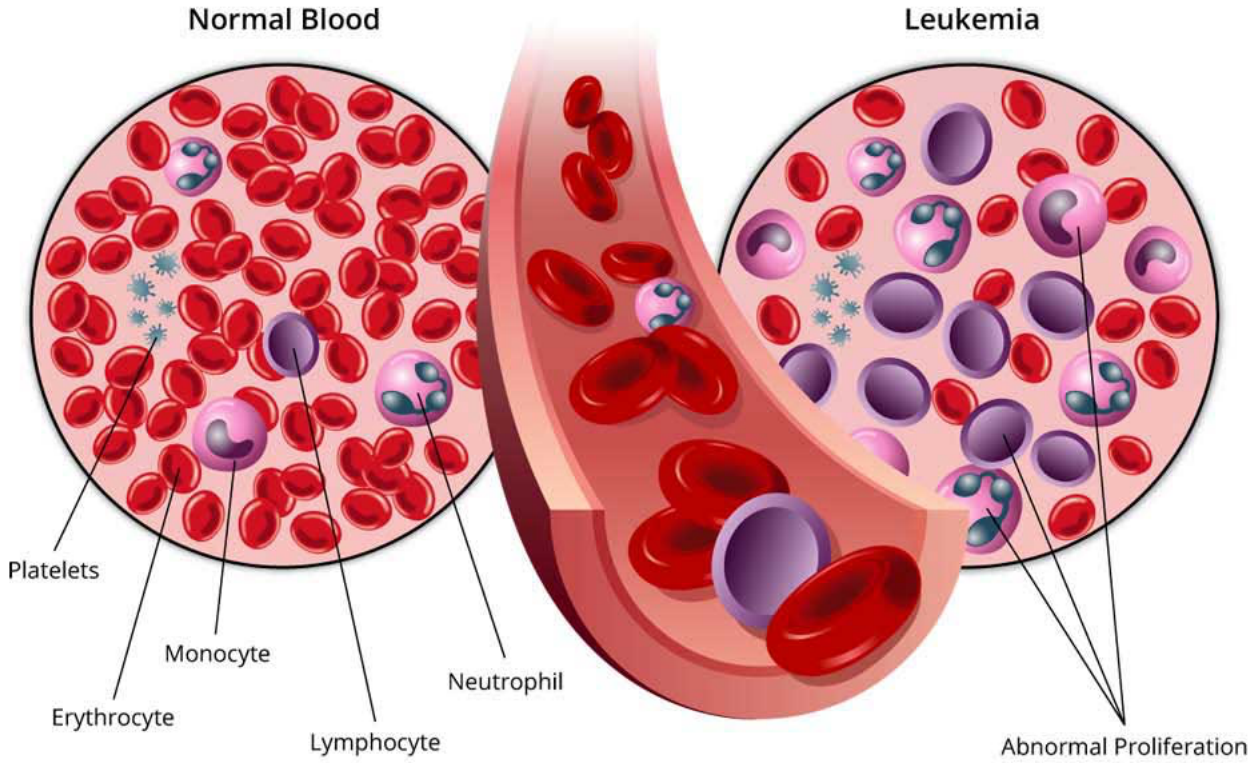
Therapeutics
Fifth Stage

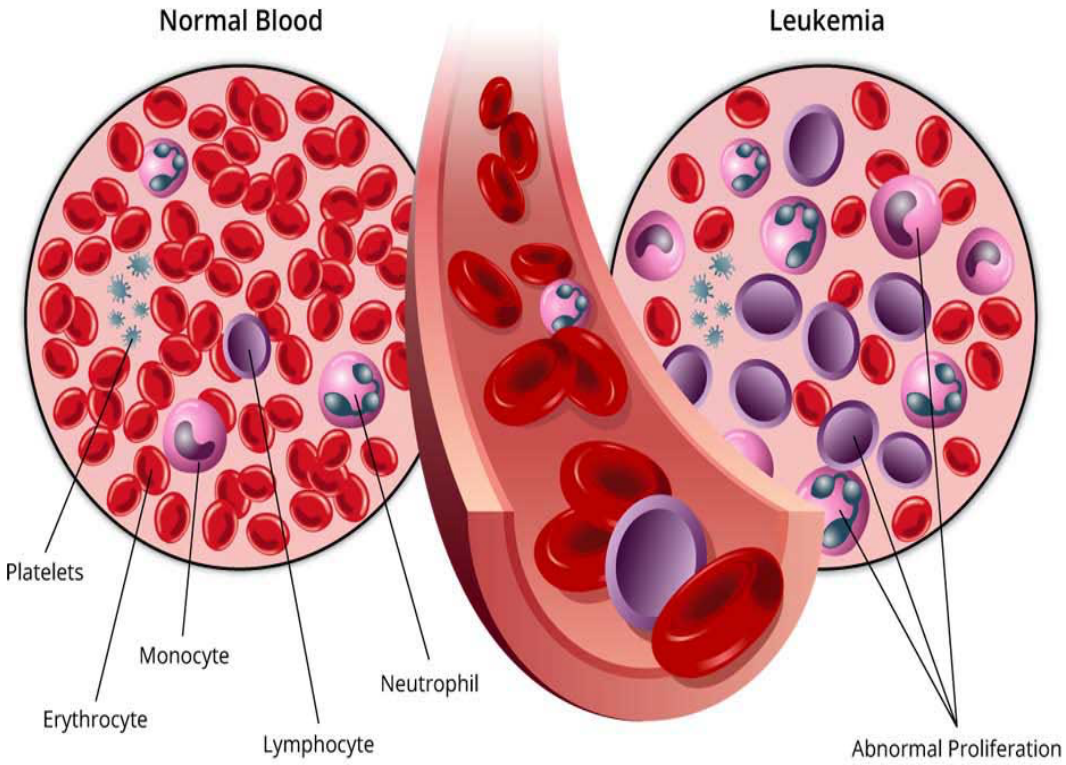


Leukemia

Acute Leukemia

Dr. Ali Al-Athari

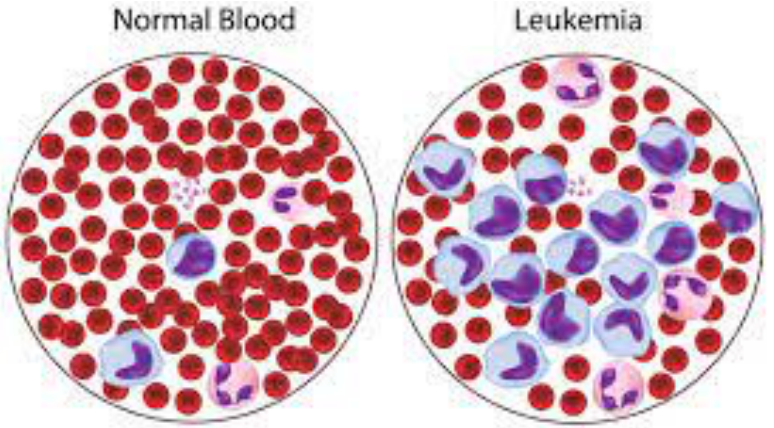
- **Acute leukemia**
- **The acute leukemias are hematologic malignancies of bone marrow precursors characterized by excessive production of immature hematopoietic cells. This proliferation of "blast" cells eventually replaces normal bone marrow and leads to the failure of normal hematopoiesis (Resulting in anemia, neutropenia, and thrombocytopenia) and the appearance in peripheral blood as well as infiltration of other organs including the liver, spleen, bone, skin, lymph nodes, testis, and central nervous system (CNS).**



