Recent advances in our understanding of the cellular and molecular pathology of cancer are facilitating the development of new treatments which are expected to be both more active and less toxic than conventional therapies. These new treatments are known as 'targeted therapies' because they target lesions underlying the disease, as opposed to conventional cytotoxic drugs which act indiscriminately on all dividing cells.

General features of the molecular and cellular pathology of cancer are summarised in Table 1. At the genetic level, the development of a cancer cell involves the:

- activation of oncogenes that confer a growth and survival advantage
- inactivation of tumour suppressor genes which normally act to regulate cell division
- reactivation of immortality genes that allow the indefinite replication of the tumour cell.

At the cellular level, the three key features of the malignant cancer cell are its ability to:

- invade local normal tissue
- develop a blood supply
- metastasise to form secondary tumours.

Drugs to target all these processes are being developed.

**Historical approaches to the development of anticancer therapies**

The major approaches to treating cancer are listed in Table 2. Surgery and radiotherapy remain widely used and are curative when the total tumour mass can be excised or irradiated with a lethal dose of ionising radiation. However, most patients have disseminated disease at the time of presentation and hence cannot be cured by surgery and local radiotherapy alone. In contrast, chemotherapy can have curative activity against disseminated malignancies. A number of childhood solid tumours, certain haematological malignancies and rare adult cancers (eg testicular teratoma) are diseases where the majority of patients can be cured. In more common adult solid tumours, notably breast and colorectal cancer, adjuvant chemotherapy can cure a subset of patients and produces valuable tumour control in more advanced disease. Experimental approaches to cancer treatment are immunotherapy and gene therapy, but these have yet to have a major clinical impact.

There are two types of conventional chemotherapy: cytotoxic drugs and anti-endocrine agents:

- **Cytotoxic drugs** prevent cell division by inhibition of DNA replication (antimetabolites, alkylating agents, platinum complexes, DNA-binding drugs and topoisoisomerase inhibitors) or chromosome segregation (tubulin binding agents). Cell division in normal tissues is also affected, giving rise to the characteristic toxicities of cytotoxic drugs – leucopenia/anaemia/thrombocytopenia, stomatitis/diarrhoea, alopecia – due to effects on the bone marrow, gastrointestinal epithelium and hair follicles, respectively.

- **Anti-endocrine agents** act by depriving tumours that arise in hormone-dependent tissues (ie breast, prostate) of the endocrine hormones they require for growth: oestrogens and androgens, respectively. In this respect, anti-endocrine agents are targeted therapies.

**Development of conventional therapies**

The processes involved in the development of conventional therapies are summarised in Fig 1. In most instances, a drug 'lead' was identified by a mixture of scientific/clinical intuition and serendipity. For example, the atrophy of lymphoid glands in soldiers exposed to sulphur mustard gas in World War I led to the development of nitrogen mustard (ie mustine) and its use to treat patients with lymphoma. Rapid disease progression in children with leukaemia given folate supplements led to the development and use of antifolate drugs (eg methotrexate). Once a first-generation drug with significant activity was identified, analogue development was undertaken in an attempt to:

- improve the pharmaceutical properties (eg solubility, stability)
• improve pharmacokinetics (eg potential routes of administration, metabolism)
• reduce the toxicities (eg to avoid non-antiproliferative side effects such as renal or cardiac damage), or
• enhance activity (eg by avoiding resistance mechanisms).

Table 3 gives examples of first-generation cytotoxic drugs and the analogues that have been developed together with the rationale for their development. Although analogue development has been extremely successful, only rarely has it resulted in an agent with a markedly greater level or spectrum of activity.

Contemporary approaches to drug development

Stages in contemporary drug development are illustrated in Fig 2. Unlike conventional cytotoxic drugs, where targets or mechanisms of action of the lead compounds were unknown at the time they were first used in patients, the drug development process now starts with the identification of a target that is linked to the molecular or cellular pathology of cancer. Specifically, using genomic and proteomic analyses, for example gene sequencing, chromosomal analysis, gene expression, protein level or, more rarely, protein function studies, an association is sought between the presence of the target and patient outcome (eg disease-free or overall survival).

Target discovery

An excellent example of this approach is provided by the studies of HER-2/C-erbB2 growth factor receptor expression in breast cancer which ultimately led to the development of trastuzumab for HER-2/C-erbB2 overexpressing breast cancer.

