AntiC: A practice tool for the safe use of oral chemotherapeutics by community and hospital pharmacists

Tibor van Rooij, BSc; Serena Rix, PharmD; Sharon Marsh, PhD

Problem

Mrs. Brown has a prescription for capecitabine 2000 mg oral, twice daily. Is this the correct dose for her? Perhaps you are the pharmacist in a busy community pharmacy, or maybe you are processing orders in a hospital, but without a comprehensive oncology background, how do you ensure you are processing these prescriptions appropriately?

Background

With an increasing number of chemotherapeutic agents available in oral formulations, it is essential to have the necessary prescribing and dispensing information in a readily accessible format that can be interpreted easily and quickly. Although resources, including electronically accessible data, already exist, much of the relevant information is in disparate, lengthy formats, and is not tailored specifically for Health Canada-approved oral chemotherapeutics.¹⁻¹⁰ It is unlikely that the pharmacist has access to multiple up-to-date texts as well as the time to consult multiple resources to find all the pertinent information for each medication. The case outlined above demonstrates the necessity for an instrument that presents relevant, concise oral chemotherapeutic data in a standardized, Canadian-specific format and automatically updates when new data are added.

The urgency of this issue was initially identified when Mrs. Brown was admitted to hospital via the emergency room for complications of metastatic breast cancer, and “at home” medications were ordered, as neither the prescribing physicians nor the pharmacists processing the order were aware of the potential harm to the patient. Hospital policy issues a 30-day automatic stop order for all medications, except opiate analgesics, antibiotics

and other medications needing more frequent assessment. Oral chemotherapeutic agents, however, are not classified in this group, so this order was processed with a 30-day stop date. Neither the physicians nor the pharmacists involved were aware that this medication is prescribed within the strict parameters of a chemotherapy protocol, including specific start and stop dates. Thus, a serious problem had been identified and a solution needed to be found.

Development of the practice tool

The resolution came in 3 stages. Initially, chemotherapeutic drugs were identified in the hospital computer system (by S. Rix) and flagged for further evaluation. Monographs were drafted (by S. Rix) for each of the oral chemotherapeutic agents available in Alberta. These were made in a standardized 1-page format so the information required could be retrieved and reviewed quickly (Figure 1). Doses, indications, common side effects and drug interactions were included, as well as basic pharmacokinetics to identify whether dose adjustments were necessary for renal or hepatic insufficiency. The authors also devised a cytochrome P450 (CYP) drug interaction table and outlined commonly used chemotherapeutic protocols, as well as including National Institute for Occupational Safety and Health (NIOSH) classification.¹⁻¹⁰

Another component to the problem is that not all medications classified as chemotherapy have the same risk if dosed inappropriately. We wanted to stratify the risk so the pharmacist would be able to identify which agents warranted the greatest concern. A literature search was performed to determine whether this had been done previously, but nothing was found, so we risk stratified based on perceived complexity of

FIGURE 1 Example of a 1-page monograph with information for capecitabine, a common oral chemotherapy agent with a high risk of toxicity¹⁻¹⁰

