Chemotherapy and Biotherapy in Non-Oncology Settings

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Objectives

- Understand non-oncologic indications for use of specific chemotherapy and biotherapy agents.
- Recognize side effects related to chemotherapy/biotherapy administration.
- Describe appropriate patient monitoring for specific chemotherapy/biotherapy agents.

Chemotherapy

- Alkylating Agents
  - Cyclophosphamide
- Antimetabolites
  - Methotrexate
  - Mercaptopurine
  - Hydroxyurea
FDA approved for various cancers

Off label indications
- Rheumatoid Arthritis
- Multiple sclerosis (MS)
- Systemic lupus erythematosus (SLE)
- Sarcoidosis
- Scleroderma
- Thrombotic thrombocytopenic purpura (TTP)
- Idiopathic thrombocytopenic purpura (ITP)
- Vasculitis
- Solid organ transplant rejection/solid organ transplant rejection prophylaxis

Drug Classification:
- Alkylating Agent
- DMARD 1

Mechanism of Action:
- Cross-links DNA strands
  - Interferes with DNA replication & RNA transcription
  - Disrupts nucleic acid
  - Causes cell death and altered cell function
- Reduces both T & B lymphocytes.
- Cell cycle non-specific

Administered: PO & IV
Metabolized:
- Prodrug
  - Phosphoramidate mustard
  - Acrolein
- Liver
  - 20 – 60 % protein bound
- CYP450
  - CYP2B6 - active
  - CYP3A4 – inactive, neurotoxic
  - CYP3A5, CYP2C9 – extrahepatic activation
- Excreted: urine
- Half-life: 3-12 hours

Pharmacokinetics
Solid organ transplant rejection prophylaxis
• 1-2 mg/kg/day PO

ITP
• 2 mg/kg PO daily
• 500 mg IV every 3—4 weeks

SLE or scleroderma
• 1—3 mg/kg PO daily in combination with corticosteroids
• 500 mg IV every 2 weeks for 6 doses

RA
• 1.5—2.5 mg/kg/day PO in combination with other agents
• 0.5—1 g/m² IV monthly for 6 months then every 2—3 months in combination with other agents.

Previous hypersensitivity reaction
Urinary outflow obstruction
Neutrophil count 1,500/mm³ or less
Platelet count < 50,000/mm³
Serious infection
Severe liver impairment
Pregnancy & Breastfeeding

Bone marrow suppression
Nausea & vomiting
Moderate alopecia
Hemorrhagic cystitis
Nasal congestion
Infertility
Development of malignancy
Monitoring

- Serum creatinine, Urea nitrogen, Electrolytes, CBC with differential
  - Every 2 weeks
- Urinalysis
  - Monthly during Tx
  - Yearly after dc
- Risk factors for cardiac toxicity/disease
- S & S of pulmonary toxicity

Methotrexate

FDA approved:
- Various oncology indications
- RA, JRA, JIA, and psoriasis

Recommended uses:
- MS
- SLE
- Active Crohn’s disease or ulcerative colitis
- Ectopic pregnancy
- Sarcoidosis, dermatomyositis, polymyositis, psoriatic arthritis
- Post-organ transplant

Drug Classification:
- Folate antimetabolite
- Folic acid antagonist
- DMARD 1
- Biologic response modifier

Mechanism of Action:
- Inhibits DNA, RNA, and protein synthesis
- Results in decreased production of proinflammatory cytokines by activated T cells and inhibits replication and function of T & B cells.
- Cell cycle specific - S-phase
- **Administered:** PO, IV, SQ, IM
- **Metabolism**
  - Liver, GI tract
  - 50-60% protein bound (albumin)
    - May be displaced by other weak acids
- **Excreted:** urine
- **Terminal half-life:** 10-12 hours

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- **RA**
  - 7.5-20mg PO/IM/SQ weekly
- **Psoriasis**
  - 10-25 mg PO/IM/SC/IV weekly
- **MS**
  - 7.5 mg PO + 20 mg SC weekly
- **Sarcoidosis**
  - 10-15 mg PO/IV weekly

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- **SLE**
  - 7.5mg weekly up to 20 mg weekly
- **Crohn's disease or Ulcerative colitis**
  - 15-25mg IM/SC weekly
- **Ectopic pregnancy**
  - 50 mg/m² IM once
- **Post-organ transplant (GVHD prophylaxis)**
  - 10-15 mg/m² IV on days +1, +3, +6 & +11

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Contraindications:

- Previous hypersensitivity reaction
- Pregnancy & Breastfeeding
- Preexisting Bone marrow suppression
- Active infection
- Immunodeficiency syndromes (AIDS)
- Alcoholism/Chronic hepatic disease
- GI disease - caution
- Renal impairment - caution