Target validation

Once a target has been identified, it must be validated. This normally involves the generation of laboratory models of the clinical disease in which the gene or protein of interest is present or absent or its function can be modulated. These target validation studies seek to establish that presence of the target promotes tumour cell growth, survival, spread etc, whereas removal or lack of the target compromises the tumour. Target validation is the most difficult aspect of drug development – but developing a drug against an invalid target will lead to an inactive agent.
Lead discovery

Having selected a valid target, there are both rational and empirical approaches to developing chemical leads that interact with the target in the desired manner:

- The rational approach uses data on the structural biology of the target, the biochemistry of the process the target controls and information on natural substrates or ligands as the starting point for the chemical synthesis of molecules designed to influence target function in the desired manner. Key techniques are X-ray protein crystallography, structural magnetic resonance spectroscopy and computational chemistry.

- The empirical approach to identifying leads, more usually referred to as ‘hits’ in the first instance, is to screen libraries of compounds in an assay that measures target function. The libraries or collections of compounds can be large and it is not unusual to screen tens of thousands of compounds in cell-free (eg enzymatic or ligand binding) or whole cell (eg reporter gene) assays.

Lead optimisation

The initial compound (ie lead or hit) identified by either a rational or an empirical approach is unlikely to be the ultimate clinical agent. The next phase of development is lead optimisation in which the chemical properties required for activity in \textit{in vitro} and \textit{in vivo} preclinical models are introduced into the drug:

- solubility
- stability
- target specificity
- cell penetration (unless the target is extracellular)
- acceptable pharmacokinetics (including oral bioavailability if possible/appropriate)
- safety (lack of mechanism-unrelated side effects).

Although it is recognised that preclinical animal tumour models are limited in their ability to predict the subsequent clinical activity of anticancer drugs, the final stage of the development process is to demonstrate that the new agent has activity at tolerated doses in an \textit{in vivo} model. Following the development of a clinical formulation and safety studies, the drug is then ready for clinical trials.

Development of imatinib as a paradigm for targeted therapy

The above approach to developing anticancer drugs has been reduced to practice by a number of pharmaceutical companies and academic groups. Drugs are now in clinical trials, and in some cases have progressed to registration and general use.

Most notably, the development of imatinib for the treatment of Bcr-Abl positive chronic myeloid leukaemia (CML) represents a paradigm for the development of targeted therapies. The Bcr-Abl oncogene is formed during the reciprocal translocation between the long arms of chromosomes 9 and 22, the resultant shortened chromosome 22 being known as the Philadelphia chromosome. The Philadelphia chromosome is detected in 90% of patients with CML, 20% of adults with acute lymphoblastic leukaemia (ALL) and 5% of children with ALL. The 9:22 translocation results in the constitutive activation of the kinase domain of the Abl protein. The downstream effects of kinase activation include:

- stimulation of the proliferation via the ras pathway
- inhibition apoptosis via PI-3 kinase
- altered cellular adhesion via phosphorylation of Crk1.

During the late 1980s and 1990s, Lydon, Matter and colleagues at Novartis initiated the development of Bcr-Abl...
inhibitors and imatinib mesylate (STI571 or Gleevec) entered clinical trial in 1998. In preclinical in vitro and in vivo models of CML, imatinib displayed potent activity, which was rapidly confirmed in clinical studies. The drug was given daily as an oral dose. When doses were escalated to 300 mg and above, 53/54 patients with chronic phase interferon refractory CML achieved a complete haematological remission, and cytogenic responses were seen in 17/31 patients. Toxicities were in general mild (grade 1 peri-orbital oedema, muscle cramps, skin rashes and diarrhoea) with grade 2 or 3 myelosuppression in 16/54 patients on a dose of 300 mg or more daily.

The outstanding activity and tolerability of imatinib are unprecedented in cancer chemotherapy. Furthermore, the clear mechanistic understanding of the reasons for the activity of the drug hold out real hope for the future management of cancer, as lesions equivalent to Bcr-Abl become identified in an ever increasing number of solid and haematological malignancies.

Building on the results of the Phase I trial in CML, Phase II and Phase III studies have confirmed that imatinib has activity in chronic phase, accelerated phase and even myeloid blast crisis CML.

Conclusion

Although notable successes have been achieved with cytotoxic drugs, the future for the management of cancer lies in the development and use of targeted therapies – agents designed to exploit the molecular and cellular pathology of the disease.

References