<u>Capecitabine</u> (Xeloda)	
Risk	High: consult clinical/oncology pharmacist
Classification	Antimetabolite Cytotoxic
Oncology uses (*Approved by Health Canada)	*Breast Cancer Pancreatic cancer *Colorectal cancer
Contraindications	Hypersensitivity to capecitabine (or components) Renal Impairment ($Cl_{cr} < 30$)
Precautions (Special populations)	Pediatrics: Safety & efficacy have not been established Elderly (> 65): may be more sensitive: consider dose reduction DPD deficiency: may require dose reduction
Pregnancy Breastfeeding Fertility	Category: D Not recommended May impair fertility
Side Effects (Clinically significant & frequent: >10%)	PPE , dermatitis, rash Diarrhea, nausea, vomiting, stomatitis , abdominal pain, anorexia, decreased appetite, constipation Cardiotoxicity, edema Hyperbilirubinemia, $\uparrow$ LFT's, myelosuppression Fatigue, pain, fever, paresthesia, dyspnea, eye irritation
Drug Interactions Metabolism: hepatic Inhibits: CYP 2C9 (s)	Avoid: natalizumab, pimecrolimus, tacrolimus (top), live vaccines $\downarrow$ effect of capecitabine: echinacea $\uparrow$ effect of capecitabine: denosumab, trastuzumab $\uparrow$ Effect of: CYP 2C9 substrates , leflunomide, warfarin Caution with other anti-neoplastic agents (unless per protocol)
Usual Oral Dose(s)	Refer to protocol
Dose Adjustments Excretion: renal	Renal Cl_{cr} : 30-50 mL/min: 75% < 30 mL/min: contraindicated Dialysis: no data available Hepatic dysfunction: moderate: no adjustment severe: no data available Myelosuppression/toxicities: dose adjust per protocol or dose adjustment for myelosuppression
Available	Tablets 150 mg & 500 mg
Administration	Oral: Do not crush tablets. Take with water, 30 mins after food
Monitoring	Disease progression & toxicities. (NCI Common Toxicity Criteria) Labs (each cycle): Renal function, LFTs, CBC (diff) INR if on anticoagulants

In addition to the risk categories, further information including contraindications, common associated toxicities and monitoring requirements is included.

dosing regimens and potential harm to patient if the medication was incorrectly prescribed (Table 1). If more detailed information was required, the pharmacist was referred to the *Compendium of Pharmaceuticals and Specialties* (CPS)³ or other drug information.

Website development

The second stage was the creation of the website. Training tools for community pharmacists have been shown to have a significant impact on pharmacist confidence in dispensing oral chemotherapeutics.¹¹ A serendipitous conversation at the

University of Alberta resulted in a collaboration to transfer this information onto an interactive website, thus enabling dissemination of the information to a wider audience, and www.oralchemotherapy.ca was born (Figure 2). The website provided the same information as the monographs but had links to pages listing CYP drug interactions and the chemotherapeutic protocols for each drug.

Mobile application development

The third phase of the project was achieved when the opportunity arose to transform the website into a mobile application (app), making

TABLE 1 Risk stratification of available oral chemotherapeutic agents in Canada*

High risk	Moderate risk	Low risk
Busulfan (Myleran)	Abiraterone (Zytiga)	Anastrozole (Arimidex)
Capecitabine (Xeloda)	Acitretin (Soriatane)	Bicalutamide (Casodex)
Chlorambucil (Leukeran)	Afatinib (Giotrif)	Cyproterone (Androcur)
Cyclophosphamide (Procytox)	Anagrelide (Agrylin)	Exemestane (Aromasin)
Estramustine (Emcyt)	Axitinib (Inlyta)	Flutamide (Euflex)
Etoposide (VePesid)	Bexarotene (Targretin)	Letrozole (Femara)
Fludarabine (Fludara)	Bosutinib (Bosulif)	Medroxyprogesterone (Provera)
Lapatinib (Tykerb)	Dasatinib (Sprycel)	Megestrol (Megace)
Lenalidomide (Revlimid)	Erlotinib (Tarceva)	Nilutamide (Anandron)
Lomustine (CeeNU)	Everolimus (Afinitor)	Tamoxifen (Nolvadex-D)
Melphalan (Alkeran)	Gefitinib (Iressa)	
Methotrexate (Trexall)	Hydroxyurea (Hydrea)	
Procarbazine (Matulane)	Imatinib (Gleevec)	
Sunitinib (Sutent)	Mercaptopurine (Purinethol)	
Temozolomide (Temodal)	Nilotinib (Tasigna)	
Thalidomide (Thalomid)	Pazopanib (Votrient)	
	Sorafenib (Nexavar)	
	Thioguanine (Lanvis)	
	Tretinoin (Vesanoid)	
	Vorinostat (Zolinza)	

