Improving the safety of community-based **chemotherapy**

Chemotherapy is predominantly managed in secondary care, but many prescriptions for oral medicines are dispensed and taken in the community. Chemotherapy medicines are cytotoxic, and their regimens are often complicated; prescribers and pharmacists need to take added care as errors can result in severe harm to patients. Defined processes when prescribing or dispensing, combined with good communication between prescribers, patients and pharmacists, improves the safety of community-based chemotherapy.

Cancer treatment in the community is increasing

As the average age of the population increases and detection techniques improve, the number of people diagnosed with cancer continues to grow. In 1950 there were 3605 new cancer diagnoses registered in New Zealand; in 2010 this number had increased to more than 21 000.[1] Improved treatments mean that people diagnosed with cancer are living longer. Chemotherapy is increasingly available in oral formulations that the patient takes at home, rather than in a hospital setting. In 2014, oral chemotherapy and immunosuppressant medicines were dispensed more than 345 000 times from community pharmacies in New Zealand to over 52 000 people.[2]

Chemotherapy has a narrow therapeutic window

Systemic chemotherapy targets malignant cells but also adversely affects normal cells. Oncologists optimise the patient's treatment plan to maximise the toxicity to cancer cells while minimising the adverse effects on the rest of the body. There is a narrow threshold between the therapeutic window and the development of serious complications. Due to this fine balance even small irregularities in prescribing or dispensing can result in serious adverse effects. If a patient receives a dose that is too low, this may allow proliferation of neoplastic cells. Over-treatment can result in complications ranging from vomiting to neurotoxicity, renal and liver dysfunction, bone marrow suppression or death.[3]

Chemotherapy regimens are often complicated

The complex and cyclical nature of some chemotherapy treatment regimens increases the potential for error during prescribing or dispensing. Doses of chemotherapy medicines may be fixed or they may be continually adjusted depending on the patient's body weight, body surface area, neutrophil count, renal or hepatic function or response to treatment. Chemotherapy dosing may be altered if other medicines are taken concurrently.

How common are errors in chemotherapy?

A study from the United States found an overall error rate of 1.4% for outpatient chemotherapy.[4] This was higher than the 0.8% overall rate of errors for patients taking non-chemotherapy medicines.[4] Paediatric patients appear to be particularly vulnerable to community-based chemotherapy treatment errors. At one paediatric cancer clinic 77% of medicine errors involved medicines taken at home.[4]

For further information, see: "The medicine errors most often associated with oral chemotherapy", Page 24.

Practice points to improve the safety of chemotherapy regimens

The Health Quality and Safety Commission (HQSC) and the Clinical Oncology Society of Australia have recommended practice points to improve the safety of chemotherapy. The theme across many of these recommendations is the need for clear, and where possible documented, communication between patients, oncologists, general practitioners and pharmacists.

Communication between prescribers, patients and pharmacists improves safety

Chemotherapy is safer when there is good communication between prescribers, patients and pharmacists. Before a patient begins treatment it is a good idea to discuss all the medicines they are currently taking including any over-the-counter (OTC) or complementary and alternative medicines (CAM). A number of CAMs have the potential to interact with chemotherapy medicines, including: gingko biloba, echinacea, ginseng, St. John's Wort and kava.[8] Discussions between prescribers and pharmacists about the chemotherapy regimen reduce the risk of errors, particularly before a patient begins chemotherapy and whenever the treatment regimen is changed.

The medicine errors most often associated with oral chemotherapy

The oral chemotherapy medicines that were most frequently involved in errors in a review conducted in the United States were:[5]

- Capecitabine – indications for cancer treatment include: breast, colon and oesophago-gastric cancers
- Imatinib – indications for cancer treatment include: leukaemia, gastrointestinal stromal tumours and dermatofibrosarcoma protuberans
- Temozolomide – indicated for: glioblastoma multiforme, recurrent high grade glioma, advanced metastatic melanoma
- Methotrexate – indications for cancer treatment include: general antineoplastic chemotherapy
- Hydroxyurea – indications for cancer treatment include: chronic myeloid leukaemia, cancer of the cervix, head or neck
- Vinorelbine – indicated for: non-small cell lung cancer and advanced breast cancer

Capecitabine is reported to be particularly prone to dispensing errors due to the number of different indications it is used for and because it has a variety of dosing algorithms;[5] it is available in 150 mg and 500 mg tablets.

