HLS Final Summary

Anti-Platelets ➔ <u>Prophylactically</u> used in cases of MI, unstable angina, TIA.

1. **Aspirin ➔ Blocks Cyclooxygenase ➔ inhibits conversion of Arachidonic Acid (AA) to Thromboxane A2.**
   - **Uses:** Baby aspirin (Antiplatelet), Analgesic, Antipyretic, Antiinflammatory.
   - **Side effects: hemorrhagic stroke, GIT bleeding**.
2. **Clopidogrel ➔ Blocks P2Y12 (ADP) Receptor on platelets ➔ Platelet inhibition (GPIIb/IIIa receptor will not be active/present to bind with fibrinogen and eventually platelets will not aggregate)**
   - He belongs to a family of drugs which have **Clop** or **grel** suffix in their names. Let's try it and see (:
     a. **Clop**ido**grel**: Metabolized (activated by **CYP2C19**). Make sure patient is not a slow metabolizer before giving it, as this drug needs activation (found in the form of a prodrug). Rarely ➔ **bleeding**
        - A loading dose of Clopidogrel is given 6 hours before **coronary stent to prevent thrombosis**
     b. Prasu**grel**, more easily activated in the body than Clopidogrel, it's given when patient doesn't respond to Clopidogrel (Slow metabolizer).
        - **SE: Hypertension, hypotension, afibrillation, bradycardia**
     c. Tica**grel**or, not a prodrug (doesn't need activation in the body as it's already activated). SE: **Dyspnea**
     d. Ti**clop**idine, not used anymore (➔ Thrombotic Thrombocytopenic Purpura "**TTP**"), **leukopenia**
     e. Can**grel**or: Given **IV** in an active form. Useful in Emergencies. SE: **Bleeding** ↑ ↑
        → Can be used in Sudden Cases (Putting a stent in 2 hrs)
3. **Abciximab ➔ Blocks GPIIb/IIIa receptors on platelets ➔ no platelet aggregation.**
   - He belongs to a family of drugs which have **<u>fib</u>** suffix in their names. With an exception to one: abciximab
     a. Given intravenous (IV) ➔ Risk of bleeding is higher. All Inhibit bridging of platelet by fibrinogen
     b. Abciximab: humanized monoclonal antibody directed against GPIIb/IIIa
     c. Epti**fib**atide & Tiro**fib**an: inhibit ligand binding to IIb/IIIa receptor by their occupancy of the receptor.
4. **Dipyridamole/ Cilostazol ➔ blocks PDE3 Enzyme ➔ levels of cAMP will increase ➔ platelets are inhibited.**
   - **inhibits phosphodiesterase→ ↑ cAMP→ potentiates effects of prostacyclin→ platelet inhibition.**
   - **dipyridamole is also a coronary vasodilator (any vasodilator in the body may ➔ Headache)**
   - **Indications:**
     a. **with aspirin for prophylaxis in angina.**
     b. **with warfarin to inhibit embolization from prosthetic heart valves.**

Anticoagulants ➔ <u>Treat</u> cases of thrombosis in Afib, DVT/PE, Post-surgery.

1. **Unfractionated Heparin**: inhibits the activated factors (2,9,10,11,12)
   - Prevents further thrombus growth, allowing the body's own thrombolytic system to dissolve clot.
   - **Activates antithrombin III (AT III) ➔ Dual inhibition: inhibits <u>mainly</u> both factor IIa & factor Xa**
     a. Other factors that are inhibited as well: factors IXa, XIa & XIIa
   - **Route of administration: IV/SC given for DVT/PE for 5-7 days**
   - **Response to drug is unpredictable & has a narrow therapeutic index**
     ⇨ **That's why UFH must be monitored using aPTT**
   - **Side effects: <u>Allergy (animal source)</u>, <u>Alopecia</u>, <u>bleeding</u>, osteoporosis, hyperkalemia, Heparin Induced Thrombocytopenia (HIT) ➔ check platelet levels before and at days 3 & 5.**
   - **Antidote: protamine sulphate**
2. **LMWH:** Enoxa**parin**, dalte**parin**, tenza**parin** & arde**parin**
   - **Activates antithrombin III (AT III) ➔ inhibits <u>mainly</u> factor Xa**
   - **Excretion: Kidneys**
   - No need to monitor aPTT unless patient is obese/pregnant or has renal disease.
   - **SE: bruising/hematoma at injection site, Bleeding, HIT**
   - **Antidote: protamine sulphate**

