

## Extension materials for lecture 3 : Chemo & Biologicals

### The Start of Chemotherapy

- ❖ Paul Ehrlich a German organic chemist, coined the term Chemotherapy in 1909. He was interested in producing stains for indoles & amino acid structures in biological material (Ehrlich's reagent)
- ❖ He inadvertently invented the first dope test! (LSD)
- ❖ 'Chemotherapy' to him meant the treatment of disease using chemical agents
- ❖ Initially referred to antimicrobial therapy
- ❖ Since 1950's, term has been synonymous with anti-cancer therapy.

### Development of chemotherapy

Chemotherapy has gone from a history of serendipity and mass screening of compounds through to rational drug design and the use of targeted therapies

- ❖ Nitrogen mustards were observed to cause lymphopaenia in (accidentally) exposed Italia soldiers
- ❖ Goodman & Gillman (Yale) used nitrogen mustard on a mouse lymphoma. Able to induce remission.
- ❖ Their boss at Yale, Milton Winternitz, signed a deal with US government to develop antidotes to nitrogen mustard agents.
- ❖ Patient JD at Yale, first person to receive chemotherapy August 25 **1942** (Lymphosarcoma of neck and cervical region, relapsed after radiation therapy).
- ❖ Written up in the notes as Substance X. September 27 – all neck nodes and masses had gone.
- ❖ Response was short lived. Tumour recurred in November, patient died in hospital in December

Antifolate therapy followed soon after Carmustine

- ❖ 1948 : Sidney Farber used a folate analogue aminopterin to induce remission in ALL
- ❖ 1950 : Actinomycin D developed as an antibiotic. Too many side effects to be useful as an antibiotic, but used as a cytotoxic
- ❖ 1951 : Hitchings and Elion (Working at Wellcome) synthesised 6-mercaptopurine
- ❖ 1951 : Methotrexate synthesised to have higher therapeutic index than aminopterin. Used to treat patients with a solid tumour (breast cancer)
- ❖ Folinic acid is used to protect from the bone marrow, liver and mucosal side effects of methotrexate, especially when given at high dose. It works by restoring folate pools in cells. You might think therefore that if you give a lot of folinic acid, it would counteract the effect of methotrexate. However, high doses of folinic acid actually inhibit thymidylate synthase, and thus have an anti-proliferative effect in their own right.

In the 1970's and 80's, the advent of cisplatin and the anthracycline agents really transformed the use of chemotherapy agents, particularly in solid tumours.

- ❖ Cisplatin was found to inhibit the growth of bacterial cells. Cells in suspension were observed not to grow close to platinum electrodes when current was running through the electrodes. If the current was turned off, then the cells grew normally. Barnbett & Noble realised that the platinum ions must somehow be combining with something in the solution and preventing the bacterial cells from dividing.
- ❖ We now use cisplatin in combination with other agents as adjuvant treatment for a whole range of cancers (squamous cancer in head & Neck and cervix, adenocarcinomas of the GI tract, paediatric brain tumours)

- ❖ Adriamycin, the first anthracycline compound used clinically, was isolated by Farmitalia from a red coloured fungus found growing on the shores of Adriatic sea, hence the drug was called Adriamycin.
- ❖ Epirubicin is a second generation agent introduced in 1980's. It was modified to facilitate clearance from body and hence reduce cardiac toxicity.

❖

Taxanes were identified by NCI drug discovery programme. Thousands of US plants collected in 1960's and screened for medicinal properties.

- ❖ On August 21 1962 the bark of Pacific Yew tree (*Taxus brevifolia*) was collected by Arthur Barclay in Washington State, and in 1971 a crystalline version of Taxol extracted.
- ❖ Hugely resource intensive – bark from 1 tree = single dose of drug
- ❖ Now made by plant cell fermentation
- ❖ Taxol is not water soluble. Has to be solubilised in modified castor oil and ethanol. Carrier frequently causes systemic allergic response.

