

18: Supportive Agents – these can be life improving or even life saving

Granulocyte macrophage colony-stimulating factor, GM-CSF (Sargramostim, Leukine)

Uses: For leucopenia to shorten time to white cell depletion recovery during chemotherapy, and to reduce the incidence of severe and life-threatening infections. Also uses within setting of BMT.

Mechanism: Induces partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways which include neutrophils, macrophages and myeloid derived dendritic cells.

Toxicities: Arrhythmia, fainting, eosinophilia, dizziness, hypotension, injection site reactions, pain (including abdominal, back, chest, and joint pain), tachycardia, thrombosis, and transient liver function abnormalities. Drugs which may potentiate the myeloproliferative effects such as lithium and corticosteroids, should be used with caution.

Note(s): Produced by recombinant DNA technology in yeast (*S. cerevisiae*) expression system. GM-CSF is a glycoprotein of 127 amino acids. The recombinant amino acid sequence differs from the natural human GM-CSF by a substitution of leucine at position 23, and the carbohydrate moieties may differ.

Granulocyte colony-stimulating factor, G-CSF (Filgrastim, Neupogen)

Uses: For neutropenia, to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever. A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy, and twice per week during G-CSF therapy to avoid leucocytosis and to monitor the neutrophil count. In phase 3 clinical studies, NEUPOGEN® therapy was discontinued when the ANC was $\geq 10,000/\text{mm}^3$ after the expected chemotherapy-induced nadir.

Mechanism: Regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation. G-CSF is not species specific and has been shown to have minimal direct *in vivo* or *in vitro* effects on the production of hematopoietic cell types other than the neutrophil lineage. Endogenous G-CSF is produced by monocytes, fibroblasts, and endothelial cells.

Toxicities: The most commonly observed adverse effect is mild-to-moderate bone pain after repeated administration and local skin reactions at the site of injection. Other adverse effects include serious allergic reactions (including a rash over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, and sweating), alveolar hemorrhage, acute respiratory distress syndrome (ARDS), hemoptysis, and spleen rupture. Persons with sickle cell disorders may suffer sickle cell crisis after receiving G-CSF. Drugs which may potentiate the myeloproliferative effects such as lithium and corticosteroids, should be used with caution. Better tolerated than GM-CSF for most people.

Note(s): Produced by recombinant DNA technology wherein the gene for human granulocyte colony-stimulating factor is inserted into the genetic material of *E. coli*. The 175 amino acid protein G-CSF is a lineage specific colony-stimulating factor (granulocyte specific).

Epoetin (Epogen, Procrit)

Uses: For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of myelosuppression caused by chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Mechanism: Erythropoiesis stimulating agents (ESAs) stimulate erythropoiesis by the same mechanism as endogenous erythropoietin. Epoetin is very similar to endogenous erythropoietin. Elimination t_{1/2} about 8 hrs.

Toxicities: Nausea, vomiting, pruritus, headache, injection site pain, chills, deep vein thrombosis, cough, and hypertension. Also, rare but serious increase in risk of death from myocardial infarction, stroke, venous thromboembolism. Also see notes below.*

Note(s): *Although ESAs are much used outside of cancer, within cancer treatments clinical data have revealed a reduction in overall survival and/or increased the risk of tumor progression or recurrence of cancer in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. Consequently, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to dispense ESAs to cancer patients. ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure. Discontinue following the completion of a chemotherapy course.

Darbopoietin (Aranesp)

Uses: As for epoetin; for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of myelosuppression caused by chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Mechanism: Stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. Darbopoietin is less similar to endogenous erythropoietin. Elimination t_{1/2} about 25 hrs.

Toxicities: Nausea, vomiting, pruritus, headache, injection site pain, chills, deep vein thrombosis, cough, and hypertension. Also, rare but serious increase in risk of death from myocardial infarction, stroke, venous thromboembolism. Also see notes below.*

Note(s): *Although ESAs are much used outside of cancer, within cancer treatments clinical data have revealed a reduction in overall survival and/or increased the risk of tumor progression or recurrence of cancer in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. Consequently, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to dispense ESAs to cancer patients. ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure. Discontinue following the completion of a chemotherapy course.

Eltrombopag (Promacta)* A small molecule thrombopoietin (TPO) receptor agonist for oral administration.

Romiplostim (Nplate)* An Fc peptide fusion protein (peptibody) that activates intracellular transcriptional pathways leading to increased platelet production via the TPO receptor. Administered IV.

*Thrombocytopenia typically not a big problem in cancer.

Bisphosphonates

Uses: Major use outside of cancer for prevention of osteoporosis. Also for reducing skeletal events associated with cancer such as multiple myeloma or breast cancer. Administered PO and IV.

Mechanism: Possess two phosphate (PO_3^{2-}) groups similar to the endogenous agent pyrophosphate which is very abundant in bones. See Figure 1. Bones undergo constant turnover and this is kept in balance (homeostasis) by osteoblasts creating bone and osteoclasts degrading bone. Bisphosphonates also inhibit the breakdown of bone by encouraging osteoclasts to undergo apoptosis, thereby slowing bone loss. High-potency IV agents have been shown to modify progression of skeletal metastasis in several forms of cancer.

Toxicities: Upset stomach and inflammation, erosion of the esophagus; chronic use associated with osteonecrosis of the jaw (ONJ).

ADME: Essentially no metabolism and no interactions with P450 enzymes; some unchanged drug excreted renally but most taken up by bones.