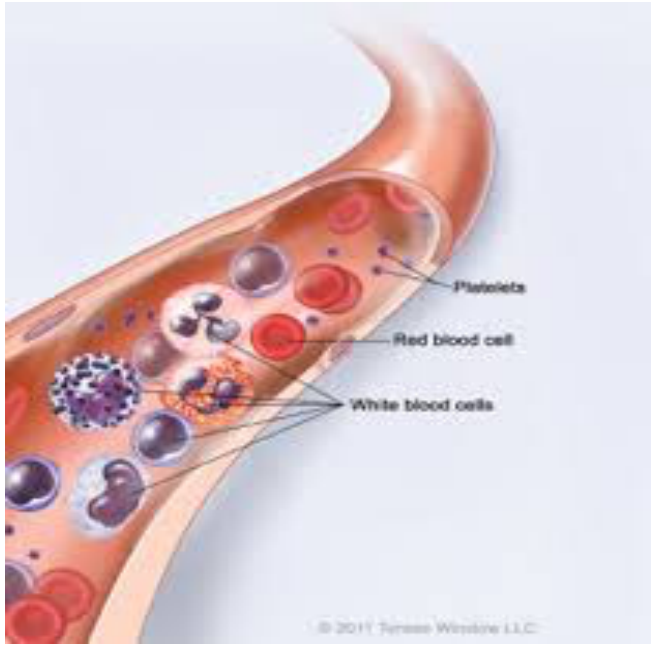
- **Types of acute leukemia:**

Acute leukemias are classified according to their cell of origin.

- **Acute lymphocytic leukemia (ALL) arises from the lymphoid precursors.**



- **Acute nonlymphocytic leukemia (ANLL) or acute myelogenous leukemia (AML) arises from the myeloid or megakaryocytic precursors.**

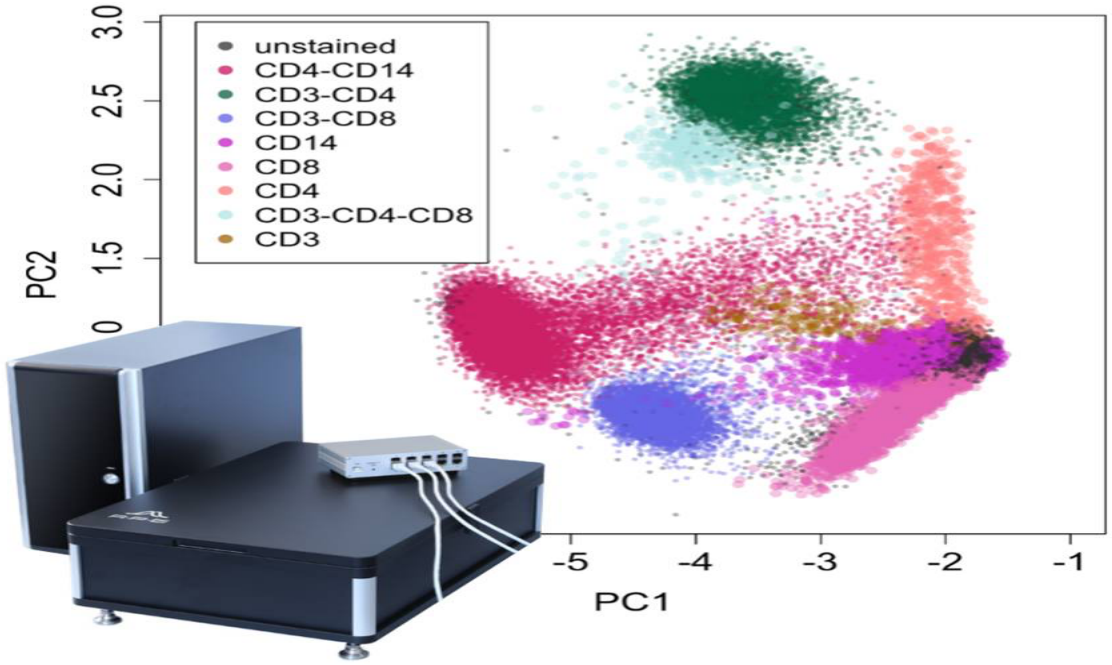


- **Epidemiology:**
- **Leukemia is a relatively uncommon disease.**
- **In the pediatric population, leukemia is a common cancer.**
- **ALL accounts for 75% to 80% of all cases of childhood leukemia.**
- **The average age of diagnosis for AML is about 65 years and is a result of an increasing incidence of AML with age.**

- **Etiology:**
- **The cause of acute leukemias is unknown; multiple influences related to genetics, socioeconomics, infection, environment (e.g. chemicals, pesticides, and radiation), hematopoietic development, and chance may play a role.**
- **Alkylating agents, such as ifosfamide and cyclophosphamide, and topoisomerase inhibitors, such as etoposide, are linked to an increased risk of AML and myelodysplastic syndrome (MDS).**

- **Diagnosis of acute leukemia**
- **Immunophenotyping by flow cytometry has taken on an increasingly important role in the diagnosis of leukemia.**
- **Flow cytometry is the preferred method for leukemic lineage as well as prognostic assignment.**

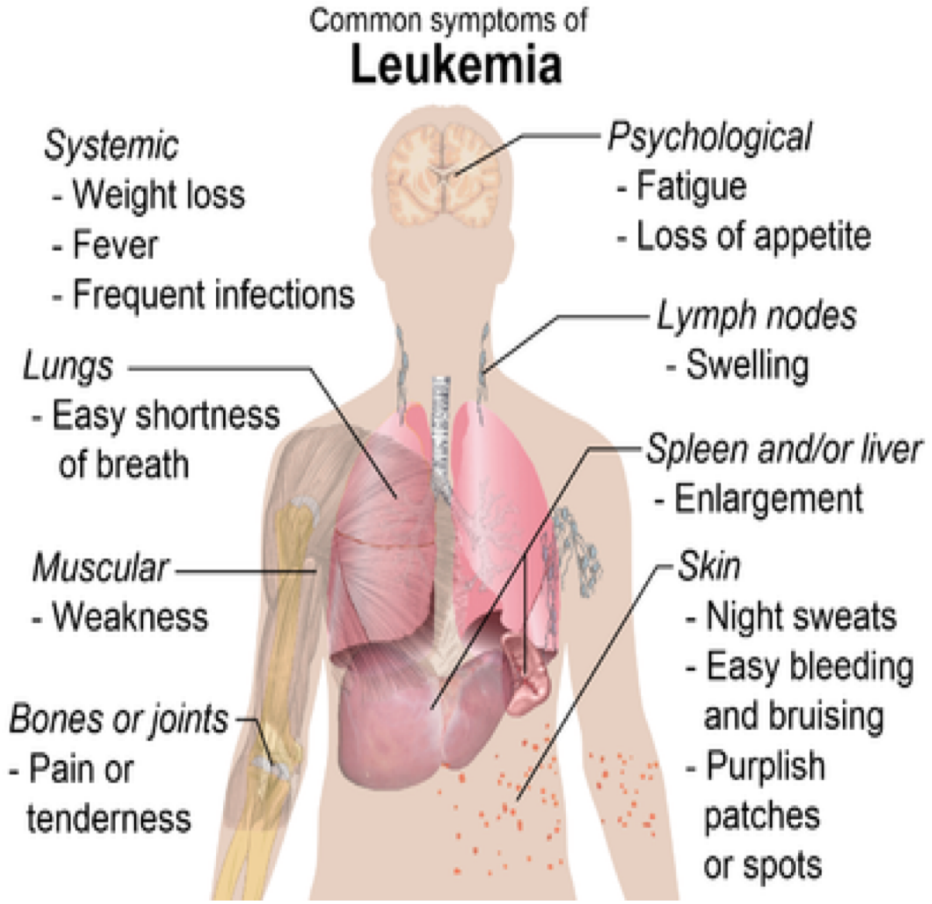
Immunophenotyping is a test used to identify cells on the basis of the types of markers or antigens present on the cell's surface, nucleus, or cytoplasm.



