Treatment results in ALL

- **Adults**
  - **Complete remission (CR) 80-85%**
  - **Leukemia-free survival (LFS) 30-40%**
- **Children**
  - **Complete remission (CR) 95-99%**
  - **Leukemia-free survival (LFS) 70-80%**

Combination chemotherapy

- **in order to :-**

1. **obtain synergestic action**

2. **minimize side effects.**

3. **attacks leukemic cells in different phases of mitosis.**

4. **delay the onset of resistance of the malignant cells.**

Effective drugs for ALL

1- vincristine-----> arrest cell mitosis

2- predinsone ----> Lyrmpholysis

3-6.M.P. ----> inhibit DNA synthesis.

4-Methotrexate ----> inhibit RNA and protein

Synthesis

5-Doxorubich (adriamycin)----> inhibit DNA synthesis

6-L- asparaginase

Chemotherapy for acute leukemias

- Phases of ALL treatment
  - induction
  - intensification
  - CNS prophylaxis
  - maintenance

} post-remission therapy

Induction

four to six weeks:

- Vincristine
- Glucocorticoid (prednisone, prednisolone or dexamethasone)
- L-asparaginase

Pharmacodynamics

- The malignant cells are dependent on an exogenous source of asparagine for survival.
- Normal cells, however, are able to synthesize asparagine and thus are affected less by the rapid depletion produced by treatment with the enzyme asparaginase.

L-Asparaginase – Mechanism of Action

- Catalyzes the conversion of L-asparagine to aspartic acid and ammonia.
- Reversal of L-asparagine synthetase activity.
- Results in rapid and complete depletion of L-asparagine.
- Lack of intracellular asparagine results in decrease of protein synthesis and apoptosis.

L-Asparaginase – Impaired Protein Synthesis

- Decreased production of insulin
  - Resultant hyperglycemia secondary to hypoinsulinemia
  - Hyperglycemia usually transient and resolves upon discontinuation
    - Blood sugar should be closely monitored

- Decreased production of albumin
  - Hypoalbuminemia can be severe resulting in peripheral edema or ascites
    - Patients with limited hepatic synthetic function may be unable to tolerate the effects of L-asparaginase

L-Asparaginase – Impaired Protein Synthesis

- Decreased production of vitamin K-dependent clotting factors and endogenous anticoagulants such as proteins C and S and antithrombin III
  - Coagulopathies, thrombosis, or bleeding due to impaired protein synthesis may occur
  - Monitor coagulation parameters during L-asparaginase therapy
  - Use cautiously in patients with a preexisting coagulopathy (e.g. hemophilia) or hepatic disease
  - Intramuscular injections may cause bleeding, bruising, or hematomas due to coagulopathy

L-Asparaginase – Toxicities

- Mild nausea/vomiting
  - Anorexia, abdominal cramps, general malaise, weight loss
- Tumor Lysis Syndrome (TLS)
  - Hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and decreased urine output
  - severe renal insufficiency

Vincristine

- Constipation is common during articularly because of the Vincristine.

- Nerve Irritation

Vincristine may cause numbness or tingling in the hands and feet. If this occurs.

GLUCOCORTICOIDS

- **have inhibitory effects on lymphocyte proliferation and are used in treating lymphomas and leukaemias.**

- **REDNISONE is an example; that used to induce remission in the treatment of lymphocytic leukaemia and in the treatment of Hodgkin and non Hodgkin lymphoma.**

Steroid Side Effects

- : Potential side effects of the steroid prednisone can include: trouble sleeping, increased appetite, fluid retention and swelling, indigestion, restlessness, nervousness, headache, blurred vision, muscle cramps and weakness, increased blood sugar level, bone pain, and high blood pressure.

Consolidation

- Once normal haematopoiesis is achieved, patients undergo **Consolidation** therapy.

- Common regimens in childhood ALL include:

1. **Methotrexate with mercaptopurine**

2. High-dose asparaginase over an extended period

3. Reinduction treatment (a repetition of the initial induction therapy in the first few months of remission).

Maintenance

- Maintenance usually consists

1. weekly methotrexate and
2. daily mercaptopurine.

- 2-3 years

CNS prophylaxis

- Patients with ALL frequently have meningeal leukaemia at the time of relapse (50-75% at one year in the absence of CNS prophylaxis) and a few have meningeal disease at diagnosis (<10%).