Note(s): Have also been used by NASA crew during long space missions to minimize bone loss.

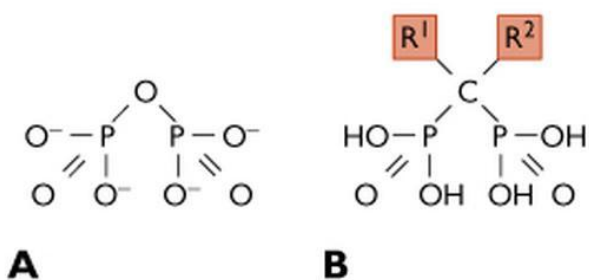

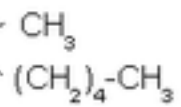

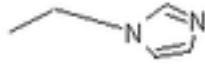


Figure 1. Structure of pyrophosphate (A) and a bisphosphonate (B)

There are two types of bisphosphonates (non-nitrogenous and nitrogenous). Nitrogenous bisphosphonates are more potent than non-nitrogenous bisphosphonates. E.g. zoledronate is about 10,000 times more potent than etidronate. See Table 1.

Table 1. Table of non-nitrogenous and nitrogenous bisphosphonates (first 3 are non-nitrogenous while all the rest are nitrogenous)

Agent	R ₁ side chain	R ₂ side chain
Etidronate	-OH	-CH ₃
Clodronate	-Cl	-Cl
Tiludronate	-H	-S-  -Cl
Pamidronate	-OH	-CH ₂ -CH ₂ -NH ₂
Neridronate	-OH	-(CH ₂) ₅ -NH ₂
Olpadronate	-OH	-(CH ₂) ₂ N(CH ₃) ₂
Alendronate	-OH	-(CH ₂) ₃ -NH ₂
Ibandronate	-OH	-CH ₂ -CH ₂ N 
Risedronate	-OH	
Zoledronate	-OH	

Antiemetics

Ondansetron (Zofran)

Uses: Prevention of nausea and vomiting caused by emetogenic chemotherapy or radiation. Administered PO as tablet, disintegrating tablet, or solution (2-3 times daily). Also IV solution.

Mechanism: A serotonin 5-HT₃ receptor antagonist; affects both peripheral and central nerves. Reduces the activity of the vagus nerve, which deactivates the vomiting center in the medulla oblongata, and also blocks serotonin receptors in the chemoreceptor trigger zone.

Toxicities: Generally well tolerated, but dizziness, headache, diarrhea, constipation. Contraindicated with apomorphine; can cause profound hypertension.

ADME: Metabolized by CYP3A4, CYP2D6, and CYP1A2. Strong P450 inhibitors and inducers can alter the PK, but the clinical impact is minimal. Elimination t_{1/2} about 4-6 hrs.

Note(s): Originally approved (1991) without QT warning. QT warning added in June 2012 (no black box).

Granisetron (Kytril)

Uses: As for ondansetron; prevention of nausea and vomiting caused by emetogenic chemotherapy or radiation. Administered PO as tablet or solution, (1-2 times daily). Also IV solution and transdermal patch.

Mechanism: As for ondansetron; a serotonin 5-HT₃ receptor antagonist.

Toxicities: Generally well tolerated, but dizziness, headache, constipation, QT prolongation (no black box).

ADME: Metabolized by CYP3A4 mainly, but some CYP2D6, and CYP1A2. Strong P450 inhibitors and inducers can alter the PK, but the clinical impact is minimal. Elimination t_{1/2} about 9-12 hrs.

Palonsetron (Aloxi)

Uses: As for ondansetron and granisetron; prevention of nausea and vomiting caused by emetogenic chemotherapy or radiation. Administered IV.

Mechanism: As for ondansetron and granisetron; more potent than either.

Toxicities: Generally well tolerated, but dizziness, headache, constipation, QT prolongation (no black box).

ADME: Metabolized by CYP2D6, CYP3A4 and CYP1A2. CYP2D6 mainly, but no evidence of CYP2D6 PM impact. Elimination t_{1/2} about 40 hrs.

Chemoprotectants

Dexrazoxane (Zinecard): Cardioprotectant that chelates iron. It provides some protection from reactive oxygen species (ROS) generated by agents such as the anthracyclines. Also (Totect) useful to protect tissues at injection sites from extravasation damage.

Mercaptoethylsulfonate sodium salt (MesNa): Very polar (ionized) molecule that contains a thiol and concentrates in the urine of the bladder and can protect from bladder toxicity (hemorrhagic cystitis) caused by agents such as ifosfamide or cyclophosphamide.

N-Acetylcysteine (NAC): A non-polar thiol-containing agent that protects from nephrotoxicity. (Also note it is used as antidote to acetaminophen (Tylenol) overdose to protect from potentially fatal hepatotoxicity.)

Amifostine (Ethyol): Actually a disulfide prodrug that is converted to a free thiol that can protect from ototoxicity and renal toxicity due to platinum agents, and xerostomia (dry mouth) from radiotherapy.

Glucarpidase (Voraxaze): For treatment of toxic plasma methotrexate concentrations (> 1 µmol/L) in patients with delayed methotrexate clearance due to impaired renal function.

Immunoprotectant

Tocilizumab (Actemra): An immunosuppressive MAB that targets cytokine IL-6. IL-6 is a potent pro-inflammatory cytokine. Initially developed for diseases such as rheumatoid arthritis, but also useful to reduce CRS (cytokine release syndrome) associated with other therapies.