New Drugs

Anticancer chemotherapy

PETER DAVEY, G R TUDHOPE

Though the selection and administration of cytotoxic drugs is usually restricted to specialist units, all doctors should be aware of both the available treatment and its associated problems. This review concerns new cytotoxic drugs and some new applications of current drugs. It is largely confined to drugs marketed in the United Kingdom in the past five years and drugs from abroad that are currently used in the United Kingdom, although some mention is made of those still undergoing clinical trial which may be more widely used in the future.

Many new drugs are analogues: they are the product of a search for a compound related to an existing cytotoxic drug that will retain or surpass its efficacy with a simultaneous reduction in toxicity.

Current drugs and their analogues

ALKYLATING AGENTS

Alkylating agents—for instance, busulphan, cyclophosphamide, melphalan, and mustine—prevent replication of nucleic acids by cross linking base pairs. Doses of all alkylating agents are limited by myelosuppression and gastrointestinal disturbance; haemorrhagic cystitis is dose limiting for cyclophosphamide.

ANALOGUES OF ALKYLATING AGENTS

Ifosfamide (Mitoxana) is structurally related to cyclophosphamide. It may have better activity against non-small cell lung cancer and soft tissue sarcoma, but otherwise there is no convincing evidence of superiority over cyclophosphamide. Gastrointestinal side effects and haemorrhagic cystitis seem to be more severe than after cyclophosphamide but this may be related to differences in dose rather than in biological activity. Disturbances of consciousness have been reported after ifosfamide.

Treosulfan (Treosulfan Leo) is a derivative of busulphan used to treat ovarian cancer. Like busulphan it is myelosuppressive and causes skin pigmentation.

NEW DEVELOPMENTS WITH ALKYLATING AGENTS

The oxazophosphorenes (cyclophosphamide and ifosfamide) cause haemorrhagic cystitis because an inactive metabolite, acrolein, is produced. The administration of -SH donors prevents the action of acrolein on the bladder mucosa. SH donors, which are used to treat overdoses of paracetamol such as N-acetyl cysteine, antagonise the cytotoxic action of the oxazophosphorene when administered systemically and must be given as a bladder irrigation. Mesna (2 mercaptoethane sulphonate) is an SH donor that has been available as a mucolytic for about 20 years. When given systemically it is excreted rapidly in the urine. Initial trials have shown that when given systemically it does protect against oxazophosphorene haemorrhagic cystitis without impairing cytotoxicity. Mesna is not marketed in the United Kingdom yet but it is available for clinical trials (from WB Pharmaceuticals as Uprometixen).

Some tumour cells are known to have hormone receptors. A cytotoxic drug might be preferentially concentrated in the tumour if it were linked to the relevant hormone. Estramustine phosphate (Estracyt) is mustine linked to an oestradiol; it has been used with some success in treating metastatic prostatic cancer. Prednimustine (trial) is chlorambucil linked to a corticosteroid; it is undergoing trials in cases of leukaemias and lymphomas.

Alkylating agents affect dividing cells in any phase of the cell cycle and theoretically their cytotoxic action should increase with dose. Experimental studies with tumours in animals have shown a steep relationship between dose and response for these agents; clinical studies are so far inconclusive, but studies with high dose alkylating agents are of considerable current interest. Two methods have been developed for protecting patients against high doses of melphalan and cyclophosphamide. Autologous bone marrow transplantation is performed by removing some of the patient's bone marrow and reinfusing it after a massive dose of the alkylating agent has been cleared from the blood. The second technique, priming, stems from the observation that exposure to an animal of a small dose of an alkylating agent protects against the haematological and gastrointestinal side effects of a subsequent high dose without protecting tumour cells. Both techniques appear to enhance haematological recovery in preliminary clinical trials.

NITROSOUREAS

Nitrosoureas such as carmustine (BCNU) and lomustine (CCNU) act as alkylating agents and by other mechanisms that are not precisely defined. Existing agents are limited by severe myelosuppression that often begins three to four weeks after treatment, is prolonged, and is cumulative with repeated dosing.

ANALOGUES OF NITROSOUREAS

Methyl CCNU is available in the United States as Semustine (National Cancer Institute of America (NCI)). Animal screening tests predicted a higher therapeutic index compared with

Department of Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee DD1 9SY
PETER DAVEY, MD, MRCP, senior registrar
G R TUDHOPE, MD, FRCP, reader and honorary consultant physician

Correspondence to: Dr Peter Davey.

CCNU or BCNU but this has not been confirmed in clinical trials.