- Intrathecal (methotrexate, cytarabine, steroids)

- **and for adult high-dose systemic chemotherapy (methotrexate, cytarabine, L-asparaginase)**

AML: INDUCTION THERAPY

- Anthracycline (Idarubicin) for 3 days and Cytosine arabinoside (Ara-C) for 7 days (3+7, Younger/fit patients only)
- Three to 5 weeks of pancytopenia
- Supportive care red cell and platelet transfusions, prophylactic antibacterial, antifungals and antivirals

AML: INDUCTION THERAPY

- Two cycles of cytosine arabinoside + daunorubicin +/- thioguanine and other agents gives remissions in 70-90%

- **Chemotherapy alone has given 30-50 % cure rates.**

- **Cure is higher after timed-sequential induction therapy (42% vs. 27%).**

- **Short (4-12 months) of post-induction therapy is adequate**
- **CNS leukemia is less common than in ALL; 'prophylaxis' may be accomplished with high dose Ara-C +/- intrathecal Ara-C**

AML Treatment: Consolidation

Following induction into Complete Remission

- 3-4 cycles of high dose cytosine arabinoside (HiDAC) administered approximately every 5-6 weeks

OR

- Bone marrow (peripheral blood stem cell) transplant

  (Depends on degree of risk)

Common side effects

More than 10 in every 100 people have one or more of the side effects listed below.

- Fatigue (tiredness) during and after treatment – most people find their energy levels are back to normal after 6 months to a year
- Soreness at the injection site (if you are having injections under the skin)
- Women may stop having periods (amenorrhoea) but this may only be temporary

