

Safe use of oral cytotoxic medicines

SUMMARY

The oral route is increasingly used to administer cytotoxic therapy for cancer and non-cancer conditions.

Oral cytotoxic therapy carries the same risk of medication errors as parenteral therapy.

It is essential that health professionals involved in providing oral cytotoxic therapies understand how they are used, what adverse effects can occur and how to minimise medication errors.

Introduction

Oral administration of cytotoxic therapy has increased over the past decade as newer drugs and formulations have become available (see Table). Cytotoxic chemotherapy is not restricted to cancer. Conditions including rheumatoid arthritis, psoriasis and other autoimmune diseases may be managed using oral medicines such as methotrexate.

The pros and cons of oral cytotoxic therapy

The oral route offers many advantages over the parenteral route of administration. Medicines can be administered in the community, without the need for venous access, and fewer visits to the hospital are needed.

While self-administration at home is convenient for both patients and carers, it can present a risk for the patient. Adverse effects can go undetected unless appropriate steps are in place to monitor the patient. Cytotoxic chemotherapy has a narrow therapeutic index and a small increase in dose can result in toxic effects, while under-dosing can lead to failure of therapy. Serious toxicities and fatal outcomes have occurred as a result of incorrect prescribing and dispensing as well as patient misinterpretation of dosing instructions.¹⁻⁶

Responsibilities of the healthcare team

The safe delivery of oral cytotoxic therapy requires a multidisciplinary approach. Patients may be managed under shared-care arrangements between hospital specialists, general practitioners and community pharmacies.

All health professionals involved should:

- have appropriate training and skills in the use of cytotoxic chemotherapy and cancer care, when therapy is being used in this context⁷
- seek advice from a practitioner experienced in cytotoxic chemotherapy when required
- follow the principles of safe medication practices for oral cytotoxic medicines.

All patients should have a treatment plan. This is completed by the specialist who initiates the treatment⁷ and should be given to the patient and all the healthcare professionals involved in their treatment. It is important that the patient has the plan with them if they see a different doctor, for instance in an emergency.

For the treatment plan to be useful, it should be explicit about:

- the patient's diagnosis
- the name of the chemotherapy protocol or specific cytotoxic medicine
- the expected number of cycles and the intended duration of treatment
- other adjuvant or concurrent treatments the patient is receiving (for example radiation therapy or surgery for cancer patients)
- expected adverse effects and their management.

Prescribing

Prescriptions for oral cytotoxic therapy should be clear and unambiguous. The term 'as directed' must not be used regardless of how long the patient has been on the therapy.

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Key words

capecitabine, methotrexate

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Table Oral cytotoxic medicines

Drug class	Drugs
Alkylating agents	busulfan, chlorambucil, cyclophosphamide*, lomustine, melphalan, procarbazine, temozolomide
Anthracyclines	idarubicin
Antimetabolites	capecitabine, fludarabine, hydroxyurea*, mercaptopurine*, methotrexate*, thioguanine
Podophylotoxins	etoposide
Vinca alkaloids	vinorelbine

* currently used for both cancer and non-cancer indications

Prescriptions should specify:

- the generic drug name, number of tablets to be taken⁷ and frequency and duration of therapy (written in full)
- whether the medicine is given on a cyclical or continuous basis. For example, capecitabine is frequently administered for 14 days of a 21-day cycle while temozolomide may be administered for 5 days of a 28-day cycle. The start and stop dates for a cycle should be clear.
- the day on which tablets should be taken. For example, methotrexate is most commonly given as a once-weekly dose (Box).⁸ Fatal errors have occurred when methotrexate has been prescribed to be taken daily or when the incorrect strength of tablets has been prescribed.⁹

Wherever possible the quantity prescribed should be the quantity needed for one cycle (cancer chemotherapy) or one month (for example methotrexate for rheumatoid arthritis). Preferably, repeat prescriptions should not be issued as doses may change according to adverse effects and therapeutic response. If a repeat prescription is

