Principles of systemic anticancer therapy

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Abstract

Cytotoxic chemotherapy remains an important component of anticancer therapy. However, newer 'targeted agents' are emerging as more effective agents in certain cancer types as determined by their molecular phenotype.

Keywords Alkylating agents; anthracyclines; antimetabolites; cancer; chemotherapy; cytotoxic; platinum compounds

Cytotoxic chemotherapy

Alkylating agents

Alkylating agents are chemically reactive drugs that react with DNA to form covalent bonds, causing single-strand or double-strand DNA breaks that lead to interstrand and intrastrand DNA cross-linking. These agents are used extensively in cancer chemotherapy. They have a steep dose–response curve and are therefore useful in dose intensification strategies (e.g. in bone marrow transplantation). There are several subclasses of alkylating agents. (See *Cytotoxic Chemotherapy*: *Clinical Aspects* on pages 25–29 of this issue for more detail of clinical use of the agents.)

Nitrogen mustards

- Melphalan is a nitrogen mustard derivative of the amino acid 1-phenylalanine. It was originally synthesized in the hope that it would be taken up selectively by tumour cells. It is now known that melphalan is taken up into cells by an active transport carrier. It is particularly active in multiple myeloma.
- Chlorambucil is used extensively in Hodgkin's disease and chronic lymphatic leukaemia.

Oxazaphosphorines: in the 1930s, it was observed that certain tumours overexpress phosphoramidase, and an attempt was made to develop mustards that would be selectively activated by this enzyme. Cyclophosphamide was synthesized in 1958 and ifosfamide and trophosphamide in the 1960s. It soon became apparent that these drugs are activated in the liver (by cytochrome P450, principally the 3A4 isoform) and not by the tumour.

Alkyl alkane sulphonates: the only member of this group used in clinical practice is busulfan, which is given in the maintenance phase of chronic myeloid leukaemia and in high doses in refractory lymphoma, leukaemia and tumours occurring in children.

Nitrosoureas: these comprise carmustine (BCNU), lomustine (CCNU), semustine, fotemustine and streptozotocin, and were developed as a result of a US National Cancer Institute screening programme in the 1960s. In general, these agents alkylate guanines at the O-(6) position. O-6-alkylguanine (O6AT)-DNA transferase is a suicide enzyme that can remove these adducts, and certain cell lines (MER+) that overexpress it are resistant to the nitrosoureas. Patients with malignant glioma, in which the O6AT-DNA transferase gene has been silenced by methylation of its promoter, are more likely to respond to nitrosoureas than those with tumours in which this is not the case.

- BCNU and CCNU are commonly used in the treatment of brain tumours.
- Streptozotocin is a naturally occurring sugar-based nitrosourea derived from *Streptomyces achromogenes* and is used in the treatment of pancreatic islet cell tumours.
- Bendamustine is more stable than many other nitrosoureas and causes more sustained DNA damage. It is particularly useful in the treatment of chronic lymphatic leukaemia.

Tetrazines: the tetrazines are dacarbazine and temozolomide. These drugs release a reactive diazonium ion that alkylates DNA.

- Dacarbazine is used in malignant melanoma, soft tissue sarcomas and Hodgkin's disease.
- Temozolomide is active in malignant glioma and melanoma. Like the nitrosoureas, temozolomide damage can be repaired by O6AT and expression of the enzyme may predict the response in patients with a glioma.

Aziridines

- Thiotepa probably undergoes a series of complex metabolic steps to form various cytotoxic moieties, including its principal metabolite tepa.
- Mitomycin is also a pro-drug, but is preferentially activated in hypoxic rather than oxygenated cells.

Platinum compounds

Three heavy metal agents are currently used in the treatment of malignancies – cisplatin, carboplatin and oxaliplatin (1,2-diaminocyclohexane platinum). All are activated intracellularly to produce reactive intermediates that form covalent bonds with nucleotides from both interstrand and intrastrand DNA cross-links.

- Cisplatin was discovered accidentally in 1969, during studies of the effect of electric currents on the growth of *Escherichia coli* using platinum electrodes in an ammonium chloride bath. It underwent early clinical trials in the 1970s and was found to be highly active in the treatment of germ cell tumours of the testis. The severe nephrotoxicity of cisplatin can be ameliorated by vigorous hydration and the drug is used routinely in the treatment of many malignancies.
- Carboplatin is less reactive than cisplatin, with little nephrotoxicity or neurotoxicity. It is excreted by

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glomerular filtration. Thus, patient exposure and degree of thrombocytopenia are related to the glomerular filtration rate. Carboplatin doses can be calculated on the basis of this, using a simple (Calvert) formula.

- The third-generation platinum analogue oxaliplatin forms intrastrand cross-links but, unlike cisplatin, its bulky 1,2-diaminocyclohexane ring fills much of the major groove of DNA. This may prevent access of DNA repair molecules. Oxaliplatin appears to be active in mismatch repair-deficient tumours whereas cisplatin is not; this may explain why oxaliplatin is active in tumours in which cisplatin and carboplatin are not active (e.g. colorectal cancer).

Antimetabolites

Antimetabolites are cytotoxic agents that structurally resemble naturally occurring purines and pyrimidines. They have two modes of action: inhibition of key enzymes involved in DNA synthesis, and incorporation into DNA and RNA to cause strand breaks or premature chain termination. They generally act on the S phase of the cell cycle; consequently (and because many of these drugs have a short plasma half-life), their action is often schedule- rather than dose-dependent. Their cytotoxic efficacy is generally greater when they are given over a prolonged period of time. Hence, they are usually given continuously, often as an intravenous infusion.

