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# Immunosuppression and chemotherapy

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## Classification

### *By class/mechanism*

#### Cytotoxics

- Antimetabolites
  - Purine antagonists
  - Pyrimidine antagonists
  - Both
  
- Topoisomerase inhibitors
  
- Agents that bind DNA covalently
  - Alkylating agents
  - Platinum compounds
  
- Spindle inhibitors
  - Vinca alkaloids
  - Taxanes

#### Non-cytotoxics

- Corticosteroids
  
- T-cell inhibitors
  
- Hormonal agents
  
- Immunomodulators
  - Interferons

**Monoclonal antibodies** (some are selectively cytotoxic)

#### Physical therapies

- Plasmapheresis
- Irradiation

#### *By interaction with cell cycle*

- Class I: non-specific for dividing/resting cells      e.g. nitrogen mustard
- Class II: specific for certain phases of division      e.g. MTX
- Class III: all phases of division      e.g. nitrosoureas

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## Indications

- Neoplasia
  - Often as part of combined modality therapy, which may also comprise radiotherapy and surgery
    - E.g. neoadjuvant/adjuvant use (to reduce bulk/to eradicate micrometastases)
    - Pulsed use to allow marrow recovery
  - Aims vary
    - Eradication/cure
    - Remission induction
    - Symptom control
- Autoimmune disease
- Transplantation
  - Differs from autoimmune disease in being predictable event, hence can prophylactically immunosuppress and monitor for rejection, rather than treating an established response (more difficult)
  - Some regimes used
    - Induction/maintenance of immunosuppression
      - Ciclosporin monotherapy

- Ciclosporin+prednisolone
- Ciclosporin+prednisolone+azathioprine
- Ciclosporin+prednisolone+azathioprine+poly-/monoclonal antibody
- Treatment of acute rejection
  - High-dose prednisolone
  - Poly-/monoclonal antibody

## Principles

How to choose

- Nature of process
  - In neurology: which side of BBB – peripheral/central
  - Type of process: ?T ?B cells
- Risks vs. benefits

Main indications in neurology

- Antibody-mediated disease (e.g. myasthenia, stiff person syndrome)
- Demyelinating disease (e.g. GBS, CIDP)
- Vasculitis
- Inflammatory muscle disease

Drug combinations

- Multiple agents used at doses close to maximum tolerated
- Use agents with different mechanisms of action/different SE profile
  - More effective
  - Less SEs

Dose usually adjusted for BSA

Resistance

- MDR1 (multidrug resistance gene) encodes ATP-dependent transporter that effluxes certain cytotoxics out of cells; higher expression in tumours

## Cytotoxics

### Shared adverse effects

Cytotoxic agents cause death of rapidly dividing tumour cells. Selectivity is based upon the high mitotic rate of the tumour. Death of normal body cells occurs related to the rate of their division, and pertains particularly to the most rapidly dividing tissues:

- |                           |                          |  |
|---------------------------|--------------------------|--|
| • Hair                    | alopecia                 |  |
| • GI epithelium           | mucositis, PU, diarrhoea |  |
| • Bone marrow suppression | pancytopenia             |  |
|                           | → prone to               | infections (incl. opportunistic), malignancy |
| • Fetus                   | teratogenic/fetotoxic    |  |

Excessive rapid cell death causes **hyperuricaemia** – can be prevented with

- Xanthine oxidase inhibitor: allopurinol, febuxostat
- Adequate hydration

**N&V** is caused by stimulation of CTZ

- Acute
  - 5HT<sub>3</sub> antagonists can be particularly useful (in combination with dexamethasone) in patients at high risk of emesis or unresponsive to other therapies
- Delayed
  - Dexamethasone plus metoclopramide or prochlorperazine
- Anticipatory
  - Good control of acute and delayed emesis
  - Addition of lorazepam (amnesic, sedative and anxiolytic)

**Extravasation** of irritant drugs into extravascular tissues causes local tissue necrosis

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## Antimetabolites

Chemical analogues of normal cell metabolites that become incorporated into nuclear material or inhibit essential enzymic steps in cellular metabolism

### Purine antagonists

- Analogues: azathioprine, 6-MP
- Inosine monophosphate dehydrogenase inhibitor: mycophenylate