Box **Safe prescribing of weekly methotrexate**⁸

Provide the patient with verbal and written information on the intended schedule of therapy including the dose as a quantity of tablets and the frequency of dosing

Ensure handwritten prescriptions are complete and legible and include in full the form, strength, dose and directions

Nominate on the prescription the day on which the dose should be taken

Do not write 'as directed' on the prescription

Consider limiting the prescribed quantity of methotrexate to four weeks

Do not override warnings and flags for methotrexate in prescribing software

Keep the strength of tablet supplied to the patient consistent to avoid confusion for the patient over the number of tablets they need to take

Be aware of signs of methotrexate toxicity or intolerance, for example dry persistent cough, vomiting and diarrhoea

Patients should be advised to contact their doctor or pharmacist straight away if a dose is missed, or they develop an infection such as gastroenteritis or fever

If a patient is admitted to hospital, strike out the six days of the week when methotrexate is NOT required in the administration section of the inpatient medication chart

issued within the Pharmaceutical Benefits Scheme regulations, the patient should be directed to destroy any repeats or return them to the prescriber if treatment is changed or stopped.

Patients should always be advised on the action to take should they experience an adverse event – for example severe diarrhoea with capecitabine requires immediate cessation of therapy. Patients should be given the name of an accessible healthcare contact they can speak to regarding any concerns.

Dispensing and supplying oral cytotoxic treatment

The dispensing of oral cytotoxic therapy includes verification of the prescription for the patient and their condition, and appropriate supply in a safe and timely manner.⁷ For cancer chemotherapy the pharmacist should have access to the treatment plan, the chemotherapy protocol and relevant patient parameters including height and weight and recent laboratory results.¹⁰ The pharmacist should ensure that the relevant supportive medicine has been prescribed or is available to the patient.

Interactions between chemotherapy, other prescribed drugs, and over-the-counter and complementary medicines can cause changes in the efficacy and safety of oral chemotherapy.¹¹ For example, analgesic doses of aspirin and non-steroidal anti-inflammatory drugs can increase the toxicity of methotrexate when they are used with cancer therapy. Low-dose aspirin can be used with weekly methotrexate. The risk associated with lower doses of methotrexate used in rheumatoid arthritis therapy is much less.

Conversely cytotoxic chemotherapy can alter the effectiveness of other drugs. For example, capecitabine significantly reduces the metabolism of warfarin, increasing its anticoagulant effect. A complete medication history should be taken from the patient or carer before dispensing a prescription and potential interactions should be discussed.

If a dose administration aid (for example a Websterpak) is required by the patient, then oral cytotoxics must be packed separately from the patient's non-cytotoxic medicines.

Medicine labelling

The labelling of oral cytotoxic therapy should clearly state the dose and the number of tablets to be taken. The label for weekly dosing for medicines such as methotrexate and vinorelbine should include the term 'once a week' and specify the day the dose should be taken. Cytotoxic chemotherapy can be carcinogenic, mutagenic and teratogenic. A warning sticker should be placed on all containers of cytotoxic chemotherapy tablets and capsules, in accordance with local health

and safety policy. An adhesive purple sticker with the wording 'cytotoxic, handle with care' is recommended. A warning label must be placed on administration aid packs that identify the contents as cytotoxic. Oral cytotoxic tablets and capsules should not be broken or crushed as this can increase the risk of exposure and alter the bioavailability of the medicine.

Information for the patient

Patient information is paramount to support the safe use of oral cytotoxic therapy. Patients should be given verbal and written information that includes dose instructions (when the medicine should be taken and if it is required to be taken before or after food), adverse effects and safe storage instructions.^{7,12} Some oral cytotoxic medicines need to be stored securely in a refrigerator, for example chlorambucil and melphalan.

Patients should be advised that oral cytotoxic medicine should only be taken out of the dispensed packaging immediately before a dose. To minimise exposure of carers and family members to cytotoxic medicines, patients should be advised that self-administration is preferable. If administration by a carer is required then disposable gloves should be worn. Unused tablets must be returned to the local pharmacy or original supplier and not disposed of at home.

