Oral Antineoplastic Chemotherapy

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ABSTRACT
Although most cancer medicines are administered parenterally, there has been an increase in the availability of oral antineoplastics. Oral antineoplastics offer several advantages, including ease of administration, convenience and cost savings. Disadvantages may include reduced patient supervision, concordance issues, inappropriate patient selection and unpredictable bioavailability. A number of safety issues, including storage and prevention of medication errors, must also be addressed. Safe handling techniques must be optimised to minimise occupational exposure. Pharmacists are in an ideal position to educate patients/carers to ensure concordance to therapy and guarantee the safe and effective use of oral antineoplastics.


INTRODUCTION
Most medications used in oncology and haematology are administered by a parenteral route. While many antineoplastics have been available for oral administration, they have been used rarely compared to intravenous therapies. Factors limiting their use have included lack of appropriate mechanisms for subsidising medication costs, less evidence for use when compared to established intravenous therapies, and an assumption that antineoplastics are best given parenterally.1 A number of new oral antineoplastics have recently been approved and many more are in various stages of development. Oral chemotherapy is appealing for a number of reasons, including ease of administration, convenience and cost savings. However, concordance with therapy and pharmacokinetic considerations may pose problems. With increasing usage expected, pharmacists will have a role in ensuring their safe and efficacious application.

ORAL MEDICATIONS
Oral antineoplastics that have been available for a number of years include busulfan, capecitabine, chlorambucil, cyclophosphamide, etoposide, hydroxyurea, idarubicin, lomustine, melphalan, mercaptopurine, methotrexate, cyclophosphamide, etoposide, hydroxyurea, idarubicin, lomustine, melphalan, mercaptopurine, methotrexate, procarbazine, temozolomide and thioguanine. Older drugs, such as thalidomide, have had a resurgence in treating conditions, such as multiple myeloma. Novel agents and new oral formulations of drugs currently given parenterally are being developed.1 Oral camptothecins, such as topotecan and irinotecan, may exhibit a better toxicity profile.1,13 The ability to administer taxanes orally offers considerable advantages in terms of drug stability following reconstitution and decreases the incidence of hypersensitivity reactions attributed to Cremophor EL (vehicle in paclitaxel formulations).1 Fluorouracil, a cell-cycle-specific agent, has greater efficacy if given over a prolonged period, therefore, there has been a focus on the development of oral alternatives. These have included prodrugs that are absorbed unchanged (capecitabine, tegafur), inhibitors of dihydroptymidine dehydrogenase, or a combination of the two strategies (emitefur).1,4 Capecitabine may potentially replace fluorouracil/calcium folinate in the adjuvant and palliative management of colorectal cancers as a single agent and in combination with oxaliplatin and/or irinotecan. Oral formulations of vinorelbine and fludarabine offer similar efficacy and safety profiles to that of their parenteral forms.5,6

The most important advances in oral chemotherapy are targeted therapies, such as protein kinases.7 Imatinib, a tyrosine kinase inhibitor, has excellent bioavailability and significant activity in chronic myelogenous leukaemia and gastrointestinal stromal tumours.7 Gefitinib, a quinazoline epidermal growth factor receptor tyrosine kinase inhibitor, has activity in non-small cell lung cancer, while erlotinib has shown activity in non-small cell lung and head and neck cancers.1,8

Due to their effects on the immune system, antineoplastics are also indicated in non-malignant conditions, such as autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis), gestational trophoblastic disease, ectopic pregnancy, and psoriasis.8 A number of drugs used to treat these conditions can be given orally (azathioprine, methotrexate).

ADVANTAGES
Ease of Administration
Oral chemotherapy avoids the need for cannulation, often a major cause of discomfort and anxiety for patients. Although these concerns may be alleviated by permanently placed venous access devices, they are expensive, require surgical admission, and can be associated with complications, e.g. infection. Oral chemotherapy can be given in a number of settings, such as the patient's home, nursing home, hospital or hospice.

Improved Quality of Life
Intravenous chemotherapy can be inconvenient for patients, adversely affect quality of life, and can be associated with toxicities, psychological distress, financial difficulties, and prolonged hospital stays.10 Additional visits to the oncology clinic may be required and, with some protocols, overnight or extended hospital admission will be needed. For some patients, this can necessitate long distance travel, keep them away from family and friends, and affect employment. Chronic oral administration may, in selected situations, provide quality of life advantages for patients who are unable to tolerate aggressive regimens, e.g. elderly patients.11

Patient Preference
Most patients prefer oral therapy as it offers a sense of control over treatment and interferes less with their lives and social activities.12 Liu et al. surveyed 103 patients with advanced cancer on their preferred method of treatment—oral chemotherapy was preferred by 89% with the major reasons being convenience (57%), problems with intravenous lines/needles (55%) and control over

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the environment (33%). Patients were not prepared to sacrifice efficacy, reduced response (70%) or shorter duration of response (74%), in preference for oral therapy.

