An overview of cancer treatments

As part of our series of science articles, Roz J. Anderson, Paul W. Groundwater, Adam Todd and Adrian Moore present the first of four articles on cancer treatments. The first provides an overview of traditional anticancer therapies, their mechanisms of action and their limitations.

There are many new anticancer agents in clinical trials, all of which are designed to improve on current treatments. This series of articles starts with an overview of traditional anticancer chemotherapeutic approaches and their limitations, develops to identify recent additions that have made significant improvements to the treatment of cancer, and progresses to introduce new agents currently in clinical trials, along with an outline of their mechanism of action and advantages they offer.

For the purposes of these articles, the vast number of anticancer agents have been classified according to their biological target: antimetabolites, agents targeting DNA and tumour-targeted monoclonal antibodies (mAbs). However, the list is not exhaustive and, indeed, only a selection is presented. But we hope these examples serve to illustrate the various approaches employed. The subject of anticancer approaches has been reviewed by a number of authors, for example, the textbook ‘Chemistry and pharmacology of anticancer drugs’ by David E. Thurston.1

Antimetabolites

An essential metabolite is a compound that is required for the normal biochemical processes in a cell, such as the synthesis of DNA. An antimetabolite is structurally similar to an essential metabolite, but cannot take its place in the biochemical process (or reaction). The antimetabolites form a group of drugs that are used to treat a variety of cancers and are often designed through bioisosteric replacement in an essential metabolite,2 with the structures of anticancer antimetabolites generally being based on the structures of pyrimidine or purine DNA bases, or folic acid — all of which are crucial to the synthesis of DNA.

Folic acid is classed as an essential metabolite and is critical for the synthesis of DNA because it forms the basis of enzyme co-factors that provide one-carbon units in the synthesis of nucleotides — the building blocks of DNA. Methotrexate, an antimetabolite of folic acid, inhibits the enzyme dihydrofolate reductase, which is used to convert dihydrofolic acid (FH$_2$) into tetrahydrofolic acid (FH$_4$). Because these folic acid co-factors have to be continuously regenerated after they donate the one-carbon unit, this enzyme inhibition ultimately leads to the depletion of one-carbon donors and disrupts DNA synthesis. Another antimetabolite often used in clinical practice is 5-fluorouracil (5-FU), in which a key hydrogen in uracil is replaced by fluorine. This bioisosteric replacement gives 5-FU powerful anticancer properties. It is a prodrg that is converted in vivo to the active metabolite 5-fluorodeoxyuridine monophosphate, which irreversibly inhibits the enzyme thymidylate synthase (required for DNA synthesis).

These drugs have formed the mainstay of antimetabolite chemotherapy but, over the past few years, there has been significant development of, for example, new antimetabolites. Indeed, the discovery of gemcitabine, capcitabine, permetrexed and fludarabine has expanded and improved this class of chemotherapeutic agents.3 More new antimetabolites are in the later stages of drug development, for example, pralatrexate has yet to reach the market, but has demonstrated activity in the treatment of non-small cell lung cancer.4 Furthermore, the US Food and Drug Administration has recently granted accelerated approval of pralatrexate for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma.5

Drugs targeting DNA

Within this broad class of anticancer agents, there are several distinct mechanisms of action that are dependent on the exact interaction with DNA. For the purposes of this article, the various types of agents have been classified into intercalators, minor groove binding agents, alkylating agents and antimetotic agents.

Intercalators

Anticancer agents, such as doxorubicin and daunomycin, that form non-covalent complexes with DNA have found great use in the treatment of a range of cancers for many years. Their planar, electron-deficient aromatic structures slide neatly between the planar, electron-rich aromatic DNA bases to form a stable complex that inhibits the replication and transcription of the genetic code around the point of intercalation, eventually leading to cell death.

Minor groove binding agents

There has been much interest in agents that bind to the minor groove of DNA since, in the 1970s, the antimicrobial DAPI and the antiprotozoal agent berenil were shown to bind to the minor groove of DNA. (The sugar-phosphate
backbone of each DNA strand forms part of the DNA double helix. The space between these backbones forms two different sized grooves, called the minor groove and the major groove. The minor groove is narrower than the major groove. Antitumour activity was also observed, which suggested potential for the treatment of cancer. Further work showed the greatest anticancer effect when there was selectivity of binding, particularly to AT-rich regions. Although these agents have had some success in the treatment of selected infections, their use and further development have been limited by their severe toxicity.

Recently, however, trabectedin, a marine natural product, was approved in Europe, which has renewed interest in these agents. Trabectedin’s maintained activity against multidrug-resistant tumours (due to suppression of the gene conferring multidrug resistance) provides a valuable addition to the arsenal available for anticancer chemotherapy.

**Alkylating agents**

Alkylating agents were the first class of anticancer chemotherapeutic agents identified. A vast group of compounds that have significant efficacy in the treatment of slow-growing cancers (eg, leukaemia, lymphomas and solid tumours).