*More than 75% of oral chemotherapy medications fall into the high- or moderate-risk categories. Parameters considered for risk category included multiple administration routes, multiple dosing regimens, potential for drug-drug interactions, high potential for toxicity and whether there was high potential that the toxicity would be life-threatening.¹⁻¹⁰

the information available via a handheld device such as a smartphone or tablet. This development resulted in the AntiC app (Figure 3). The oralchemotherapy.ca website infrastructure was modified to connect with the AntiC app. This allows all the information on the website to be accessed at the bedside. A template was created for the app, which is compatible with both Apple and Android devices. This template format allows a pharmacist or other non-computer expert to add and manage the data.¹² There are obvious advantages to this system. Data can be input by personnel with administrative access, who are familiar with the drug names and

understand the relevant medical terms, thus reducing the risk of error. Also, the template can be reused for other data sets such as psychiatry medications or antibiotics. Therefore, it is relatively simple and inexpensive to build other apps using this template, which may also be used to access local information, such as regional or provincial formularies.

Another unique feature of this system is that adding to or editing the database on the website will automatically confer the changes to the app the next time it is connected to the Internet, thus saving time and reducing the risk of transcription error. Finally, the app can be used even in

FIGURE 2 Screenshot of AntiC website Oral Chemotherapeutics page. Users can click on the drug of interest for more information.

Name	Risk
Abiraterone (Zytiga)	!!
Acitretin (Soriatane)	!!
Anagrelide (Agrylin)	!!
Anastrozole (Arimidex)	!
Bexarotene (Targretin)	!!
Bicalutamide (Casodex)	!
Busulfan (Myleran)	!!!
Capecitabine (Xeloda)	!!!
Chlorambucil (Leukeran)	!!!

FIGURE 3 AntiC Android application

the absence of a network connection, allowing pharmacists to access data regardless of their location.

Clinical use of the practice tool

In the case of Mrs. Brown, if you look at the entry for capecitabine on the website (Figure 1; <http://oralchemotherapy.ca/drugs/Capecitabine>), you will see that this medication is coded in the high-risk category and therefore has the potential to cause patient harm if dosed incorrectly. We see that the dose is protocol dependent. In this case we are using capecitabine as a single agent for metastatic breast cancer. Referring to the protocol (Figure 4), we note that the usual dose for single-agent capecitabine for metastatic breast cancer is 1000 to 1250 mg/m² orally, twice daily × 14 days in a 21-day cycle. Mrs. Brown is approximately 1.6 m², so 2000 mg is a suitable dose, providing there have been no prior dose modifications. However, the drug should be dosed × 14 days in a 21-day cycle, so a definite stop date should have been indicated. This information would have to be verified by obtaining the start date and dose using the provincial drug record (if available) or by contacting the originating pharmacy or prescriber, or from medication containers. If Mrs. Brown is still in your care beyond day 21 and is unable to return to the prescriber, you will need to contact the prescriber to determine how to proceed to the next cycle.