- **Prognostic Factors**
- **Patients with leukemia are categorized based on clinical and biological features that mirror their risk of relapse.**
- **Risk assessment is an important factor in the selection of treatment (minimized overtreatment or undertreatment).**
- **Age, WBC, leukemic cell-surface markers, DNA content, and specific cytogenetic abnormalities predict response to therapy and are used to assign risk and associated treatment.**
- **On the basis of these prognostic variables, patients are assigned to standard-, high-, or very-high- risk groups that determine the aggressiveness of treatment.**
- **For ALL patients: Minimal residual disease (MRD) is a quantitative assessment (By PCR) of subclinical remnant of leukemic burden remaining at the end of the initial phase of treatment (induction) when a patient may appear to be in a complete morphologic remission. This measure has become one of the strongest predictors of outcome for patients with acute leukemia. The elimination of MRD is a principal objective of postinduction leukemia therapy.**
- **MRD is an important indicator of disease recurrence**

- **Clinical Presentation of acute leukemia**
- **Typically, patients with acute leukemia have non-specific symptoms (fatigue, pallor and fever) with no obvious distress for 1 to 3 months before presentation.**

- **Patients with acute leukemia may present with malaise and weakness (due to anemia); bleeding due to thrombocytopenia; fever and high susceptibility to infection (due to neutropenia), bone pain (due to leukemic infiltration) and weight loss.**



- **Lymphoadenopathy is common seen in ALL patients.**

Lymphoadenopathy

- **Chloromas (localized leukemic deposits named after their color) may be seen, especially in the periorbital regions and as skin infiltrates in AML patients. Gum hypertrophy is indicative of AML M4 and M5 subtypes.**
- **Potassium and phosphorus often are elevated. Uric acid is increased in approximately 50% of patients secondary to rapid cellular turnover.**

Chloromas

- **Treatment**
- **Desired outcomes**
- **The primary objective in treating patients with acute leukemia is to achieve a continuous complete remission (CCR). Remission is defined as the absence of all clinical evidence of leukemia with the restoration of normal hematopoiesis.**
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- **For both ALL and AML, remission induction is achieved with the use of myelosuppressive chemotherapy. Failure to achieve remission in the first 7 to 14 days of therapy is highly predictive of later disease recurrence. This again represents the growing importance of MRD in prognosis and treatment.**
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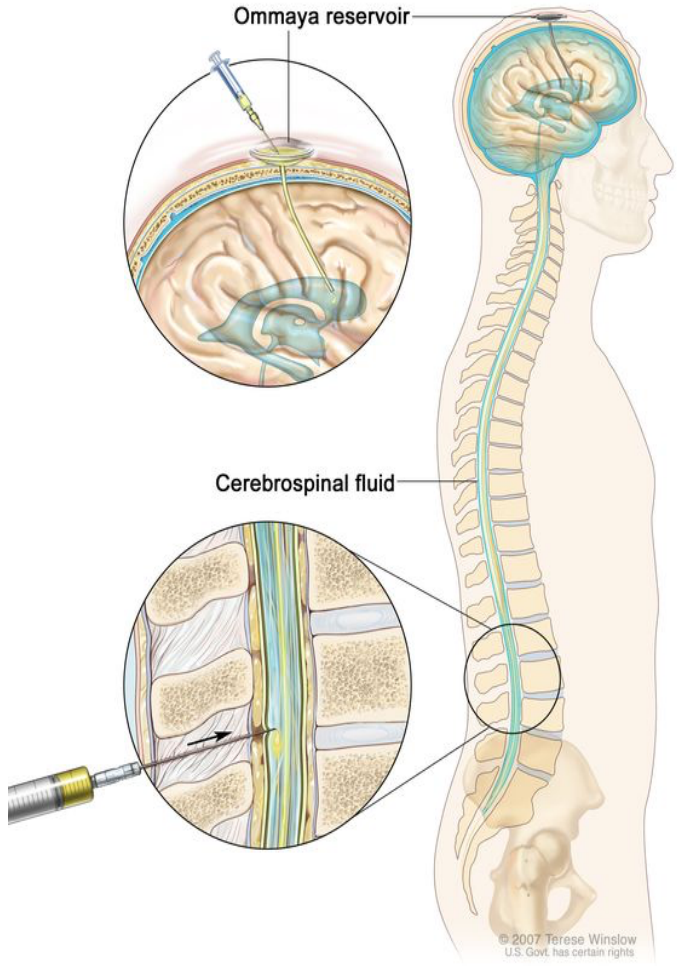
- **Non pharmacological treatment of acute leukemia**
- **Cancer survivors are at greater risk for developing second malignancies, cardiovascular disease, diabetes, and osteoporosis than those in the general population.**
- **Thus, it is important to provide supportive care and counseling related to nutrition, smoking cessation, and exercise as a part of their active treatment.**

- **Pharmacologic Therapy: ALL**
- **The treatment for ALL consists of the following main elements:**
- **1- Initial therapy : is called induction (sometimes called remission induction) which aim to induce a remission, a state in which there is no identifiable leukemic cells in the bone marrow or peripheral blood with light microscopy.**
- **Current induction therapy for ALL typically consists of vincristine, L-asparaginase, and a steroid (prednisone or dexamethasone). An anthracycline is added for higher risk patients (e.g. adults).**
- **Dexamethasone often replaces prednisone because of its longer half-life and better CNS penetration.**

- **2- CNS-directed treatment,**
- **3- Post remission therapies include:**
- **A- Intensive post remission consolidation regimens (for 1 month) to reduce the burden of residual leukemic cells.**
- **B-Reinduction (Interim maintenance for 2 months and delayed intensification by repetition of initial induction therapy given 3 months after remission): followed by**
- **C- A prolonged maintenance phase to further eliminate leukemic cells and produce an enduring continuous complete remission (CCR). Maintenance chemotherapy is a combination of oral methotrexate and 6-mercaptopurine.**