Streptozocin (NCI) is a glucose derivative of methyl nitrosourea. Animal screening showed two interesting differences from other nitrosoureas: it was not myelosuppressive and it was diabetogenic. In clinical trials its lack of myelosuppression was confirmed but this was offset by nephrotoxicity and by a narrow range of antitumour activity. Streptozocin is rarely diabetogenic in man but it acts against islet cell tumours and possibly also against metastatic carcinoid tumours. It is being investigated in combination with other drugs for the treatment of Hodgkin's disease.

ANTIMETABOLITES

Antimetabolites—for instance, fluorouracil, mercaptopurine, methotrexate, thioguanine—act by irreversible inhibition of enzyme systems for deoxyribonucleic acid (DNA) or protein synthesis or by incorporation into nuclear material with subsequent prevention of replication. Methotrexate and fluorouracil are the only antimetabolites with wide activity. Both have dose limiting myelosuppression, and methotrexate is further limited by mucositis, nephrotoxicity, neurotoxicity, and hepatic fibrosis. Fluorouracil may be given by mouth but its absorption is erratic. Disturbance of consciousness occurs at high doses.

ANALOGUES OF FLUOROURACIL

Several fluorinated pyrimidines are under investigation. Ftorafur (trial) has been most widely tested. When used intravenously it causes toxicity of the central nervous system and does not have superior cytotoxic action to fluorouracil. This toxicity, however, is less after oral administration. Comparative trials of oral ftorafur and fluorouracil are under way.

NEW DEVELOPMENTS WITH ANTIMETABOLITES

The toxic effects of methotrexate may be prevented by large doses of folinic acid (Calcium Leucovorin). Massive doses of methotrexate have been given with subsequent folinic acid "rescue" with the aim of increasing intracellular concentrations of methotrexate in tumour cells relative to normal cells to obtain an increased therapeutic index. The benefit of this technique has not yet been proved with the possible exceptions of osteosarcoma and head and neck tumours; it should be used only in specialist centres.

The interaction of fluorouracil with other compounds that affect nucleotide metabolism has been investigated intensively. Clinical trials of combinations of fluorouracil with methotrexate, allopurinol, and thymidine may establish a way of increasing the therapeutic index of fluorouracil.

CYTOTOXIC ANTIBIOTICS

Antitumour antibiotics—for example, actinomycin, bleomycin, doxorubicin, and mitomycin—act by intercalation between strands of DNA. Until recently bleomycin and doxorubicin were the most widely used antitumour antibiotics. Special mention must be made of mitomycin, which has been available since the 1950s but has been little used in Britain because of severe delayed myelosuppression. Recently it has been shown that intermittent high doses avoid this problem. Mitomycin is now being increasingly used to treat stomach cancer and is under trial for breast and lung cancers. Less common side effects are microangiopathic haemolysis, nephrotoxicity, and pulmonary toxicity.

Bleomycin is not myelosuppressive but its cumulative dose is limited by pulmonary fibrosis. Doxorubicin has a wide range of activity but causes severe alopecia, vomiting, dose limiting myelotoxicity, and cumulative cardiotoxicity—leading to irreversible heart failure. Several analogues of bleomycin—for instance, pepleomycin, tallysomycin—and doxorubicin—for instance, aclacinomycin A, rubidazone—are undergoing clinical trials. Preliminary results suggest that less toxic alternatives to both drugs may be available in the near future.

One mechanism that may be responsible for doxorubicin cardiotoxicity is the generation of superoxide radicals that cause cell death because of hydrogen peroxide formation. Experimental doxorubicin cardiotoxicity may be prevented by -SH donors such as n-acetyl cysteine or by compounds such as vitamin E that are free radical "scavengers" without affecting antitumour activity; clinical trials are awaited.

VINCA ALKALOIDS (VINCRISTINE, VINBLASTINE)

Vinca alkaloids act principally by binding to microtubules and preventing metaphase and cell division. Vincristine and vinblastine have been marketed in the United Kingdom for several years and are used mainly to treat lymphoma, leukaemia, and testicular teratoma, but they also show activity against bronchial carcinoma, breast cancer, and melanoma. Both drugs are relatively non-toxic: vincristine is only slightly myelosuppressive but causes peripheral neuropathies and occasionally toxicity of the central nervous system; vinblastine is less neurotoxic but is myelosuppressive.

