Cancer chemotherapy: identifying novel anticancer drugs

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This is the ninth in a series of articles examining developments in cancer and updating what we know about the disease

There are now around 60 cytotoxic drugs licensed for use in cancer therapy in the United Kingdom. For certain malignancies such as childhood cancers, haematological malignancies, and germ cell tumours chemotherapy has been pivotal to the substantial improvement in therapeutic outcome achieved over the past 10 years. In contrast, improvements in the systemic management of adult solid tumours have been less dramatic. There is a clear and urgent need for new, more effective drugs for lung, breast, and colorectal malignancies. This paper examines the processes in identifying, developing, and evaluating new drugs with anticancer activity.

Current cytotoxic drugs

Cytotoxic drugs can broadly be grouped into classes relating to their action at the cellular level (box). Most drugs in current use inhibit cellular proliferation, commonly by inhibiting DNA or RNA synthesis. In contrast, other anticancer agents, including hormone analogues such as tamoxifen, induce growth inhibition through interaction with specific nuclear receptors.

Origin of current cytotoxic drugs

The search for active new anticancer drugs over the past decade has proved difficult, but one approach has been by review of the origin of our current compounds. Certain compounds, such as vincristine, were isolated through large scale drug screening programmes, whereas others were produced via analogue development, as illustrated by the new platinum compounds. In contrast, comparatively few cytotoxic drugs have been specifically designed to attack particular cellular targets, though this type of approach did lead to the development of particular antimetabolites used today, such as aminopterin and methotrexate. Serendipity has undoubtedly played a major part in identifying other important cytotoxic drugs—for instance, cisplatin.

SCREENING PROGRAMMES

For the past 40 years the National Cancer Institute in the United States has carried out large scale screening of compounds with potential anticancer activity.¹ The screen has been used to evaluate a wide range of agents, including natural products and synthetic chemicals developed in the laboratory.

The natural product programme has identified several compounds with biological activity. One of these is the taxene taxol, a plant alkaloid derived from the bark of the Pacific yew tree.² Taxol has been shown to have anticancer activity against a range of solid tumours, including breast cancer and ovarian cancer, and is now available for routine clinical use. Fascinating alternative sources of new cytotoxic compounds are continually under assessment. For example, many products are being derived from tropical rain forests for further evaluation. Similarly, compounds derived from marine species have been evaluated,³ yielding interesting new compounds such as bryostatin, a macrocyclic lactone derived from the marine invertebrate *Bugula neritina*.⁴ Bryostatin modifies the activity

of protein kinase C, an important enzyme in second messenger systems concerned in signal transduction from the plasma membrane. Bryostatin is currently under clinical evaluation in Britain by the Cancer Research Campaign.

The first screening programme by the National Cancer Institute entailed testing agents in mice against the rapidly growing mouse leukaemia cell lines L1210 and P388. Agents having activity against these tumour models were subsequently included in a secondary screen using various mouse solid tumours and then human tumour xenografts growing in immune deprived mice.¹ As might have been predicted, this screen was very successful in identifying drugs with activity against rapidly growing tumours such as the leukaemias and lymphomas, but was less effective at identifying active drugs for treating the more slowly growing adult solid tumours. This led to fundamental change in the screening programme in 1985, with the introduction of the in vitro disease oriented screening programme.¹

The in vitro disease oriented screening programme utilises a large panel of human tumour cell lines grown initially in vitro and assessed for cytotoxicity by the MTT assay⁵ and subsequently the sulforhodamine B protein assay.⁶ The aim of this screen is to select drugs exhibiting selective activity against different histological tumour types, particularly solid tumours. There are obvious limitations to an in vitro approach, in that drugs requiring metabolic activation and those active via immunomodulation would not be identified. Despite these limitations, early reports are encouraging