Prolonged Drug Exposure
Oral therapy of the cell-cycle-specific agents avoids daily intravenous or continuous infusions. In contrast to the intermittent, short-term use of traditional antineoplastics, which is compatible with intravenous administration, novel agents, such as signal transduction inhibitors, may need to be taken continually for months or years. In the evolving area of chemoprevention, oral therapy may improve efficacy by facilitating continuous drug exposure. Oral chemotherapy is more easily combined with radiation therapy as chemosensitisers, than intravenous therapies. Infusional fluorouracil is likely to be replaced as a chemosensitiser by oral fluoropyrimidines in the concurrent treatment of many tumours.

Cost Benefits
Savings in direct drug costs may not be apparent when changing to oral chemotherapy. Lower bioavailability may translate into increased expenditure where higher doses of oral drugs are needed for an equivalent therapeutic dose. Patients may also be required to pay the Pharmaceutical Benefits Scheme contribution for oral chemotherapy, which may not occur with parenteral treatment given in a public institution. The advantages of oral therapy lie in the reduced workload of the oncology clinic and savings from decreased costs of chemotherapy reconstitution and intravenous administration. Administration costs can include hospitalisation, salaries, infusion equipment and consumables, intravenous fluids, manufacturing costs and capital equipment.

Disadvantages
Reduced Supervision
Fewer oncology clinic visits are expected with oral chemotherapy. This reduced contact with the oncology team can be a disadvantage to many patients (physically and psychologically). Patients will have less contact with oncology pharmacists, and the burden for supply and counselling may fall on less experienced dispensary staff. Oral antineoplastics are increasingly likely to be dispensed through community pharmacies, placing the onus on these pharmacists to be able to counsel patients effectively on dosing regimens and the hazards of these medications. It is essential that patients are educated to recognise adverse effects so that treatment can be promptly ceased, if required.

Patient Concordance
Concordance is a major consideration in any switch to oral therapy as dose intensity, and hence treatment outcome, may be affected. Patient concordance to oral chemotherapy is variable and not easily predicted. In a review of published studies, concordance rates ranging from 20 to 100% were reported, with particular problems in certain populations, such as adolescents. A number of factors were identified as leading to non-concordance with oral regimens. These included complex regimens, inadequate supervision, poor communication with health providers, inadequate social support, history of non-concordance, and history of mental illness. Concordance also tends to fall with chronic therapy.

Unpredictable Bioavailability
Oral drugs may have low and unpredictable bioavailability compared to the immediate and complete bioavailability following intravenous administration. In general, antineoplastics have a narrow therapeutic index and tend to be used at maximum tolerated administration. The bioavailability of some oral antineoplastics may be too low to achieve therapeutic plasma levels. This, along with considerable inter-patient variability, complicates dosing and may easily lead to either subtherapeutic treatment or unexpected toxicity. The bioavailability is contingent on adequate intestinal absorption and the circumvention of intestinal and, subsequently, hepatic metabolic systems. When considering absorption, the limitations imposed by saturability and structural stability in gastric and intestinal pH must be addressed. Saturable absorption has been reported for etoposide with doses above 200 mg/day, whereas lower doses were associated with increased bioavailability, although they were characterised by high inter and intra-patient variability. This has also limited the use of oral calcium folinate in regimens for colorectal cancer.

The intestinal epithelium has several mechanisms that limit the absorption of oral antineoplastics. These include extrusion from the epithelium (before reaching the general circulation) back into the intestinal lumen by P-glycoprotein and metabolic breakdown to inactive or less active metabolites by mainly cytochrome P450 (CYP) enzymes. Oral antineoplastics known or suspected to be P-glycoprotein substrates include paclitaxel, docetaxel, etoposide, vinorelbine, idarubicin, topotecan and irinotecan. Investigations are under way using P-glycoprotein inhibitors, such as cyclosporin, to enhance oral bioavailability of P-glycoprotein substrates.

First-pass metabolism by the liver is an important factor in the overall bioavailability of medications. However, metabolism in the gut wall may contribute substantially to this metabolic breakdown. The CYP isoenzyme 3A4, abundantly present in the liver, is also primarily responsible for enteric metabolism. Substrates of CYP3A4 include cyclophosphamide, etoposide, paclitaxel and vinorelbine. Bioavailability may be enhanced by pharmacological manipulations of this system, involving the use of CYP3A4 inducers, such as ketoconazole or cyclosporin.

