New drugs for colorectal cancer – mechanisms of action

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SYNOPSIS
Several new drugs have recently been approved for the treatment of advanced colorectal cancer. Raltitrexed is a folate-based inhibitor of thymidylate synthase. Capecitabine is an orally active prodrug of 5-fluorouracil which undergoes some tumour selective activation. Irinotecan is the first registered topoisomerase I poison with activity against this tumour, whereas oxaliplatin is a platinum analogue. The lack of cross-resistance between these drugs has sparked preclinical and clinical studies of a multitude of combination regimens. These regimens may improve the outcomes for patients in the near future.

Index words: oxaliplatin, irinotecan, capecitabine, raltitrexed.

Introduction
Colorectal cancer has long been considered as moderately resistant to chemotherapy. Previously 5-fluorouracil (5-FU) was the only proven treatment for this indication, but it has been slowly replaced by other drugs. It is hoped these newly approved regimens will provide the building blocks for the combination chemotherapy of the future.

Anticancer drug mechanisms
Anticancer drugs act by a variety of mechanisms including:

- DNA damage by direct (e.g. alkylating agents), protein-mediated (e.g. topoisomerase poisons) and fraudulent base pathways (e.g. nucleoside analogues)
- interference with synthesis of vital co-factors and DNA/RNA/protein precursors (e.g. antimetabolites, asparaginase)
- interference with other cellular structures and processes (e.g. anti-microtubule drugs such as docetaxel, paclitaxel and Vinca alkaloids)
- inhibition of growth/anti-death signal (e.g. tyrosine kinase inhibitors such as imatinib mesylate, trastuzumab).

These mechanisms induce acute cell death (necrosis), programmed cell death (apoptosis), growth arrest or differentiation. Many anticancer drugs have multiple actions on the cell. For example, 5-FU is activated to 5-fluorodeoxyuridylate (also known as fluorodeoxyuridine monophosphate), which in the presence of a reduced folate co-factor inhibits the enzyme thymidylate synthase. This blocks the production of thymidine phosphate which is required for DNA synthesis. The 5-fluorodeoxyuridylate may also be fraudulently incorporated into DNA causing a form of DNA damage.

Mechanisms of action of new drugs active against colorectal cancer (Table 1)

Raltitrexed
Natural folates are vital co-factors for many cellular enzymes, specifically those that catalyse one carbon transfer reactions. Thymidylate synthase is a critical enzyme in the synthesis of the thymidine nucleotides required for DNA synthesis. This enzyme requires a reduced folate co-factor, 5–10-methylene tetrahydrofolate, to act as a carbon donor for the synthesis of thymidylate from deoxyuridylate. Raltitrexed has been specifically developed as a potent mimic of 5–10-methylene tetrahydrofolate and therefore inhibits thymidylate synthase. Many antifolate drugs are polyglutamated within cells. These polyglutamate forms are retained in the cells and, in the case of raltitrexed, this increases its potency and selectivity against thymidylate synthase.

Capecitabine
5-FU was until recently the only drug used extensively for advanced colorectal cancer in Australia (usually in combination with leucovorin). There is now some evidence to suggest that 5-FU is most active when given by prolonged intravenous infusion. This is not very convenient for patients because it

<table>
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<th>Drug</th>
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<td>5-fluorouracil</td>
<td>Inhibition of thymidylate synthase (potentiated by addition of leucovorin)</td>
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<tr>
<td></td>
<td>Incorporation of fraudulent bases into DNA and RNA</td>
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<td>Raltitrexed</td>
<td>Direct inhibitor of thymidylate synthase</td>
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(Aust Prescr 2002;25:108–10)
requires protracted venous access and infusion devices. Oral treatment is not a viable alternative because the absorption of 5-FU from the gastrointestinal tract is low and unpredictable. This problem has led to the development of orally bioavailable 5-FU prodrugs, such as capecitabine.

Oral capecitabine undergoes sequential hydrolysis and deamination reactions in the liver to produce 5'-deoxy-5-fluorouridine. This is converted to 5-FU by thymidine phosphorylase (also known as platelet-derived growth factor). As this enzyme is abundant in tumour tissue there is some tumour specificity in the patient’s exposure to 5-FU.

The adverse effects of treatment resemble those of 5-FU when given by protracted infusion. Hand and foot syndrome (plantar-palmar erythroderma) occurs commonly, the mechanism of which is unknown.

Other oral 5-FU prodrugs (e.g. S-1, UFT) have been the subject of extensive clinical trials, particularly in Japan. These are mostly combinations of 5-FU prodrugs with uracil, which is an inhibitor of dihydropyrimidine dehydrogenase, a ubiquitous enzyme that rapidly degrades 5-FU. This results in higher and more sustained concentrations of 5-FU in the tumour tissue. Surprisingly, these drugs do not appear to produce hand and foot syndrome to the same extent as capecitabine.

