

Antineoplastic drugs - recent developments

by John Hammond

Cancer is worldwide a healthcare problem affecting one in three people in the developed world, and killing one in four. Worldwide, 12.5 million new cases are diagnosed each year, and this is predicted to reach 15 million by 2020. As a result, the total market for cancer therapies is predicted to reach \$55-70 billion by 2010.

Comparison data for 2004 show that the prevalence of cancer has increased as other aspects of healthcare have improved. For example new cases of malignant neoplasms, excluding non-melanoma skin cancer, diagnosed in England in 1971 were 143,880, and 240,283 in 2005. At least part of this increase is likely to be caused by ageing of the population; there is a sharp increase in cancer cases from age 55 onwards.

Although we know that mutation of genes controlling cell division causes cancer, the large variety of cancers, and the range of tissues which they affect has made understanding of the molecular and cellular mechanisms a complex challenge. There are still many aspects of cancer biology, for example metastasis, which are poorly understood.

This has not prevented development of antineoplastic drugs (drugs which act against newly proliferating cells), because therapies for cancer have focused mainly on agents which target dividing cells. Since most cancer cells are rapidly dividing they are selectively targeted.

The first antineoplastic compound to be tested was the chemical warfare agent mustard gas. We now know that this modifies DNA, leading to cell death by apoptosis when the damage cannot be repaired. Mustard gas produced a short-term improvement, and stimulated research into more effective drugs. Cyclophosphamide (Cytosan, Neosar), a derivative of mustard gas, is still used in cancer treatment. Cisplatin also acts through DNA modification.

Drugs such as floxuridine, 5-fluorouracil are incorporated into new DNA, also interfering with cell division. Paclitaxel interferes with the separation of chromosomes during cell division by interfering with microtubule function. These drugs also cause cell death.

There are drawbacks to drugs which aim to kill cancer cells through interfering with cell division. Some healthy tissues, such as gut epithelium, contain rapidly dividing cells and these will also be susceptible to such drugs, causing serious side effects. Additionally, some cancer cells, for example those within tumours, grow more slowly and are less susceptible. Cancer cells may also develop resistance to some drugs.

These problems have led to a demand for drugs which can target cancer cells more precisely. Research into the molecular mechanisms of cancer is still in progress, and development of new and effective antineoplastic drugs has been slow. Despite this, GlaxoSmithKline reports 32 drugs from phase I onwards for cancer and associated problems in its development pipeline, while Pfizer reports 24.

The main targets for antineoplastic drug in development are colorectal cancer, non-small cell lung cancer, breast and ovarian cancer. This reflects the frequency of the diseases. Lung cancer is the most common type of cancer, causing 24% of cancer deaths in UK males and 19% in females. Breast cancer and prostate cancer are the next most common cancers at 17% and 13% in the UK, while colorectal cancers account for around 10% of UK cancer deaths. There is also interest in drugs effective against less prevalent forms of cancer, partly because they may eventually provide treatments for other cancer types.

The toxicity of many current antineoplastic is a major concern. Drugs which interfere with DNA and the cell's ability to divide are also likely to introduce mutations, and are therefore potential carcinogens. For example, cyclophosphamide is listed as a human carcinogen and cisplatin as a probable carcinogen, by the International Agency for Research on Cancer.

This means that these drugs can lead to development of new cancers in patients being treated with them, and lead to risks to healthcare and home care workers who prepare and administer the drugs. As well as potential carcinogenicity in these workers, symptoms such as hair loss, hypersensitivity and headaches have been recorded, as well as reproductive problems in female workers.

To reduce the risk to workers a range of recommendations for safe handling of antineoplastic drugs have been made by the US National Institute for Occupational Safety and Health. These include use of adequate personal protective equipment and procedures and correct cleanup of working surfaces and equipment. Also it is recommended that preparation is carried out in containment cabinets and spills cleaned up with safe disposal. Routine monitoring of work and treatment areas for contamination, and routine medical testing for staff should also be maintained.

One of the main areas of interest in antineoplastic development is to target proteins involved in the systems which relay the signal for the cell to divide. Drugs acting in this way are likely to be cytostatic, preventing tumour growth, rather than cytotoxic. This should mean that they present a lower risk to patients and medical staff.

Tamoxifen was the first antineoplastic drug to target a signal receptor. It blocks the oestrogen receptor in breast tumour cells, so preventing their growth and division. However, this is not free from risk, since the drug stimulates the same receptor in the endometrium, leading to the possibility of endometrial cancer.

