

## Chemotherapy Teaching Points

1. Antimetabolites - These drugs are analogs of vital co-factors in DNA or RNA synthesis. They competitively inhibit DNA or RNA production, or are directly incorporated into the DNA/RNA yielding a defective product. These drugs require that cells are in a phase when they are preparing to divide (S-phase specific).
  - a. Methotrexate – A structural analog to folic acid, a required cofactor for purine and thymidine synthesis. Methotrexate blocks dihydrofolate reductase which converts folic acid to its active form which is necessary for DNA synthesis.
    - i. Methotrexate is active in leukemias, lymphoma, histiocytosis, and osteosarcoma.
    - ii. Common toxicities include myelosuppression and mucositis both of which are preventable with leucovorin rescue
    - iii. Other toxicities include hepatitis, pneumonitis, dermatitis, and arachnoiditis.
    - iv. Methotrexate is contra-indicated if effusions are present because it will tend to concentrate there and be released slowly, increasing patient's overall exposure to the medication.
  - b. Ara-C or Cytarabine- A structural analog to cytosine, this drug is converted to Ara-CTP which is incorporated into newly synthesized DNA strands. The abnormal nucleotide blocks the advancing DNA polymerase, which blocks chain elongation.
    - i. Ara-C is active in most leukemias
    - ii. Side effects include: Myelosuppression, GI – nausea, vomiting, mucositis, pancreatitis, Neurologic – cerebellar toxicity, Ocular – conjunctivitis, Dermatologic – palmar/plantar erythema, Pulmonary – edema
  - c. Mercaptopurine (6-MP) and Thioguanine (6-TG). Analogs of purines, these compounds are incorporated into DNA like Ara-C, but also inhibit de novo purine synthesis.
    - i. Useful in ALL, AML, and histiocytosis.
    - ii. Side effects include myelosuppression and hepatitis. 6-TG can cause hepatic veno-occlusive disease.
  - d. Hydroxyurea: This drug inhibits the conversion of ribonucleotides to deoxyribonucleotides
    - i. Hydroxyurea is useful in chronic myelogenous leukemia, some solid tumors – melanoma, head and neck tumors, and myeloproliferative disorders.
    - ii. Side effects include neutropenia, diarrhea, mucositis, and skin rash

2. Alkylating Agents – These agents bind irreversibly to DNA and RNA. These drugs are not S-phase specific (cells do not need to be in act of dividing at time of exposure), and so can be used in combination with the antimetabolites for synergistic tumor kill. Alkylating agents include:
  - a. Cisplatin/Carboplatin
    - i. Active in multiple solid tumors, especially germ cell tumors, hepatoblastoma, neuroblastoma, Ewings sarcoma
    - ii. Side effects include: severe nausea and vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, and myelosuppression
    - iii. Secondary malignancy and sterility are serious long-term side effects seen as a result of these drugs.
  - b. Cyclophosphamide(Cytoxan)/Ifosfamide
    - i. Useful in a wide variety of malignancies
    - ii. Side effects include:
    - iii. Hemorrhagic cystitis is a toxicity unique to these two drugs, and is preventable with hydration and MESNA,
    - iv. SIADH is another idiosyncratic side effect of these two drugs. Watch urine output and serum sodium closely, and if urine output decreases, use furosemide and not fluid restriction.
    - v. Cardiotoxicity is a rare side effect following use of these drugs.
    - vi. Renal dysfunction, especially Fanconi's syndrome, is associated with Ifosfamide.
    - vii. CNS toxicity can also be seen mainly with Ifosfamide.
  - c. Temozolomide (Temozar): Is an oral alkylating agent.
    - i. Useful in brain tumors
    - ii. Side effects are few including myelosuppression, nausea and vomiting, fatigue, constipation, and transaminase elevations.
  - d. Busulfan: Another oral alkylating agent.
    - i. Wide range of activity
    - ii. Side effects include extreme myelosuppression, and so this drug is useful as a condition agent in bone marrow transplant. It can also cause pneumonitis, hepatic veno-occlusive disease or with BMT dosing, seizures (requires anti-seizure medication when giving BMT doses), and skin hyperpigmentation.
  - e. Melphalan: Designed specifically to be taken up by melanin producing cancers (melanoma).
    - i. Wide range of activity in adults, but used mainly in transplant in children.
    - ii. Side effects include myelosuppression (also useful in BMT), skin rash, pulmonary fibrosis, and secondary leukemia.

### 3. Natural Products

- a. Anthracyclines – such as Doxorubicin, Daunorubicin, and Mitoxantrone, these bind to DNA between base pairs, a process called intercalation. The anthracyclines interfere with DNA uncoiling which is necessary for replication. They also impair the action of Topoisomerase II leading to strand breaks, and can also form free radicals damaging DNA.
  - i. Wide range of activity
  - ii. Side effects include myelosuppression, N/V, cardiotoxicity (is cumulative), radiation recall (causes late skin burn at prior site of XRT), and severe mucositis
  - iii. Highly pigmented, and will see pigment in the urine (red for doxo and daunorubicin, blue for mitoxantrone).
- b. Bleomycin.
  - i. Useful in germ cell tumors and Hodgkin's disease.
  - ii. Pulmonary fibrosis a common side effect. We monitor pulmonary function tests in these patients.
- c. Actinomycin D –
  - i. Active in Wilm's tumor, Ewing's sarcoma, rhabdomyosarcoma
  - ii. Side effects include myelosuppression, N/V, mucositis, diarrhea

### 4. Plant Products:

- a. Vincristine/Vinblastine – disrupts microtubules preventing mitosis
  - i. Wide range of activity
  - ii. Side effects include peripheral neuropathy – jaw pain, constipation, loss of deep tendon reflexes, hand and foot drop, possibly SIADH, myelosuppression (with Vinblastine only)
- b. Etoposide or VP-16 – inhibits Topoisomerase II and therefore prevents DNA uncoiling and recoiling
  - i. Wide range of activity
  - ii. Side effects include myelosuppression, secondary AML, skin rash – possibly Stevens-Johnson syndrome
- c. Camptothecins- Topotecan and Irinotecan: These drugs induce DNA strand breaks by blocking activity of topoisomerase I.
  - i. Topotecan is active against neuroblastoma and rhabdomyosarcoma. Myelosuppression and diarrhea are side effects.
  - ii. Activity of irinotecan is being tested in rhabdomyosarcoma. Diarrhea is a major side effect of this drug.