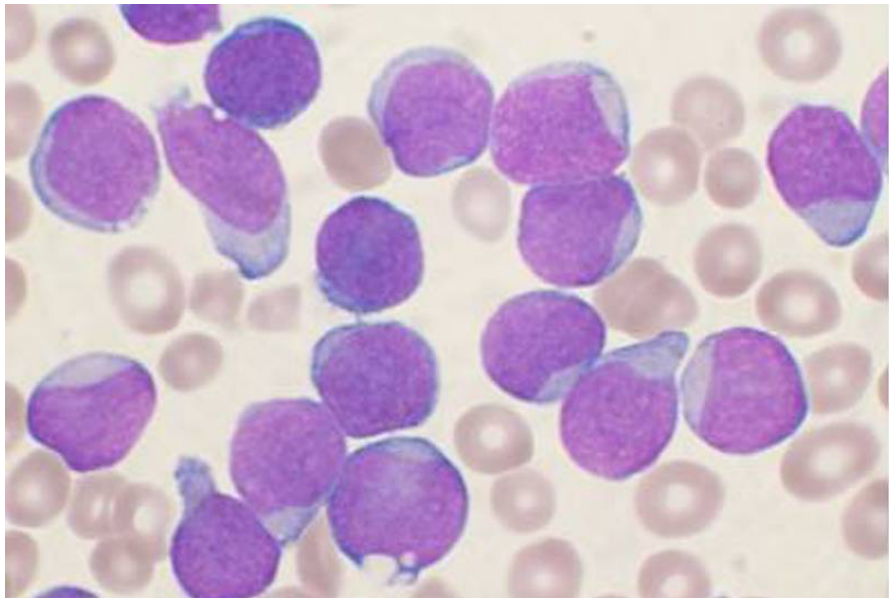
- **The total duration of treatment is 2 to 3 years**
- **Note: Improved outcome is associated with increasing 6-mercaptopurine doses to the limits of individual tolerance based on absolute neutrophil count (ANC).**
- **CNS Prophylaxis**
- **Leukemic invasion of the CNS is an almost universal event in patients. Thus, all patients with ALL and AML leukemia receive intrathecal (IT) chemotherapy.**
- **CNS prophylaxis relies on IT chemotherapy (eg, methotrexate, cytarabine, and corticosteroids), systemic chemotherapy with dexamethasone and high-dose methotrexate, and craniospinal irradiation (XRT) in selected high-risk patients (T-cell ALL).**

IT



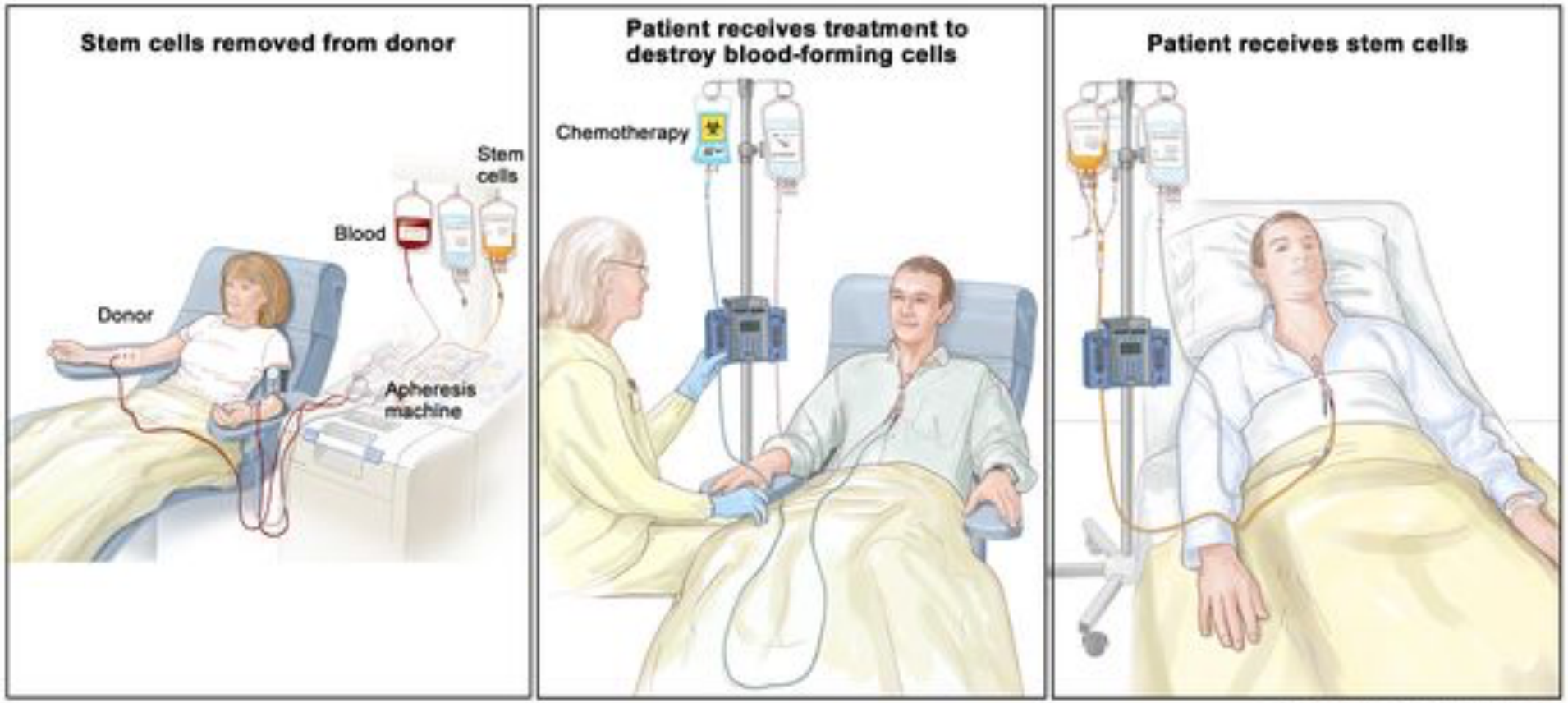
- **Relapsed ALL**
- **Relapse is the recurrence of leukemic cells at any site after remission has been achieved.**
- **Bone marrow relapse is the major form of treatment failure in 15% to 20% of patients with ALL. Most relapses have the same immuno-phenotype and cytogenetic changes seen of the original disease. Extramedullary sites of relapse include the CNS and the testicles**
- **Site of relapse and the length of the first remission are important predictors of second remission and overall survival (OS).**