Side Effects:

- Symptoms of myelosuppression
- Nephrotoxicity
- Hepatotoxicity
- Nausea & Vomiting
- Reddening of skin
- Infertility
- Pneumonitis

Monitoring:

- Pregnancy test
  - Before therapy initiation
- Hepatitis B & C testing
  - Before therapy initiation
- CBC with differential & platelets
  - Before therapy initiation & monthly
- LFTs
  - Before therapy initiation
  - Every 4 to 8 weeks
- Liver biopsy
  - Psoriasis – periodically for long-term Tx
  - RA – if persistent LFT abnormalities; baseline if increased risk of hepatotoxicity
- Serum creatinine/BUN
  - Before therapy initiation
  - Every 4 to 8 weeks
- Serum uric acid
- Serum albumin
  - Before therapy initiation
- Chest X-ray
  - Before initiation of therapy
- PFTs
  - If MTX-induced lung disease suspected
- Hepatitis B & C testing
  - Before therapy initiation
- CBC with differential & platelets
  - Before therapy initiation & monthly
- LFTs
  - Before therapy initiation
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LFTs:
- Before therapy initiation
- Every 4 to 8 weeks

Liver biopsy:
- Psoriasis – periodically for long-term Tx
- RA – if persistent LFT abnormalities; baseline if increased risk of hepatotoxicity

Serum creatinine/BUN:
- Before therapy initiation
- Every 4 to 8 weeks

Serum uric acid:

Serum albumin:
- Before therapy initiation

Chest X-ray:
- Before initiation of therapy

PFTs:
- If MTX-induced lung disease suspected
**Indications:**
- FDA approved:
  - Acute Lymphocytic Leukemia (ALL)
- Off label:
  - Crohn's disease, ulcerative colitis

**Dose:**
- 75-125 mg PO daily
- Max 1.5 mg/kg/day

**Drug Classification:**
- Antineoplastic antimetabolite
- Purine analog

**Mechanism of Action:**
- Inhibits DNA synthesis
- Cell cycle specific – S phase

**Administration:** PO, IV

**Metabolism**
- Liver
  - Significant 1st pass metabolism

**Excreted**
- Urine
  - After 24 hours – greater than 50% of dose can be recovered as intact drug & metabolites

**Half-life:** 1-2 hours
Contraindications

- Previous hypersensitivity reaction
- Prior resistance to Mercaptopurine Tx
- Prior myelosuppressive Tx (extreme caution)
- Severe bone marrow suppression
- Concurrent use of thiopurine methyltransferase inhibitors (TPMT)
- TPMT deficiency
- Active Infection
- Pregnancy & Breastfeeding
- Renal failure (use with caution)
- Vaccination < 2 weeks previous to Tx

Side Effects

- Dose-related bone marrow suppression
- Increased risk of infection
  - Especially opportunistic viral or fungal infections
- Reactivation of varicella zoster, herpes simplex or other viral infections
- Hepatotoxicity

Monitoring

- Serum Creatinine/BUN, uric acid
  - baseline
- CBC w/differential
  - weekly
- LFTs
  - weekly at treatment start then every month
  - more frequently if taking other hepatotoxic drugs or pre-existing hepatic disease
- TPMT genotyping/phenotyping
  - prior to Rx
**Indications:**
- Various oncologic
  - CML, blast crisis in acute leukemia, metastatic melanoma, ovarian cancer
- FDA approved
- Sickle cell disease
- Off-label
  - Psoriasis

**Dosing:**
- Sickle cell disease: 15 mg/kg PO daily; Max: 35 mg/kg/day; titrate by 5 mg/kg/day q12wk
- Psoriasis: 1000-1500 mg PO daily; Max: 80 mg/kg/day

**Drug Classification:**
- Miscellaneous antimetabolite

**Mechanism of Action:**
- Interferes with DNA synthesis
- Increases RBC hemoglobin F levels increasing water content in RBCs increasing deformability of sickled cells
- Slows basal cell-layer replication (psoriasis)
- Cell-cycle specific S-phase

**Administration:** PO

**Metabolism:**
- Liver (up to 60%)
- GI (minor)

**Excretion:**
- Urine

**Peak concentration:**
- 1-4 hours
Contraindications

- Previous hypersensitivity reaction
- Preexisting myelosuppression
- Pregnancy & Breastfeeding
- Renal impairment
- HIV with concomitant use of stavudine and didanosine

Side Effects

- Nausea
- Myelosuppression
- Radiation recall
- Folic acid deficiency
- Secondary malignancy
  - Leukemias
  - Skin cancer

Monitoring

- Serum Creatinine/BUN
- LFTs
  - Baseline, then periodically
- CBC w/differential, platelets
  - Baseline
  - Weekly/biweekly
- Monitor for skin erythema
  - If previous radiation therapy
T.X. is a 28-year-old female diagnosed with Crohn’s Disease who has not shown a positive response from treatment with 5-aminosalicylates, antibiotics or corticosteroids. T.X. is considering starting a family in the next year.

