Capecitabine and Temozolomide: Design, Implementation, and Preliminary Outcomes From a Pilot Project to Ensure Safe Prescribing of Oral Chemotherapy

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Introduction

ASCO and the Oncology Nursing Society (ONS) recently released recommendations to ensure the safe administration of chemotherapy.¹ These standards call for two qualified personnel to review independently the accuracy of name, dose, and route of cytotoxic therapy. The recommendations convey an implicit understanding of the inclusion of oral cytotoxic chemotherapy. And so they should. Currently, oral chemotherapy constitutes 10% of all cancer chemotherapy administered, and by 2013, this percentage will increase to 25%.² The increasing use of these agents—coupled with a narrow, dose-dependent safety margin of agents such as capecitabine and temozolomide—underscores the importance of double checking all aspects of their administration in a manner analogous to that of intravenous cancer chemotherapy.

However, oral cancer chemotherapy presents unique and challenging circumstances. The fact that nursing staff are not handling these drugs strips away the safety checks routinely provided with intravenous chemotherapy. Moreover, the portable nature of these written prescriptions can lead to drugs being filled at retail pharmacies, which might lack familiarity with cytotoxic agents and might also lack critical patient-specific information on height, weight, and other parameters necessary to check calculations. In the absence of adequate safety measures, oral chemotherapy could lead to undetected dosing errors. Thus, our institution launched a safety project to ensure that each prescription for capecitabine and temozolomide receives an independent double check. This report describes our project and preliminary outcomes.

Methods

The institutional review board at the Mayo Clinic (Rochester, MN) deemed this project exempt. The project itself was designed and implemented within the Division of Medical Oncology at the Mayo Clinic. This solid tumor oncology practice includes more than 70 health care providers, some of whom are fellow-level trainees. Two health care providers at a nearby outreach site were also included. A multidisciplinary task force, which included physicians, pharmacists, nurses, and fellow-level trainees—all of whom were willing to serve in this capacity—was formed to devise, implement, and track the safe prescribing of oral chemotherapy.

Identification of Prescriptions

The task force focused on capecitabine and temozolomide because both agents require a dose calculation. All outpatient prescriptions involving these two drugs were to undergo a safety double check,

regardless of whether patients had their prescriptions filled at a Mayo Clinic pharmacy (where such a double-check procedure would have already been in place) or at an off-site location. The intention was to ensure that safety mechanisms were comprehensive.

Preexisting Safety Mechanisms

This project integrated preexisting and new safety mechanisms (Fig 1). The former mandated that all health care providers prescribe only previously published and internally approved chemotherapy regimens; that they use a calculator embedded within an established electronic chemotherapy ordering system, which would automatically calculate the proper dose when patient height and weight and any clinically indicated dose reduction were entered; that they encounter a flag if a calculation were to yield an extremely high dose; and that they order all paper prescriptions exclusively by means of an electronic ordering system.

Designing and Implementing the Safety Double Check

The task force resolved four design and implementation questions (Fig 1):

First, what would this double check entail? As formulated, this double check required that an oncology pharmacist review an electronic version of the patient's prescription; make sure that the prescription given to the patient included the correctly calculated, clinically appropriate dose, which was in alignment with the previously published, internally approved chemotherapy regimens described earlier; and discuss and resolve dose discrepancies directly with the prescribing health care provider in a timely manner. A discrepancy between prescribed and intended dose of 10% or greater, a threshold based on clinical judgment and precedent,^{3,4} was to prompt a telephone call and electronic message to the prescribing health care provider. In turn, the pharmacist was to provide medical record documentation that a double check had occurred with a description of outcome.

Second, did this safety double check have to occur before a patient's departure? In view of large patient volumes (daily chemotherapy census of more than 100 outpatients), the need to control patient waiting times, the recognition that 1 day of dosing would represent only a fraction of the total chemotherapy dose, the option (as discussed with all oncology health care providers)

Preexisting safety mechanisms:

- Mandated use of only previously published and internally approved chemotherapy regimens
- Automatic calculator embedded within an established electronic chemotherapy ordering system
- Exclusive use of an electronic ordering system for all outpatient prescriptions
- Flags generated by extreme, unjustified chemotherapy dosing

Double-check for capecitabine and temozolomide:

- 6 AM electronic download of all capecitabine and temozolomide prescriptions from the day before
- Pharmacist reviews the electronic version of prescription within 24 hours of patient's receipt
- Direct phone communication between pharmacist and provider for 10% or greater dose discrepancies followed by electronic communication
- Health care provider communicates dose discrepancies directly to patient

Figure 1. Integration of preexisting and new safety mechanisms.

that patients could be told to begin therapy after the double check, and the fact that safety checks were already in place to alert health care providers to high, unjustified doses of chemotherapy, the task force decided that the answer was no. A double check that occurred within 24 hours of a patient's receipt of the prescription seemed acceptable.

Third, who would take responsibility for communicating a prescription change to the patient? The task force obtained consensus among oncology health care providers that they (the health care providers) would take on this duty. Thus, it would be the prescribing health care provider who would inform and re-educate the patient on the correct dosing. If a health care provider were to be absent, a covering health care provider would assume this responsibility.