Relapsed ALL

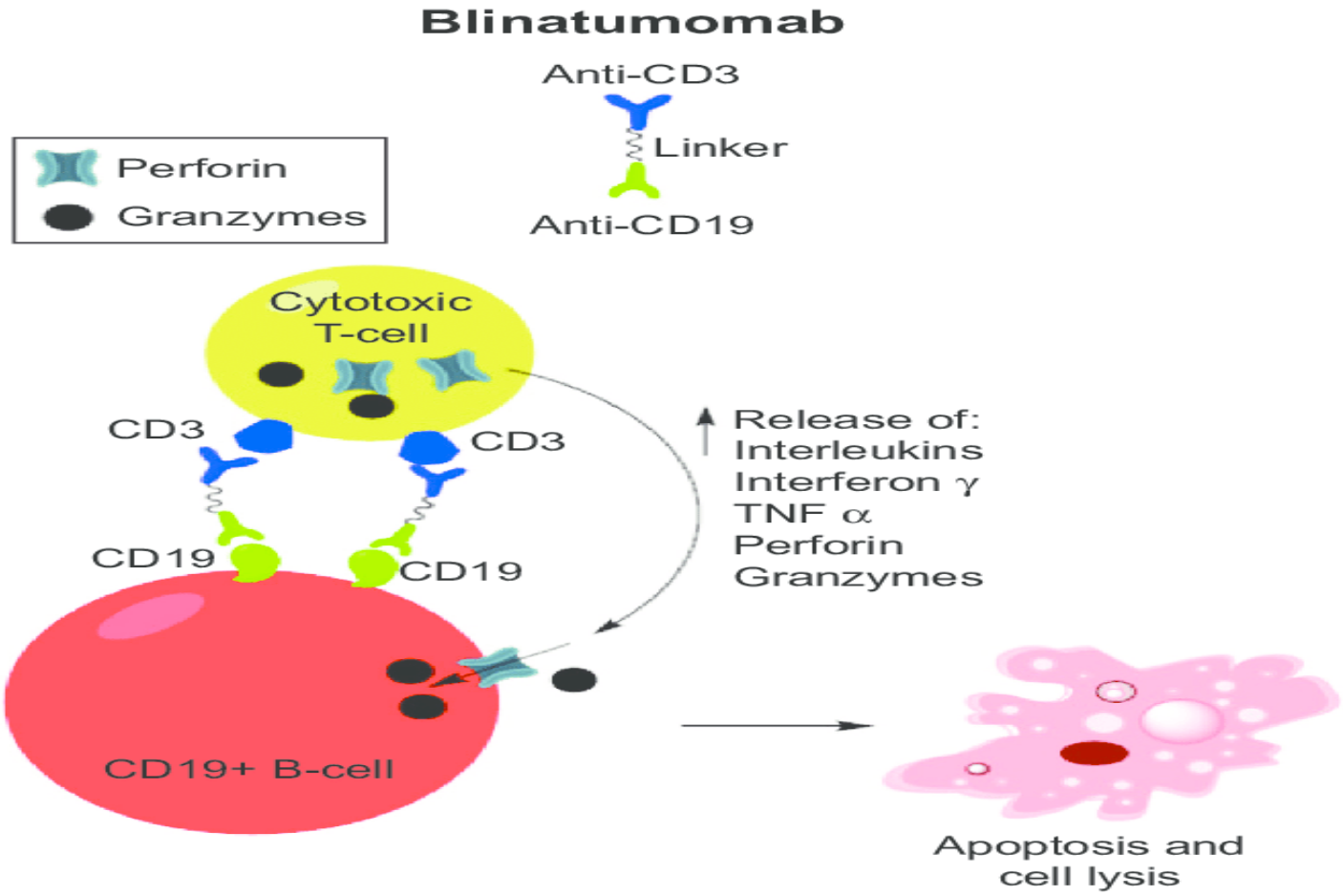


- **Treatment strategies for relapsed ALL**
- **Treatment strategies for relapsed ALL include chemotherapy or allogeneic hematopoietic stem cell transplant (allo-HSCT).**
- **Clofarabine has shown considerable activity in refractory acute leukemias.**
- **Blinatumomab, a monoclonal antibody that targets CD19, was approved for Ph negative relapsed or refractory ALL.**
- **Inotuzumab ozogamicin (anti CD-22) is also used in relapsed and refractory B-ALL.**
- **Tisagenlecleucel is an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that has been shown to induce durable remissions in patients with relapsed and refractory B-cell ALL.**
- **Nelarabine is used in patients with relapsed or refractory T-lineage ALL.**

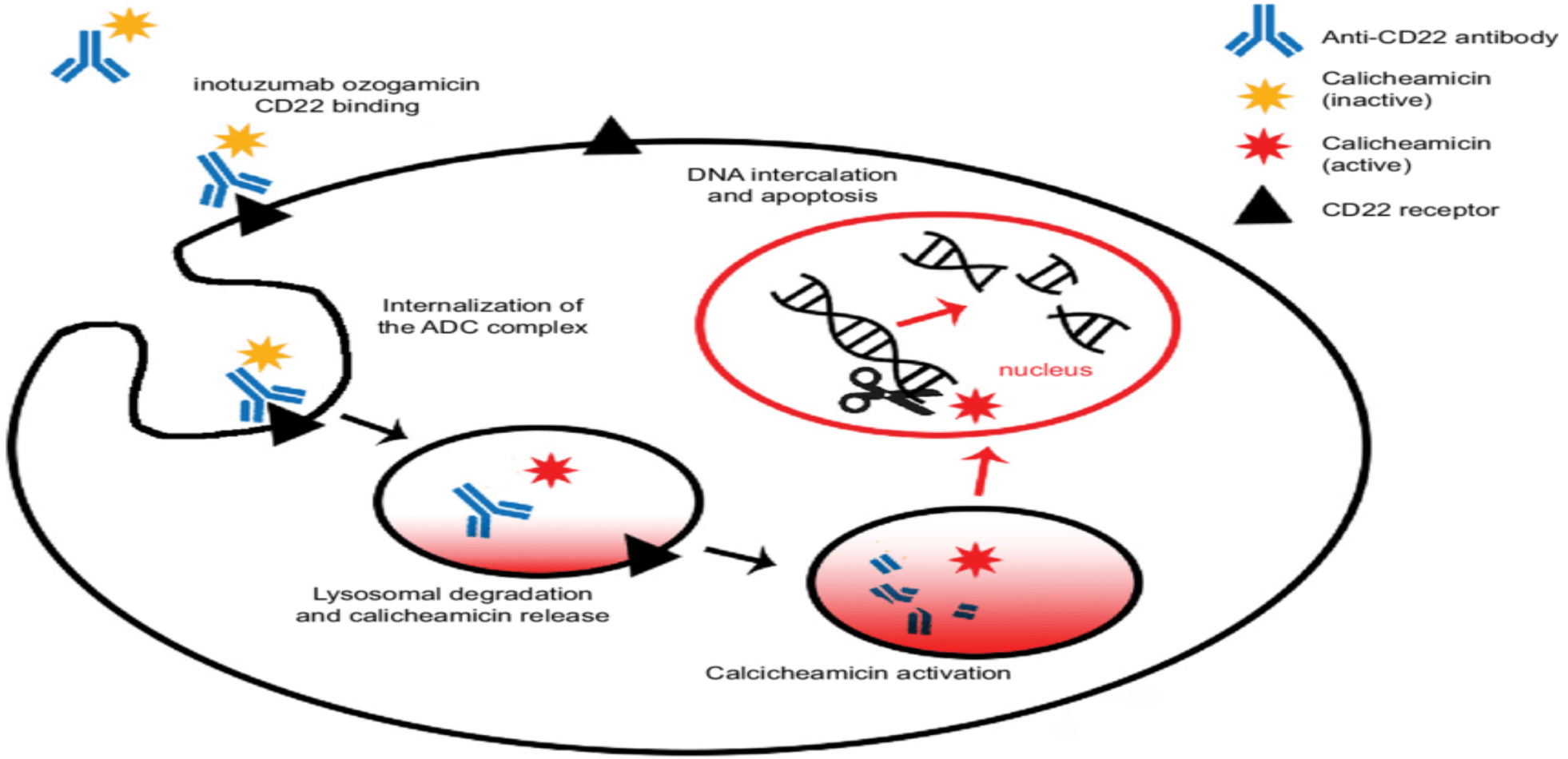
- **allogeneic hematopoietic stem cell transplant (allo-HSCT)**