Cytotoxic drugs currently in use in Britain

- *Alkylating agents*
Bifunctional agents:
Cyclophosphamide
Chlorambucil
Melphalan
Nitrosoureas
Platinum drugs
- *Antimetabolites*
Methotrexate
Cytarabine
Fluorouracil
- *Topoisomerase poisons*
Etoposide
Doxorubicin
Mitozantrone
- *Spindle poisons*
(inhibitors of microtubule assembly)
Vincristine
Vinblastine
Taxenes
- *Biological agents*
Interferons
Interleukin 2
- *Miscellaneous agents*
Dacarbazine
Mitomycin

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BMJ 1994;308:1288-90

that this programme will detect important drugs for treating solid tumours. There are several groups also pursuing a screening approach, including the European Organisation for Research and Treatment of Cancer, permitting the early identification of interesting new drugs with rapid transit into clinical practice.⁷

RATIONAL DRUG DESIGN

The alternative to large scale screening is to utilise our understanding of cellular biology and biochemistry in order to design drugs to attack particular targets, such as the important enzymes concerned in cellular proliferation. This approach was first used in the development of antifolate drugs such as aminopterin and methotrexate, following the important observation of the growth stimulation of human leukaemia by folate supplementation.⁸ Subsequently other antimetabolites such as fluorouracil have been designed, aimed at specific enzyme targets. The activity of fluorouracil is primarily attributed to inhibition of thymidylate synthetase by its metabolite 5-deoxy uridine monophosphate.⁹ Inhibition of thymidylate synthetase can be enhanced by the addition of folinic acid, resulting in stabilisation of the 5'dump-TS complex with a resultant increase in therapeutic benefit.¹⁰ Of interest, more specific inhibitors of thymidylate synthetase have recently been developed and are currently under clinical evaluation.

New cytotoxins: the next 10 years

The next 10 years are likely to herald a significant change in anticancer drug discovery. Analogue development is still likely to produce some interesting drugs that may substantially reduce the toxicity associated with treatment. In addition, drugs will continue to be discovered in large scale screening programmes. However, broad based random screening is likely to decrease in frequency, with many drug discovery screening programmes focusing on specific cellular targets in the future. An increasing proportion of the new drugs will arise from rational design based on our increasing scientific understanding of the malignant process. These compounds may arise from various sources (figure).

Possible sources of new cytotoxins

Improved systemic treatment could be achieved by modulating the activity of currently available drugs. This approach would include the development of effective drugs to control the toxicities associated with chemotherapy and the use of drugs to overcome drug resistance. Modulating drug resistance has primarily focused on multidrug resistance,¹¹ but the next few years should also see the development of agents capable of modifying repair of DNA damage associated with cytotoxic drug treatment.¹²

Alternatively, novel therapeutic strategies (see below) may prove to be a more effective approach.

NUCLEAR TARGETS

Though many classic anticancer treatments, such as the alkylating agents, are currently directed at nuclear targets, DNA is also the target for many new anticancer strategies. The development of DNA sequence specific drugs may result in growth inhibition with the potential for antitumour selectivity,¹³ some of these compounds achieving antitumour activity via inhibition of important transcription factors.¹⁴ Alternatively, antisense oligonucleotides may be used selectively to modulate gene expression,¹⁵ oncogenes being an obvious target. At present, however, this strategy is limited by cellular uptake and rapid degradation problems which need to be overcome. Many groups have evaluated gene therapy strategies experimentally and in limited clinical studies. These have included attempts to enhance the host immune response¹⁶ and modulate tumour cell growth or behaviour¹⁷ by using various techniques to achieve gene transfer.¹⁸ However, the precise role for gene therapy in malignancy remains unclear, in contrast with the treatment of single gene disorders.