FIGURE 4 Screenshot of protocols for capecitabine

Capecitabine Protocols	Use	V	Dose	Days of cycle	Days	# Cycles
Capecitabine (single agent)	Metastatic Breast	1	1000 mg/m ²	1-14	21	
Capecitabine (single agent)	Metastatic Breast	2	1250 mg/m ²	1-14	21	
Capecitabine (single agent)	Colorectal	1	1250mg	1-14	21	
Bevacizumab-capecitabine (XELOX)	Colorectal	1	850 mg/m ² bid	D1 (pm) - D15 (am)	21	
Bevacizumab-capecitabine (XELOX)	Colorectal	2	1000mg/m ² /bid	1-14	21	
Capecitabine-Docetaxel	Breast	1	1250mg/m ² bid	1-14	21	DP/toxic
Capecitabine-Docetaxel	Gastric	1	1000mg/m ² bid	1-14	21	9 cycles/DP/toxic
Capecitabine-Docetaxel	Gastric	2	1000mg/m ² bid	1-14	21	DP/toxic
Capecitabine-Docetaxel	Gastric	3	825mg/m ² bid	1-14	21	DP
Capecitabine-Docetaxel	Gastric	4	1250mg/m ² bid	1-14	21	6 cycles/DP
Capecitabine-Gemcitabine	Pancreatic	1	650mg/m ² bid	1-14	21	24wks/DP
Capecitabine-Gemcitabine	Pancreatic	2	830mg/m ² bid	1-21	28	DP/toxic
Capecitabine-Ixabepilone	Breast	1	1000mg/m ² bid	1-14	21	DP/toxic
Capecitabine-Lapatinib	Breast	1	1000mg/m ² bid	1-14	21	DP/toxic
Capecitabine-Trastuzumab	Breast	1	1250mg/m ²	1-14	21	DP/toxic
Capecitabine-Trastuzumab	Breast	2	1250mg/m ²	1-14	21	
Capecitabine (CAPOX)	Biliary	1	1000mg/m ² bid	1-14	21	
Capecitabine (CAPOX)	Pancreatic	1	1000mg/m ² bid	1-14	21	DP or toxic
Capecitabine (CAPOX)	Pancreatic	2	750mg/m ² /bid	1-14	21	DP or toxic
Cisplatin-capecitabine	Esophageal	1	1000mg/m ² bid	1-14	21	DP or toxic
Cisplatin-capecitabine	Gastric	1	1000mg/m ² bid	1-14	21	DP or toxic
Epirubicin-cisplatin-capecitabine (ECX)	Esophageal	1	625mg/m ² bid	1-21	21	up to 8
Epirubicin-oxaliplatin-capecitabine (EOX)	Esophageal/Gastric	1	625mg/m ² bid	1-21	21	up to 8
Gemcitabine-capecitabine	Biliary	1	650mg/m ² bid	1-14	21	DP or toxic
Gemcitabine-capecitabine	Pancreatic	1	650mg/m ² bid	1-14	21	DP/tox. M 24wks
Gemcitabine-capecitabine	Pancreatic	2	830mg/m ² bid	1-21	28	DP or toxic
Gemcitabine-docetaxel-capecitabine	Pancreatic	1	750mg/m ² bid	1-14	21	
Gemcitabine-docetaxel-capecitabine	Pancreatic	2	500mg/m ² bid	1-14	21	DP or toxic
Irinotecan-capecitabine	Esophageal	1	1000mg/m ² bid	1-14	21	DP or toxic
Irinotecan-capecitabine	Esophageal	2	1000mg/m ² bid	1-14	21	up to 24 weeks
Irinotecan-capecitabine	Gastric	1	1000mg/m ² bid	1-14	21	DP or toxic
Irinotecan-capecitabine	Gastric	2	1000mg/m ² bid	1-14	21	24 weeks
Capecitabine (XELOX)	Colorectal	1	1000mg/m ² bid	1-14	21	8 cycles
Capecitabine (XELOX)	Colorectal	2	1000mg/m ² bid	D1 (pm) - D15 (am)	21	
Capecitabine (XELOX)	Colorectal	3	850 mg/m ² bid	D1 (pm) - D15 (am)	21	
Trastuzumab-cisplatin-capecitabine	Gastric	1	1000mg/m ² bid	1-14	21	DP/toxic

Assuming Mrs. Brown does not have renal impairment (the monograph states that capecitabine is renally cleared; Figure 1) and is not suffering from febrile neutropenia, serious side effects of the drug or disease progression, then it should be safe to proceed for the remainder of the 14 days. If there is any doubt it is always prudent to contact the prescriber for further direction. As it is likely that a hospital admission would result in the prescribing of new medications, we should also perform a drug interaction check, using the website or app (Figure 5).

Using Mrs. Brown as an example, we have demonstrated how a non-oncology pharmacist can navigate the necessary triaging steps with ease and process chemotherapy orders with confidence.