The common errors associated with oral chemotherapy

The most frequent types of errors involving oral medicines prescribed for chemotherapy reported by the same study from the United States are shown in Figure 1.

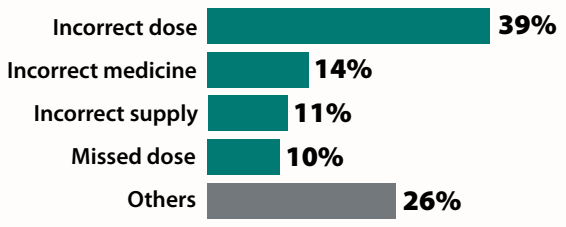


Figure 1: Types of oral chemotherapy errors[5]

The majority of errors involved "near misses" where the error was identified before any harm was caused to the patient.[5] Errors involving chemotherapy medicines were intercepted by a pharmacist before serious harm was done to patient in 38% of cases.[5]

Incorrect doses cause patient harm

Incorrect dosing resulted in patient harm in approximately 40% of reported cases.[5] Problems with prescribers writing prescriptions accounted for almost 60% of these errors.[5] For example, a patient died after a doctor prescribed a ten-fold overdose of temozolomide;[5] this can easily occur when medicines have formulations with many different strengths.

Medicine administration errors accounted for 27% of dosing errors.[5] These errors included patients taking medicines daily instead of weekly, or not stopping medicines when intended.

Dispensing errors accounted for 3% of dosing errors.[5] In one case a pharmacist misinterpreted a prescription for mercaptopurine 50 mg, twice daily, as 300 mg, daily; the patient experienced serious bleeding.[5] Mercaptopurine indications include acute leukaemias and chronic myeloid leukaemia.[6]

Multiple formulations of medicines can cause errors

Different formulations of oral chemotherapy medicines can cause confusion when patients need to take multiple tablets of different strengths to make up a dose. For example, temozolomide is available in four different subsidised strength capsules and patients may need to take multiple strengths to achieve the correct dose.[6]

Supplying the incorrect number of days treatment

Chemotherapy medicines that are taken on specific days, rather than daily, may be supplied in the wrong quantity if the prescription is not processed correctly. For example, lomustine is indicated for patients with brain tumours, Hodgkin's lymphoma and small cell lung carcinoma and is taken as a single dose, once every six weeks.[7] A patient taking lomustine died of complications of bone marrow suppression after they were dispensed, and took, 190 mg of lomustine, daily, rather than every six weeks.[5]

It is important that patients understand why they need to take chemotherapy medicines as prescribed. Treatment non-adherence is a frequent finding in studies of patients taking chemotherapy in the community, sometimes because prescriptions are not collected from the pharmacy. One study found that approximately one in four women with early-stage breast cancer who were prescribed anastrozole did not have sufficient supply to take the medicine for at least 80% of the days they were prescribed it.[9] Chemotherapy regimens usually need to be taken at the full, or near-full, dose to maximally benefit patients. An early study of postoperative breast cancer treatment with cyclophosphamide, methotrexate and fluorouracil (CMF) found that patients given ≥ 85% of the planned dose had a five-year relapse-free survival of 77%.[10] This compared with a five-year relapse-free survival of 48% for patients who received less than 65% of the planned dose due to reasons such as toxicity, the patient's age or their preference.[10] The equivalent survival rate in patients treated by surgery alone was 45%.[10]

Practice points for general practitioners

General practitioners involved in the care of patients with cancer should be provided with a copy of the patient's treatment plan from the clinician who is managing their care.[3] The treatment plan should include the name of the chemotherapy protocol and all medicines the patient is taking, as well as how to manage any adverse effects.

General practitioners are recommended to discuss the treatment plan with the patient. Patients who recognise the medicine and formulation they are taking can help to detect any prescribing or dispensing errors before they cause harm. Asking the patient what they know about a medicine and how frequently they should take it is one way of assessing their understanding and uncovering any misinformation. Patients need clear instructions, including how to identify different strengths of a medicine and when medicines should be taken. When chemotherapy medicines are prescribed the information that is discussed with the patient should be documented.