The intermittent, cyclical treatment that is characteristic of many cancer chemotherapy protocols is difficult for some patients to understand and they may misinterpret instructions. Medication guides, patient calendars and dose administration aids are often useful to help patients follow complex dose regimens, particularly those on multiple medicines. Adherence to oral therapy is important to maximise the benefits and reduce the risks of treatment. This should be discussed with the patient.

If appropriate, Consumer Medicine Information leaflets should be given to patients, however the context in which cytotoxic chemotherapy is used often limits their suitability. Patient information leaflets on many of the commonly used cancer chemotherapy protocols can be found on the eViQ Cancer Treatments Online website.¹³ This website also provides information about how to safely take oral chemotherapy treatments at home.* The Australian Rheumatology Association provides patient information on drugs such as methotrexate and cyclophosphamide.⁸

Patients should be advised of the importance of notifying dentists, doctors and other healthcare professionals who may be involved in their care about their cytotoxic therapy.

Identifying and managing adverse effects

Cytotoxic chemotherapy causes many adverse effects such as nausea, vomiting, bone marrow suppression, stomatitis, diarrhoea, hand-foot syndrome, peripheral and central neurotoxicity, renal and liver dysfunction and hair loss. The effects require careful monitoring, and supportive therapies may be needed to minimise them. Antiemetics should be prescribed according to the emetogenic potential of the chemotherapy.¹⁴ Nausea and vomiting can continue for several days after a dose of chemotherapy and the duration of antiemetic therapy should take this into consideration. Guidelines exist for prescribing antiemetics with cancer chemotherapy.^{15,16}

Blood counts need to be frequently checked with cytotoxic therapy. Patient monitoring, including laboratory tests and the parameters for initiating the next cycle of chemotherapy, should be clearly defined in the protocol or treatment plan. For example, a neutrophil count of greater than 1×10^9 is usually required for a cycle of cancer chemotherapy to proceed.

Particular care should be taken with patients when the cytotoxic therapy is taken continuously, for example cyclophosphamide or chlorambucil, as severe myelosuppression can develop. Cytotoxic chemotherapy can adversely affect liver and renal function and these should be monitored before each course of therapy.

Live vaccines are contraindicated in patients with impaired immune function which includes those receiving oral cytotoxic therapy. These vaccinations should usually be delayed until at least six months after the completion of any chemotherapy. Inactivated vaccines are generally safe, but patients may have a diminished immune response to the vaccine. The influenza vaccine should be administered before each influenza season and pneumococcal vaccine should be considered before starting therapy.

Recommendations

Despite the convenience that oral cytotoxic therapy offers, it carries the same risk of medication errors and adverse effects as parenteral therapy. Oral

Patient information is paramount to support the safe use of oral cytotoxic therapy

* www.eviq.org.au/Protocol/tabid/66/categoryid/449/id/492/Patient+Information+-+Oral+Chemotherapy.aspx

cytotoxic medicines have a narrow therapeutic index and monitoring the patient for safety and efficacy is essential. Written and verbal communication with patients and carers is critical for the safe and appropriate use of cytotoxic therapy.

If a patient unknown to the prescriber, pharmacist or healthcare professional presents for oral cytotoxic therapy, the risk of continuing therapy should be balanced against the risk of stopping therapy until

a full history and safety checks are done. In many cases delaying therapy for a short time while a full patient review is conducted and laboratory counts are obtained is safer than continuing therapy. <

Dr Carrington served on advisory boards for Amgen and Merck Sharp & Dohme and has received honoraria from Roche and Merck Sharp & Dohme for educational presentations.

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FURTHER READING

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Dental note

Safe use of oral cytotoxic drugs

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The increasing use of oral cytotoxic drugs for non-oncological diseases has resulted in an increased likelihood that dental patients will be taking them. The oral mucosa has a very high cell turnover rate and these drugs will invariably result in thinning of the mucosa, and often, concurrent salivary hypofunction.

These patients are likely to require increased care and, if they have complex dental treatment needs, may require specialist management. Good communication with the treating doctors and appropriate referral where necessary will significantly help these patients.