**Irinotecan**

Irinotecan is a water-soluble camptothecin analogue. Camptothecin was first isolated in extracts of the Chinese Happy Tree (*Camptotheca acuminata*) in the 1960s, but the mechanism of action and the anticancer potential have only recently been recognised.

Camptothecins function by ‘poisoning’ a nuclear enzyme, topoisomerase I. Topoisomerase I acts as a ‘swivelase’ in the cell, relieving topological problems (hence the name) that arise from the torsional strain that is introduced into long strands of DNA during processing (e.g. replication). This enzyme normally introduces a transient nick into one of the two strands of the DNA, which enables strand rotation and relief of the torsional strain. In the presence of camptothecins, the nick is stabilised which is equivalent to a single-strand DNA break (Fig. 1). Collision with a replication fork during DNA replication then leads to the formation of a potentially lethal double-stranded break. These breaks occur at concentrations of camptothecins that are usually much lower than those that inhibit topoisomerase I-mediated DNA relaxation. This is why these drugs are termed poisons and not inhibitors.

The anticancer activity of doxorubicin, mitozantrone, etoposide and amsacrine is partly mediated by a similar action on DNA. These drugs, however, act on topoisomerase II.

Irinotecan is a prodrug and requires activation to the metabolite SN-38. This metabolite is then conjugated in the liver to an inactive glucuronide by the enzyme UDP glucuronosyltransferase 1A1. The activity of this enzyme is deficient in people with Gilbert’s disease. It is relatively common (1 in 5) and those individuals so affected have greatly reduced capacity for conjugation of SN-38 so they have an increased risk of severe toxicity when treated with irinotecan. Although Gilbert’s disease is not a specific contraindication for irinotecan, affected patients should be treated with great caution.

Irinotecan is also an inhibitor of acetylcholinesterase and patients may experience an acute onset of cholinergic-like symptoms including lacrimation, sweating, abdominal cramping and diarrhoea during or within minutes of the end of infusion. The acute diarrhoea should not be confused with a delayed diarrhoea which can arise 3–10 days after treatment.
Oxaliplatin

Oxaliplatin is a diaminocyclohexane platinum derivative with a broad spectrum of activity which includes colorectal cancer. It undergoes rapid non-enzymatic activation with the displacement of the oxalate ring by two chlorines and subsequent formation of a variety of aquated species. These species react with macromolecules within the cell (Fig. 2). Specifically, the bis-aquated diaminocyclohexane platinum is a bifunctional alkylator capable of reacting with adjacent guanine residues in DNA. This provides either intra- or inter-strand DNA cross-links, which interfere with DNA processing. The lack of cross-resistance with cisplatin in tumour cell models may be due to the retained bulky di-amino cyclohexane residue of the adduct prevents or slows considerably the DNA repair machinery which otherwise removes such aberrant structures.

Interference of oxaliplatin with DNA processing

Oxaliplatin (top left) is activated to a bis-aquated species through a number of reactions. The bis-aquated species then reacts with neighbouring guanine residues either on the same or neighbouring strands of DNA. In the illustrated case, an inter-strand link is depicted (i.e. a bridge is formed between the two strands of DNA). This prevents the strand separation required for DNA processes such as replication, thereby blocking the replication fork (large arrow). It is thought that the bulky di-amino cyclohexane residue of the adduct prevents or slows considerably the DNA repair machinery which otherwise removes such aberrant structures.

The lack of cross-resistance between the thymidylate synthase inhibitors (5-FU, capecitabine, raltitrexed), oxaliplatin and irinotecan means that they could potentially be combined. Indeed, the clinical data gathered so far indicate a definite role for combination regimens in the treatment of advanced colorectal cancer. Oxaliplatin, for example, is only registered for use in combination with 5-FU and leucovorin.

Summary

Recently, several conventional cytotoxic drugs have been registered for use in the management of advanced colorectal cancer. These drugs do not represent a revolution in the treatment of this disease, but they target novel processes (irinotecan), are less prone to deactivation (oxaliplatin), are more selective (raltitrexed) or enable oral therapy (capecitabine). Combining these drugs has additive or synergistic effects in cell culture. These combinations, because of their largely non-overlapping toxicities, are being studied in clinical trials of advanced disease and post-surgical adjuvant treatment.

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Further reading


Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 123)

1. Capecitabine enables cancer cells to be exposed to 5-fluorouracil without the need for prolonged intravenous infusion.
2. Patients may be more prone to the adverse effects of oxaliplatin in cold weather.

Personal information: None declared

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