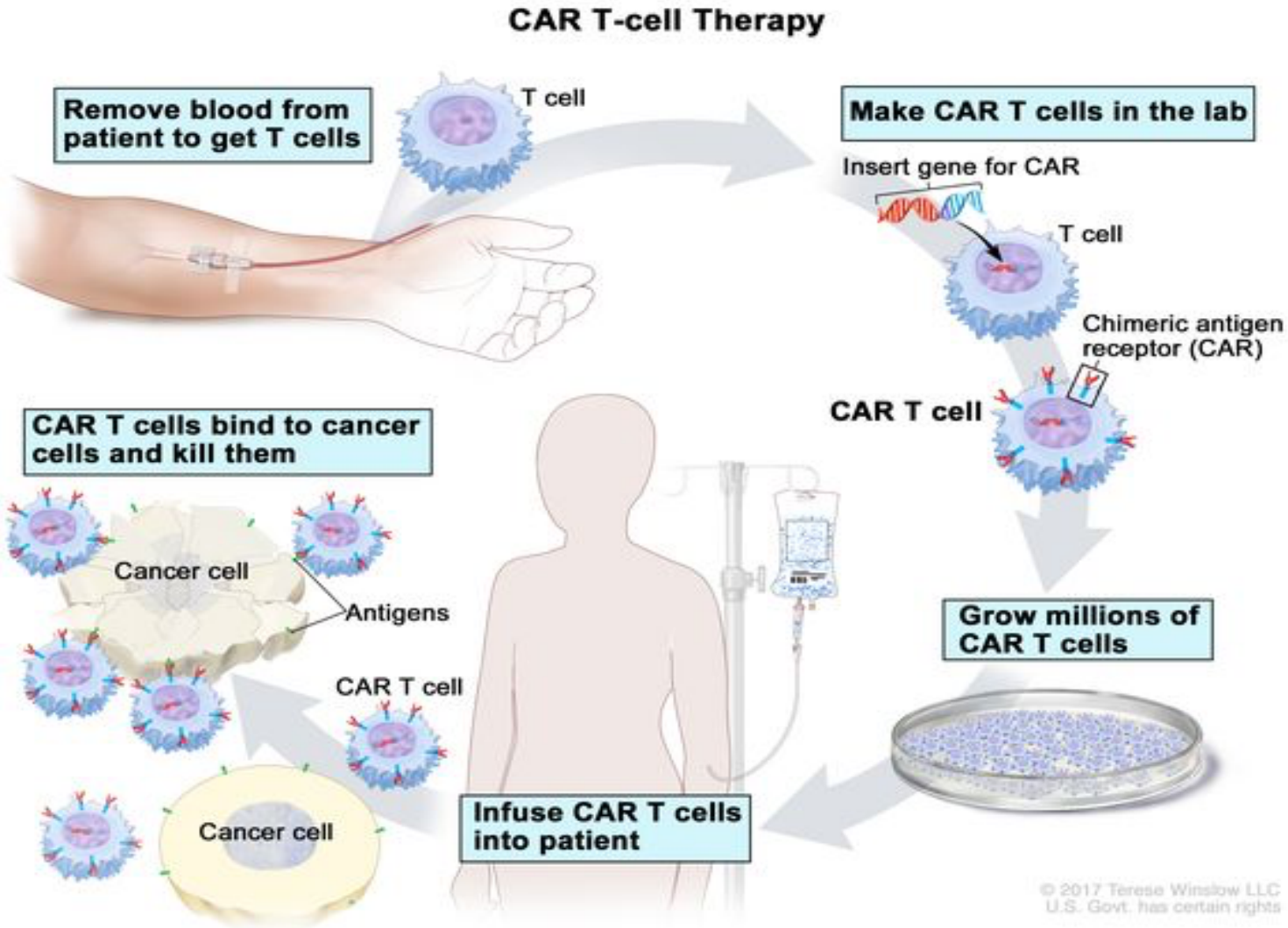
- **Mechanism of actions:** للاطلاع
- **Blinatumomab:**
- a monoclonal antibody that targets CD19, was approved for Ph negative relapsed or refractory ALL



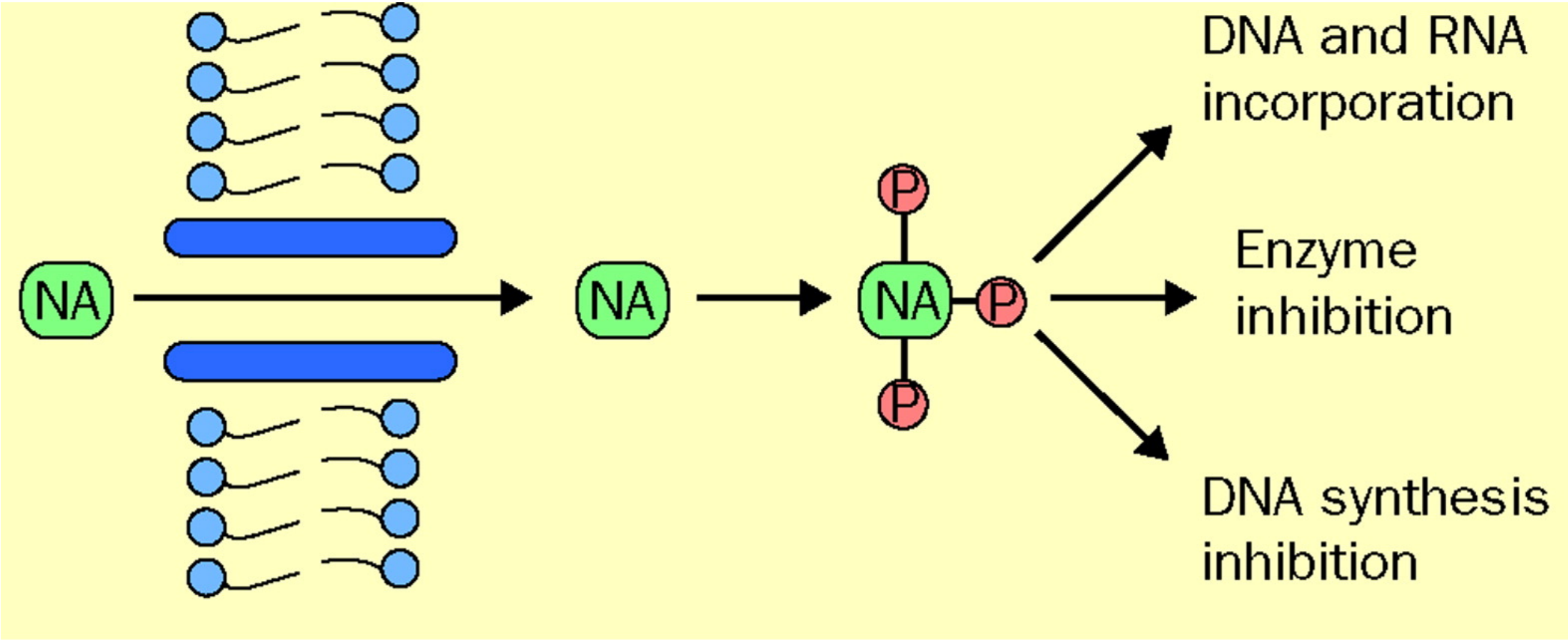
- **Inotuzumab ozogamicin:** (anti CD-22) is also used in relapsed and refractory B-ALL



- **Tisagenlecleucel**
- anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that has been shown to induce durable remissions in patients with relapsed and refractory B-cell ALL.