Should therapy with an antimetabolite (Methotrexate or Mercaptopurine) be considered for T.X.’s refractory Crohn’s disease? Why or Why not?

### Case Study

### Mitoxantrone

- **Indications:**
  - FDA approved
  - AML
  - Secondary progressive, progressive relapsing or worsening relapsing-remitting MS
- **Dose:**
  - MS 12mg/m2 IV every 3 months
**Drug Classification:**
- Synthetic anthracenedione

**Mechanism of Action:**
- Inhibits topoisomerase II
- Inhibits DNA & RNA synthesis
- Not cell cycle specific
  - Most active late G-2

**Administered:** IV

**Metabolism:**
- Liver
  - 78% protein bound

**Half-life:**
- 75 hours

**Excretion:**
- Feces
- Urine (minor)
  - Bluish green

**Active infection**

**Severe bone marrow suppression**
- ANC <1500

**Pregnancy & Breastfeeding**

**Vaccinations < 2 weeks**

**LVEF < 50% or clinically significant LVEF decrease during therapy**
- Mild myelosuppression
- Moderate nausea & vomiting
- Severe cardiotoxicity (dose-related)
- Secondary malignancy

**Side Effects**

**Monitoring**

- CBC with differential & Platelets
  - Prior to each course
  - If S&S of infection
- Chest x-ray
- Cardiac evaluation - ECG & Ejection Fraction
  - Prior to each course
  - LVEF yearly after discontinuation of therapy
- LFTs
  - Prior to each course
- Pregnancy test
  - Prior to each course

- A laboratory-produced protein or antibody that is engineered to attach to specific antigen. Monoclonal antibodies mimic the antibodies your body naturally produces as part of your immune system’s response to germs, vaccines and other invaders (cancer).
- **How do they work?**
  - Act as a marker to target certain cells or proteins for destruction by the immune system
  - Block antigens that help cells grow
  - Target immune system check points – marks cells as “foreign”
**Indications:**
- FDA approved
- CLL
- Non-Hodgkin lymphoma (NHL)
- Rheumatoid Arthritis (RA)
- Wegener’s granulomatosis, and microscopic polyangiitis
- Off-label
  - Various oncologic diseases
  - ITP, TTP, autoimmune hemolytic anemia
  - Autoimmune mucocutaneous blistersing diseases

**Dose:**
- RA = 1,000 mg on Days 1 & 15 with Methotrexate every 16-24 weeks based on clinical need
- ITP & TTP = 375 mg/m² IV per week for 4 weeks

**Drug Classification:**
- anti-rheumatic, anti-neoplastic, monoclonal antibody (anti-CD20 antibody)

**Mechanism of Action:**
- binds to CD20 antigen on B-lymphocytes

**Pharmacokinetics:**
- Administration: IV
- Half-life: 18-32 days
Severe infusion reaction
- Hypotension, acute bronchospasm, angioedema
- Fever/Rigors/Chills
- Rash/Pruritus/Urticaria
- Headache
- Nausea/Vomiting
- Myalgias/Back pain

Side Effects

Hepatitis B screening
- Baseline & if S&S of hepatitis or HBV reactivation
- CBC with differential/platelet count
- Baseline & q2-4 months during Tx
- ECG
- During infusion, immediately post infusion if Hx arrhythmias, angina
- Serum creatinine/BUN
- Serum electrolytes
- Serum uric acid

Monitoring

Indications:
- FDA Approved:
  - CLL
  - MS
- Off-label:
  - T-cell lymphoma
  - GVHD prophylaxis
  - PLL
  - Stem cell transplant prep

Dose:
- Relapsing MS
  - 12mg IV/daily for 5 days
  - then 1 year later, 12 mg IV/daily for 3 days

Alemtuzumab
Drug Classification:
- Monoclonal Antibody

Mechanism of Action:
- Binds to CD52 surface antigen of multiple cells types, resulting in lysis

Pharmacokinetics:
- Administration: IV, SQ
- Half-life: 2 weeks

Side Effects:
- Pain
- Nausea/vomiting
- Fatigue
- Insomnia
- Diarrhea
- Arthralgia
- Anxiety
- Muscle weakness
- Bone Marrow Suppression
  - Moderate to Severe

