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- vincristin*e*-----> 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.**

- **The mechanism is unclear, may related to decrease glucose transport and decrease the available energy, or may related to the inhibition of protein synthesis and retard mitotic division in the cells.**

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**

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

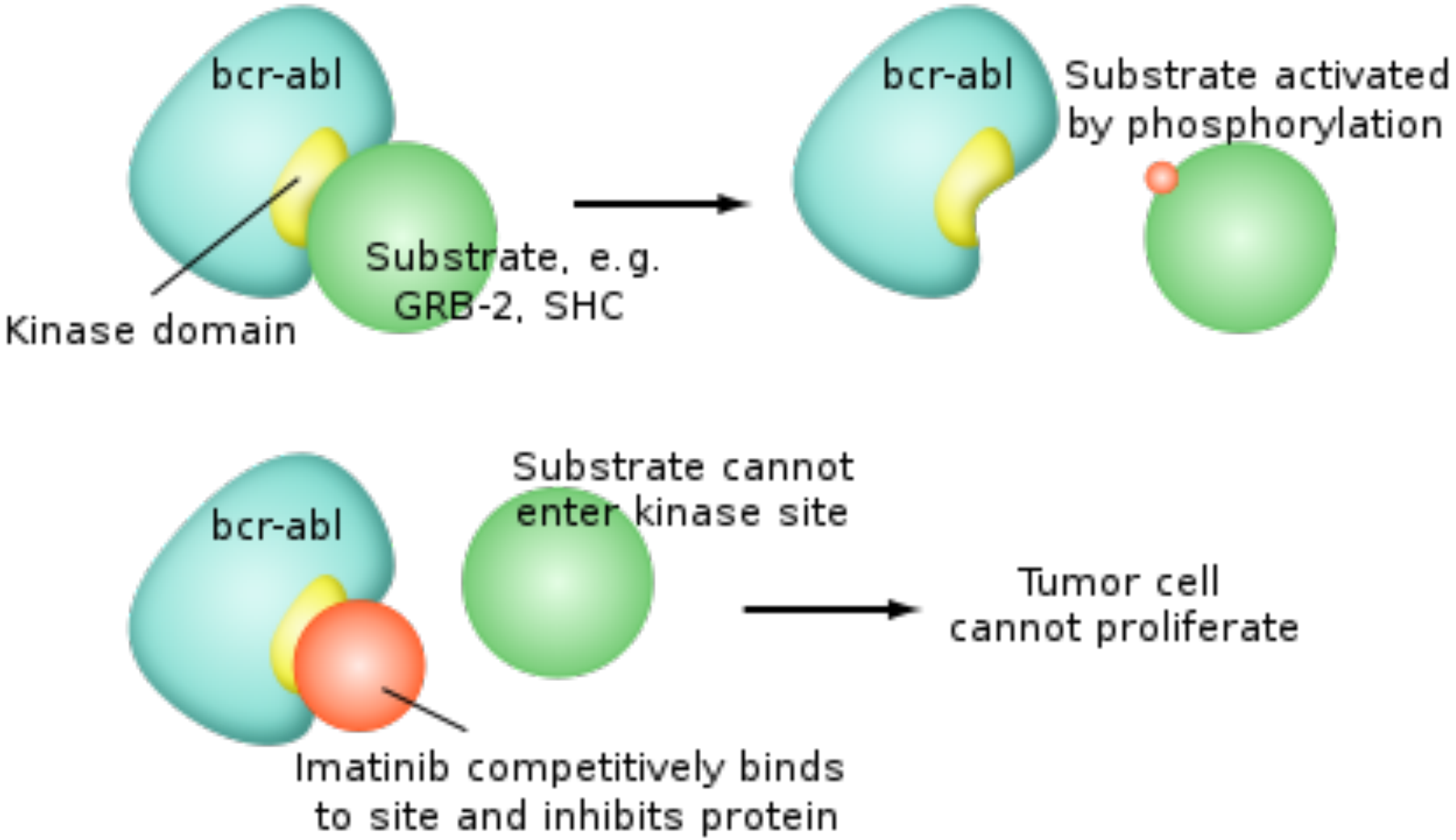
Determining when to start treatment and by what means is often difficult; studies have shown there is no survival advantage to treating the disease too early.