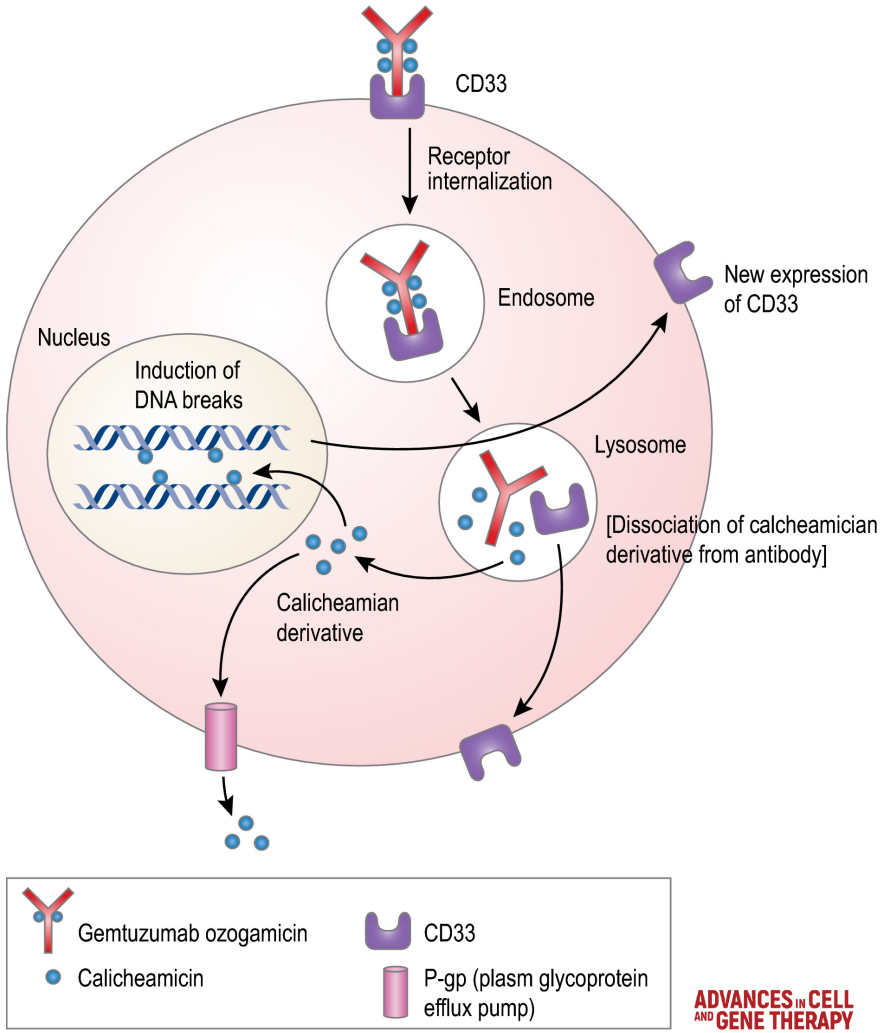
- **Nelarabine** is used in patients with relapsed or refractory T-lineage ALL.
- **Clofarabine** acts by inhibiting DNA polymerases and ribonucleotide reductase as well as by inducing apoptosis in cycling and non-cycling cells.



- **Outcome evaluation**
- **Failure to obtain morphologic bone marrow remission by day 28 is a very adverse prognostic sign and dictates further induction treatment.**
- **For those who have a morphologic remission, quantification of MRD has become an increasingly important prognostic factor.**
- **Levels of residual less than 0.01% appear to be associated with better outcome.**

- **Treatment of AML**
- **Treatment of AML is divided into two phases:**
- **Induction (to achieve remission): consists of a combination of cytarabine, and daunorubicin. Adding gemtuzumab ozogamicin to induction therapy for older patients improved relapsed rates and OS.**
- **Consolidation (postremission) to further enhance remission with more cytoreduction and prevent relapse. Mainly through the use of 2-4 cycles of high-dose cytarabine**
- **Note: Midostaurin, an oral multi- target kinase inhibitor, was recently approved by the FDA for treatment of Fms-like tyrosine kinase 3(FLT3) positive AML**

- gemtuzumab ozogamicin للاطلاع



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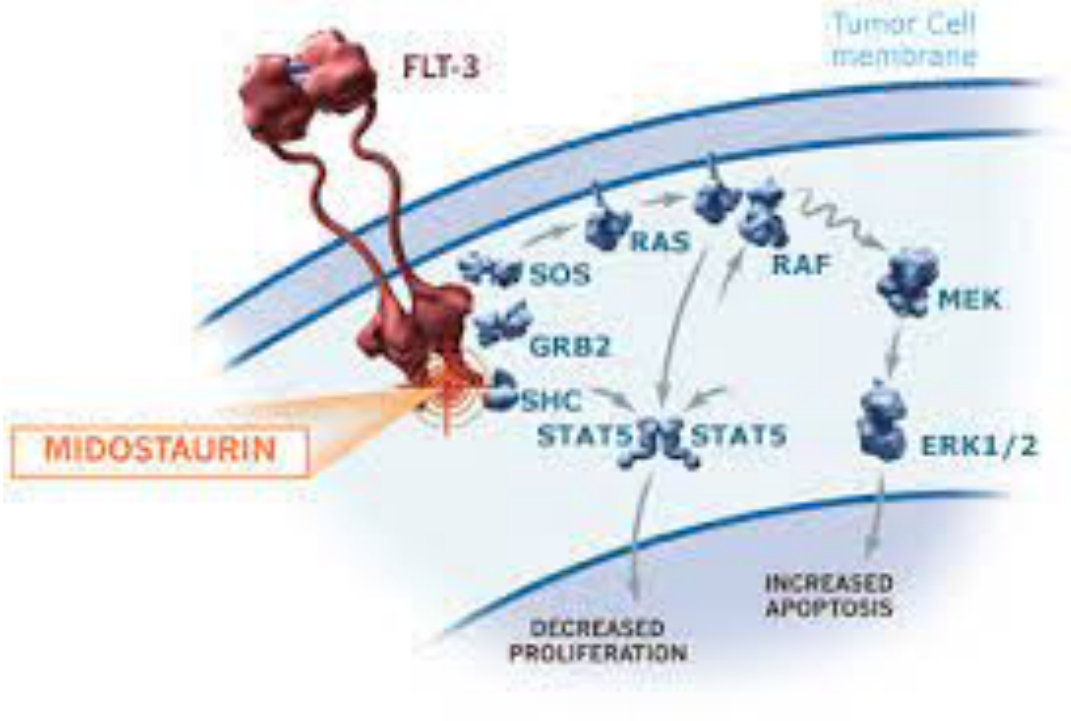


