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Principles of Cancer Therapy

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Learning Goals

- Define chemotherapy, selective toxicity and therapeutic index
- Understand how selective toxicity is achieved in chemotherapy
- Know the eight main classes of cancer chemotherapy drugs, a lead example of each class and its mechanism of action
- Be able to predict the major adverse effects of a cancer chemotherapy drug from its mechanism of action

Slide 3

Cancer in New Zealand

- Cancer is a common clinical problem in NZ
  - 21,050 new cancer registrations and 8,891 cancer deaths in 2011*
- Learn about the most common types of cancer
  - Top 5 Cancers in NZ*
    1. prostate
    2. colon, rectum and anus
    3. breast
    4. melanoma of the skin
    5. trachea, bronchus and lung
  - The principles of managing common cancers are also relevant to management of less common types of cancer

* http://www.health.govt.nz/publication/cancer-new-registrations-and-deaths-2011

Slide 4	**Clinical presentation of cancer** • Primary tumour – Local effects due to expansion (mass), breach of epithelial surfaces (bleeding), narrowing of body tubes (bowel obstruction) or invasion of local structures (hoarseness). • Metastasis – Distant effects of metastatic disease involving lymph nodes (mass), lungs (breathlessness), brain (headache), liver or bone (localised pain). • Paraneoplastic syndromes – Generalised effects due to hormonal (hypercalcaemia), autoimmune (myasthenia gravis) or undefined mechanisms (finger clubbing)	
Slide 5	**Principles of Cancer Diagnosis and Investigation** • Diagnosis – Cancer is a pathological diagnosis, requiring tumour biopsy and histopathology to exclude benign pathology, identify tissue of origin, tumour grade and prognostic markers • Staging – Determination of extent of involvement according to staging systems, eg. TNM system • Functional assessment – Assessment of how patient is likely to cope with the disease and treatment	
Slide 6	**Principles of Cancer Treatment** • Key Questions: – Is surgical resection or curative treatment possible? (or will the benefits of therapy be limited to palliation) – What treatment modalities are required for the best outcome? (surgery, radiotherapy and chemotherapy) – Are different treatment options available? (eg, mastectomy versus lumpectomy plus radiotherapy). • Multidisciplinary approaches usually required	

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Principles of Cancer Surgery

- For Cure
  - Surgery most effective cancer treatment
    - >40% of cancer is cured by surgery
  - Complete excision with margin of normal tissue
- Other Indications
  - Diagnosis (excision biopsy)
  - Staging (assess lymph node spread)
  - Local control
  - Palliation (bypass obstruction)

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Principles of Radiation Therapy

- Ionising Radiation Mode of Cell Death
  - Energy from radiation damages DNA (double-strand breaks) and generates free radicals from water that damage membranes, proteins and organelles
- Therapeutic Radiotherapy
  - External beam radiotherapy
  - Planned according to treatment fields, dose to tumour and normal tissue, and number of treatment fractions
  - Component of curative treatment
    - Head and Neck Ca

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Principles of Cancer Chemotherapy

Definition of Chemotherapy:

- using chemicals to kill disease causing cells in the body
- eg. bacteria, fungi, viruses, cancer

In contrast, Drug Therapy:

- using chemicals to modulate body processes
- eg. arterial blood pressure, mood

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Selective Toxicity

- Selective toxicity is the goal of cancer chemotherapy
- Occurs when toxicity is produced in the cancer cell without (or with less) effects in the host cells (cf drug therapy)
- Selective toxicity is achieved by exploiting differences between normal host cells and the disease-producing cells, when:
  - there is an unique target in the pathogen
  - the target is structurally different in the pathogen
  - the target is functionally different in the host

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Therapeutic Index (TI)

- important indicator of selective toxicity
- ratio of dose required to produce toxic effect divided by dose required to produce desired effect
- $TI = \frac{ED_{50} \text{ for unwanted toxicity}}{ED_{50} \text{ for therapeutic activity}}$

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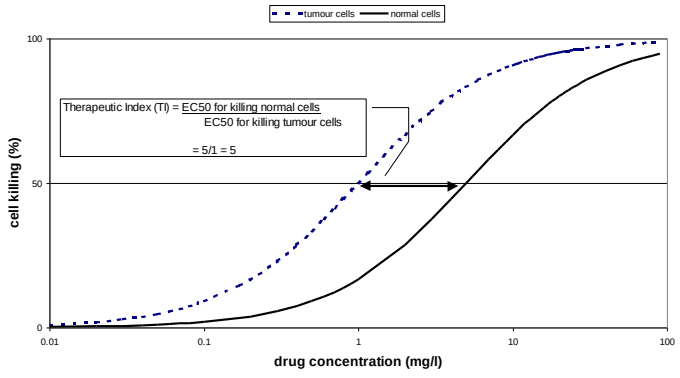
Pharmacodynamics of cancer chemotherapy



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Classification of cancer chemotherapy drugs: according to mode of action

1. Alkylating agents
   - Binds DNA
   - eg. cyclophosphamide
2. Platinum-based drugs
   - Binds DNA
   - eg cisplatin
3. Antimetabolites
   - Inhibit DNA synthesis
   - eg methotrexate
4. Topoisomerase-interactive drugs
   - Inhibit topoisomerases
   - eg. doxorubicin
5. Antimicrotubule drugs
   - Bind microtubules
   - eg. paclitaxel
6. Hormonal agents
   - Block production or action of sex steroids
   - eg. tamoxifen
7. Targeted therapies
   - Block oncogenic proteins
   - imatinib
8. Vascular targeting therapies
   - Inhibit angiogenesis
   - eg. bevacizumab

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First Order Kinetics of Tumour Cell Growth and Chemotherapy Killing