VINCA ANALOGUES

Vindesine (Eldisine) is a newly marketed vinca alkaloid that has shown activity in acute lymphoblastic leukaemia, lymphomas, melanoma, bronchial carcinoma, and testicular teratoma. Interestingly, despite having a similar range of action, vindesine is often active against tumours that have become resistant to the other vinca alkaloids. Vindesine is moderately myelosuppressive but is neurotoxic and also causes local phlebitis even without extravasation of injections. It remains to be seen whether vindesine has considerable advantages over vincristine and vinblastine.

New cytotoxic drugs

CISPLATIN

Cisplatin acts by intercalation of DNA strands. It is licensed for the treatment of cancers of the testis, ovary, cervix, head, and neck. It is also under trial against non-small cell lung cancer, prostatic cancer, neuroblastoma, and childhood osteogenic sarcoma. Cisplatin causes severe acute gastrointestinal disturbance and myelosuppression. Nephrotoxicity is manifested by both renal magnesium wasting and impaired glomerular filtration and neurotoxicity by deafness, particularly in children, and occasionally by peripheral neuropathy.

Because of the toxicity of cisplatin a vigorous search has been made for analogues with equal activity but less toxicity; several of these analogues will go into clinical trial in the near future.

ETOPOSIDE (VEPESID)

Etoposide (Vepesid) is a plant alkaloid derived from podophyllotoxin. Until recently it was known as VP 16-213. Its precise mode of action is not yet clear. It is licensed for treating small cell lung cancer and testicular teratoma and is being investigated for the treatment of lymphomas. Side effects are alopecia, myelosuppression, and slight gastrointestinal dis-

turbance. Teniposide, also known as VM-26, is an analogue that is not active against small cell lung cancer but may have a place in treating acute myeloid leukaemia.

HEXAMETHYLMELAMINE (TRIAL)

The precise mode of action of hexamethylmelamine is not known but it may act both as an alkylating agent and an antimetabolite.

Hexamethylmelamine must be given by mouth because it is not water soluble and gastrointestinal intolerance is dose limiting. It shows good activity against ovarian cancer even when the tumour is resistant to alkylating agents, and it is also being tested for cancers of the breast and cervix. Water soluble derivatives that may be given intravenously are being developed. Pentamethylmelamine has entered clinical trials but is unlikely to continue because of severe toxicity of the central nervous system.

HEXITOLS

Hexitols are sugar derivatives that are alkylating agents. Mitobronitol (Myelobromol) has comparable activity to busulphan in treating chronic myeloid leukaemia. It is given by mouth, and the dose is limited by myelosuppression.

Mitolactol (trial; also known as dibromodulcitol) has a wider range and has shown activity against head and neck tumours, melanoma, and cancer of the breast and lung. Mitolactol is particularly interesting because it shows some penetration into cerebrospinal fluid; a related drug, dianhydrogalactilol (trial) crosses the blood-brain barrier even more effectively and is being tested for the treatment of brain tumours.

RAZOXANE (RAZOXIN; ICRF 159)

Razoxane is at present used to treat acute myeloid leukaemia and acute transformation of chronic myeloid leukaemia. Activity has also been reported against tumours of the large intestine. Razoxane appears to act as a radiosensitiser; clinical trials of radiotherapy with razoxane are in progress, but no clinical role has been established. One major problem is that the drug must be given by mouth and has unreliable absorption; a more soluble analogue which may be given intravenously (ICRF-187) is just entering clinical trials. The precise mode of action of razoxane is uncertain; it is highly specific for cells in the premitotic and early mitotic phases of the cell cycle. The dose limiting toxicity is leucopenia; gastrointestinal disturbance and alopecia are mild.

BIOLOGICAL RESPONSE MODIFIERS

Biological response modifiers, or biologicals for short, are naturally occurring substances that modify the host's normal response to a tumour. Biologicals encompass agents such as BCG which act as general immunostimulants and were formerly referred to as immunotherapy. There are several new biologicals: the interferons; retinoids, which are derivatives of vitamin A; thymic hormones; and the monoclonal antibodies. These newer agents have a variety of known and potential activities. They may increase host resistance to the tumour and also restore host immunity (thymic hormones; levamisole); they may have direct cytotoxic activity (interferons; monoclonal antibodies); or they may prevent neoplastic transformation (retinoids).

BCG and related non-specific stimulants have failed to find any place in the treatment of cancer. It was hoped that immune stimulation would help to "mop up" micrometastatic residual disease after other treatment. A major problem has been that these agents have no activity in advanced cancer, and it is therefore impossible to establish the best dose to use. The dose used tends to be the maximum one that can be tolerated by the patient but quite possibly a lower dose has a greater antitumour activity. Also the trials of adjuvant immunotherapy may have been in tumours resistant to this approach. The interferons do have intrinsic antitumour activity against several haematological and solid tumours. It should therefore be possible to define optimum doses for different tumours and then to design trials rationally using interferons with other forms of treatment.

