# Cytotoxic drugs

## Updated learning objectives

1. Summarise the epidemiological findings and main hallmarks of cancer
2. Describe the actions of drugs used for adjuvant chemotherapy of colorectal cancer
3. Describe the actions of drugs used for adjuvant chemotherapy of early non-small cell lung cancer
4. Describe the actions of drugs used for treatment of advanced non-small cell lung cancer
5. Describe the actions of the cytotoxic drugs used for adjuvant chemotherapy of breast cancer
6. Summarise the different categories of cytotoxic drugs

## Cancer Background & Epidemiology

Cancer constitutes a group of conditions and can be defined as a disease that is caused by the uncontrolled proliferation and growth of abnormal cells. There are thought to be over 200 different types of cancer and their prevalence varies depending on a number of factors. Although it is generally thought that a cell only becomes cancerous due to multiple genetic mutations they are associated with typical ‘hallmarks’ as outlined by the seminal Hanahan & Weinberg publication (2000) and updated in 2011. Discussion of these aspects is behind the scope of this lecture but readers should refer to the aforementioned article.

In terms of epidemiology a large analysis recently carried out by the American Cancer Society (2013) found that the four most commonly occurring forms of cancer were in the:

1. Digestive system (colorectal, pancreatic, liver stomach etc)
2. Respiratory system (lung cancer accounts for 90%)
3. Genitalia (prostate cancer accounts for 70%)
4. Breast (99% occurs in females)

These statistics closely correlate with the most recent data from the United Kingdom where the same four systems accounted for more than 50% of the new cases each year.

Although, the overall rates have significantly improved over the years, the prognosis varies between different types of cancer. For example, whilst the 5 year survival rates for prostate and breast cancer patients are around 80%, the 5 year survival rates for pancreatic and oesophageal cancer are only 20%.

The main staple of treatment for cancer is surgical resection and this can be accompanied by radiotherapy and/or adjuvant chemotherapy. The treatment schedule varies depending on the type cancer and the stage, which it has progressed to. The number of drugs available for the treatment of cancer is increasing at a steady rate, mainly due to the relaxation of regulatory procedures in the United States. In the UK there are currently almost 90 different drugs licensed for the treatment of cancer.

## Colorectal cancer

### Background & disease staging

### Around 80% of colorectal cancer (CRC) cases are due to colon cancer and most are adenocarcinomas, which develop from polyps. Common symptoms are rectal bleeding, change in bowel habits and anaemia.

### 25% are due to genetic defects, e.g. familial adenomatous polyposis (FAP) & non-polyposis colorectal syndrome (NPCS). Inflammation, meat consumption & smoking are major risk factors whereas high fibre diets, folic acid intake and NSAID use reduce CRC incidence.

### The spread of CRC is described using Dukes’ staging (see table 1) or TNM (tumour, nodes, metastasis) classification

**Table 1: Dukes’ staging for colorectal cancer**

|  |  |  |  |
| --- | --- | --- | --- |
| **Dukes’ stage** | **Definition** | **Frequency (%)** | **5 year survival** |
| **A** | Localised within bowel wall | 10 | 80% |
| **B** | Penetrating bowel wall | 35 | 65% |
| **C** | Within lymph nodes | 25 | 40% |
| **D** | Distant metastases | 30 | 5% |

*Adjuvant chemotherapy*

Chemotherapy is given as an adjuvant to surgery in a minority of patients (~25%). It is offered to all Dukes’ stage C patients who are able to tolerate drugs following surgery.

Standard treatment is fluoropyrimidine-based therapy with **5-fluorouracil** (5-FU) & folinic acid (FUFA) given intravenously over 6 months. 5-FU is an **antimetabolite**. Folinic acid is tetrahydrofolic acid derivative that will allow for some purine and pyrimidine synthesis to occur.

**Antimetabolites**

5-FU is a widely used cytotoxic drug that is used for the treatment of various solid tumours. It is thought to exert its cytotoxic action by different mechanisms including:

* Inhibition of thymidilate synthase thus interfering with DNA synthesis and repair
* Incorporation into DNA and RNA thus inhibiting RNA processing and DNA synthesis

The main toxicities associated with 5-FU include bone marrow suppression, diarrhoea and neutropenia.

**Bevacizumab** (I-V) is licensed as secondary treatment for metastatic CRC. It is a monoclonal **antibody** that inhibits vascular endothelial growth factor (VEGF). Bevacizumab is always given as combination treatment with FUFA and is not recommended for first-line treatment. Its use has been associated with higher incidences of certain cardiovascular events and bleeding. It is also licensed, in combination therapy, for number of other metastatic solid tumours (e.g. metastatic breast, renal cell, non-small cell lung cancer).