A different mechanism is responsible for the variable bioavailability of oral fluorouracil. This variability is caused by inter-individual differences in the activity of dihydropyrimidine dehydrogenase, an enzyme catalysing the breakdown of fluorouracil. Dihydropyrimidine dehydrogenase is primarily found in the liver, but is also present in many other tissues. Activity in the intestinal epithelium seems mainly responsible for the erratic oral bioavailability. Several inhibitors of dihydropyrimidine dehydrogenase have been examined in an attempt to modulate the oral bioavailability of fluorouracil.

Inappropriate Patient Selection
Oral therapy should be avoided in patients who are unlikely to be able to reliably take their medicines, some patient populations and patients with an underlying gastrointestinal motility disorder limiting absorption. These disorders may be related to surgical procedures (e.g. gastric resection), complications of their cancer (e.g. bowel obstruction), result of hormonal secretions from tumours, or side effects of antineoplastics or other medicines (e.g. nausea). Swallowing may be difficult with
severe mucositis or significant oropharyngeal disability, such as in head and neck cancer. Oral chemotherapy is not advisable in patients with nasoenteric or gastrostomy tubes as this may necessitate crushing of medicines leading to potential occupational exposure.

Age-related factors, involving comprehension and the ability to physically take tablets/capsules, are important in the young and elderly. Elderly patients may have limited sight and/or manual dexterity. Oral medicines should be avoided in patients with major depression or dementia, and those who have demonstrated unreliable behaviour or a lack of motivation in the past. For patients taking multiple oral medicines, the addition of oral chemotherapy to their regimen may not be feasible, due to increased complexity or potential drug interactions.

SAFETY ISSUES

Occupational Exposure

Occupational exposure to antineoplastics has been recognised as a health hazard for over 25 years. Apart from their well-documented acute and chronic adverse effects, antineoplastics have been proven in clinical and animals studies to be mutagenic, teratogenic and carcinogenic. Pharmacists and technicians often come in contact with antineoplastics during the manufacturing process. Nurses are also at potential risk of exposure when administering these drugs. Patients receiving antineoplastics may also pose a hazard to family members and caregivers through contact with body fluids. With oral chemotherapy the greatest risks of occupational exposure lie with absorption of powdered drug or contact with active drug or metabolites that have been excreted from the body. Possible routes of absorption include inhalation, dermal, oral and ocular. Excretion is possible via urine, faeces, saliva, tears and breast milk. Davis et al. have developed a concise reference table on the potential effects of exposure to 50 of the most commonly used antineoplastics. Pharmacokinetic parameters listed include pregnancy risk category, route of excretion, route of absorption, estimated time for drug clearance, and signs or symptoms of exposure.

Studies of occupational exposure have demonstrated contamination of the operator and the work environment, even when protective measures have been taken. However, the specific use of oral antineoplastics has not been extensively studied. Dorr et al. examined the extent of percutaneous absorption of several antineoplastics, including crushed melphalan tablets, and showed negligible or non-existent transdermal uptake. They concluded that these results were not surprising as most topically applied drugs achieve little systemic bioavailability (< 1 to 5%) even when administered in optimised topical preparations. However, significant amounts of drug were recovered from the ambient air in close proximity to the mortar and pestle used to crush the melphalan tablets, indicating a risk of exposure to airborne drug particles during mechanical manipulations.

Safe Handling

The development of cytotoxic drug handling guidelines, incorporating the use of cytotoxic drug safety cabinets or isolators and improved handling techniques, have greatly reduced the potential for exposure in health workers. While specific guidelines for oral antineoplastics have not been developed, the SHPA standards of practice recommend that tablets/capsules must be handled in a manner which avoids skin contact, liberation of powdered drug into the air and chemical cross-contamination with other medications. All equipment used in the dispensing of cytotoxic solid dosage forms must be dedicated to this purpose and clearly labelled. Tablets/capsules must not be counted using a counting machine. For staff administering oral antineoplastics, a no-touch technique is advised. If touching is unavoidable, gloves and thorough hand washing are essential to avoid the risk of skin exposure.

Exposure can also occur through contact with contaminated body fluids and precautions should be taken for around 48 to 72 hours after treatment is stopped, and sometimes longer with faeces. Continual oral dosing means that bodily waste is always contaminated.