We encourage systems to flag oral chemotherapeutic agents and direct the user to the website or app, where the necessary information is available to dispense the medications correctly, paying particular attention to the high- and intermediate-risk medications. Although the website/app may not be able to solve all the possible problems encountered when prescribing/

dispensing oral chemotherapy, we can alert pharmacists to potential issues and encourage further follow-up if they are still uncertain.

We plan to provide some instruction in the form of online tutorials; for example, we will provide cases on the website homepage (<http://oralchemotherapy.ca>), similar to Mrs. Brown's, where you have the opportunity to resolve the drug-related problems using the website. There is also an opportunity to request the mobile app and to provide feedback (<http://oralchemotherapy.ca/about>) so we can improve the service to better fit the needs of the users.

Limitations

Although creating an updatable app and website is a powerful method of disseminating information quickly and efficiently, it is not without drawbacks. There is a need to update the technology as new operating systems become available and to ensure that the data are continually updated and accurate.

Only medications licensed for use in Canada are included, with Canadian-specific data. It is

FIGURE 5 Screenshot of drug interactions table for capecitabine

Interactions:	Interaction	Compound	Enzyme Effect
	Increases effect of	Carvedilol	-
	Increases effect of capecitabine	Cimetidine	-
	Avoid concomitant use	Clozapine	-
	Increases effect of capecitabine	Denosumab	-
	Increases effect of	Diclofenac	-
	Decreases effect of capecitabine	Echinacea	-
	Increases effect of	Fosphenytoin	-
	Decreases effect of	Inactivated vaccines	-
	Increases effect of	Lacosamide	-
	Increases effect of	Leflunomide	-
	Avoid concomitant use	Live vaccines	-
	Avoid concomitant use	Natalizumab	-
	Increases effect of	Ospemifene	-
	Increases effect of	Phenytoin	-
	Avoid concomitant use	Pimecrolimus	-
	Increases effect of capecitabine	Roflumilast	-
	Avoid concomitant use	Tacrolimus (topical)	-
	Increases effect of capecitabine	Trastuzumab	-
	Increases effect of	Warfarin	-
	Increases effect of	CYP2C9	Substrate
	Other Interactions	n/a	-

also important to acknowledge that oncology is a specialized area of practice. However, pharmacists in nononcology environments are expected to handle these medications, with limited training. No website or mobile app can replace knowledge or education, and this is not the intention. AntiC is merely a tool designed to provide information in a concise and convenient format.

Next steps

The next phase of the project will entail testing and dissemination. We are asking pharmacists to test the website/app, assess the information and provide feedback. The system is currently being tested at a community hospital pharmacy in Edmonton, and any edits will be incorporated into the database fueling the website and app immediately. We also welcome feedback from pharmacists across Canada. The team currently meets monthly to update the practice tool

with newly approved drugs, to curate and edit the existing data and to address any technical issues.

For education, we will continue to provide training through the website, including a streamlined triage process for non-oncology-trained pharmacists. One proposed training mechanism is to devise a series of questions to be answered before and after training using the information provided on website or app and determine whether the quality of the responses improves. We also propose to introduce workshops that include all aspects of oral chemotherapy use, including monitoring side effects and how and when to adjust doses safely.

Future work includes a plan to devise and test a tool to determine the risk stratification of oral chemotherapeutics. This will ensure the stratification process is reproducible and robust for the rapid assessment of newly approved drugs.

Conclusion

We identified a need to ensure safer dispensing of oral chemotherapy. The information to do this

was incorporated into an updatable website and mobile app specifically designed to help the pharmacist in an efficient, user-friendly manner. ■

From the Faculty of Pharmacy and Pharmaceutical Sciences (van Rooij, Rix, Marsh), University of Alberta, Edmonton; and Grey Nuns Community Hospital (Rix), Edmonton, Alberta. Contact Serena. Rix@covenanthealth.ca.

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