## Non-small cell lung cancer

### Background & disease staging

Around 80% of lung cancers cases are classed as non-small cell lung cancer (NSCLC) and common symptoms include haemoptysis, cough, shortness of breath.

NSCLC can be categorised as:

* Squamous cell carcinoma (most common)
* Adenocarcinoma
* Large cell carcinoma

Although 90% of NSCLC cases are due to cigarette smoking, epidermal growth factor receptor (EGFR) mutations are found in ~15% of lung cancer patients.

Surgery can involve lobectomy or pneumonectomy and this is often combined with adjuvant chemotherapy and/or radiotherapy. NSCLC staging is described both numerically (see table 2) and using the TNM classification.

**Table 2: Staging for non-small cell lung cancer**

|  |  |  |
| --- | --- | --- |
| **Stage** | **Definition** | **5 year survival** |
| **1** | < 5cm diameter and localised within the lung | 40-70% |
| **2** | 5-7 cm diameter  May be within lymph nodes | 25-45% |
| **3** | > 7cm diameter  and has metastasised | 7-24% |
| **4** | In both lungs and has metastasised | 2-13% |

## *Adjuvant chemotherapy*

## Chemotherapy is given post-surgery to patients with stage 2 and above NSCLC and standard treatment is platinum-therapy, which consists of either:

## Cisplatin & etoposide

## Carboplatin & etoposide

## Carboplatin & gemcitabine

## Cisplatin & carboplatin

## Alkylating agents- Platinum compounds

## Cisplatin (I-V) and carboplatin (I-V) are alkylating (-like) agents that crosslink DNA guanine residues forming DNA adducts. Cisplatin has a broad range of activity but also a broad range of toxicity. Carboplatin is associated with lower incidences of emesis and nephrotoxicity but more bone marrow toxicity.

**Topoisomerase inhibitors**

## The topoisomerase enzymes play an essential role in separating the DNA strands during replications. The type I enzymes are only able to cut a single DNA strand whilst the type II enzymes are able to cut both strands of the DNA double helix. Etoposide (oral) is a natural product that is a type II topoisomerase inhibitor. The main toxic side-effect associated with etoposide is myelo-suppression.

## Gemcitabine (I-V) is an anti-metabolite (see table X) that:

## Inhibits ribonucleotide reductase

## Inhibits DNA polymerase

## Incorporates into DNA cause chain termination

Gemcitabine is also licensed for advanced pancreatic cancer, advanced bladder cancer (with cisplatin) and metastatic breast cancer (with paclitaxel).

### Advanced chemotherapy

For advanced or metastatic NSCLC a third-generation drug (**docetaxel**, **paclitaxel**, **vinorelbine**) is also recommended in combination with platinum therapy.

**Microtubule inhibitors**

**Docetaxel** (I-V) & **paclitaxel** (I-V) are taxanes that bind to the β subunit of tubulin, which form microtubules. They prevent microtubule disassembly thus inhibiting important processes such as treadmilling and dynamic instability

**Vinorelbine** (I-V) is a vinca alkaloid that also binds to tubulin within microtubules but has a different binding site and mechanism of action to the taxanes. It binds at the inter-dimer interface between the α and β tubulin subunits and inhibits microtubule assembly rather than disassembly.

**Erlotinib** & **gefitinib** are also recommended for patients with the EGFR mutation in NSCLC. These are selective inhibitors of the EGFR tyrosine kinase. Erlotinib is also licensed as combination treatment for metastatic colorectal cancer.

## Breast cancer

### Background & disease staging

The main symptom of breast cancer is a lump within the mammary gland (although approximately 90% of lumps within breasts are not cancerous) but other other common symptoms include breast/ nipple shape change, skin dimpling and discharge.

There are four main types of breast cancer:

1. Luminal A, B & C
2. Normal
3. Basal-like
4. HER-2 enriched

Age, weight, breast tissue density, alcohol consumption & exposure to oestrogen are all risk factors for developing breast cancer. Whilst numerous gene mutations are also implicated, especially BRCA1, BRCA2 & TP53

Non-pharmacological treatment involves a lumpectomy in combination with radiotherapy or a mastectomy and surgical reconstruction.

**Table 3: staging for breast cancer**

|  |  |  |
| --- | --- | --- |
| **Stage** | **Definition** | **5 year survival** |
| **1** | < 2cm diameter and found within breast or nearby lymph nodes | 90% |
| **2** | 2-5 cm diameter and found within breast or 1-3 lymph nodes | 70% |
| **3** | > 5 cm diameter and found within breast or 4-9 lymph nodes | 50% |
| **4** | Has metastasised to other regions | 13% |

*Adjuvant chemotherapy*

Hormone therapy (e.g. Aromatase inhibitors, tamoxifen) can be given before or after surgery for eostrogen receptor positive tumours and the TAC regimen (docetaxel, **doxorubicin** & **cyclophosphamide**) is recommended for early node-positive breast cancer. Cyclophosphamide (I-V) is a nitrogen mustard that acts as an **alkylating agent**.

