD9a.
- Pre-T-cell type: Typically positive for CD1, CD2, CD3, CD5, CD7.

Biochemical

- Raised serum uric acid
- Raised LDH

Treatment

25.46 Preparation for specific therapy in acute leukaemia

- Existing infections identified and treated (e.g. urinary tract infection, oral candidiasis, dental, gingival and skin infections)
- Screen for COVID-19
- Anaemia corrected by red cell concentrate transfusion
- Thrombocytopenic bleeding controlled by platelet transfusions
- If possible, central venous catheter (e.g. Hickman line) inserted to facilitate access to the circulation for delivery of chemotherapy, fluids, blood products and other supportive drugs
- Tumour lysis risk assessed and prevention started: fluids with allopurinol or rasburicase
- Therapeutic regimen carefully explained to the patient and informed consent obtained
- Consideration of entry into clinical trial

25.47 Drugs commonly used in the treatment of acute leukaemia

Phase	Acute lymphoblastic leukaemia	Acute myeloid leukaemia
Induction	Vincristine (IV) Prednisolone (oral) L-Asparaginase (IM) Daunorubicin (IV) Methotrexate (intrathecal) Imatinib (oral)*	Daunorubicin (IV) Cytarabine (IV) Etoposide (IV and oral) Gentuzumab ozogamicin (IV) All-*trans* retinoic acid (ATRA) (oral) Arsenic trioxide (ATO) (IV)
Consolidation	Daunorubicin (IV) Cytarabine (IV) Etoposide (IV) Methotrexate (IV) Imatinib (oral)*	Cytarabine (IV) Amsacrine (IV) Mitoxantrone (IV)
Maintenance	Prednisolone (oral) Vincristine (IV) Mercaptopurine (oral) Methotrexate (oral) Imatinib (oral)*	
Relapse	Fludarabine (IV) Cytarabine (IV) Idarubicin (IV)	Fludarabine (IV) Cytarabine (IV) Arsenic trioxide (ATO) (IV) Idarubicin (IV)

There are currently 3 phases of specific treatment for AML :

1. **Remission Induction phase**

- n this phase, a fraction of the tumour is killed by combinations of chemotherapy drugs
- daunorubicin with cytosine arabinoside given for 7-10 days in two cycles
- Patients with a good or standard risk karyotype, benefit from the addition of the antibody drug conjugate gemtuzumab ozagomicin which targets CD33 on AML cell and delivers DNA damaging drug calicheamicin directly into the cell.
- In AML with FLT3-ITD mutations- FLT3 inhibitor midostaurin - midostaurin

• Risk for severe bone marrow hypoplasia lasting 3-4 weeks and requires intensive support

Aim- to achieve normal blood count and marrow blast count<5%

Remission Consolidation

- Attacking the residual disease once remission achieved
- 1-2 courses of high dose cytosine arabinoside
- In poor prognosis AML, defined by poor risk cytogenetic/molecular genetic abnormalities or persistent MRD(mesurable residual disease) this may include allogeneic HSCT (hematopoietic stem cell transplantation)

- **Remission Maintenance**

  - Patients not undergoing allogenic HSCT with FLT3 mutation receives 1 year maintenance with midostaurin / Azacitdine

RELAPSE AML

- Very poor prognosis
- Pre-empted by monitoring MRD and intervening before haematological relapse occurs.
- However,the aim is to attempt to achieve further remission and deliver a HSCT,if possible

Remission induction

(ALL)

• Aim is to achieve remission and to retore normal hematopoesis in the bone marrow with less than 5% blasts

• using a combination of chemotherapy drugs given over a 4-week

• Dexamethasone, vincristine,antrhracyclines, methotrexate, mercaptopurine and asparaginase are commonly used

• Better tolerated than AML therapy

• Due to high dose steroid coupled with neutropenia – increases risk for infection

BCR-ABL rearrangement occurs in adult pts & TKI (TKI = tyrosine kinase inhibitor)therapy is included eg:dasatinib, imatinib

Remission Consolidation

•Consolidation phase builds on remission by decreasing leukemic burden

• Intensity depends on MRD (level at the end of induction)

Allogenic HSCT in adults

REMISSION MAINTENANCE

If the patient is still in remission after the consolidation phase for ALL

• May extend upto 3 yrs (if relapse does not occur.)