Contraindications:
- HIV+
- Immunesuppression
- Active infection
- Pregnancy/Breastfeeding
- Vaccinations less than 6 weeks prior to Tx
- Pregnant/Breastfeeding
- Active infection
- HIV+ Immunesuppression
- Active infection
- Vaccinations less than 6 weeks prior to Tx
Monitoring

- **Indications:**
  - Moderate to severe plaque psoriasis
  - Psoriatic arthritis

- **Dose:**
  - Psoriasis
    - <100 kg – 45mg SC q12w; Start: 45 mg SC x1 wk 0, 4, then 12wk
    - >100 kg – 90mg SC q12w; Start: 90mg SC x1 wk 0, 4, then q12w; may decrease to 45 mg if dose intolerable

- **Serum creatinine**
  - Baseline
  - Monthly for 48 months after last dose

- **Thyroid function tests (TFTs)**
  - Baseline
  - Every 3 months until 48 months after last dose

- **Urinalysis with cell counts**
  - Baseline
  - Monthly for 48 months after last dose

- **TB test**
  - Baseline

- **S&S of thyroid cancer**
  - S&S of depression or suicidal behavior

- **Dermatologic exam (melanoma)**
  - Baseline
  - Yearly

- **CBC with differential**
  - Baseline
  - Monthly for 48 months after last dose

- **Test for varicella antibodies**
  - If no Hx of varicella or vaccination

- **Hepatitis B & C screening**
  - Baseline

- **HPV test (females)**
  - Yearly

- **Varicella antibodies**
  - If no Hx of varicella or vaccination

- **Drug Classification:**
  - Monoclonal Antibody

- **Mechanism of Action:**
  - Binds to and interferes with interleukin-12 and interleukin-23 cytokines, reducing inflammation and altering immune response

- **Pharmacokinetics:**
  - Administered: SQ
  - Steady-state serum concentration: 28 weeks
  - Half-life: 15-46 days

Ustekinumab

Ustekinumab (Stelara)
- Headache
- Fatigue
- Arthralgia
- Nausea
- Diarrhea
- Back pain
- Dizziness
- Pruritis, infection, injection site redness

### Side Effects

- Hypersensitivity reaction to Ustekinumab
- Allergy immunotherapy (caution)
- Hx of malignancy or current malignancy
- TB vaccine (foreign-born)
  - 1 year before or after Tx
- Serious Active infection
  - Sepsis, Influenza, TB
- Predisposition to infections
  - Chronic/recurrent infections, immunosuppression

### Contraindications

- TB test
  - Baseline
- Monitor for active TB S&S
  - during Tx
  - after DC.
- Dermatologic exams
  - Hx of ultraviolet light therapy (PUVA)
You are considering prescribing Ustekinumab to treat T.X.’s refractory Crohn’s Disease.
What is included in the pre-treatment evaluation?
How will T.X. need to be monitored during therapy?

- Adalimumab (Humira)
- Certolizumab pegol (Cimzia)
- Etanercept (Enbrel)
- Golimumab (Simponi)
- Infliximab (Remicade)

DMARD 2: TNF inhibitor

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<th>Arthritis</th>
<th>Psoriasis</th>
<th>Ankylosing Spondylitis</th>
<th>Ulcerative Colitis</th>
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**Mechanism of Action:** Binds and inhibits tumor necrosis factor alpha, reducing inflammation and altering immune response

**Contraindications/Cautions:**
- Hypersensitivity reaction to drug
- Infection
- Active, chronic or recurrent, or risk; immunosuppression
- TB infection/risk
- HBV carrier
- Uncontrolled Diabetes Mellitus
- Congestive Heart Failure
- Greater than 65 years old
- Cancer risk/hx
- CNS demyelinating disease (MS)
- Hypersensitivity to latex (autoinjector forms)

**Monitoring:**
- HBsAg
  - Baseline
- Active HBV infection S&S
  - Baseline,
  - During & several months after DC if HBV carrier
- TB test
  - Baseline
  - Then periodically
- Active TB S&S
- Dermatologic exams

**Dosing:**
- **Adalimumab**
  - 40mg SC q2wk
- **Certolizumab**
  - 200 mg SC q2wk or 400 mg SC q4wk
- **Etanercept**
  - 50mg/wk SC
- **Golimumab**
  - 50mg/month SC
- **Infliximab**
  - 5mg/kg IV q8wk
  - Weeks 0, 2, 6 (Induction)
  - ankylosing spondylitis – q4 wk
  - RA - 3mg to 10 mg/kg with Methotrexate q3 wk
T.X. failed Ustekinumab. You are considering a TNF-inhibitor: Infliximab, Adalimumab, or Certolizumab pegol.

Which of the 3 has the fewest side effects?
Which has the most convenient dosing schedule?
What pre-treatment screening should be completed for any TNF-Inhibitor?
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