### Pyrimidine antagonists

- Analogues: 5-FU, cytarabine (cytosine arabinoside)
- Dihydroorotate dehydrogenase inhibitor: leflunomide

### Both

- Folate antagonist: MTX
- Ribonucleotide reductase inhibitor: hydroxyurea

### Azathioprine

#### Mechanism

- Prodrug, metabolised to **6-mercaptopurine**, a purine nucleotide analogue that competes with inosine monophosphate in synthesis of AMP and GMP
- Blocks DNA/RNA synthesis, toxic to dividing lymphocytes

#### Adverse effects

- Affects all rapidly dividing cells as above
- Also hepatotoxic
  - Toxic bone marrow suppression/hepatitis probably secondary to TPMT deficiency
  - Opportunistic/bacterial infections possible, esp. if monitoring stopped
- PUO/flu-like symptoms
  - Unrelated to TPMT

Thiopurines (azathioprine, 6-MP, thioguanine) are eliminated via

- Thiopurine methyltransferase (TMTP)
  - Polymorphic: 90% high activity (risk of undertreatment), 10% intermediate activity, 0.3% low activity (risk of toxicity)
  - Check TMTP activity before starting drug.
    - Normal           2-4mg/kg/day
    - 50-100%        1-2mg/kg/day + monitor
    - <50%           use alternative
- Xanthine oxidase. Inhibitors predispose to toxicity though allopurinol is used to counter hyperuricaemia – must at least halve dose of azathioprine.

#### Note

- Monitor FBC and LFT
- Widely used in organ transplantation and auto-immune disease
- Used at high dose when aiming to eliminate all dividing lymphocytes e.g. pre-marrow transplantation

### Mycophenylate

#### Mechanism

- Active drug, and converted in body to more active metabolite mycophenolic acid
- Reversible inhibitor of inosine monophosphate dehydrogenase, a key enzymic step in purine nucleotide biosynthesis
- Highly selective for T and B cells, as lymphocytes have no salvage pathway for purine synthesis
- More selective than azathioprine, and more effective in preventing acute rejection

#### Adverse effects

- Similar to those of azathioprine
  - Side-effects related to inhibition of lymphocyte proliferation may be more severe (i.e. intercurrent infection with organisms largely cleared by lymphocyte activity)

- Effect on other dividing tissues may be less severe
- GI side-effects are prominent

*Note*

- Monitor FBC and LFT
- Currently licensed for prophylaxis of acute renal transplant rejection only

**Methotrexate**

- Inhibits
  - DHFR, required for purine, pyrimidine and protein (methionine and serine  $\alpha\alpha$ s) synthesis
  - 5-amino-imidazole-4-carboxamide-ribonucleotide (AICAR) transformylase
- Folinic acid helps prevent methotrexate-induced myelosuppression/mucositis – can now give myelotoxic doses and then ‘rescue’ the marrow with folinic acid after e.g. 24h

**Adverse effects**

- Mucositis
- Hypersensitivity pneumonitis (5%)
- Hepatitis
- Teratogenic

**Interactions**

- ↑levels by NSAIDs (displace MTX from protein), penicillin, probenecid

*Note*

- Check baseline CXR and lung function tests
- Start at 7.5mg PO *weekly*, increase in steps of 2.5mg to maximum of 25mg
- Monitor FBC and LFT
- Ensure patient receives NPSA information leaflet – fertility can be impaired

**Hydroxyurea (hydroxycarbamide)**

Urea analogue, inhibits ribonucleotide reductase.

**Adverse effects**

- Leg ulcers – may not heal unless drug stopped
- N, V, D
- Bone marrow suppression
- Rashes

**Topoisomerase inhibitors**

E.g. doxorubicin, daunorubicin, etoposide

**Mechanism**

- Stabilise cleavable complex formed by topo 2 + DNA → double strand break
- Anthracyclines also possess hydroxyquinone moiety that generates free radicals; not necessary for antitumour effect, but explains increased cardiotoxicity

**Adverse effects**

GI side-effects are a particular problem

**Alkylating agents**

**Mechanism**

Form reactive ion that alkylates N7 of guanine (most nucleophilic part of DNA)  
DNA strands then either break or cross-link