Prescribers are recommended to include the start date and duration of treatment on chemotherapy prescriptions.[11] It is recommended that only one cycle of chemotherapy be prescribed at a time, e.g:[11]

- Fludarabine 30 milligrams, daily, for three days (days 1 – 3)
- Cyclophosphamide 200 milligrams, daily, for five days (days 1 – 5)
- Day 1 is 1st October, 2015

The patient's height, weight and body surface area should be included on the prescription along with the name of the chemotherapy treatment protocol, e.g. "FC protocol for chronic lymphocytic leukaemia".[11] All units should be recorded in full to prevent quantities such as microgram and milligram amounts being confused.[12] Abbreviations should also be avoided when specifying how frequently medicines should be taken.[12] The term "as directed" should never be used when prescribing chemotherapy medicines.[3] Prescribers should avoid hand writing prescriptions for chemotherapy medicines. Patients should be given advice on how to manage missed doses and what to do if they vomit shortly after taking a chemotherapy medicine.

Managing the adverse effects of chemotherapy

Patients may take oral chemotherapy medicines at home for weeks without direct clinical supervision. The clinician who is responsible for the patient's care will generally manage any adverse effects. However, general practitioners may treat mild symptoms and need to be alert to the possibility of serious adverse effects requiring urgent referral to secondary care.

Nausea and vomiting is expected to occur in 70–80% of patients and may be experienced before chemotherapy, i.e. anticipatory, or up to 72 hours later.[8] Prophylactic lorazepam, metoclopramide or prochlorperazine are often prescribed when the patient has low to moderate risk of chemotherapy-induced nausea.[8] Serotonin antagonists, e.g. ondansetron, are appropriate for more severe chemotherapy-induced nausea; these are highly effective and have minimal adverse effects.[8] Antiemetics are taken between 30 and 90 minutes before the administration of oral chemotherapy, unless the protocol specifies otherwise.[12]

Diarrhoea can be caused by variety of mechanisms in patients undergoing chemotherapy, depending on the treatment regimen. A stool sample is generally recommended to exclude the possibility of an infective organism.[8] Antibiotics may be appropriate if the stool sample is positive for bacteria, otherwise treatment with loperamide may be considered.[8]

Infection can be life-threatening in patients undergoing chemotherapy. Patients who present with an elevated temperature should be carefully assessed, particularly if they are at risk of neutropenia, as clinical signs may be reduced. The risk of serious complications due to infection is proportional to the severity of any finding of neutropenia on full blood count.[8] Clinicians should have a low threshold for requesting further investigations and contacting the clinician managing the patient's care if a patient undergoing chemotherapy presents with signs of infection.

Rarer but serious adverse effects of chemotherapy that require immediate referral to secondary care include: tumour lysis syndrome, superior vena cava syndrome and spinal cord compression.[8]

Be aware of clinically significant interactions

There are a number of clinically significant interactions that can occur between chemotherapy medicines and medicines commonly prescribed in primary care. For example, the toxicity of methotrexate can be increased in patients taking analgesic doses of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) for arthritis or gout. N.B. this risk is much less when methotrexate is used in lower doses for rheumatoid arthritis.[3] Capecitabine significantly reduces the metabolism of warfarin and increases its anticoagulant effect;[3] the increased risk of bleeding should be discussed with patients taking warfarin who are being treated with capecitabine, and warfarin doses and INR frequency may need to be adjusted.

The New Zealand Formulary has a medicine interaction checker available from: **www.nzf.org.nz/nzf_1**

Practice points for pharmacists dispensing chemotherapy medicines

Pharmacists need to recognise when they receive a prescription for medicines as part of a chemotherapy protocol and have additional safety procedures in place for checking, handling and dispensing cytotoxic medicines. This includes confirming that:[11]

- The medicines dispensed match those on the treatment protocol and none have been confused with another medicine of a similar name
- Any calculations involving the patient's body surface area are still accurate
- The dose and formulation of the medicine are correct
- The patient understands the treatment regimen

The NZF has a body surface area calculator available from: **www.nzf.org.nz/nzf/resource/body%20surface%20Area%20Calculator.htm**

Patients undergoing cyclical chemotherapy are usually clinically reassessed between treatment cycles, therefore only enough medicine for one cycle is recommended per dispensing.[11] Dispensing more medicine than is required may create confusion and increase the risk of a dosing error.