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,.

Hodgkin's D e

- Histologically & clinically a distinct malignant disease
- Predominantly, B-cell disease
- Course of the disease is variable, but the prognosis has improved with modern treatment

Treatment

- Stage IA , Stage IIA with 3 or < 3 areas involved: ***Radiotherapy***

- Stage IB, Stage II A with > 3 areas , Stage IIB: ***Chemotherapy*** every 3-4 weeks, 6-8 cycles; either alone, or in combination with *radiotherapy*

- *Stage III & IV* : ***Chemotherapy*** + ***Radiotherapy*** (for bulky disease or palliation of symptoms)

Chemotherapy

- **ABVD**:
  *A*driamycin,
  *B*leomycin,
  *V*inblastine,
  *D*acarbazine

- Higher dose for relapse or younger pts with poor prognostic features

Prognosis

- Overall 10 yr survival – 80%

- In long term survivors there is a risk of
  - secondary malignancy: (leukemia , NHL), Solid tumors- Lung, breast
  - Infections
  - Cardiac, pulmonary, endocrinal abnormalities

Non Hodgkin's lymphoma

- Incidence is increasing
- NHL>HD
- Median age of presentation is *65-70 yrs*
- *M>F*
- More often clinically disseminated at diagnosis
- B-cell-70% ; T-cell-30%

NHL Lymphoma Biology

- Aggressive NHL
  - short natural history (patients die within months if untreated)
  - disease of rapid cellular proliferation
  - Potentially curable with chemotherapy
- Indolent NHL
  - long natural history (patients can live for many years untreated)
  - disease of slow cellular accumulation
  - Generally incurable with chemotherapy