Attention has now moved away from hormone receptors to more general growth receptors. Erbitux (cetuximab), Avastin (bevacizumab) and Tarceva (erlotinib) are more recent examples of antineoplastics which target receptors. Their targets are growth factor receptors. When growth factors bind to their receptors, a signal is transmitted from the receptor via protein kinases to the nucleus, stimulating cells to grow, divide and spread. Blocking the receptor stops cell growth (i.e. is cytostatic). These drugs are effective in the treatment of a range of cancer types.

Both Erbitux and Tarceva target the activity of the epidermal growth factor receptor (EGFR). Erbitux is a monoclonal antibody which binds to the receptor, preventing its activation. It is used to treat metastatic colon cancer. Tarceva blocks the tyrosine kinase signalling system of the receptor, and is used in treatment for lung and pancreatic cancers.

Cells within a tumour are often difficult to eliminate because of their low growth rates, and poor blood supply within the tumour, leading to low drug access. Avastin, another monoclonal antibody, binds to, and blocks vascular endothelial growth factor (VEGF). This prevents the growth of blood vessels, cutting off the supply of blood and nutrients to developing tumours. It has been approved for treatment of breast cancer and colorectal cancer, and has activity in renal cell cancer and ovarian cancer when used as a single agent, and in combined therapy for lung cancer.

Trastuzumab (Herceptin) is a monoclonal antibody that acts on the ErbB2 receptor, a member of the same receptor family as EGFR. Trastuzumab's principal use is against breast cancer in patients whose tumours produce increased amounts of the receptor.

There are more drugs targeting receptors and signalling kinases in the manufacturer's pipelines.

Further into the future there is interest in the mechanisms that allow cancer cells to metastasise, in oncogene regulation and in the process of programmed cell death, or apoptosis.

Interference with metastasis would allow the physicians to treat the original tumour without exposing the patient to the danger of spread of cancer to other tissues. Tykerb (lapatinib ditosylate) inhibits the tyrosine kinase of both EGFR and ErbB2. It is under development by GlaxoSmithKline to treat solid tumours such as breast and lung cancer. Combination therapy of breast cancer patients with Tykerb and capecitabine reduced the incidence of CNS and brain metastases. Inhibiting both receptors may also be a means of overcoming drug resistance.

Current research on metastasis suggests that a match between the receptors carried by specific cancer cells and their chemokine activators expressed in the tissues where metastases develop is important. For example, breast cancer cells carry large numbers of the CXCR4 chemokine receptor, and lung tissue where metastases develop, expresses high levels of CXCL12, a soluble activator for the receptor. Breast cancer metastasis does not occur in skin where CXCL12 is not expressed. Similarly, melanoma and skin cells have matching chemokine receptor and activator in common. The activation of chemokine receptors in wandering cancer cells may switch on genes enabling tissue invasion. If this is a general pattern, blocking the chemokine receptor could reduce metastasis.

We now have extensive knowledge of the genes which are mutated to initiate cancer. Another part of the puzzle now seems to be falling into place. Over the last few years research has shown that heritable changes in gene expression can occur without a change in DNA sequence.

Such epigenetic changes are due to methylation of cytosine in regions of the DNA. This turns off the production of proteins from genes in these regions. Study of cancer cells has shown that genes connected with cancer may be affected by incorrect methylation. There is also evidence that methylation increases with ageing.

If faulty methylation has a role in switching cells towards uncontrolled proliferation and cancer, treatments which remove it may be therapeutic. Hydralazine and valproic acid are drugs used to treat cardiovascular and neurological conditions. Hydralazine inhibits DNA methylation, and valproic acid inhibits a related process, the removal of acetyl groups from the histones associated with DNA. Trials have suggested that combined use of these drugs may limit the growth of cancer cells.

Although current drugs target protein activity, it is now becoming possible to reduce or block the production of these proteins at the cell level. This may be achieved through the use of either antisense oligonucleotides or small interfering RNAs (siRNAs). Both of these technologies prevent the translation of the target mRNA into protein. For example, siRNA has been shown suppress H-ras oncogene expression, indicating potential for application in therapy of ovarian cancer.

Although effective cancer treatment once seemed an intractable problem, painstaking research has led to the development of a range of drug therapies. Improved understanding of cancer biology is allowing the development of more specific antineoplastic drugs. These will help to reverse the rising world trend of the disease.

copyright: J.B.W. Hammond 2008