- Tumour Growth
  - starts as one malignant cell
  - divides with constant doubling time
  - clinical evident at 10^8 cells;
  - lethal at 10^{12} cells
- Chemotherapy killing
  - Each dose kills a constant proportion of tumour cells
  - repeated doses required
  - Continued after clinical disappearance of disease

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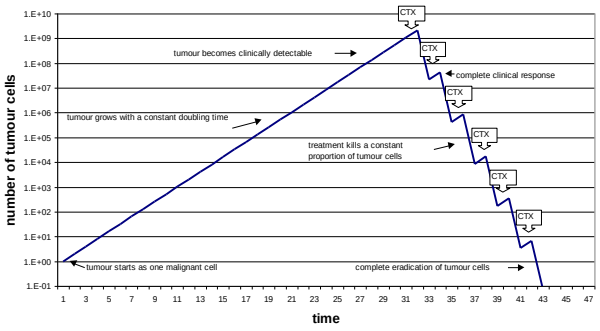
Model of tumour growth and response to treatment



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Combination Chemotherapy

- more effective than use of single agents
- criteria for combination therapy
  - some activity as a single agent
  - differing mechanisms of action
  - different side-effect profiles

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BEP combination chemotherapy for testicular cancer

Drug	Mechanism of action	Limiting toxicity
Bleomycin	induces DNA breaks	lung
Etoposide	topoisomerase II poison	bone marrow
Cis**P**latin	induces DNA crosslinks	peripheral nerves

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Adverse effects of cancer chemotherapy

- Common
- Most related to the main pharmacological action
- determine the dose and dosing interval of chemotherapy
- May be annoying, dangerous, and limit compliance of patients with therapy
- Most are reversible or clinically manageable, eg. chemotherapy induced nausea and vomiting

Slide 19	**Adverse effects of cancer chemotherapy related to pharmacological mechanism** • Antiproliferative – myelosuppression, mucositis, alopecia, sterility • Mutagenesis – second cancers, teratogenecity • Microtubule disturbance – peripheral neurotoxicity • Sex steroid deficiency – decreased libido, impotence, flushing	
Slide 20	**Indications for cancer chemotherapy** • Cure – High cure rates achieved in acute lymphoblastic leukaemia, testicular cancer, Hodgkin's disease • With surgery – Adjuvant chemotherapy for node-positive breast and colorectal cancers • With radiotherapy – Combined modality therapy for Head and neck, cervical cancer etc • Palliation – Improve symptoms and survival time, eg. Lung cancer	
Slide 21	**Oncology Clinical Case: Presentation** • Adult ex-smoker • Cough + haemoptysis for 5 weeks • Left lung mass on chest x-ray • Suspected primary lung cancer • Also, back pain and finger clubbing 	

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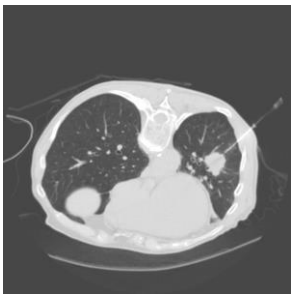
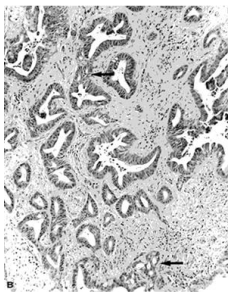
CT-guided needle biopsy and pathological diagnosis of non-small cell lung cancer





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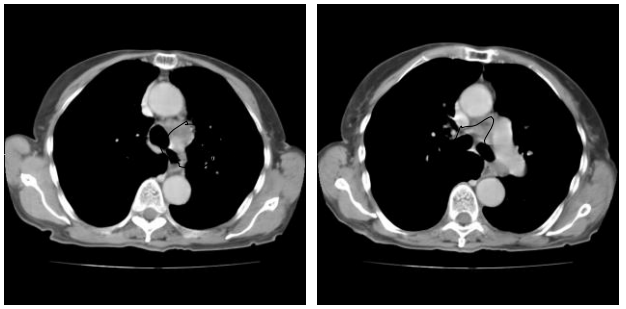
Staging CT Scans



Mediastinal lymphadenopathy

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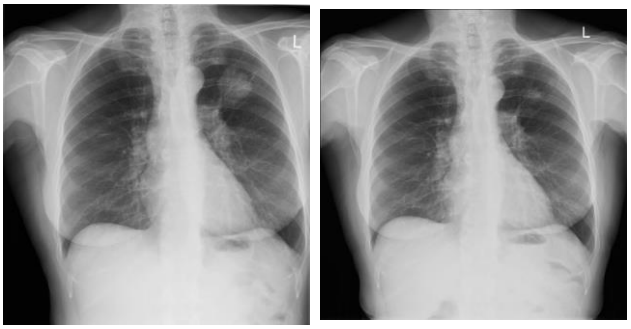
Investigations and treatment plan

- Assessment Summary
  - Primary non-small cell cancer of left lung with mediastinal lymph node and bone metastases
- Treatment plan
  - Palliation (rather than cure)
  - Radiotherapy to symptomatic bone lesions
  - Palliative chemotherapy with carboplatin and paclitaxel

Slide 25	Chest X-ray showing response to chemotherapy  Before Chemotherapy After Chemotherapy x3	
Slide 26	Short answer question: example For this patient, an oncologist recommended treatment with combination chemotherapy including paclitaxel, an antimicrotubule drug that binds to microtubules and thereby inhibits the formation of the mitotic spindle and cell division 1. Define selective toxicity? 2. What is the mechanism of action of paclitaxel? 3. How is selective toxicity achieved in cancer chemotherapy by paclitaxel? 4. List two Type A (augmented pharmacological effect) adverse drug reactions expected from paclitaxel?	