3. **Warfarin (derived from Coumarin)**
   - It Blocks carboxylation of factors 1972 (10,9,7,2) "procoagulants" as well as the proteins C and S "anticoagulants"
     a. **By inhibiting Vitamin K epoxide reductase (which normally reduces Vitamin K)**
   - **Full therapeutic effect is not achieved until existing factor II is cleared (t1/2: 60 hours)**
     a. **That's why patient is bridged on heparin for 4-5 days until INR becomes between 2-3.**
   - **> 99% is bound to plasma albumin → small volume of distribution, long half life. 100% bioavailability.**
   - **Drug interactions with warfarin are either:**
     a. **Pharmacokinetics (CYP2C9-related):** examples**:** ***Azapropazone*** which displaces warfarin from plasma protein & inhibits its metabolism (warfarin levels in plasma ↑). ***Allopurinol*** & ***Amiodarone***, too inhibit warfarin's metabolism increasing the risk of bleeding.
        - **CYP2C9 enzyme induction ➔ warfarin levels will go down (as more is metabolized)**
        - **CYP2C9 enzyme inhibition ➔ warfarin levels will go up (as less is metabolized)**
     b. **Pharmacodynamics (Vitamin K-related)**
   - **Side effects: A**bnormal bone formation and hemorrhage in ***fetus***, **B**leeding, **C**holesterol microembolisation (purple toe syndrome) , **V**enous thrombosis (*reduced protein C synthesis*)
   - **Absolute contraindicated in pregnancy**
   - The best oral agent to use for anticoagulation in a **mechanical prosthetic heart valve.**
   - **Antidote: Vitamin K**

4. **Dabigatran: Direct thrombin (factor IIa) inhibitor (one of the Direct Oral Anticoagulants "DOACs")**
   - Given orally
   - Response is almost the same in all people (no variation in response as in warfarin) ➔ monitoring isn't required unless **bleeding** occurs.
   - Side effects: **GI upset (most common), Dyspepsia, Bleeding, Esophagitis**
   - The only type of hemorrhage that's more in Dabigatran than warfarin is (GI hemorrhage)x
     a. The reason is thought to be related to **tartaric acid** which reduces gastric pH (make it more acidic)
        - To avoid these complications ➔ give PPI or H2 blocker ➔ Increase gastric pH (make it less acidic)
   - Drug interactions
     a. **P-Gp (p-glycoprotein) inducers** ➔ Less dabigatran will enter the blood ➔ **thrombosis** may result.
     b. **Amiodarone, P-Gp inhibitors** ➔ more Dabigatran will enter the blood ➔ **bleeding** may occur
   - Contraindications:
     a. Active pathological **bleeding**
     b. Anticoagulation in a patient with **mechanical prosthetic heart valves** ➔ more likely **bleeding** & **thrombosis**
   - **Antidote: Idarucizumab**

5. **Rivaroxaban, Apixaban: Factor Xa inhibitor (Direct Oral Anticoagulants "DOACs")**
   - Given orally
   - CYP3A4 is responsible for its metabolism.
   - **CYP3A4/P-glycoprotein inhibitors ➔ High levels of rivaroxaban ➔ bleeding**
   - Warning: Patients undergoing **spinal anesthesia or puncture** are at ➔ Higher risk of **hematoma** & **paralysis**
   - **Antidote: Andexanet**

6. **Fondaparinux: Factor Xa inhibitor (injectable)**
   - Given subcutaneously
   - **Used in cases of Heparin Induced Thrombocytopenia (HIT)**
   - **Antidote: no known antidote**

7. **Thrombolytics (**streptokinase, urokinase, t-PA, alteplase, tenecteplase, reteplase**) ➔ activate plasminogen ➔ fibrinolysis**
   - Given **IV** ➔ Multiple Pulmonary Emboli, Central deep venous thrombosis (superior vena caval syndrome), Acute MI, stroke (within 6 hrs)
   - Given **Intra-arterially** ➔ Peripheral Vascular Disease.
   - We always want to activate the plasminogen which is only present in the clot (and the not the circulating one)
   - **Streptokinase**, **Anistreplase** & **urokinase** ➔ Higher risk of bleeding as they activate both clot-bound and circulating plasminogen
   - **T-PA**: ***endogenous*** direct plasminogen activator (fibrinolysis is confined to formed thrombi) ➔ less risk of bleeding
   - **Alteplase**: most widely used (recombinant t-PA)
   - **Reteplase**: less fibrin selective than t-PA
   - **Tenecteplase**: most selective to plasminogen found in the clot and has longer half-life.
   - As the clot dissolves, concentration of thrombin ↑ locally→ ↑ platelet aggregation & ↑ formation of new thrombi ➔ Give an antiplatelet or anticoagulant to prevent thrombosis
   - Side effects: **Bleeding, Hypotension, Reperfusion Arrhythmia, Hypersensitivity**

Lecture 5+6: Cancer Treatment

- **Introduction: a common side effect between anti-cancer drugs**
  a. Bone marrow suppression (may need to use a **colony stimulating factor** either GM-CSF or G-CSF)
     - Low WBC = leukopenia
     - Low RBCs = Anemia ➔ give these patient **Erythropoietin** (EPO) to stimulate BM to increase RBC synthesis.
  b. Alopecia (hair loss)
  c. Nausea, Vomiting & Diarrhea

- **Why do we use Combination chemotherapy?**
  a. Synergistic action, to Minimize side effects, To Attack leukemic cells in different phases of mitosis & delay the onset of resistance of the malignant cells.