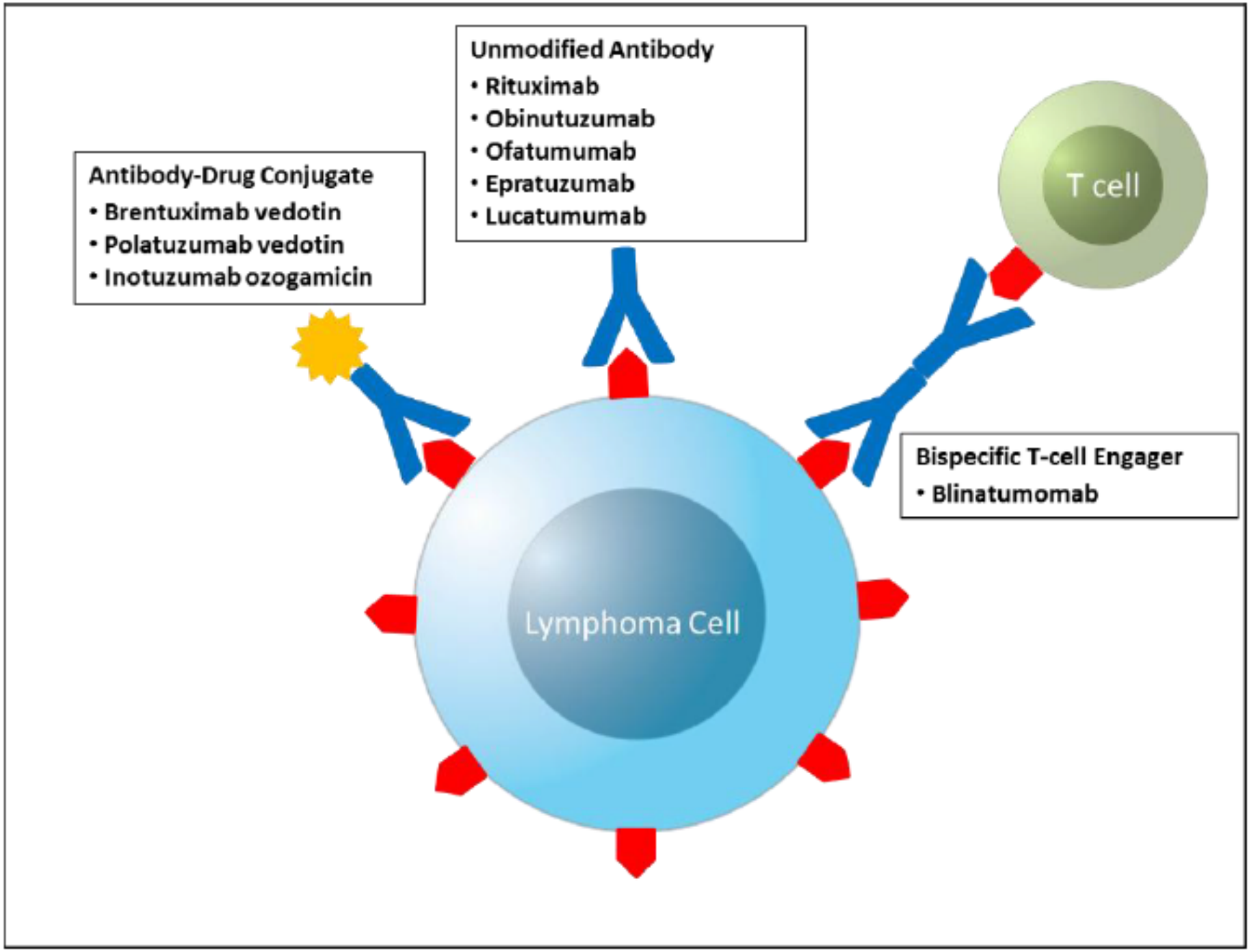
NHL: Approach to the Patient

- Approach dictated mainly by histology
  - reliable hematopathology crucial
- Aggressive NHL
  - Cure is often the goal
- Indolent NHL
  - Cure is rarely the goal
  - Control is the goal

Aggressive (high / intermediate grade):

- *Chemotherapy*: mainstay
  CHOP -every 3 weeks,
  at least 6 cycles
  D*C*yclophosphamide,
  D*O*xorubicin *H*ydrochloride,
  *V*incristine,
  *P*rednisolonone

The results of the treatment of patients with NHL have been improved impressively by the use of antibodies directed against the lymphoma cells