TREATMENT OF TOXIC REACTIONS

A review of the management of toxic effects of chemotherapy is beyond the scope of this article. In general any problems arising in patients who are receiving chemotherapy should be referred to the specialist who administered the drugs. For further information readers are referred to the article by Spiegel (see bibliography).

The future

Several new classes of cytotoxic drug are being investigated and may be available in the near future. Amsacrine, also known as M-AMSA, is an acridine that acts by intercalation of DNA. It has dose limiting myelotoxicity; it is active against various tumours but is most promising against acute myeloid leukaemia and the lymphomas. Bisantrene and mitoxantrone are anthracenediones and are structurally related to the anthracycline antibiotics doxorubicin and daunorubicin. The anthracenediones have impressive activity against breast cancer but both are myelotoxic and mitoxantrone may be cardiotoxic, particularly in patients who have received anthracyclines. The ellipticines are plant alkaloids that act by intercalation of DNA. Trials in animals have shown minimal toxicity with apparently useful antitumour activity. Initial trials in man have confirmed that the ellipticines are not myelotoxic, but unfortunately they do have other dose limiting toxic effects.

These new classes of drugs and the other new drugs reviewed act principally by the same mechanisms as existing drugs—that is, as alkylating agents, as antimetabolites, or by intercalation with DNA. Although these new drugs may have some advantages, it is not surprising that they are not tumour specific and have low therapeutic indices. Indeed, the animal tumour models used to screen compounds for cytotoxic activity may not identify highly selective compounds. For example, deoxycoformycin is a drug which selectively kills lymphocytes and may be valuable in T cell lymphoid malignancies but which is completely inactive in animal tumour models. The biologicals offer one alternative approach but clearly other ways of selectively killing tumour cells must be found, which will in turn require new screening methods. The review by Connors (see bibliography) outlines some ideas on this subject.

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Bibliography

Pinedo M, ed. *Cancer chemotherapy*. Vol 1, 1979; vol 2, 1980; vol 3, 1981. Amsterdam: Excerpta Medica.

The most up to date and comprehensive reference source. Volume I reviewed current drugs and practice in 1979 whereas the subsequent two volumes review the world publications for their respective years. It is intended to continue an annual publication. This is a cumulative work and it is necessary to have access to all the volumes. Each volume contains chapters on all established and new cytotoxic drugs and chapters that review the treatment of individual malignancies.

Carter SK. Cancer chemotherapy: new developments and changing concepts. *Drugs* 1980;**20**:375-97.

A review of analogue development, with particular reference to

anthracyclines and nitrosoureas as well as some important topics that could not be covered in our review such as scheduling of drugs to manipulate cell kinetics, in vitro sensitivity testing, and autologous and allogenic bone marrow transplants.

Martin DS. The scientific basis for adjuvant chemotherapy. *Cancer Treat Rev* 1981;**8**:169-89.

A stimulating review of the theory and experimental evidence behind adjuvant chemotherapy. If adjuvant chemotherapy works, and there is increasing evidence that it does, there will be a major increase in the use of cytotoxic drugs and anybody who sees patients with cancer should be familiar with the evidence.

Spiegel RJ. The acute toxicities of chemotherapy. *Cancer Treat Rev* 1981; **8**:197-207.

A practical guide on how to deal with problems such as extravasation of cytotoxic drugs, vomiting, allergic reactions, mucocitis, and alopecia.

Connors TA. Basic research in cancer. In: *Collected papers from cancer topics.* Gosport, Hants: Lederle Ltd, 1981. (Fareham Road.)

An analysis of the deficiencies in current drug development programmes with suggestions for new approaches. This volume also contains short reviews on the pharmacokinetics of cytotoxic drugs, treatment of individual solid tumours, monoclonal antibodies, and the long term consequences of cytotoxic treatment.

Mathe G, Muggia FM, eds. *Recent results in cancer research 74: Chemopharmacology.* Berlin: Springer Verlag, 1980.

Contains individual chapters on the following drugs: cisplatin and some of its analogues; aclacinomycin and other doxorubicin analogues; ellipticines; mesna, pepleomycin; VM 26 and VP 16; vindesine; and leucovorin rescue of high dose methotrexate. There are also reviews of long term side effects, stem cell assays, cell kinetics, and correlation of animal models with clinical trials.