When dispensing chemotherapy medicines ensure that patients understand all the information that is on the medicine label; medicine information should also be printed if it has not already been supplied to the patient by the clinician managing their care.

If a medicine is not to be taken every day patients need to be told this; it should be clearly stated what the interval between each dose should be and that a dose should not be repeated until that interval has passed. Particular care should be taken when consulting with patients with English as a second language and all information should be appropriate to the patient's stage of health literacy.

To ensure the pharmacokinetics of the treatment is not altered patients taking oral chemotherapy should never crush or chew tablets, unless advised to do so.

Pharmacists who are aware which patients are taking chemotherapy medicines can contact prescribers if prescriptions are not being collected.

Provide the patient with "trusted" sources of information

People with cancer and their families may search the internet for information about their condition or the medicines that they are prescribed. It is important that patients make treatment decisions based on evidence-based information from reliable sources.

The Cancer Society of New Zealand has patient-centred cancer treatment information, for further information see: **www.cancernz.org.nz** keyword search = chemotherapy

The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) have safety information available for chemotherapy medicines, e.g.:

www.medsafe.govt.nz/consumers/cmi/m/methotrexatesandoz.pdf

Other reliable international sources of cancer-related information for patients include:

www.nhs.uk/conditions/chemotherapy/pages/definition.aspx

www.cdc.gov/cancer/index.htm

A case of mistaken medicine identity

The office of the Health and Disability Commissioner recently released findings from an investigation as to whether a pharmacist provided a patient with an appropriate standard of care when they were mistakenly dispensed a chemotherapy medicine instead of an immunosuppressant. Although this example does not involve a patient intentionally on a chemotherapy regimen, it shows how care needs to be taken when processing prescriptions for medicines with similar names that are not routinely dispensed.

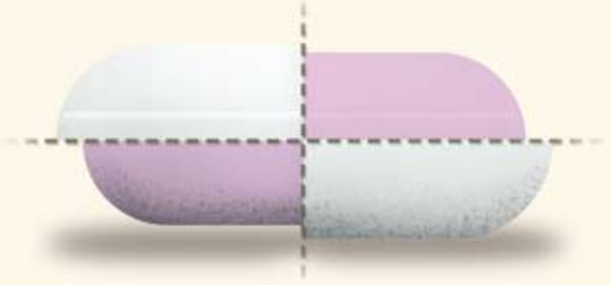
The incident occurred when a patient who had previously had an organ transplant presented at a pharmacy to collect a repeat of their medicines, which included cyclosporin 50 mg (also referred to as ciclosporin and cyclosporine). Cyclosporin is an immunosuppressant with a range of indications and was prescribed to the patient to prevent organ transplant rejection.[13]

A pharmacy technician processed the prescription and selected cyclophosphamide 50 mg capsules, instead of cyclosporine 50 mg capsules.[13] Cyclophosphamide is a chemotherapy medicine indicated to treat patients with leukaemia, lymphomas, some solid tumours and rheumatoid arthritis.[6] Cyclophosphamide tablets are smaller than cyclosporin capsules, pink, and dispensed "loose" in a bottle. Cyclosporin capsules are white, sealed in foil, and dispensed in a cardboard box.

The processed prescription was checked and signed as correct by the attending pharmacist who then supplied this to the patient.[13]

Approximately six weeks later, when the patient presented at the pharmacy again, the same pharmacist was asked why the tablets were different from their regular cyclosporin capsules; an investigation was triggered which uncovered the error.[13] The patient did not appear to have experienced any long-term harm despite taking cyclophosphamide for approximately three weeks.

This is an example of a "mix-up" between medicines with similar names that were both in 50 mg tablets. The pharmacist was found to be in breach of the Code of Health and Disability Services Consumer's Rights for making a serious dispensing error.[13] An adverse comment was also made about the technician's error in selecting the incorrect medicine.[13] The pharmacy has reviewed its standard procedures for dispensing and reporting incidents.[13]



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