Alkylating agents are classified as either monofunctional methylating agents, such as temozolomide, or bifunctional cross-linking agents, such as platinum compounds (eg, cisplatin, oxaliplatin).

Although the alkylating agents differ significantly in their clinical activity and indications, their mechanism of action is essentially the same. Nucleophilic groups on DNA (particularly, but not exclusively, N7 of guanine) readily react with the drug, resulting in irreversible alkylation, which triggers the fragmentation of DNA by repair enzymes. There are attempts to replace the alkylated bases. Alkylation prevents DNA synthesis and RNA transcription from the affected DNA. It also induces mispairing of the nucleotides, leading to mutations (eg, alkylated G bases may erroneously pair with T bases). If this altered pairing is not corrected, it may lead to a permanent mutation.

Finally, bifunctional agents can form cross-bridges between two different parts of the DNA. Bridges can be formed within a single molecule of DNA or may connect two different DNA molecules. Cross-linking prevents DNA from being separated for synthesis or transcription and the cell dies eventually.

**Antimitotic agents**

The mitotic spindle that separates the chromosomes during the mitosis phase of cell division is made up of microtubules formed by polymerisation of the structural protein tubulin. During mitosis, microtubules are assembled and disassembled by means of tubulin polymerisation and microtubule depolymerisation mechanisms, which are in dynamic equilibrium. Several important chemotherapeutic agents derived from natural products block mitosis by causing metaphase arrest (they are cell-cycle specific) through disruption of this equilibrium, either by binding to tubulin and inhibiting polymerisation to microtubules (classified as microtubule destabilisers) or binding to tubulin in microtubules and inhibiting their disassembly (microtubule stabilisers). At low, clinically relevant concentrations, both classifications of agent may act by slowing microtubule dynamics resulting in mitotic arrest and eventual cell death.

The vinca alkaloids vincristine and vinblastine, and the second generation semi-synthetic analogues vindesine, vinorelbine and the recently introduced vinflunine, act as potent microtubule destabilising agents. Despite the similarities in the structures of these clinically useful vinca alkaloids, their ranges of clinical applications and toxicities are different. For example, vincristine is indicated for the treatment of leukaemias, lymphomas and sarcomas, whereas vinblastine is indicated for advanced testicular carcinomas, Hodgkin’s disease and lymphoma and vinorelbine for non-small cell lung carcinomas. Of these agents, vincristine exhibits the greatest neurotoxicity, but the least myelosuppression.

In contrast to the vinca alkaloids, the taxanes paclitaxel and its semi-synthetic analogue docetaxel act as potent microtubule stabilising agents. The taxanes are primarily indicated in the treatment of solid tumours (eg, breast, lung and ovarian carcinomas), with dose-limiting toxicities of immunosuppression and peripheral neuropathy.

Despite the clinical efficacy of the vinca alkaloids and the taxanes, there are limitations to their use, particularly acquired drug resistance, so there is significant interest in the development of novel agents with related mechanisms of action. Examples currently being investigated that are derived from natural sources include combretastatins, dolastatins, epothilones, spongistatins and tactalonolides and a range of semi-synthetic analogues.

**Monoclonal antibody agents**

There has been an explosion in the use of biologics to treat a variety of diseases, including psoriasis, arthritis and cancer. Many of the problems previously encountered with the use of large proteins as therapeutic agents have now been satisfactorily overcome to allow their successful application to chemotherapy.

Monoclonal antibodies use the specific antigen-antibody recognition process to target identified extracellular proteins or peptides associated with certain diseases. Advances in the understanding of particular cancers have resulted in the identification of surface proteins associated with malignancy that provide characteristic targets to which a chemotherapeutic agent can be directed. The identification of the HER-2 (human epidermal growth factor receptor-2) tyrosine kinase receptor as a biomarker of metastatic breast cancer was followed by the development of trastuzumab, which binds to HER-2 and results in a number of anticancer events, such as cell-cycle arrest, down-regulation of angiogenesis and inhibition of DNA repair mechanisms.

Conversely, instead of targeting a receptor, bevacizumab binds specifically to the angiogenic peptide vascular endothelial growth factor (VEGF), which inhibits the binding to, and activation of, vascular endothelial growth factor receptor-2, resulting in contraction of the tumour vasculature and the blocking of the angiogenic cascade. Further mAb anticancer agents have followed, such as rituximab and cetuximab, and more are in development, targeted at a range of extracellularly expressed proteins linked to cancer progression.

**Conclusion**

It may appear surprising that so many different anticancer agents exist and that more are being developed, but the variation in cancer biochemistry, metabolism and pathophysiology causes significant differences in the approaches required for their treatment. Cancer is not a single disease, but a collection of over 200 diseases, which often bear little resemblance to one another. Furthermore, the inherent difficulty in selectively targeting highly cytotoxic chemicals to cancer cells gives rise to major problems with toxicity and side effects, while resistance to chemotherapeutic agents also contributes to the need for new and improved anticancer agents with novel mechanisms of action.

In the articles that will follow, a selection of recent, current and future advances in cancer chemotherapy will be discussed.

**References**