بسم الله توكلت على الله

* Lec 5 *

• بهاي المحاضرة (5) في جزئين جزء تكملة ال Chemo وجزء بداية ال Antivirals.
بس هون رح تلاقوا جزء ال Chemo من المحاضرة + محاضرة 6 يلي هي آخر جزء ال Chemo عشان تتابع المعلومات
1/2 Lec 5 + Lec 6 (Chemo Part)

Acute Leukemia Treatment and Pharmacology Overview

A) Induction
four to six weeks:
- ***Vincristine***
- ***Glucocorticoid (prednisone, prednisolone or dexamethasone)***
- ***L-asparaginase***

For adults, doxorubicin-related drugs such as daunorubicin are added; for infants under one year, different drugs are used due to varying responses. (مش مهم الفكرة تفهم كيف جسم الكبير يختلف كليًا عن جسم الطفل)

*Key drug discussed: **1) asparaginase** – reduces asparagine levels in the blood, which affects normal cells and cancer cells differently.*
Pharmacodynamics of asparaginase: it depletes asparagine, leading to impaired protein synthesis, especially affecting insulin, albumin, and coagulation factors.
Consequences of asparaginase use include: "side effects"
1) Hypoinsulinemia → hyperglycemia
Hyperglycemia requires close monitoring and potential endocrine intervention.

2) Edema and ascites due to water retention (hypoalbuminemia)
Diuretics are used to manage it.

3) Coagulopathy due to impaired synthesis of clotting proteins (protein C, antithrombin III), leading to bleeding or thrombosis risks. (Remember Lec 1)
Management of coagulation disorders includes balancing treatments to reduce bleeding or thrombosis, e.g., using vitamin K or warfarin.
During L-asparaginase therapy, monitor blood coagulation closely.
Use it carefully in patients with bleeding or liver disorders, as it may cause bleeding, bruising, or hematomas, especially with intramuscular injections.

L-Asparaginase toxicities:
- *Mild effects: nausea, vomiting, loss of appetite, abdominal cramps, fatigue, weight loss.* (الدكتور ماركز عليهم)
- *In ALL, rapid cell destruction releases DNA, phosphate, potassium, and uric acid, leading to Tumor Lysis Syndrome (TLS) → characterized by high K⁺, phosphate, uric acid; low calcium; decreased urine output; and possible kidney failure.*

Tumor Lysis Syndrome and Chemotherapy Agents:

Tumor Lysis Syndrome (TLS) is highlighted as a critical acute complication, especially after induction therapy in leukemia.
TLS results from rapid death of leukemia cells releasing large amounts of intracellular contents:
Potassium (hyperkalemia)
Phosphate (hyperphosphatemia)
Uric acid (hyperuricemia)
Calcium (hypocalcemia due to phosphate binding calcium)

***2) Vincristine**: antimitotic agent causing nerve irritation and constipation; it inhibits mitotic spindle polymerization and halts cell division at the M phase.*
Vincristine is preferred over other agents because it has relatively low bone marrow toxicity. (it's cell-cycle dependent, it is considered BM-sparing drug)

***Taxoids** (paclitaxel, docetaxel) : inhibit depolarization, more neurotoxic than vincristine.*

***3) Glucocorticoids** (e.g., dexamethasone, prednisone):* (* Steroids *)
Have broad systemic effects: increase blood pressure, blood sugar, cause muscle weakness, osteoporosis, and immune suppression.
They alter gene expression extensively, affecting up to thousands of genes. (one-third)
Important in leukemia for immune suppression and inducing apoptosis in lymphocytes.
Their cytotoxic effect helps kill leukemia cells but also suppresses normal immune function.

After induction, some **resistant leukemic cells may remain** (~5% or less), necessitating **B) consolidation** therapy with higher or different drug doses to eliminate residual disease.
Increasing dose intensity or switching mechanisms of action (e.g., from asparaginase to antimetabolites) helps overcome resistance, this is called:

C) Maintenance therapy involves prolonged use of drugs like weekly methotrexate and daily 6-mercaptopurine to suppress DNA synthesis and maintain remission.
Maintenance lasts 2-3 years, longer in boys due to immune differences.
Compliance is critical; skipped doses due to side effects or parental fear can cause relapse.

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6-MP and methotrexate cause bone marrow suppression and febrile neutropenia by killing normal cells,
while vincristine, asparaginase, and prednisolone only stop bone marrow cell division without major cell death.

D) Prophylaxis and management of infections are vital.
CNS protection in leukemia:

- Children: receive intrathecal chemotherapy (methotrexate, cytarabine, steroids) injected into the cerebrospinal fluid.
- Adults: get high-dose systemic chemotherapy (methotrexate, cytarabine, L-asparaginase) to reach the brain through the blood.
- Purpose: destroy cancer cells that escape to the brain.
- If this fails → bone marrow transplantation is used, more often in AML cases.