**Alkylating agents- Nitrogen mustards**

The alkylating agents have electrophilic alkyl groups that form covalent bonds with nucleophilic cellular sites. The active alkylating species from cyclophosphamide (phosphoramide mustard and acrolein) preferentially bind to the oxygens present in phosphate groups of RNA and DNA and the oxygens of purines and pyrimidines. Although these agents react with cells in all phases of the cell cycle they are more efficacious in rapidly proliferating cells. These drugs are associated with severe nausea, bone marrow toxicity and alopecia.

**DNA intercalators**

The DNA intercalators include **doxorubicin** (I-V) and **daunorubicin** (I-V) and they can also be termed as type II topoisomerise inhibitors. They ‘poison’ topoisomerase II by intercalating DNA and stabilising the topoisomerase-DNA complex thus preventing re-ligation. They are primarily used for the treatment of liquid tumours (e.g. leukaemias & lymphomas), although doxorubicin has a number of indications. They are both are associated with myelosuppression, alopecia, nausea & vomiting.

**Trastuzumab** is recommended for HER-2 positive breast cancer and is a monoclonal antibody that binds to the extracellular region of the HER-2 neu receptor.

## Other cytotoxic drugs

### Other Antimetabolites (also see tables 4 & 5))

**Methotrexate** is also an antimetabolite that exerts its effects by inhibiting the critical enzyme in folate metabolism, dihyrofolate reductase. It is effective against a range of solid and liquid tumours but is associated with myelo-suppression and gastrointestinal toxicity. **Capecitabine, cytarabine, gemcitabine** (see later) and **mercaptopurine** are other prominent antimetabolites.

### Other topoisomerase inhibitors (also see tables 4 & 5)

**Irinotecan** (I-V) and **topotecan** (I-V) inhibit the type I topoisomerase enzyme and neither are indicated for NSCLC. Irinotecan is licensed as combination therapy and monotherapy for the treatment of metastatic colorectal cancer. Topotecan is licensed for the treatment of relapsed small cell lung cancer and metastatic ovarian cancer. Both drugs are associated with myelosuppression.

**Table 4: Selected cytotoxic drugs**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug category** | **Selected examples** | **Mechanism of action** | **Common side-effects** |
| **Antimetabolites** | Methotrexate | DHF reductase inhibitor | Myelosuppression, gastrointestinal toxicity, oral mucositis |
| Mercaptopurine | Inhibits the phosphoribosyl transferase enzymes involved in purine synthesis | Myelosuppression, gastrointestinal toxicity |
| 5-Fluorouracil, Capecetabine | Thymidylate synthase inhibitor | Bone marrow toxicity, diarrhoea, hand-foot syndrome, oral mucositis |
| Cytarabine, Gemcitabine | Potent inhibitors of DNA polymerases α,β and γ. Gemcitabine also inhibits ribonuclease reductase | Myelosuppression, leukopenia, thrombocytopenia |
| **Topoisomerase inhibitors** | Irinotecan | Inhibits the type I enzyme that is able to cut one DNA strand | Myelosuppression, diarrhoea |
| Etoposide | Inhibits the type II enzyme that is able to cut two DNA strands | Myelosuppression, leukopenia |
| **DNA intercalators** | Daunorubicin,  Doxorubicin | Intercalate DNA and ‘poison’ type II topoisomerase | Myelosuppression, nausea, vomiting, alopecia |
| Dactinomycin,  Bleomycin | Intercalate DNA between adjacent G-C bases and ‘poison’ type II topoisomerase | Myelosuppression, nausea, vomiting, alopecia |
| **Alkylating agents** | Nitrogen mustards:  Cyclophosphamide,  Chlorambucil | Form covalent bonds with DNA & RNA preventing replication, transcription | Bone marrow toxicity, **nausea, vomiting** |
| Platinum agents:  Cisplatin,  Carboplatin | Crosslink DNA guanine residues forming DNA adducts | Thrombocytopenia, **nausea, vomiting** |
| **Microtubule inhibitors** | Vinca alkaloids: Vincristine, Vinblastine | Inhibit assembly | Myelosuppression, nausea, vomiting, alopecia |
| Taxanes:  Docetaxel, Paclitaxel | Inhibit disassembly | Myelosuppression, nausea, vomiting, alopecia |
| **Monoclonal antibodies** | Rituximab | Chimeric B-cell CD20 antibody | Cytokine release syndrome, progressive multifocal leucoencephalopathy |
| Trastuzumab | Humanised IgG HER2/neu antibody | Cardiotoxicity |
| Bevacizumab | Humanised IgG VEGF antibody | Cardiotoxicity |
| **Tyrosine kinase inhibitors** | Gefitinib & Erlotinib | EGFR | Hepatotoxicity, keratitis |
| Sunitinib | Multiple receptor tyrosine kinases | Cardiotoxicity |