**Groups**

Nitrogen mustards: cyclophosphamide, melphalan, chlorambucil	bifunctional
Aziridines: mitomycin	bifunctional

Nitrosoureas: lomustin, carmustin  
Alkylsulphonates: busulphan  
Methylating agents: procarbazine

bifunctional  
bifunctional  
?also mild MAO-I/disulfiram actions

**Adverse effects** (esp. relevant for cyclophosphamide and chlorambucil)

- Dose-dependent lymphopenia, B>T cells, CD8>>CD4 cells
- Gametogenesis is severely affected
  - All males and most females become infertile
  - Consider sperm banking or ovarian preservation
- Haemorrhagic cystitis is a common manifestation of urothelial toxicity of cyclophosphamide, due to a metabolite. This can be prevented by the use of Mesna which specifically reacts with the metabolite in the urinary tract and inactivates it.
- Bladder tumours (10x baseline risk). Monitor for haematuria and proceed to cystoscopy if develops.
- NHL (11x baseline risk)
- Opportunistic infections
  - Need PCP prophylaxis (1<sup>st</sup> line co-trimoxazole, 2<sup>nd</sup> line azithromycin, 3<sup>rd</sup> line atovaquone)
  - Watch for TB, VZV, PML
- Monitor FBC weekly, discontinue if lymphocytes<0.4·10<sup>9</sup> or neutrophils<1-1.5·10<sup>9</sup>

*Note*

- Particularly used to treat haematological malignancies
- Cyclophosphamide dosing
  - PO 2-4mg/kg/day
  - IV pulse 10mg/kg/day or 0.75-1g/m<sup>2</sup>, variable pulse intervals, faster onset
- Carmustin implants (Gliadel<sup>®</sup> wafer) used in GBM debulking

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## Platinum compounds

E.g. cisplatin, carboplatin

### Mechanism

Interacts with purine and pyrimidine bases in DNA to cause inter- and intra-strand cross-links

### Adverse effects

- Neuro-, nephro- and ototoxicity are a problem
- Very emetic – needs 5-HT<sub>3</sub> antagonist cover

*Note*

Useful for ovarian, lung and testicular tumours

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## Vinca alkaloids

E.g. vincristine, vinblastine

### Mechanism

Bind to tubulin and inhibit its polymerisation

*Note*

Also inhibit other activities linked to microtubules:

- Phagocytosis
- Axonal transport (→ peripheral neuropathy – sensory>autonomic>>motor)

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## Taxanes

Paclitaxel (Taxol<sup>®</sup>) – from bark of yew  
Docetaxel (Taxotere<sup>®</sup>) – synthetic

### Mechanism

Stabilise microtubules → mitotic spindle cannot contract during mitosis

### Adverse reactions

Severe hypersensitivity reactions are common and routine prophylactic therapy to prevent reactions should be employed

#### Note

- Considered by oncologists to be a major advance in solid tumour chemotherapy
- Licensed/embraced by NICE for treatment of advanced solid tumours, e.g. ovarian cancer (paclitaxel), NSCLC (paclitaxel), and breast cancer (docetaxel, paclitaxel – if anthracycline failed/inappropriate)

## Corticosteroids

### Mechanism

- All pharmacological derivatives of glucocorticoids
  - Bind to ubiquitous intracellular receptors, steroid-receptor complex enters nucleus and regulates transcription of specific genes (up to 1% of all genes)
  - Exaggerated glucocorticoid response due to supra-physiological concentrations of ligand
- Prednisolone is most commonly used
  - Four times more potent anti-inflammatory action than cortisol

### Physiological effects

Suppression of

- Phagocyte function
- Lymphocyte recirculation
- T-cell activation
- Cytokine release

Lymphocytotoxic for >20mg prednisolone/day

Increased endonuclease activity and induction of apoptosis of lymphocytes and eosinophils

