# CANCER 12

# BIOLOGICAL BASIS OF CANCER THERAPY

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**Objectives**

* Describe the main chemotherapeutic and radiotherapeutic approaches to treating cancer
* Explain why many cancer treatments cause side effects such as nausea, hair loss, anaemia and immunosuppression, and indicate the approaches which have been tried to minimise these
* Explain the rationale for the newer drugs in cancer therapy
* Discuss the prospects for new therapies based on the biology of cancer development

# Hallmarks of a cancer cells

## Keep on growing

## Keep on dividing

## (Invade & Spread)

# Targeting cancer cells

## Keep on growing - target DNA synthesis

## Keep on dividing - target mitotic spindle

# The discovery of chemotherapy

## By mistake

## By luck

## By trial and error

# Cytotoxic discovery by mistake

# Mustard Gas

## Bis (2-chloroethyl) sulphide (C4H8Cl2S)

# Mustard gas in warfare

## 1925 Geneva protocol signed

## 1925 Spain against Morocco

## 1930 Soviet Union against China

## 1935 Italy against Ethiopia

## 1937 Japan against China

## 1965 Egypt against North Yemen

## 1985 Iraq against Iran

## 1988 Iraq against Kurds

# US Chemical Warfare Service

## Established 1940

## ‘Chemical warfare antidotes’

## Director Cornelius Rhoads

## (later founded Memorial Sloane Kettering Hospital)

# 1943 Bari Harbour

## German raid on US fleet in Bari harbour sunk USS John Harvey

## USS John Harvey was carrying 2000 M47A1 bomb containing a total of 100 tonnes of mustard gas

# Bari Harbour victims

## Survivors developed conjunctivitis & skin blistering

## 4 died the next day, 9 the following day…..etc

## 83 of 617 survivors died within a month

## Colonel Stewart Alexander noted steep fall in white cell count on day 3-4 after exposure…mustard gas was stopping bone marrow cells dividing to make white cells

