Major toxicities of cytotoxic cancer chemotherapy

- Haematological toxicity- most important dose-limiting toxicity for the majority of cytotoxics
  - Myelosuppression- risk of infection
  - Thrombocytopaenia (platelets) risk of haemorrhage- may be delayed with some drugs (mitomycin C, nitrosoureas) or cumulative (chlorambucil, melphalan)
- Gastrointestinal toxicity
  - Nausea and vomiting: maybe early onset (within 6 hours) or delayed (up to 2 weeks) (cisplatin, cyclophosphamide, doxorubicin)- maybe alleviated by 5HT3 receptor antagonists (Ondansetron) with dexamethasone
  - Diarrhoea (irinotecan, 5FU, mitomycin C)
  - Mucositis (doxorubicin, 5FU, methotrexate)

Other toxicities

- Alopecia (hair loss)
  - Cyclophosphamide, doxorubicin, etoposide, vincristine, ifosfamide
- Pulmonary toxicity
  - Bleomycin, busulphan
- Cardiac toxicity
  - Doxorubicin, epirubicin
- Renal
- - Cisplatin (decreased GFR), high-dose methotrexate
- Bladder toxicity
  - Ifosfamide, cyclophosphamide (cystitis- MESNA)
- Neurological toxicity
  - Vincas, cisplatin, paclitaxel, ifosfamide, cyclophosphamide
- Local toxicity
  - At injection site (doxorubicin, mitomycin C, vinca alkaloids)

Tumour Response

- CR (Complete Response)
  - Complete resolution of all measurable disease for at least 1 month
- PR (Partial Response)
  - 50% reduction in the product of 2 perpendicular diameters for 1 month or more
- SD (Stable Disease)
  - No change in size of measurable tumour over a period of 1 month or more

- Pancreatic cancer
  - Erlotinib (increased 1 year survival- 24% vs 17%)
- Renal cell carcinoma
  - FDA approved sorafenib and sunitinib
- Non-small cell lung cancer
  - Erlotinib (2 month gain in survival)
  - Bevacizumab
- Breast cancer
  - Trastuzumab

Mechanisms of Anticancer Agents - Drug Resistance (Lecture 2)

Drug Resistance

- Most important reason for cancer treatment failure
  - Genetic instability of tumours allows for environmental adaption
- Heterogeneity, low growth fraction & slow doubling time of most solid tumours results in low fractional cell kill
- Hypoxia reduced drug access & tumour sensitivity to many drugs (& radiation)
- Low drug levels can select for resistance

Chemrsensitivity of cancer

- Group 1: Sensitive, cures common
  - Burkitt's lymphoma, acute lymphoblastic leukaemia in children, choriocarcinoma, germ cell tumours, Hodgkin's disease, Wilms tumour
- Group 2: Moderately sensitive, may prolong survival
  - Ovarian cancer, breast cancer, gastrointestinal cancer, small cell lung cancer, AML
- Group 3: Resistant, no definite effect on survival
  - Non small cell lung cancer, melanoma, pancreatic, renal, gliomas, metastatic colorectal cancer, soft tissue sarcoma
  - Due to cell types involved - very difficult to treat

Drug Resistance

- Mutation of target stops drug binding/working
- Gene amplification of target
  - Drug can't inhibit enough of the enzyme to cause cell death
- Increased tolerance
  - Decreased cell surveillance
    - Won't trigger apoptosis