While manufacturers have improved formulations and packaging of oral antineoplastics over the years, it is still not ideal. Tablets should be coated to prevent the development of dust residue and presented in blister or strip packaging in child-resistant containers. At present, many of the older cytotoxics are packaged loose in glass or plastic containers, most of which are not child-resistant.

The need for extemporaneous preparations from oral antineoplastics is uncommon; however, if necessary, manufacturing must be done by trained staff in a cytotoxic drug safety cabinet.

Storage

Oral antineoplastics need to be stored securely and out of the reach of children. Ideally, they should be dispensed with child-resistant lids, but this may cause problems for patients lacking dexterity. Some medicines may require refrigeration, but most can be stored at room temperature away from excessive heat and moisture. Patients should be advised to return unused oral antineoplastics to their pharmacy to ensure proper disposal.

Medication Errors

The consequences of errors involving antineoplastics can be devastating due to their narrow therapeutic index. In addition, regimens are becoming more complex and intensive as supportive care has improved. Errors are just as likely to occur with oral as with parenteral administration. In a review of 106 methotrexate errors, mostly associated with oral therapy, 25 deaths were reported (24%) and 48 other serious outcomes were identified. Over 50% of errors were due to overdose, primarily giving the drug daily instead of weekly.

In an Australian study of medication errors occurring in prescriptions for chemotherapy, 20% of errors were related to oral administration despite this route accounting for only 3% of doses prescribed. While it is recognised that all antineoplastics should be written on the basis of a referenced protocol on a specifically designed prescription form, this standard is not always applied to oral chemotherapy. Reasons vary but may include the need to use the Pharmaceutical Benefits Scheme to enable reimbursement of the drug. This issue has become relevant with the introduction of the Pharmaceutical Benefits Scheme into public hospitals. A standard antineoplastic prescription will usually contain a reference to the protocol being used and may require the body surface area of the patient to enable doses to be checked. However, this type of information is not generally transcribed onto a Pharmaceutical Benefits Scheme prescription. Whereas parenteral antineoplastics, in most institutions, will be
subject to a clinical validation procedure from an oncology pharmacist, many centres direct the dispensing of oral agents to the outpatient pharmacy or a community pharmacy where there may not be a person with the knowledge and expertise to validate the prescription. The Pharmaceutical Benefits Scheme encourages original packaging of oral cytostatics but, with antineoplastics, doses and quantities may vary according to body surface area and the protocol used. Dispensing a whole pack to a patient requiring a lesser quantity can lead to confusion and potential overdosing. Strategies must be put in place to ensure the supply of oral antineoplastics is carried out to the same exacting standards as parenteral antineoplastics.

Guidelines on the prevention of errors with antineoplastics published by the American Society of Health-System Pharmacists contain recommendations for oral chemotherapy.36 The British Oncology Pharmacy Association has also published a statement on the safe practice and pharmaceutical care for oral antineoplastics <www.bopa-web.org/Publications/oralchemofinal.htm> and a similar document is being prepared by the SPHA Committee of Specialty Practice in Oncology.

Patient Education

Pharmacists must ensure that patients are educated so that the full benefit of oral chemotherapy is achieved. Effective counselling promotes safety, optimal dosing, concordance, accurate assessment of adverse effects, and implementation of self-care measures.37 Vital components for patient education include: drug name and indication; dose; route and frequency of administration; length of treatment; action to take for missed doses; interactions; storage, handling and disposal of drugs and body fluids; adverse effects; strategies for managing adverse effects; and when to seek professional guidance for adverse effects. Patients must recognise symptoms that can be self-managed as opposed to those that should prompt a phone call or immediate visit to a healthcare facility.38 As monitoring may be less frequent with oral chemotherapy, patients may need to contact oncology staff sooner when adverse effects that may necessitate a break from treatment occur. Personalised verbal counselling must be reinforced with written information.

Strategies should be put in place to ensure concordance to therapy with oral antineoplastics. Interventions that have produced some improvement in concordance in this population include educational programs, behavioural modification techniques (practice pill-taking), and the use of reminder systems and clues.39 A patient diary with a symptom management log may be an effective tool to help promote concordance and safe administration.23 Devices, such as pill boxes, may be used, but appropriate safe handling techniques must be employed when these devices are filled.

In summary, pharmacists are in an unique position to ensure the effective and safe use of oral antineoplastics. Knowledge of their distinctive characteristics and properties, as well as a thorough assessment of each patient’s ability to self-administer is critical to successful treatment outcomes. The key to success lies with comprehensive patient/carer education and continued monitoring of therapy.

Competing interests: None declared.

References

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