## Sulphur mustard Nitrogen mustard

## (Mustard gas) (mechlorethamine)

## CH2-CH2-Cl CH2-CH2-Cl

## S N

## CH2-CH2-Cl CH2-CH2-Cl

# US Military research programme

## 1942 Alfred Gilman & Louis Goodman (Yale)

## Nitrogen mustard in mouse with lymphoma led to tumour regression

# The first chemo patient

## 1944 Mr JD (48 year old silversmith) with non-Hodgkin’s lymphoma

## Treated with nitrogen mustard

## Tumours regressed and he lived 2 months before dying of marrow failure

# Drug discovery by luck

# Cisplatin

## 1965 Barnett Rosenberg (physicist at Michigan State university)

## Studied effects of electric currents on E.coli using platinum electrodes in a water bath

# Cisplatin

## E coli stopped dividing but not growing leading to long bacteria up to 300 times longer than normal

## Cisplatin a product from the platinum electrodes is responsible

# Drug discovery by trial and error

# Nixon declares “War on Cancer”

# Drug testing program at NIH

# Classes of chemotherapy from nature

## Vinca alkaloids

## Taxanes

## Camptothecans

## Anthracyclines

## Bleomycin

## Epipodophyllotoxins

## Actinomycin

# How does chemotherapy work?

## Cancer cells divide too fast:

## 1. Target formation of DNA bases

## 2. Target DNA to inhibit synthesis

## 3. Target mitotic spindle

# Antimetabolites – inhibit base synthesis

## False bases

## Purine analogues

## Pyrimidine analogues

## Inhibit enzymes that synthesise DNA bases

## Dihydrofolate reductase inhibitors

## Thymidylate synthetase inhibitors

# Purine analogues

# Pyrimidine analogues

# Antimetabolites

## 1933 Dr Lucy Wills reversed anaemia in Bombay textile workers by giving Marmite

## The anaemia was due to folic acid deficiency which was described in 1943

# Anti-folates

## 1945 Sidney Farber (Harvard) gave folic acid to patients with acute leukaemia where it accelerated the leukaemia

## Dr Subba Row of Lederle commissioned to make folic acid antagonists

# Aminopterin

## First anti-folate synthesised

## 1947 Faber treated 16 children with acute leukaemia with aminopterin and 10 achieved temporary remission

# Methotrexate

## Synthesised in 1949 and superseded aminopterin

## First ever cures (durable remissions) with chemotherapy alone reported with methotrexate for choriocarcinoma in 1963 by Roy Hertz & Min Chiu Li

# Disrupt DNA double helix & interfere with DNA synthesis

## Alkylating agents -bind to DNA bases

## Intercalating agents -disrupt double helix

## Topoisomerase inhibitors -disrupt DNA supercoiling

# Alkylating agents

# Consequences of DNA alkylation

# Actions of topoisomerases

# E*topo*side – a topoisomerase inhibitor

# Cancer- too many cells dividing

# Mitosis

# Microtubule growth

# Taxanes

## Paclitaxel -Pacific Yew bark

## Docetaxel -European Yew needles

# Taxanes bind β-tubulin

# Why the drugs don’t work

# Multi-drug resistance

## MDR-1 Pglycoprotein efflux pump overexpression

## Pumps out toxins from cells including most cytotoxics

# Cytotoxic drug specific resistance

# Methotrexate

# Actions of methotrexate

# Antifolate in pyrimidine (A,T) synthesis

# Inhibits DHFR

# DHFR gene amplification

## Methotrexate resistance due to amplification of DHFR gene as double minutes (d min*) and homogenously staining regions (HSR)*

# The good, the bad and the ugly

# Predictable side effects

## Fast growing normal cells

### 1. Inhibit cell division

### 2. Cell cycle specific drugs

### Bone marrow, GI tract epithelium, hair & nails,

### Spermatogonia

## Slow growing normal cells

### 1. Introduce DNA mutations

### 2. Cell cycle independent (alkylating agents)

### Secondary tumours

# The commonest side effect ?

# Side effects ranked by severity by patients

## Nausea

## Tiredness

## Hair loss

## Concern about effect on friends & family

## Vomiting

# Classification of toxicities

## Immediate: Nausea & Vomiting

## (Hours after) Anaphylaxis (allergy)Extravasation (tissue damage)

## Delayed: Myelosuppression (low blood cells)

## (Days-weeks) Stomatitis (sore mouth)

##  Alopecia (hair loss)

##  Neuropathy (nerve damage)

## Late: Infertility

## (Years) 2nd tumours

# How to be struck off and do time….

# Wayne Jowett of Nottingham

# Manslaughter

## Dr Feda Mulhem was only 3 days into his first post as SpR in haematology was supervising Dr David Morton (SHO), who had been at the hospital for 4 months and had never given the treatment before.

## Dr Feda Mulhem was given 8 months in jail for manslaughter.

# How to be struck off and do time….

## Since 1985 at least 13 patients in the UK have died

# Radiotherapy

# Topical radium

# Linear accelerator in 1940s

# How radiotherapy kills

# Radiation damage to DNA

# Radiation dose & effect

## 1 Gray is the dose absorbed when 1 joule is deposited in 1kg of tissue

## Each Gray per cell causes:

##  10,000 damaged DNA bases

##  1,000 damaged deoxyribose sugars

##  1,000 single strand breaks

##  40 double strand breaks

##  150 DNA-protein cross links

##  30 DNA-DNA cross links

# 8:15 am August 6, 1945

# Hiroshima

## Kengo Futagawa was crossing the Kannon Bridge (1,600 meters from the hypocenter). He jumped into the river, terribly burned. This is his watch – stopped at 8.15am when the bomb landed.