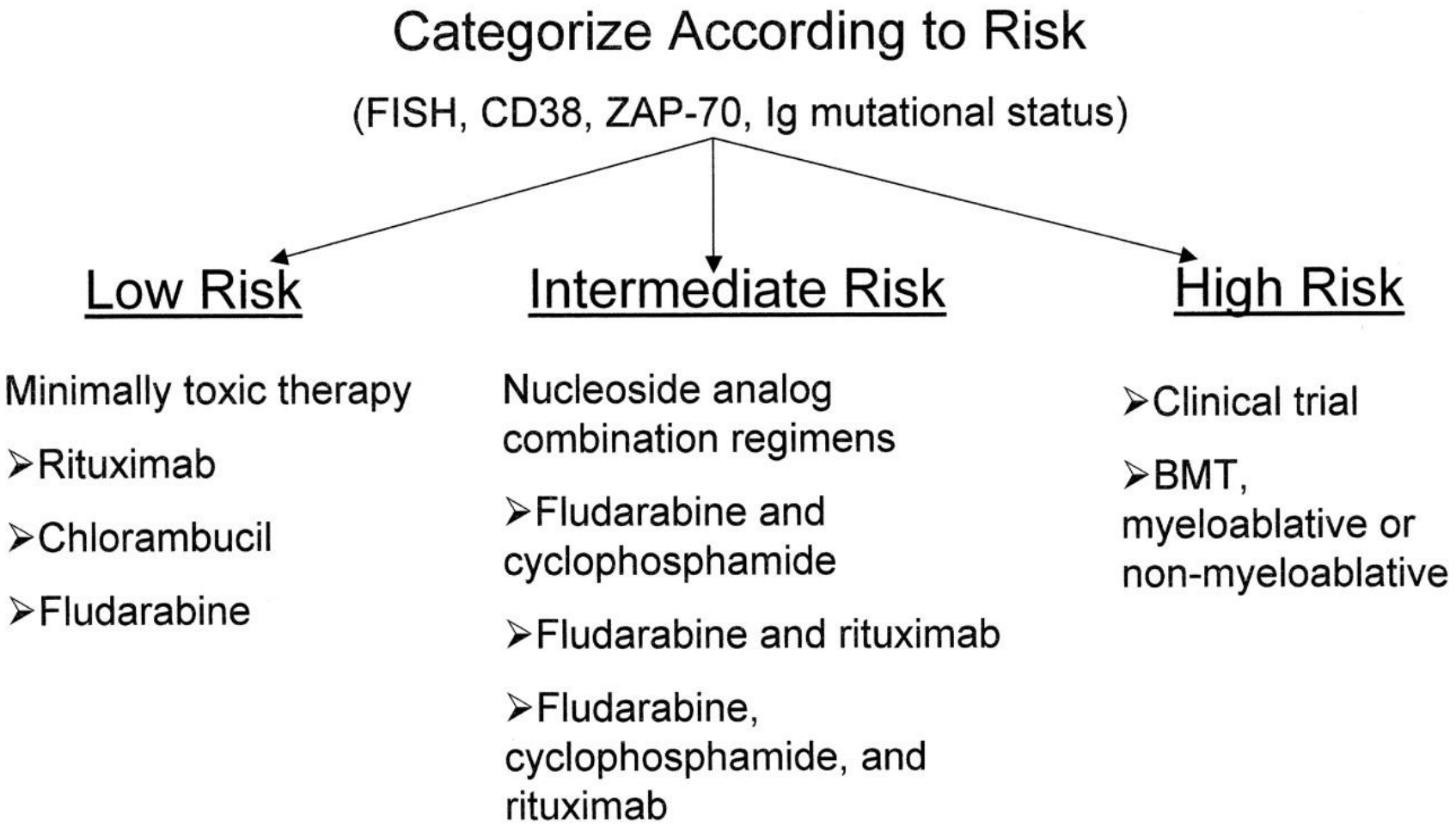
Occasional side effects

- Dizziness However

CLL – treatment

- **Watch and wait**
- **Monotherapy**
  - glucocorticoids
  - alkylating agents (Chlorambucil, Cyclophosphamide)
  - purine analogues (Fludarabine, Cladribine, Pentostatin)
- **Combination chemotherapy**
  - Chlorambucil/ Cyclophosphamide + Prednisone
  - Fludarabine + Cyclophosphamide +/- Mitoxantrone
  - CVP, CHOP
- **Monoclonal antibodies (monotherapy and in combination)**
  - Alemtuzumab (anti-CD52)
  - Rituximab (anti-CD20)

Treatment of CLL



Rituximab as part of first-line therapy for CLL: Rationale

- Rituximab monotherapy is moderately active in CLL
  - Activity is dose dependent (between 500–2250 mg/m^2)[1]
- Rituximab acts synergistically with other cytotoxic agents *in vitro*
  - Increases fludarabine activity in NHL cell lines
  - Increases activity of bendamustine, mitoxantrone and other chemotherapeutic agents in CLL cells

CLL

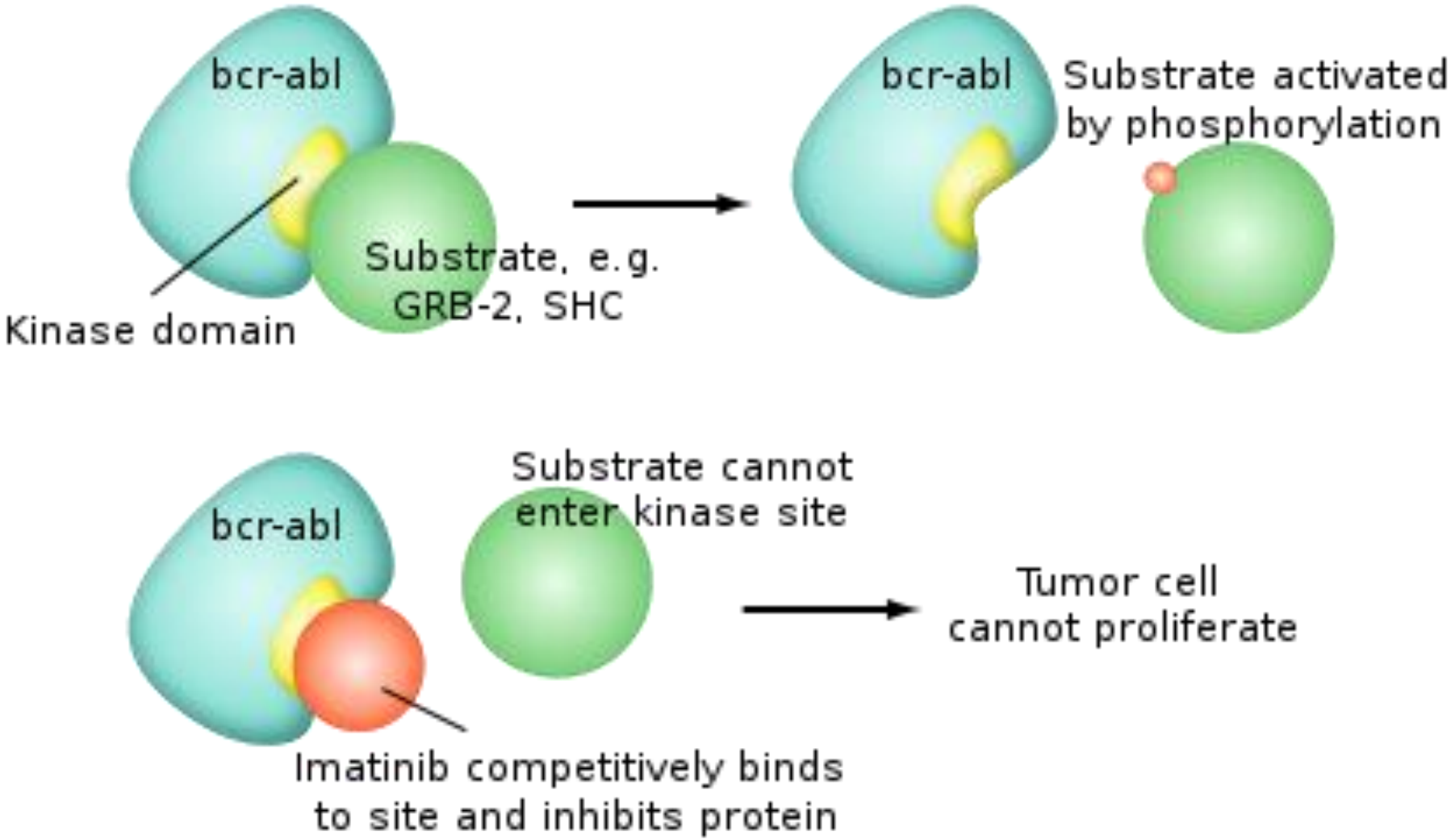
Determining when to start treatment and by what means is often difficult; studies have shown there is no survival advantage to treating the disease too early.