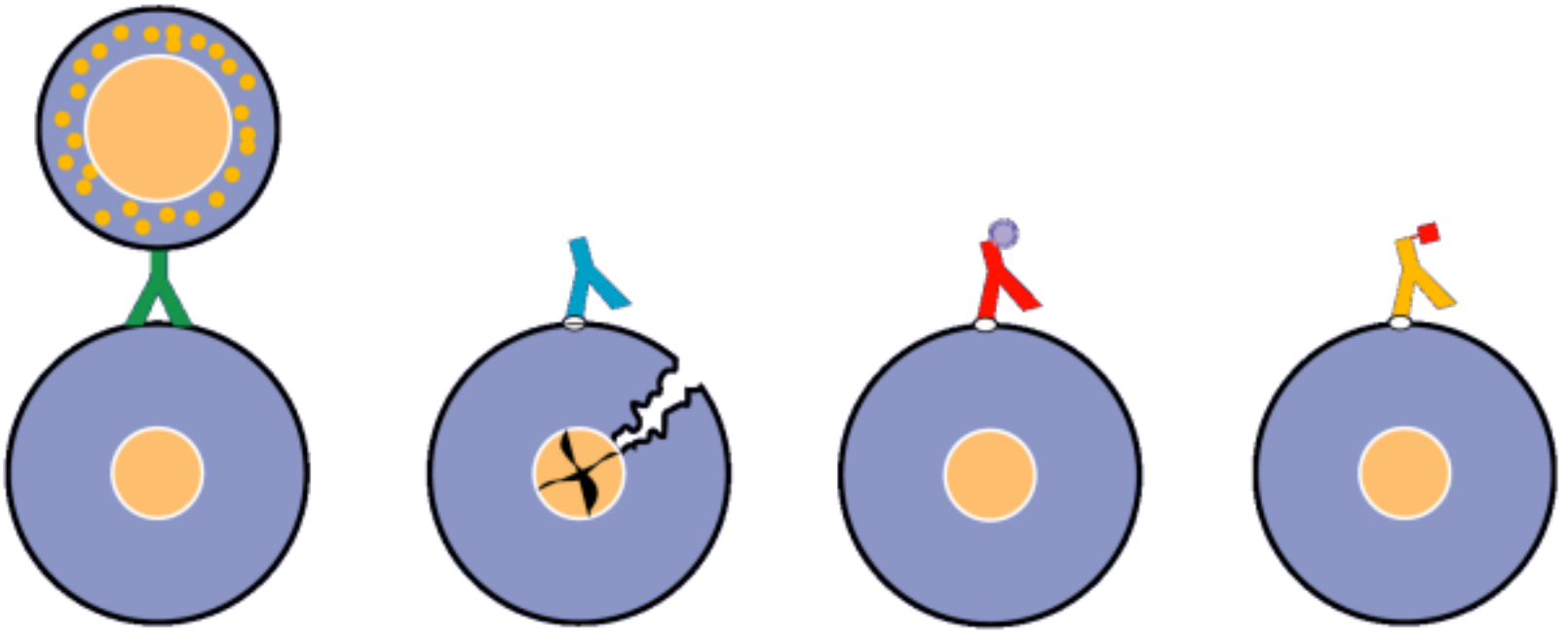

Unmodified Antibody
• Rituximab
• Obinutuzumab
• Ofatumumab
• Epratuzumab
• Lucatumumab
Antibody-Drug Conjugate
• Brentuximab vedotin
• Polatuzumab vedotin
• Inotuzumab ozogamicin
T cell
Bispecific T-cell Engager
• Blinatumomab
Lymphoma Cell

non-Hodgkin's lymphoma

Why treatment with antibodies?

- With present chemotherapy no or insufficient cure
- Treatment of minimal residual disease after chemotherapy might improve prognosis
- Antibodies are more specific than cytostatic drugs
- Antibodies are less toxic
- Antibodies have a different mechanism of action

