Major toxicities of cytotoxic cancer chemotherapy

- Haematological toxicity - most important dose-limiting toxicity for the majority of cytotoxics
  - Myelosuppression - risk of infection
  - Thrombocytopenia (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
  - Vinca, 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, rectal, breast cancer, colorectal 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

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Dose → Level → Damage → Death

"pharmacological"
  - Increased drug efflux (PgP, MRP)
  - Decreased drug influx (RFC)
  - Cytoplasmic drug inactivation (GSH)
  - Gene amplification of target (DHFR, TS)
  - Mutation of target (tubulin, topoisomerase II)

"post-target"
  - Increased DNA repair (AGT, NER)
  - Increase tolerance (loss of mismatch repair)
  - Failure to undergo apoptosis (loss of p53, increased BCL-2)
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