Imatinib

- **Philadelphia chromosome** or **Philadelphia translocation** is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).

- **This translocation results in the Bcr-Abl fusion protein, the causative agent in CML, and is present in up to 95% of patients with this disease.**

- **Imatinib is an inhibitor of the tyrosine kinase domain of the Bcr-Abl oncoprotein and prevents the phosphorylation of the kinase substrate by ATP.**



Gleevec is one of the most effective modern medications for cancer treatment,.

Myeloid Growth Factors

- -**Granulocyte colony-stimulating factor (G-CSF)** plays a central role in neutrophil formation.
- -Usually levels are low but may be increased during infections or inflammatory states.
- -Mutation in the G-CSF receptor will cause severe congenital neutropenia.
- -**Filgrastim** -> recombinant form of G-CSF produced in E coli used in the US.
- -**Lenograstim** -> G-CSF used outside the United States.

Sargramostim (GM-CSF)

- -**Granulocyte-Macrophage** colony stimulating factor (GM-CSF).
- -Increases production of neutrophils as well as macrophages.
- -Increases antigen presentation by macrophages.
- -**Deficiency of GM-CSF will not cause cytopenias but human **pulmonary alveolar proteinosis** (since macrophages do not clear the excess surfactant in the alveoli).

Myeloid Growth Factors

- **-FDA approved indications for use of filgrastim:**
- 1-Severe chronic neutropenia (congenital, cyclical, idiopathic).
- 2-Mobilize peripheral blood stem cells for transplantation.
- 3-Accelerate neutrophil recovery in neutropenic patients receiving chemotherapy (either hematologic or oncologic malignancies).

Filgrastim Side Effect

- 40 year old man serving as a stem cell donor **receiving granulocyte colony stimulating factor (G-CSF)** develops worsening **left upper quadrant pain** which progresses to **rigid abdomen and hypotension with falling hematocrit** -> what happened? Splenic rupture.

- -Filgrastim is known to cause **splenomegaly** which may lead to **splenic rupture.**

- -It can also cause **bone pain (up to 30% of patients).**

Febrile Neutropenia

- -Febrile neutropenia is associated with **significant mortality** -> patient needs broad spectrum antibiotics **immediately**.
- -Two randomized trials have demonstrated that **prophylactic use of G-CSF reduced the time of neutropenia by half, as well as, neutropenic fever**.
- -Typically would need to use G-CSF for 7 days (once each day) after each round of chemotherapy.

FDA approved indications for use of GM-CSF

- -Improve neutrophil production in patients with delayed engraftment after transplantation.
- -Mobilize autologous peripheral blood stem cells for collection.
- -Promote neutrophil recovery after autologous or allogeneic stem cell transplant.
- -Reduce risk of death due to infection in patients > 55 years old undergoing induction chemotherapy for AML.