MoAbs citotoxic mechanisms



Effector cells/ Complement

Apoptosis

Radionuclide

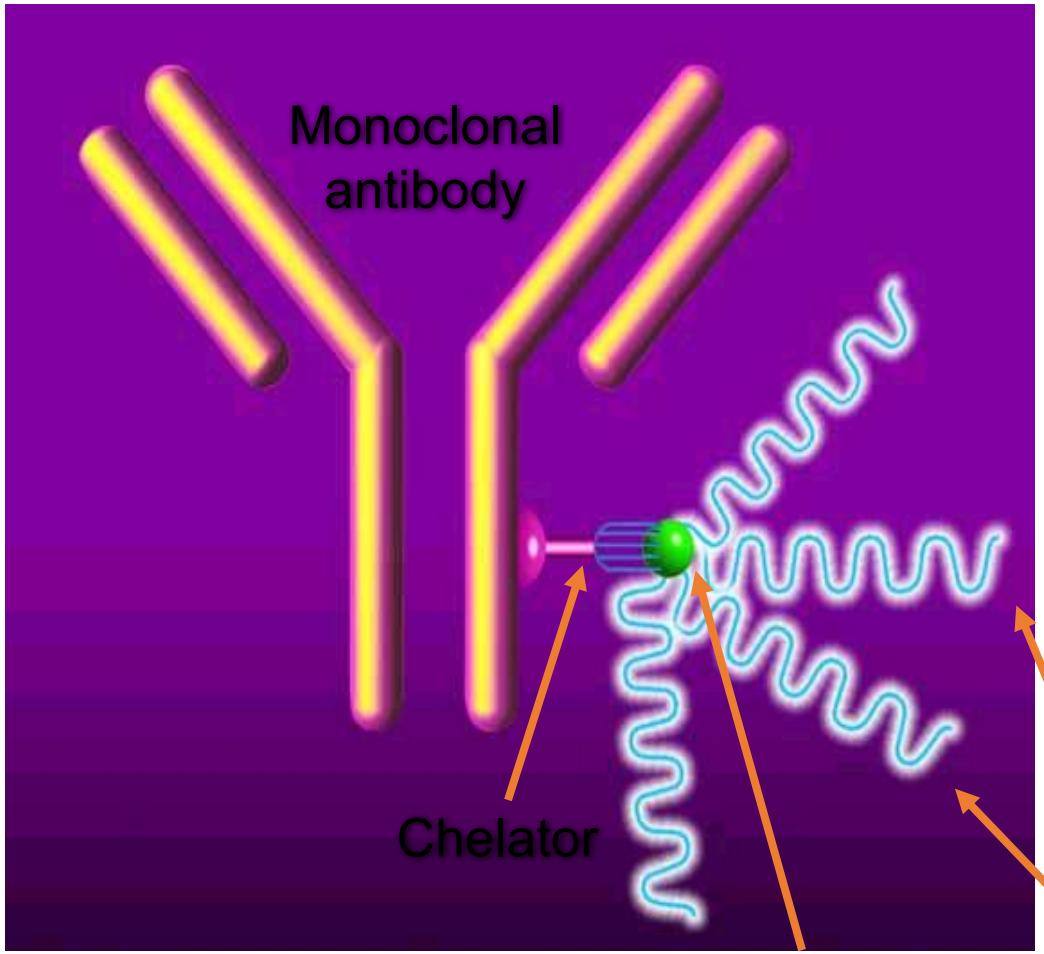
Toxin/Antibiotic

Radiolabeled anti-CD20 antibodies in the treatment of relapsed folicular lymphoma

- Response % higher than with "naked" anti-CD20
- Response duration ~ similar to "naked" anti-CD20
- High dose : response (5-10 years)

  cure ?
- Also effective in patients resistant to "naked" anti-CD20

Radioimmunotherapy with Y-90 Zevalin



- Ibritumomab
  - Murine monoclonal antibody parent of Rituximab
- Tiuxetan
  - Conjugated to antibody, forming strong urea-type bond
  - Stable retention of Y-90

Anti-CD20 (Rituximab= Mabthera®) side effects

- Mild and transient, mainly during first infusion
- Fever, chills (prevention)
- Temporary drop in blood pressure, dyspnea
- Rare: antibodies against rituximab

Myeloid growth factor

- Play a central role in neutrophil formation.
- Increase during infection and inflammatory states
- Mutation in G-CSF receptor results in congenital neutropenia
- Filgrastin is a recombinant drug

Saragramostin GM-CSF

- Granulocyte- Macrophage colony Stimulated Factor
- Increase production of neutrophil and macrophages
- Increase antigen presentation by macrophages

Febrile Neutropenia

- Associated with significant mortality
  - Needs broad spectrum antibiotic immediately

  Trials showed that prophylactic use of G=CSF reduce time of neutropenia y half as well as neutropenia fever

  7 days of one injection after each round of chemo

Filgrastin side effect

- Splenomegaly and may be spleen rapture
- Bone pain 30%

GM-CSF

- Improve neutrophil production in patient with delayed engraftment after transplantation

- Mobilize autologous peripheral blood stem cells for collection
- Promote neutrphils recovery after autologous or allogenic tem cell transplantation

- Reduce risk of death due to infection in patients over 55 years old undergoing induction chemotherapy.