# Effects of nuclear bomb irraditation

# New targets, so new drugs…

## (There’s more to cancer than DNA replication and mitosis)

# Six Steps to Cancer

## 1. Self sufficiency in growth stimuli

## 2. Insensitivity to inhibitory stimuli

## 3. Evasion of apoptosis

## 4. Immortalisation

## 5. Neoangiogenesis

## 6. Invasion and metastasis

# 1. Autonomous growth signals

# Targeting EGFR

# Antibodies = -mab

# “Humanisation” = -zumab

# cerbB2/Her2 in breast cancer

# Anti-cErbB2 (Her 2) staining

# Herceptin (Trastuzumab)

## Cost: 1 year adjuvant trastuzumab £21,000

## Benefit:

## HERA trial Increase DFS 8.4%.

## No difference in overall survival.

## US studies Increase DFS 12%

## Increase in overall survival at three years is 2.5%

## Risks:

## HERA trial Cardiac events 0.5-2.2%. Treatment withdrawals due to cardiac events in 5.5%

## Combined US studies Heart failure/death from cardiac causes was 0.8% in control group and 4.1% in Herceptin group.

# 2. Ignore cell cycle arrest points

# Cell cycle

# 3. Evade apoptosis

## Bcl2 prevents apoptosis and is over produced by cancer cells

## Turning off bcl2 production should lead to programmed cell death

# Antisense oligonucleotide to bcl-2

# 4. Immortalisation

## Cancer cells (and normal germinal cells) avoid senescence by producing telomerase (hTERT) that restores the telomere ends.

# 5. Neo-angiogenesis

# Angiogenesis inhibitors

# 6. Invasion & metastasis

# 26 human matrix metalloproteinases

# How can you tell if it works?

# Phase I trials

## Aim: Determine toxicity & dose scheduling

## Who: Few patients for whom no known alternative therapy is available

## Endpoints: Activity in humans

##  Maximum tolerated dose

##  Pharmakokinetics

##  Side effects related to different doses

# Phase II trials

## Aim: Identify promising tumour types

## Who: More patients than phase I trials treated at the dose and schedules determined in phase I

## Endpoints: Activity in human tumour types

##  Side effects

# RECIST criteria for response

## Complete response: disappearance of all known disease

## Partial response: >50% reduction in measurable lesions and no new ones

## Stable disease: lesions unchanged (<50% smaller or <25% larger)

## Progressive disease: new lesions or measurable lesions >25% larger

# A sustained complete response

# A partial response

# What are the consequences for a cancer survivor?

# Cancer prevalence in UK

## 2% of the population of the UK (1.2 million people) are alive having received a diagnosis of cancer

## Mainly breast cancer (180,000)

# Childhood cancer survivors

## 1 in 600 children (often inherited risk)

## 7 in 10 are cured (3 in 10 in 1960s)

## In UK 55,000 young adults (16-40y) who are cancer survivors

# Late side effects

## Late effects of surgery

## Late effects of radiotherapy

## Late effects of chemotherapy

## Psychological consequences

# Common psychological problems

## Lazarus syndrome

## (difficulty with returning to normal life)

## Damocles syndrome

## (fear of recurrence and terror of minor symptoms)

## Survivor syndrome

## (guilt about surviving where others have died)

# Conclusions 1- Biological basis of chemotherapy

## Molecular basis of chemotherapy – DNA and mitotic spindle

## 5 Classes of cytotoxics -

##  Antimetabolites

##  Alkylating agents

##  Intercalating agents

##  Topoisomerase inhibitors

##  Spindle poisons

# Conclusions 2- Biological basis of radiotherapy

## High energy Ionising Radiation damages DNA

## Ionisation

## Delivery of radiotherapy

##  External beam

##  Brachytherapy

##  Radio-isotopes

# Conclusions 3- Biological basis of new treatments

## Target 6 molecular mechanisms

## -Nibs & -Mabs

# Further reading

Bower, M. & Waxman, J. Oncology, Blackwell Publishing