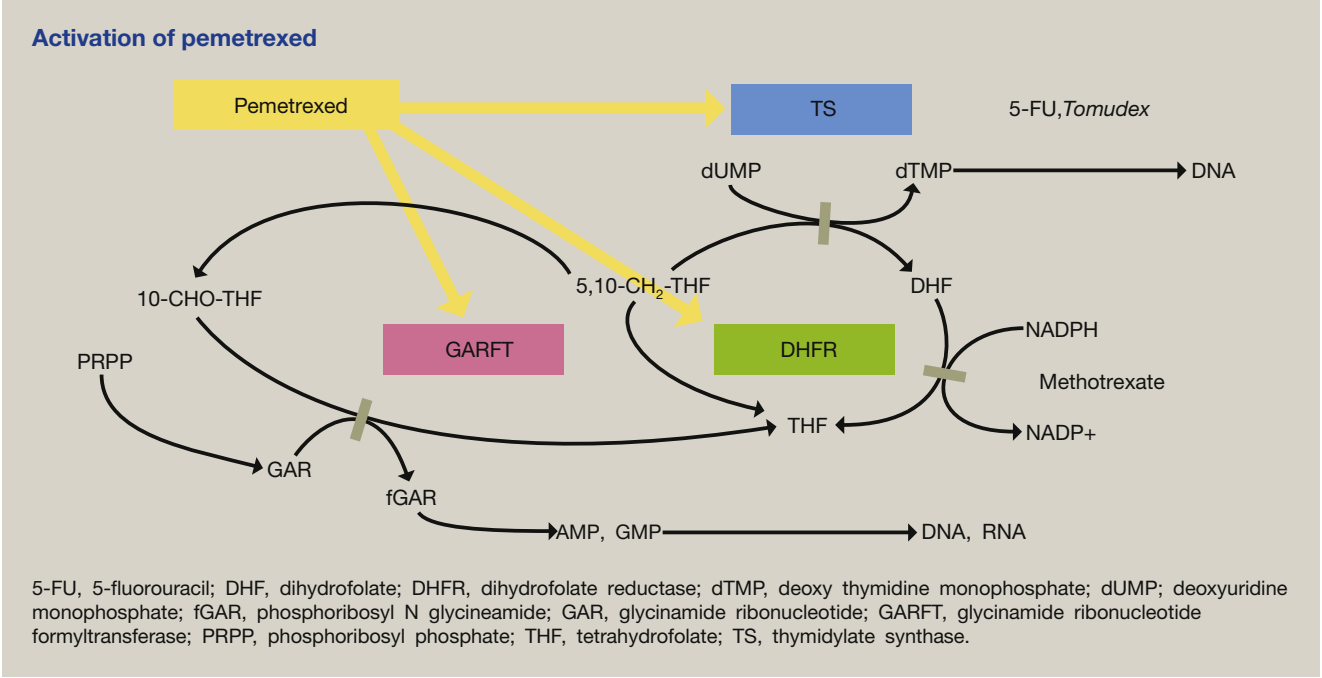
Antifolates

Methotrexate is the most commonly used antifolate. It is structurally related to folic acid. Once it has been transported into the cell, it inhibits dihydrofolate reductase (DHFR), which is responsible for the regeneration of oxidized folates following thymidine synthesis (Figure 1). Inhibition of DHFR leads to reduced intracellular folate pools and decreased thymidine synthesis. Intracellular methotrexate can be metabolized to form polyglutamate derivatives that are not as readily extruded from the cell as the parent drug. Intracellular accumulation of polyglutamated species can also inhibit thymidylate synthase and DHFR.

The biochemical toxicity of methotrexate can be reversed by the restoration of cellular reduced folate pools, usually by exogenous administration of folinic acid (*N*-5-formyltetrahydrofolate). Folinic acid can therefore be used to rescue normal tissues from the toxic effects of methotrexate. Methotrexate has a terminal plasma half-life of 2–4 hours, which can be longer in patients with renal dysfunction because a substantial portion of the dose is eliminated by renal excretion, increasing the risk of toxicity. Rescue is generally continued until plasma methotrexate concentration falls to less than 10^6 M.

Methotrexate has limited penetration into the cerebrospinal fluid. When given to treat meningeal disease, it must be administered in high systemic doses (about 3 g/m^2) or intrathecally (generally 12.5 mg).

Pemetrexed is a novel antifolate that is polyglutamated. In this form, it inhibits both DHFR and thymidylate synthase. Additionally, pemetrexed polyglutamates are inhibitors of glycinamide ribonucleotide formyltransferase, which is essential for *de novo* purine synthesis (Figure 1). The advantage of such a compound is that it may be active in cells that are resistant to antifolates by virtue of amplification of a particular target. Pemetrexed appears to be active in malignant mesothelioma and non-small cell lung cancer, particularly in non-squamous cancers.[1]



5-FU, 5-fluorouracil; DHF, dihydrofolate; DHFR, dihydrofolate reductase; dTMP, deoxy thymidine monophosphate; dUMP; deoxyuridine monophosphate; fGAR, phosphoribosyl N glycineamide; GAR, glycinamide ribonucleotide; GARFT, glycinamide ribonucleotide formyltransferase; PRPP, phosphoribosyl phosphate; THF, tetrahydrofolate; TS, thymidylate synthase.

Figure 1