1. Acute Lymphocytic Leukemia (ALL)

What drugs can we use in ALL?

- **Induction phase (4-6 weeks ➔ to achieve remission)**
  a. **Vincristine: Cell cycle specific (affects M-phase of cell cycle)**
     - **MOA: inhibit tubular polymerization ➔ prevent spindle formation ➔ mitotic arrest in metaphase**
     - **SE: Constipation, Neuropathy (nerve irritation ➔ numbness/tingling in hands/feet.**
  b. **Glucocorticoid:**
     - **MOA: inhibitory** effects on **lymphocyte proliferation** and are used in treating **lymphomas** and **leukemias**.
     - **SE:" HIGGGH HOMIE": HTN, Immunosuppression, Go crazy (mood changes), Glaucoma, Growth retardation, Hyperglycemia, Hair growth (hirsutism), Osteoporosis, Muscle weakness, increased appetite & Edema.**
  c. **L-Asparaginase:**
     - **MOA**: this enzyme **hydrolyzes** serum **asparagine** to nonfunctional aspartic acid and ammonia, depriving tumor cells of asparagine, resulting in **decreased protein synthesis** and **apoptosis** in cancer cells.
       - **Decreased Insulin production ➔ Hyperglycemia**
       - **Decreased albumin ➔ edema or ascites**
       - **Decreased activation of Vitamin K dependent factors (10,9,7,2) & protein C,S & antithrombin III**
         - **Coagulopathy may occur ➔ Thrombosis/bleeding may occur.**
     - **SE: Nausea, Vomiting, Anorexia, Cramps, Malaise, weight loss, Hepatotoxicity (not used in liver diseases), Tumor lysis Syndrome ➔ hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia & low urine output**
- **Consolidation phase**
  a. **Methotrexate + Mercaptopurine**
  b. *High Dose* **Asparaginase** over an extended period
  c. Reinduction treatment (less common)
- **Maintenance phase** (Females: lasts for 2 years, Males: lasts for 3 years)
  a. **Weekly methotrexate + Daily mercaptopurine**
- **CNS Prophylaxis (meningeal Leukemia is frequently)**
  a. Intrathecal ➔ Cytarabine, steroids & methotrexate
  b. Adults ➔ High dose systemic chemotherapy (Cytarabine, L-asparaginase & methotrexate)

2. Acute Myeloid Leukemia (AML)

What drugs can we use in AML?

- **Induction phase** (2 cycles of cytarabine + daunorubicin +/- thioguanine) give remissions in 70-90%
- **"7+3" induction regimen: 7 days of cytarabine & 3 days of Daunorubicin**
    a. **Cytarabine: Cell cycle specific (affects S-phase of cell cycle)**
        - MOA: antimetabolite chemotherapy agent . It kills cancer cells by stopping them from making and repairing DNA that they need to grow and multiply.
        - **SE: Dizziness .**
    b. **Daunorubicin (topoisomerase poisonous)**
        - MOA: cytotoxic anthracycline antibiotic which damages DNA by intercalating between base pairs resulting in uncoiling of the helix, ultimately inhibiting DNA synthesis and DNA-dependent RNA synthesis.
        - **SE: Cardiotoxicity**
    c. **Thioguanine:**
        - **MOA**: A purine analogue which inhibits purine metabolism, thus blocking DNA, RNA and subsequent protein synthesis
- **Consolidation Phase**: Following induction into Complete Remission
    a. **3-4 cycles of high dose cytosine arabinoside (HiDAC) administered approximately every 5-6 weeks**
    b. **OR Bone marrow transplant (because high rate of recurrence).**
- Common side effects:
    a. Fatigue (tiredness) during and after treatment –
    b. Soreness at the injection site (if you are having injections under the skin) .
    c. Temporary amenorrhea

3. Chronic Myeloid Leukemia (CML):

Main point CML has Philadelphia chromosome or Philadelphia translocation; This translocation results in the Bcr-Abl fusion protein ➔ tyrosine kinase overactivation

Options of management:

a. Imatinib ➔ inhibits tyrosine kinase ➔ best to start with as it has less side effects
b. Dasatinib/nilatinib ➔ if patient developed mutations to imatinib ➔ more cardiovascular side effects including thrombosis and pleural effusion. More diarrhea and skin rash
c. Ponatinib ➔ if patient developed T315I