### Adverse effects

- ↑WCC
  - Due to ↓margination/emigration
  - Lasts 7-10 days
- Cushing's!
  - Hence often combined with other ('steroid-sparing') agents to minimise dose necessary
  - Start bone protection immediately – majority of bone loss occurs in first 3m
  - Monitor glu/BP
- Growth retardation if young
- Potentially teratogenic (fetal growth retardation, ?cleft palate)
- Not present in breast milk at low (<40mg/day) dose
- Risk of opportunistic infections >20mg prednisolone/day (e.g. PCP, fungal, viral)
- Anaphylaxis (IVMP pulses – give dilute and slowly)

### Interactions

- ↑metabolism by hepatic enzyme inducers

## Drugs interfering with T-cell signalling

**Ciclosporin** = fungal peptide product

**Tacrolimus** (FK506) and **sirolimus** (rapamycin) = macrolides made by soil-dwelling bacteria

Big advance esp. in organ transplantation (now >80% 1-year survival for kidneys)

Ciclosporin has for many years been the leading compound in immunosuppression in organ transplantation; its position is now being challenged by the macrolide-based agents.

### Mechanism

Block the expression of several cytokine gene products required for T-cell activation

## Ciclosporin and tacrolimus

- Calcineurin blockers
- Bind to immunophilins (family of intracellular proteins) – complex prevents calcineurin-dependent dephosphorylation of NFAT-P (nuclear factor of activated T-cells), which is produced in response to antigen binding. Thus no stimulation of antigen receptor response element in IL-2 promoter.

## Sirolimus

- Non-calcineurin blocking immunosuppressant
- Binds to MTOR (mammalian target of rapamycin)
- Can be combined with ciclosporin or tacrolimus

## Adverse effects

- Dose-dependent nephrotoxicity
  - Narrow therapeutic window/variable pharmacokinetics → monitor levels
  - HT, oedema, K<sup>+</sup> retention (?hyporeninaemic hypoaldosteronism)
  - ARF (vasoconstriction), CRF (fibrosis)
- Hyperlipidaemia
- Hepatotoxicity
- Gum hyperplasia
- Hirsutism; *not* alopecia
- Burning hands and feet (esp. 1<sup>st</sup> week)
- Tremor
- DM
- Skin/lymphoproliferative malignancy
- Oligodystrophy
- Opportunistic infections, esp. viral (warts, EBV lymphoma)

Tacrolimus is more nephrotoxic and also neurotoxic

## Interactions

↑by hepatic enzyme inhibitors, non-DHP CCBs, OCP

↓by hepatic enzyme inducers

## Note

- Monitor trough levels
  - Ciclosporin – aim for 100-200ng/ml
  - Tacrolimus – aim for 5-10ng/ml

## Monoclonal antibodies

There is currently great interest in monoclonal antibody therapy in transplantation and immune disease.

## Nomenclature

1. Prefix
  - Distinct syllable to make unique
2. Disease/target
  - Viral vir-
  - Bacterial bac-
  - Immune lim-
  - Infectious les-
  - Cardiovascular cir-
  - Carcinoma
    - Colon col-
    - Melanoma mel-
    - Mammary mar-
    - Testis got-
    - Ovary gov-
    - Prostate pr(o)-
    - Miscellaneous tum-
3. Animal source
  - Human u

- Mouse o
  - Rat a
  - Hamster e
  - Primate i
  - Chimaeric xi [drop consonant for class]
  - Humanised zu
4. Suffix
- Monoclonal antibodies and fragments -mab
  - Toxin -tox
  - Fusion protein -cept

### Examples

#### Infliximab/adalimumab/etanercept

- Prevent TNF $\alpha$  action
  - Infliximab = chimeric antibody – mouse F<sub>ab</sub>, human F<sub>c</sub>
  - Adalimumab = fully human antibody
  - Etanercept = P75 binding domain genetically engineered to IgG F<sub>c</sub>
- Licensed for treatment of
  - RA
    - NICE recommends either infliximab or etanercept for highly active RA which has failed to respond to at least 2 standard DMDs, incl. methotrexate (unless methotrexate is contraindicated or not tolerated)
    - Withdraw if no response by 3m
    - No evidence to support treatment beyond 4y (but the agents are still very new) – make an individual decision
  - Infliximab: IBD (severe active Crohn's refractory to steroids/other immunosuppressants, refractory fistulas), AnkSpond
  - Etanercept: AnkSpond, juvenile idiopathic arthritis
- Absolute and relative contraindications: STOIC (sepsis, TB, optic neuritis/demyelination, infusion reaction, cancer)
- Main adverse effects
  - Infections (esp. TB → get baseline CXR)
  - Malignancy: esp. lymphoma; risk yet poorly defined, as drugs are quite new
  - Blood dyscrasias
  - SLE-like syndrome (infliximab>>etanercept), autoantibody formation
  - Hypersensitivity
  - Demyelination: central (MS, optic neuritis) and peripheral
  - Development of inhibitory antibodies – combine with MTX