MEMBRANE AND CYTOPLASMIC TARGETS

Better understanding of the biological events controlling malignant cell progression has identified multiple potential targets for anticancer drug design. The process of cellular proliferation in malignant cells is frequently associated with the binding of growth factors to specific receptors on the cell membrane, leading to activation of intracellular proteins, enhanced DNA synthesis, and ultimately leading to stimulation of cell growth or differentiation.^{19,20} There are several important molecules in this second messenger cascade which are prime targets for anticancer drug development through the production of inhibitory molecules. Aberrant control of this cascade is frequently observed in cancer, allowing the potential for selective antitumour activity. Inhibitors of growth factors, their receptors, and many intracellular molecules concerned in the transmission of signals from the cell membrane to the nucleus are being developed, though current attention is primarily focused on inhibitors of tyrosine kinases²¹ and protein kinase C.²²

Another class of important membrane targets includes the molecules involved in cell-cell and cell-matrix interactions, which are important in malignant cell invasion and metastasis.^{23,24} New classes of inhibitors for these targets could form the basis of second generation antimetabolites.

Evaluation of new anticancer agents

Currently the development of new cytotoxic agents follows a standard pattern. The initial step includes identifying anticancer activity in preclinical evaluation by means of in vitro or in vivo models. After this the drug undergoes standard toxicology testing in animals before being entered into clinical trials.

Phase I studies establish a safe dose and schedule, with subsequent phase II clinical trials responsible for identifying anticancer activity against particular

cancers. Phase III/IV trials compare new treatments with current "standard" treatments. In the current NHS these studies should include cost-benefit analyses. However, the selection of an appropriate end point for these studies is of fundamental importance. Although "cure" is obviously desirable, for many advanced cancers this is not achievable at present and quality of life may be a more rational end point for comparison of treatment modalities.²⁵ It is anticipated that new classes of anticancer agents should be more cancer specific and not randomly directed at "proliferating cells." Therefore, different dose limiting side effects may well be encountered. This will make the design of future clinical trials of these new drugs a great challenge.

Conclusion

Over the next 10 years a large number of potential anticancer drugs will be evaluated, many being novel structures with different mechanisms of action compared with those of currently available drugs. Though many will still be targeted at cancer cells, some will be inhibitory to normal tissues such as vascular endothelial cells. They will originate from various sources, including the pharmaceutical industry and large scale screening programmes. It is difficult to predict which strategy holds the greatest promise, though drugs directed against new targets such as angiogenesis, tumour invasion and metastasis, and signal transduction have great potential as comparatively selective anticancer agents. Greater understanding of the mechanisms underlying cell death after cytotoxic drug treatment is urgently required²⁶ and may lead to the identification of important new targets for the next generation of anticancer drugs.

This is an exciting time clinically, as our increased understanding of the biology and biochemistry of the malignant phenotype is leading to the development of new classes of drugs, which it is hoped will prove to be dramatically more effective and possibly no more expensive than their predecessors.

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ANY QUESTIONS

What is the evidence that the reaction to the live mumps vaccine is confined to transient meningitis?

Mumps vaccination is usually delivered in the form of the combined vaccine for measles, mumps, and rubella. The vaccine has been successful, and the incidence of the severe complications of mumps infections—meningitis and encephalitis—has been reduced.¹ An association of aseptic meningitis with a particular strain of mumps antigen (Urabe) was shown in Britain² and other countries. The cases seen in Britain were mild and transient compared with the encephalitis seen in infections with wild virus.³ The measles, mumps, and rubella vaccine, including the Urabe vaccine, was discontinued in Britain in 1992, and increased use was made of a vaccine containing another mumps vaccine (Jeryl Lynn), which has been used extensively in the United States and Scandinavia and has not been shown to be associated with meningitis.¹

There have been isolated reports of other adverse events after mumps immunisation, including transient parotitis, orchitis, thrombocytopenia, deafness, and the triggering of the onset of insulin dependent diabetes mellitus. But

with the exception of parotitis and the thrombocytopenia these events are all rare and explained by chance association rather than causation. There seems to be more of a case for a causal association of measles, mumps, and rubella vaccine with thrombocytopenia.³ But it is impossible to distinguish an effect associated with mumps rather than the other components in measles, mumps, and rubella vaccine, and a recent comprehensive review by the American Institute of Medicine concluded that there was no evidence to accept the case for a causal relation for any of these conditions for either mumps or measles.⁴—ANGUS NICOLL, consulting epidemiologist, Public Health Laboratory Service Communicable Disease Surveillance Centre, London

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