Lec 6:

Acute Myeloid Leukemia

AML vs. ALL:

- AML is more aggressive and treated differently from ALL.
- Reason: AML cells can synthesize asparagine, so Asparaginase (effective in ALL) doesn't work.
- Therefore, AML needs a stronger regimen — the "3+7 protocol":

AML – (1) **Induction Therapy** (3+7 Regimen)

- Goal: Induce remission using cytosine arabinoside (Ara-C) ⊕ daunorubicin ± thioguanine.
- Two cycles achieve 70–90% remission; chemotherapy alone cures 30–50%.
- Timed-sequential induction (repeating Ara-C cycles 2–3 times) improves results — 42% cure rate vs. 27% with a single round.
- Post-induction therapy lasts 4–12 months.
- CNS involvement is rare but prevented with high-dose Ara-C, given IV or intrathecally.

a. **Daunorubicin** (3 days) → non-cell-cycle specific
Anthracycline that intercalates into DNA and inhibits topoisomerase II, causing DNA breaks; more effective in AML.

b. **Cytarabine arabinosides** (7 days) → antimetabolite
Antimetabolite that mimics deoxycytidine; acts in the S phase, blocks DNA synthesis, and induces apoptosis.

c. **Thioguanine** (optional): Purine analog that blocks purine synthesis and DNA replication, preventing cell division.

- The drugs aren't given together because both suppress bone marrow.

AML – **2) Consolidation** Therapy

- After induction and complete remission (CR), two main options:

1. 3–4 cycles of high-dose cytosine arabinoside (HiDAC) every 5–6 weeks
2. Bone marrow / peripheral blood stem cell transplant (depending on risk)

- Reason: AML has high relapse rates and a maximal cure rate ~42%.
- Consolidation should not rely solely on induction drugs to avoid resistance or reduced efficacy.

Common Side Effects of AML/ALL Chemotherapy

Frequent (>10% of patients):

- *Fatigue (from anemia, bone marrow suppression, low energy) – usually improves within 6–12 months*
- *Injection site soreness*
- *Temporary amenorrhea in women*

Occasional / drug-specific:

- *Ara-C: dizziness (especially at high doses or intrathecal)*
- *Vincristine: constipation*
- *Doxorubicin / Daunorubicin: cardiotoxicity*

CLL (Chronic Lymphocytic Leukemia):

- *Often slow-growing, taking 10–15 years before symptoms appear.*
- *A "watch and wait" approach is commonly used.*
- *Early treatment does not improve survival, so deciding when and how to treat can be challenging.*

(Chronic Myelogenous Leukemia):

Imatinib and CML

- *CML is driven by the Philadelphia chromosome translocation, which creates the BCR-ABL fusion protein, a constitutively active tyrosine kinase that promotes cell proliferation, survival, and tumor growth.*
- *Pharmacogenetics is important: cancer drugs are often designed based on genetic abnormalities of the cancer, and sometimes the patient's genetics are considered.*
- ***Imatinib (Gleevec):***
- *Mechanism: binds competitively to the ATP-binding site of BCR-ABL → blocks its kinase activity → prevents phosphorylation of downstream proteins (e.g., SHC, GRB2) → inhibits multiple signaling pathways driving tumor growth.*
- *Effect: stops CML progression, transforming it into a manageable chronic disease.*
- *Administration: must be taken daily for continuous kinase inhibition and to prevent relapse.*
- *Impact:*
- *Highly effective, used for over two decades.*
- *Enables patients to live normal lives with long-term therapy.*

Imatinib Mechanism of Action:

- *Binds competitively to the ATP site of BCR-ABL tyrosine kinase, blocking its phosphorylation activity.*
- *Inhibition of BCR-ABL deactivates all downstream oncogenic pathways (GRB2/RAS/MAPK, JAK/STAT, BCL-2).*
- *Effects: stops abnormal cell proliferation, restores apoptosis, and allows leukemic cells to die.*
- *Key point: targeting the single driver mutation shuts down all malignant signaling in CML.*

CML Resistance to Imatinib:

- *BCR-ABL mutations can cause resistance, with T315I being the most problematic (threonine → isoleucine at position 315), which prevents imatinib binding.*
- *Mutations may exist before treatment or develop during therapy, leading to loss of response.*
- *Regular molecular monitoring is essential to guide therapy.*
- *Patients with non-T315I mutations can often be treated with second-generation TKIs like Nilotinib or Dasatinib, chosen based on side-effect profile.*

Choosing Tyrosine Kinase Inhibitors (TKIs) in CML Based on Mutations and Side Effects

1. ***Nilotinib***
   - *Main adverse effect: cardiovascular events – incidence ~4% for 300 mg BID, ~10% for 400 mg BID, versus 2% with imatinib.*
   - *Risk increases over time → more patients develop cardiovascular disease.*
   - *Nilotinib can also cause progressive peripheral arterial occlusive disease and clotting.*
   - *Conclusion: Generally avoided as first-line therapy due to serious side effects.*

2. ***Dasatinib***

   - *Main side effects: pleural effusion and peripheral edema.*
   - *Both Dasatinib and Nilotinib can be cardiotoxic, so caution is needed in patients with preexisting heart disease.*

3. ***Ponatinib***

   - *Specifically effective for patients with the T315I mutation, which confers resistance to first- and second-generation TKIs.*
   - *Mechanism: binds BCR-ABL ATP-binding pocket even in the closed conformation → retains activity despite structural changes.*
   - *Superior potency compared to earlier TKIs.*
   - *Major side effects: hepatotoxicity, cardiotoxicity, arterial and venous occlusions, thrombosis.*
   - *Used only when necessary due to serious risks.*

4. *Mutation-Guided Therapy Approach*

   - *Non–T315I mutations: choose Dasatinib or Nilotinib, weighing side effects.*
   - *Dasatinib → pleural effusion, peripheral edema.*
   - *Nilotinib → arterial blockages, clots, cardiotoxicity.*
   - *T315I mutation: Ponatinib is the drug of choice despite its high-risk profile.*

Key Principle:

TKI selection depends on the BCR-ABL mutation profile and patient's comorbidities, balancing efficacy against serious adverse effects.