Goldin A, Chirigos MA, MacDonald JS, Fefer A, Mitsich E. Biologic-response modifiers and adjuvant chemotherapy: consideration of selected preclinical investigations in relation to clinical potential. *Recent Results Cancer Res* 1982;**80**:351-6.

A good concise review of the mechanisms of action of biologicals, the results of initial trials with interferons, and possible ways of combining these agents with other treatment.

Individual reviews of newly marketed drugs

Cisplatin: Anonymous. *Lancet* 1982;i:374-5.

VP-16-213 (Etoposide): Vogelzang NJ, Raghaven D, Kennedy BJ. The Mandrake Root from Issyk-Kul. *Am J Med* 1982;**72**:136-44.

Ifosfamide: Trissel LA, Kleinman LM, Cradock JS, Davignon JP. *Drug Intell Clin Pharm* 1979;**13**:340-1.

Razoxane: ICRF 159. Bakowski MT. *Cancer Treat Rev* 1976;**3**:95-107.

Vindesine: Proceedings of the Vindesine International Workshop, Frankfurt. *Cancer Chemother Pharmacol* 1979;**2**:No 4.

Mesnum: Scheef W, Klein HO, Brock N. Controlled clinical studies with an antidote against the urotoxicity of oxazaphosphorines: preliminary results. *Cancer Treat Rep* 1979;**63**:501-5.

Letter from . . . France

No red roses for doctors' ladies

PETER BAXTER

A good skiing season has just ended, with tans and some late plaster casts counterpointing the new bright cotton fashions; the street markets' wares increase daily in colour, variety, and smell; a rousing dawn chorus indicates that trees which have looked like sprout plants all winter have now grown branches; and the local cartoonist has changed theme from politics to couples communing with nature. In contrast to this atmosphere, the teaching hospitals remain wintry; the students' three month strike, which has included ugly scenes with riot police, has only just ended; the juniors have only suspended their six week stoppage and may continue it in June; resulting budget deficits have caused capital projects to be shelved; and the professors have threatened not to mark exams or do any administration.

The students started in mid-February by protesting against a law introducing a new and additional final year exam which would stream their career choice into specialist, *liberale* or community medicine, or research, and which they fear will become a tool to control the number qualifying—a hurdle jumped at present in a first year exam with a 25% pass rate and in which only two attempts are allowed. They solemnly cremated their curriculum, with a funeral cortege and coffin up the Champs Elysées, and then publicised their cause: they plastered up parking meters, statues, and the gates of the Paris metro; blocked motorways, railways, and urban traffic all over the country; built barricades; occupied the spire of Strasbourg cathedral, the Arc de Triomphe, the ministry of health, and other public buildings; invaded a television studio during a programme; let 300 mice loose in a mairie; and collected blood for injured comrades and medicines for Poland. All this showing comparable ingenuity to an event last year when 400 got into a hospital being opened by the prime minister; while half interrupted his speech, the rest ate the official banquet. The public has been "gently amused," although one minister asked sourly if the steel or car workers would get the same sympathy. But the mood has changed: relatively peaceable encounters—for example, at the eviction from the Arc de Triomphe the local police chief simply pointed out that his men were not a crowd of choirboys—have turned into battles where paving stones are exchanged for truncheon blows. Bystanders and journalists have also found themselves the objects of assaults: one photographer was attacked because, apparently, the police were feeling tired after 30 charges.

The juniors have been more sedate and more effective: confining themselves to marches with slogans like "Internes with white coats and black futures," they have guaranteed essential services, halved bed occupancy, and received a new minister of health. They are fighting proposed reforms which would abolish their special status, won in a difficult exam with a 9% pass rate, and their promotion prospects by replacing the *chef de clinique* post (equivalent to a senior registrar) with permanent grade B subconsultant positions. Equally important, the autonomy of the medical schools would disappear, with them becoming part of, and thus controlled by, faculties of science, which provoked the professors' reaction.

Presented with all this, the culmination of some years of unprecedented unrest for a profession that traditionally sorted out its problems behind closed doors, the newspapers' diagnosis is chronic system failure with acute deterioration due to clumsy treatment. Decreasing morale is reflected by difficulty in filling some of the more demanding posts—why work long hours for nothing? The reforms of 1968 opened medical education to huge numbers (8000 qualified in 1978; numbers

Hôpital Debrousse, Lyon, France
PETER BAXTER, MB, MRCP, médecin résident etranger