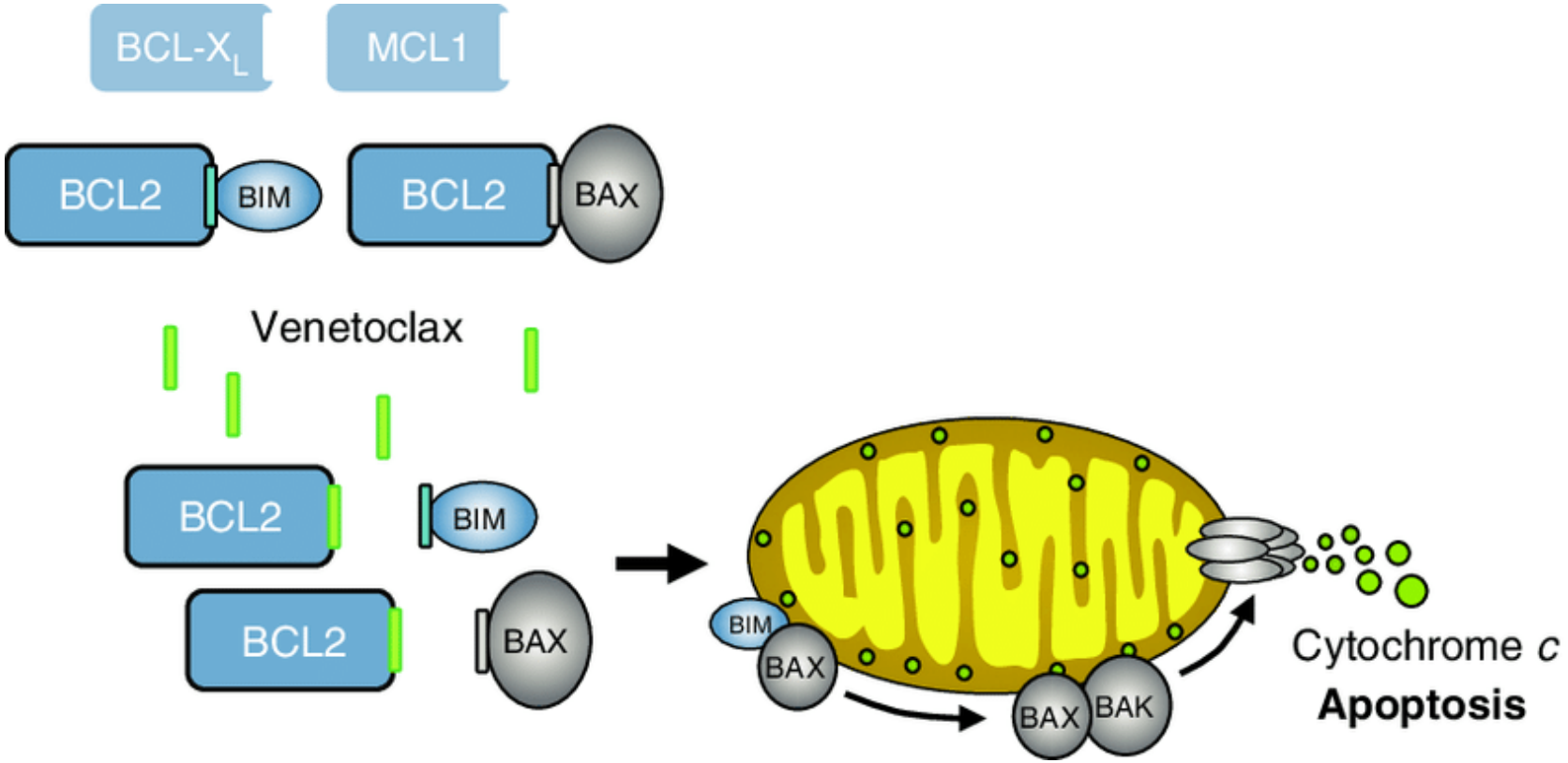
- **Allogeneic Hematopoietic Stem Cell Transplantation**
- **Hematopoietic stem cell transplantation (HSCT) is the most effective treatment for AML.**
- **Its promising benefit must be weighed against the potential risk of transplantation related sequelae.**
- **Patients who do not have an HLA-matched sibling proceed to post remission therapy with chemotherapy alone.**
- **The role of HSCT, particularly whether it should be performed during the first CR or reserved for second remission, remains the most controversial issue in pediatric AML.**
- **In certain institutions, HSCT is often reserved for patients that are considered high risk.**

- **CNS therapy**
- **Patients with CNS disease at diagnosis can be cured with IT therapy. In most cases, IT cytarabine with or without methotrexate and systemic high-dose cytarabine provide effective treatment.**

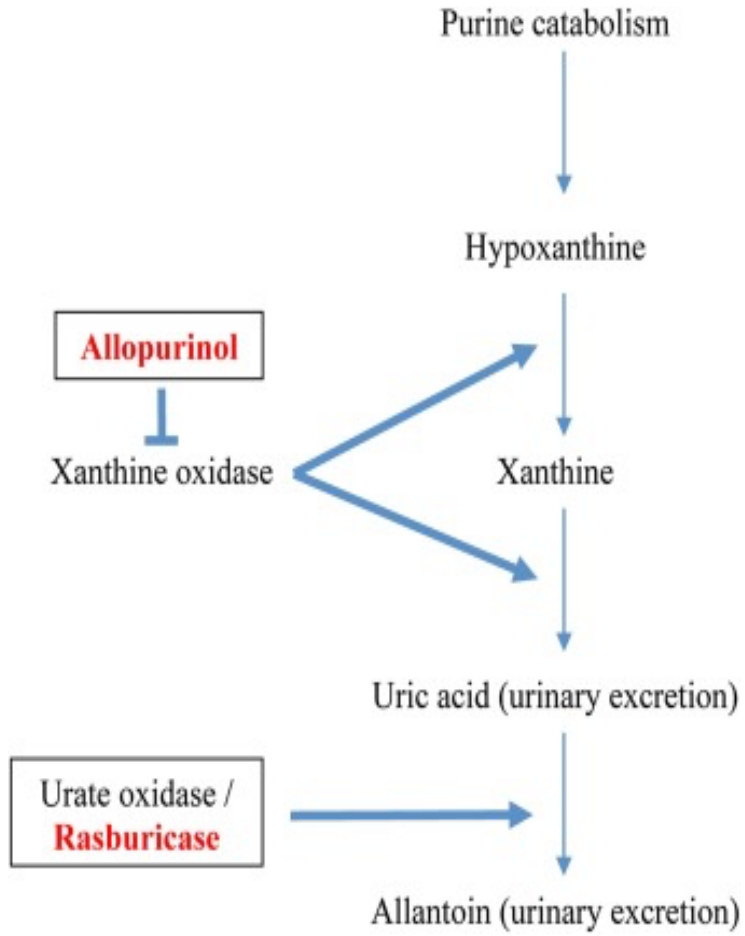
- **Relapsed AML**
- **Even though there is no standard therapy for relapse, most studies have shown that high-dose cytarabine-containing regimens have considerable activity in obtaining a second remission. Cytarabine has been used in combination with mitoxantrone, etoposide, fludarabine, 2-chlorodeoxyadenosine, and clofarabine.**

- For patients unable to tolerate intensive chemotherapy, low dose cytarabine and the hypomethylating agent, azacitidine, are also options for relapsed disease.
- Venetoclax in combination with either decitabine or azacitidine is also an alternative in the relapsed setting.
- Gilteritinib is an FLT3 inhibitor approved for AML patients with an *FLT3-ITD* mutation in relapsed setting.
- Enasidenib is an oral inhibitor of mutant *IDH2* proteins and is approved for use in patients with relapsed AML who harbor *IDH2* mutations.
- Similarly, ivosidenib is an *IDH1* inhibitor that is approved for use in relapsed AML patients with an *IDH1* mutation.
- After a patient has achieved a second remission with conventional chemotherapy, allo-HSCT is the therapy of choice.

Venetoclax للاطلاع



- **Complications of Treatment**
- ***1- Tumor Lysis Syndrome***
- **Tumor lysis syndrome (TLS) is an oncologic emergency that is characterized by metabolic abnormalities resulting from the death of blast cells and the release of large amounts of purines, pyrimidines, and intracellular potassium and phosphorus.**
- **Measures to prevent TLS include aggressive hydration to increase urine output, and allopurinol to reduce uric acid production. Rasipuricase is indicated in some cases.**



- ***2- Infection***
- **Infection is a primary cause of death in acute leukemia patients.**
- **Both the disease and aggressive chemotherapy cause severe myelosuppression, placing the patient at risk for sepsis.**
- **Because the progression of infection in neutropenic patients can be rapid, empirical antibiotic therapy (usually 4th generation cephalosporins) is started whenever a fever is documented.**

- **3- Secondary malignancy:** discussed in previous lecture

- **Supportive care**
- **Platelet transfusions are a common tool to prevent hemorrhage.**
- **Patients with uncomplicated thrombocytopenia can be transfused when the platelet count falls below 10 × 103/mm3.**
- **Patients who are either highly febrile or actively bleeding may require transfusions at higher levels.**
- **Red blood cell transfusions generally are not necessary for a hemoglobin concentration greater than 8 g/dL.**
- **The use of CSFs (G-CSF most commonly) generally is limited to those chemotherapy regimens that place the patient at highest risk for prolonged neutropenia.**

Thank you