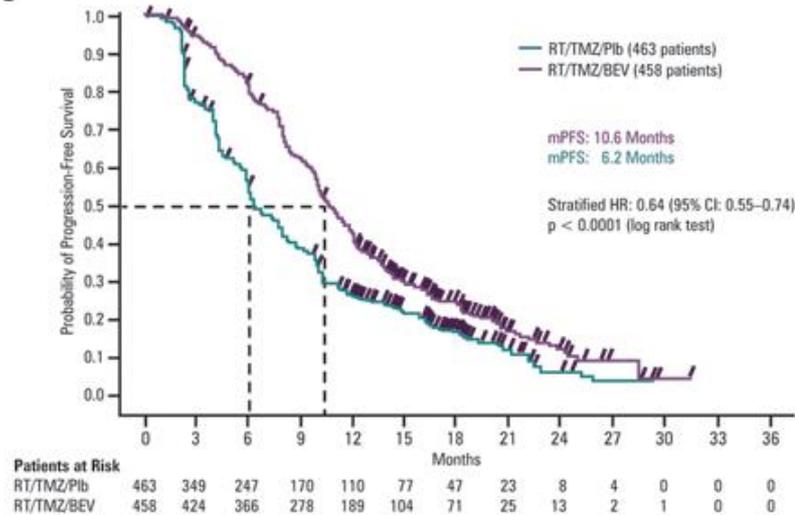
### **Biological therapies**

- ❖ Unlike early chemotherapy discovery, biological agents are developed using a very rational paradigm.
  - First a biochemical pathway is identified that is upregulated or dysregulated in tumour cells, and not in normal cells
  - Nest combination chemistry is used to design a drug that fits the target
  - Drug development cost is much higher, but as the drug has been designed to fit a particular mechanism, it should be quicker to get to studies that demonstrate efficacy of the drug
  - Many side effects relate to non-specific immune system activation and effects on health cells (mucositis, diarrhoea)
- ❖ There is a long & expensive lead time for discovery of the drugs. The development cost of the drug must be recouped in the retail costs. Manufacturers retain longer patents for biological therapies.
- ❖ Just as there are generic version of many medicines, it is possible to produce analogues of biological agents called 'Biosimilars'. There are of course concerns as to whether or not a biosimilar is the same drug

### **The top 5 biologicals**

- ❖ Avastin was developed by Genentech / Roche. It was first licensed in 2004 for treatment of metastatic colon cancer. Now used in range of tumours (lung, breast, kidney, GBM) as well as treatment of macular degeneration and for vestibular schwannomas in patients with Neurofibromatosis type 2
- ❖ Avastin can induce dramatic initial response in some tumours, but they are not always maintained (pseudoresponse). The Avaglio study of adjuvant Avastin in Glioblastoma shows the classic effect of a cytostatic agent. There is an initial apparent response, but eventually the survival advantage was lost after 12 months in the study.

## AVAglio



- ❖ Herceptin was also developed by Genentech, and was first licensed in September 1998. Dennis Slamon established efficacy in breast cancer models.
- ❖ Herceptin has proven efficacy in metastatic breast cancer in patients with HER2+ tumours, and is now also used in adjuvant breast cancer therapy in women with high risk HER2+ tumours.
- ❖ Iressa is a very interesting drug that nearly didn't make it to clinical use, due to genetic variation in EGFR mutations found in non-small cell lung cancer. Initial Japanese studies were performed showing really impressive responses in trial patients, but the same response rates were not observed in US, or European patients.
- ❖ It transpires that the rate of EGFR mutation is higher in Japanese population and in non-smokers with NSCLC (20-25%), compared to our average Cambridge patient (8%). Now we use pre-treatment EGFR mutation testing as a predictive assay, and confirm whether or not the tumour is likely to respond to therapy.

## Rational approaches to the treatment of tumour recurrence

- ❖ When tumours recur after previous chemo and biological therapies, it can be hard to determine which drug would be the best to use for a patient.
- ❖ A novel approach now being adopted in clinical practice is to resect a recurrent tumour and examine its expression profile of certain key gene sequences using high throughput screening techniques.
- ❖ The screen may determine an active pathway with a druggable target. Treatments are then chosen on the basis of this expression profile. Thus a patient with a recurrent Glioblastoma may be found to have cKit overexpression and treated with Imatinib.

## Resistance to biological therapies

- ❖ For tyrosine kinase inhibitors (TKIs), resistance typically typically sets in 8-12 months after starting treatment.
- ❖ It may lead to what is known as a differential response, where some tumours continue to respond to the drug, whilst other do not.
- ❖ It is sometimes possible to switch TKI and continue getting a response, but again it may not be a lasting response.