#### Anakinra

- Inhibits IL1
- Licensed for treatment of
  - RA, in combination with methotrexate, if RA has not responded to methotrexate alone; NICE does not recommend it unless used in a controlled long-term clinical study
- Role in myeloma?

#### Rituximab (MabThera<sup>®</sup>)

- Anti-CD20
- Causes complement-mediated B-cell lysis
- Marked ↓Ig and ↓B cells – check lymphocyte subsets after Rx
- Licensed for treatment of (NICE guidance)
  - NHL
    - Follicular lymphoma
      - First treatment if stage III/IV
      - Maintenance treatment in relapse/refractory disease responding to induction therapy
      - Treatment in chemoresistance, or in second or later relapse
    - CD20-positive diffuse large B-cell NHL (hence CHOP → rCHOP)
  - RhA: in combination with methotrexate, in severe disease, in patients with inadequate response/intolerance to DMDs incl. at least one anti-TNF therapy
- Can cause severe cytokine release (“capillary leak syndrome”) – give under analgesic+antihistamine+steroid cover
- High risk of opportunistic/bacterial infections – incl. PML



**Imatinib (Glivec®)**

- Blocks tyrosine kinase that is overexpressed in CML

**Trastuzumab (Herceptin®)**

- Licensed for treatment of metastatic breast cancers overexpressing HER2 (human epidermal growth factor receptor 2)
  - In combination with paclitaxel (a taxane), in patients who have not received chemotherapy and in whom anthracycline treatment is inappropriate
  - As monotherapy, in patients who have received at least 2 chemotherapy regimes

**Basiliximab**

- Chimeric antibody, prevents IL2 action
- Licensed for prophylaxis of acute rejection in allogenic renal transplants

**Alemtuzumab (Campath®)**

- Anti-CD52 antibodies for the treatment of Wegener's granulomatosis; hence particular interest in Cambridge
- Similar to Rituximab but less specific for B cells, also kills T cell → greater immunosuppression
- SEs similar

**Immunomodulators****Interferon alfa**

Lymphotoxic

Possible indications

- Hairy cell leukaemia
- Chronic hepatitis B and C

Pegylated varieties persist have a longer duration of action.

**Interferon beta**

Possible indications

- Relapsing, remitting MS (at least two attacks of neurological dysfunction over previous 2-3 years, followed by complete or incomplete recovery) in patients who are able to walk unaided
  - Recent study shows that may be effective in first episode if clinically and radiologically very suggestive
- IFN beta-1b is also licensed in secondary progressive MS
- Neither of the above is currently recommended by NICE

**Physical therapies****Plasmapheresis**

- Removal of serum Ig by extracorporeal circuit
- Rapidly removes pathogenic antibody
- Must be combined with B lymphotoxic drug to prevent rebound (e.g. cyclophosphamide, steroids)
- Combination with IVIg very powerful
- Risks include cardiovascular instability

**IVIg**

- Mode of action unclear – putative mechanisms
  - Inhibits cytokine production, T-cell activation, antibody production
  - F<sub>c</sub> blockade
  - Complexing of cytokines
- Exclude IgA deficiency
  - Send baseline even if unable to check before starting
  - Even IgA depleted preparations contain some IgA
- Risks include
  - Hyperviscosity with ultra-rapid infusion 2g/kg/day, esp. in arteriopathy

- Renal failure, esp. if pre-existing renal disease (sugar load), rheumatoid factor, cryoglobulins
  - Daily UE – stop if ↑crea by >10%
- Aseptic meningitis
- Transmission of infection
  - Written consent, record batch no, check pre-IVIg LFTs and HCV status