### 5. Other Agents:

- a. Asparaginase – An enzyme derived from bacteria that deprives leukemia cells of asparagine by blocking the formation of asparagine from aspartic acid.
    - i. Useful in ALL and AML
    - ii. Side effects include hypersensitivity reactions, impaired hepatic protein synthesis with possibly subsequent bleeding or thrombosis, CNS toxicity including confusion or coma, and pancreatitis.
  - b. Corticosteroids- Prednisone, Dexamethasone. These drugs are directly toxic to lymphoid cells. Binding to glucocorticoid receptors leads to apoptosis of these cells.
    - i. Useful in lymphomas, lymphocytic leukemia, and histiocytosis.
    - ii. Numerous side effects, including hypertension, behavior changes, glucose intolerance,
6. Targetted Therapies. Many new drugs are being tested in patients with cancer that are targeted to affect the cancer cell while sparing normal tissue.
- a. Antibody targeting. This approach uses an antibody that is complexed to a toxin, radioactive particle, or that activates the immune system to kill the tumor cell.
    - i. Rituximab: A highly specific mouse/human chimeric antibody. Useful in B-cell lymphomas, lymphoproliferative disorders, and autoimmune disorders (ITP). Thought to achieve tumor kill by activating antibody-dependent cellular toxicity.
    - ii. Myelotarg: Used for relapsed acute myelogenous leukemia. Is an antibody to the cell surface protein CD33 complexed to calicheamycin, an antibiotic that intercalates between DNA strands.
  - b. Imatinib Mesylate or STI-571 (Gleevec). This drug was is a specific inhibitor of the Abl class of protein tyrosine kinases and inhibits the function of the BCR-ABL fusion protein produced by the t(9;22) or Philadelphia Chromosome that is the cause of chronic myeloid leukemia (CML). Gleevec is now the standard of care for treatment of CML and gastrointestinal stromal tumor (GIST) caused by over-expressed of c-kit, a tyrosine kinase related to Abl. Gleevec is also being tested to determine its role in treatment of Philadelphia chromosome positive ALL.

### **Case Studies:**

1. Your patient is receiving Cisplatin and mannitol infusions. You are called because his urine output has diminished. You should:
  - A. Given furosemide.
  - B. Give a 20ml/kg fluid bolus.

C. Check I's and O's prior to making decision.

Answer: C. Patient may have over diuresed with mannitol and may need fluids, or the patient may be retaining fluids and need lasix.

2. Your patient who is being treated for acute lymphoblastic leukemia presents to your clinic with a 1 week history of clumsiness, and actually fell down the stairs. On exam, you notice that he has a “slapping gait”, and decreased patellar reflexes. You should:

- A. Get a myelogram.
- B. Do an LP.
- C. Check if vincristine was given recently.

Answer: C. Foot drop is a common side-effect of vincristine. Doses are only changed for severe symptoms (ie patient can't walk).

3. Your patient is receiving high dose methotrexate. You are trying to keep urine pH > 7. It has dropped to 6 and has been checked twice. What should you do:

- A. Blow it off.
- B. Give Diamox.
- C. Recheck

Answer: B. Diamox can be given to alkalinize the urine. You could also increase the sodium bicarbonate fluid rate if the patient's I's and O's are balanced. Finally, you could give a bolus of sodium bicarbonate at a dose of 1 mEq/kg/ over 1-2 hours.

4. Your patient is receiving cisplatin and his IV fluids are D5 ½ NS with 10 mEq of KCl/L and 150 mg MgSO<sub>4</sub>/L. You are paged because your patient is unresponsive. You arrive, and the patient has stable vitals but is not responsive to pain. His limbs are flaccid, and DTR's are decreased. You should:

- A. Change IV fluids.
- B. Check meds given recently. Is patient on morphine?
- C. Send electrolytes and magnesium stat.
- D. Verify magnesium sulfate in the IV fluids is in milligrams and not milliequivalents.

Answer: All of the above. It is not unheard of to have the wrong amount of magnesium in the IV fluids, such as the bag containing 150 milliequivalents rather than milligrams. Additionally, patients on PCA pumps can become overmedicated on morphine, and can present with acute mental status changes.

5. Your patient is hot to trot. He had received high dose methotrexate, and was experiencing delayed excretion. His MTX level yesterday was 0.9. You are on the telephone, and the nurse hands you a note saying that the patient's methotrexate level is now 0.05, and asks, using hand signals, whether she can discharge the patient. You should:

- A. Ask nurse to wait, and check the level on the computer.
- B. Discharge the patient.

Answer: It is not unusual for mistakes to be made based on the incorrect position of a decimal point. In this case, a seasoned nurse at another institution called the laboratory and then wrote down both on the note to the MD and in the chart that the MTX level was 0.05. In actuality, the level was 0.5. The child went home, and returned with severe mucositis, burns on his hands and feet, and pancytopenia that lasted 1 month.