• CNS preventive therapy - triple intrathecal chemotherapy (cytarabine/ methotrexate/hydrocortisone)

Relapse

ranges from

1. positive MRD(Measurable Residual Disease
2. iso-lated CNS or testicular relapse
3. full blown haematological relapse

Newer therapy for relapse includes

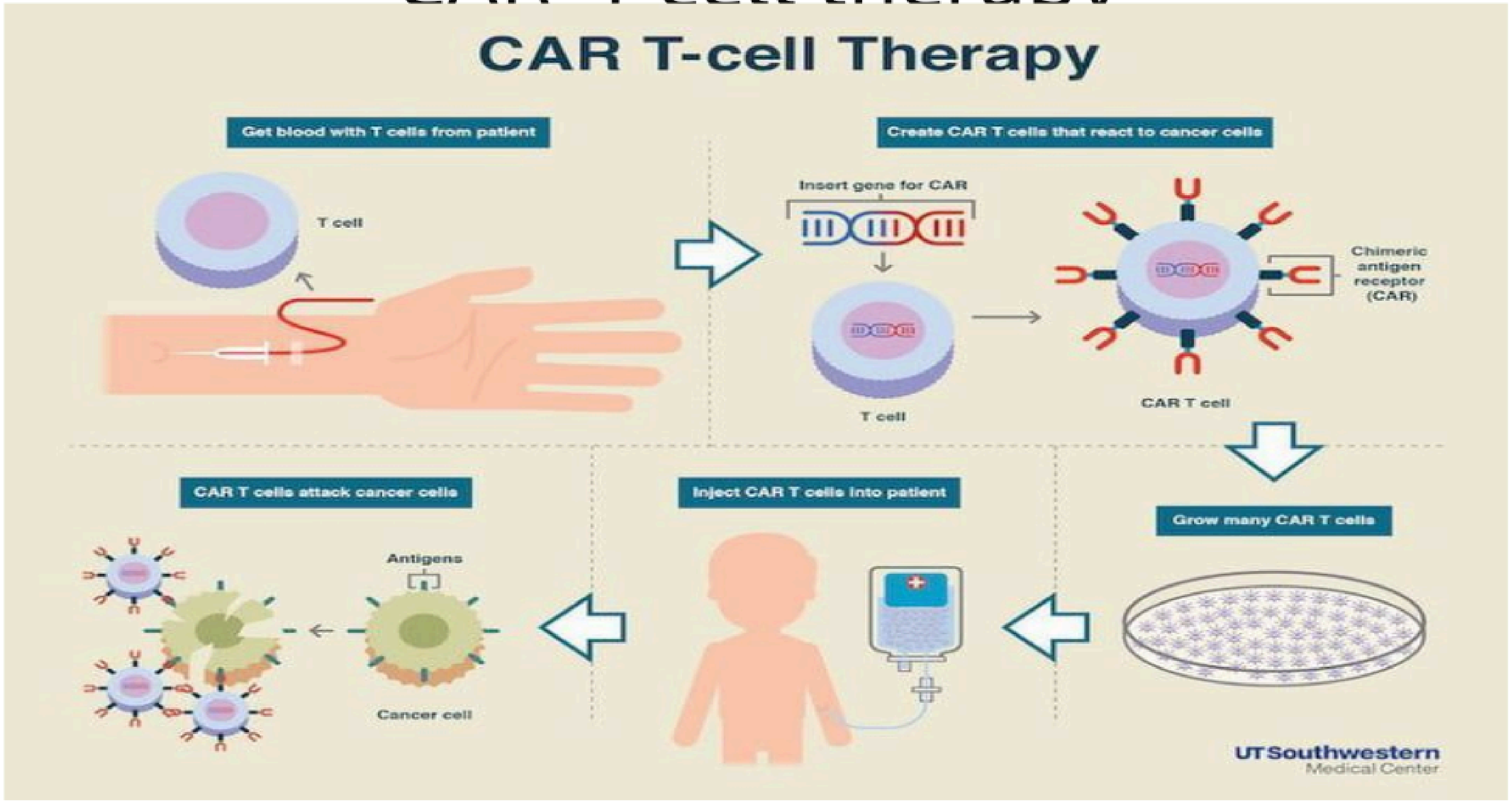
blinatumomab (antibody against CD19 and CD3)

inotuzumab ozogamicin(CD22)

Nelarabine in Tcell ALL

CART-T-cell therapy

CAR-T cell therapy



THANK YOU