**Table 5: Licensed indications of selected cytotoxic drugs**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Anti-metabolites** | | | | | **Topo-i inhibitors** | | **DNA intercalators** | | **Nitrogen mustards** | | **Platinum agents** | **Microtubule inhibitors** | | **Monoclonal antibodies** | | | **TyR kinase inhibitors** | |
| **Type of cancer** | | **1a** | **1b** | **1c** | **1d** | **1e** | **2a** | **2b** | **3a** | **3b** | **4a** | **4b** | **5a** | **6a** | **6b** | **7a** | **7b** | **7c** | **8a** | **8b** |
| **Digestive** | **Colorectal** |  |  | **X** |  |  |  |  |  |  |  |  | **X** |  |  |  |  | **X** |  |  |
| **Pancreatic** |  |  |  |  | **X** |  |  |  |  |  |  |  |  |  |  |  |  | **X** |  |
| **Lung & Bronchi** | |  |  |  |  | **X** |  | **X** |  |  |  |  | **X** | **X** | **X** |  |  | **X** | **X** |  |
| **Breast** | |  |  | **X** |  | **X** |  |  | **X** |  |  |  |  | **X** | **X** |  | **X** | **X** |  |  |
| **Urinary** | **Kidney** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **X** |  | **X** |
| **Bladder** |  |  |  |  | **X** |  |  |  |  |  |  | **X** |  |  |  |  |  |  |  |
| **Melanoma** | |  |  | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Leukaemia** | **Lymphocytic** | **X** | **X** |  |  |  |  |  | **X** |  | **X** | **X** |  | **X** |  |  |  |  |  |  |
| **Myeloid** |  | **X** |  | **X** |  |  |  |  |  | **X** | **X** |  | **X** |  |  |  |  |  |  |
| **Non-Hodgkin lymphoma** | | **X** |  |  |  |  |  | **X** | **X** | **X** | **X** | **X** |  | **X** |  | **X** |  |  |  |  |

1. **Antimetabolites**
   1. Methotrexate (DHF reductase inhibitor)
   2. Mercaptopurine (purine precursor)
   3. Fluorouracil, capecetabine (thymidilate synthase inhibitor)
   4. Cytarabine (DNA polymerase inhibitor)
   5. Gemcitabine (ribonuclease reductase inhibitor)
2. **Topo-isomerise (Topo-i) inhibitors**
   1. Irinotecan (type I)
   2. Etoposide (type II)
3. **DNA intercalators**
   1. Doxorubicin (also a topo-I inhibitor)
   2. Bleomycin
4. **Nitrogen mustards**
   1. Cyclophosphamide
   2. Chlorambucil
5. **Platinum agents**
   1. Cisplatin
6. **Microtubule inhibitors**
   1. Vinca alkaloids (inhibit assembly)
   2. Docetaxel, paclitaxel (inhibit disassembly)
7. **Monoclonal antibodies**
   1. Rituximab (B-cell CD20)
   2. Trastuzumab (HER2/neu)
   3. Bevacizumab (VEGF)
8. **Tyrosine kinase inhibitors**
   1. Gefitinib & Erlotinib (EGFR)
   2. Sunitinib (multiple receptor tyrosine kinases)

NB: Shaded cancer types indicate liquid tumours

**Prof. Nigel Gooderham’s learning objectives**

1. To be able to define the term ‘Cancer.’

Cancer can be defined as a disease that is caused by the uncontrolled proliferation and growth of abnormal cells

1. To be able to describe the characteristics of cancer cells.

Cancer cells display: self-sufficient growth; angiogenesis; evasion of apoptosis; avoiding immune detection; limitless replication potential

1. To be familiar with the molecular basis of chemotherapy.

Antimetabolites affect enzymes involved in nucleic acid synthesis; cisplatin forms DNA adducts, alkylating agents form covalent bonds with nucleic acids; the taxanes & vinca alkaloids inhibit microtubules

1. To be able to discuss the potential targets for chemotherapy.

DNA, topoisomerase, microtubules, tyrosine-kinase linked receptors

1. To be able to identify the major classes of anticancer drugs and describe their mechanisms of action.

Antimetabolites: e.g. 5-fluorouracil; Topoisomerase inhibitors: e.g. Etoposide; DNA intercalators: e.g. Doxorubicin; Alkylating agents: e.g. Cyclophosphamide; Microtubules: e.g. Vinca alkaloids; TyR receptor inhibitors: e.g. Trastuzumab, erlotinib