Fourth, how would pharmacists gain access to all capecitabine and temozolomide prescriptions written the previous day? Because our institution relies exclusively on an outpatient electronic prescribing system, the Task Force worked with technology staff to receive a download by 6 AM the following day of all patients who had received a capecitabine or temozolomide prescription. This download enabled oncology pharmacy staff to double-check dosing Tuesday through Saturday as a high-priority, daily task, in the manner described earlier.

Intended Dose and Near Miss

The definition of intended dose was based on previously published and internally reviewed chemotherapy regimens, output generated from the electronic chemotherapy ordering system, a correct calculation derived from clinical information in the medical record, and a reconciliation of dosing between pharmacist and health care provider in the event of a discrepancy. Electronic ordering systems enabled health care providers to offer clinical justification for dose modifications, thus making it easier for pharmacy staff to understand their rationale. The term near miss—as opposed to error or mistake—seemed appropriate. The early detection and rapid cor-

rection of any dose discrepancy would purportedly result in no patient harm.

Results

Over 4 months, these new safety mechanisms detected 12 prescriptions with a 10% or greater discrepancy from the intended dose, thus yielding monthly near-miss rates of 3.7%, 4%, 1.7%, and 0.8%, respectively, from project initiation (Table 1). Although more temozolomide than capecitabine prescriptions were issued, the problematic drug in all but one of these situations was capecitabine. Capecitabine dose discrepancies involved treatment duration, frequency of dosing, and incorrect data for the calculation, such as the wrong height and/or weight (Table 1). None of these discrepancies represented a nonsensical, extremely high dose, and most appeared to trend toward under-dosing. A review of the medical records of patients with a 10% or greater dose discrepancy did not provide evidence of compromised clinical outcomes attributable to the near miss.

Discussion

This project found that a safety double check can be accomplished and that more importantly, a safety double check is, in fact, valuable. After 1 month, our near-miss rate was 3.7%, but it improved, perhaps because health care providers learned of their shortcomings and subsequently strove to improve their prescribing practices. This high rate raises the question of what might have happened had we not implemented safety mechanisms. In addition to enabling our institution to be compliant with the recent ASCO/ONS guidelines,¹ this safety double check now remains an inherent part

Table 1. Information on Near-Miss Events

Month Interval	Rate (%) [*]	Nature of Near Miss [†]
1	3.7	<ul style="list-style-type: none">—Body mass index was wrongly used instead of weight in capecitabine dose calculation—Capecitabine dose frequency was intended to be twice a day but was wrongly indicated as three times a day—Capecitabine was to be prescribed as continuous dosing over 3 weeks but was wrongly denoted as every-other-week dosing—Capecitabine was to be prescribed as two tablets twice a day but was wrongly written as one tablet twice a day—Capecitabine was to be prescribed for 10 days but was wrongly written to be administered for 14 days
2	4	<ul style="list-style-type: none">—Capecitabine dose was wrongly prescribed in 150-mg tablets when 500-mg tablets were to be prescribed—Capecitabine was wrongly prescribed for 7 days per week when it was to be prescribed only from Monday through Friday—Capecitabine was wrongly prescribed as a 1-mg dose—Capecitabine was wrongly prescribed for 7 days per week when it was to be prescribed for 5 days per week with concurrent radiation
3	1.7	<ul style="list-style-type: none">—Capecitabine dose wrongly included 20% dose reduction for unclear reasons—No capecitabine dose was entered in prescription
4	0.8	<ul style="list-style-type: none">—Temozolomide was wrongly prescribed at 350 mg per day for 5 days when 14% dose reduction was intended

^{*} Rate represents percentage based on oral chemotherapy prescriptions for that time interval, with total No. of monthly prescriptions slightly more than 100.

[†] Explanatory comment is provided for every near miss.

of the Mayo Clinic infrastructure within the Division of Medical Oncology, and it serves to ensure the safe and accurate prescribing of these drugs. Over time, we anticipate the potential expansion of this double check to include other oral agents.

Our project emphasized three other points, the first of which focused on ensuring that each chemotherapy prescription was written accurately the first time. Prescribing capecitabine is challenging and complicated; it can include twice-a-day dosing, weekend interruptions of therapy, regimens of different durations, two different pill strengths, different drug doses in different regimens, and the need to sometimes round dose calculations, all of which could generate prescription errors. Our initially high near-miss rates suggest that other institutions should perhaps consider putting in place safety mechanisms to ensure the safe prescribing of at least this chemotherapy agent.

Second, the Mayo Clinic environment may differ from those of other institutions, and this report does not advocate that other institutions adopt the same methodology we have described here. Rather, this report suggests that patient volumes and current prescribing and safety mechanisms all need to be taken into account as institutions devise oral chemotherapy safety systems that will work best within their specific environments. For example, other institutions that do not incorporate an initial flag for extreme, unjustified doses of chemotherapy may find that a real-time double check is more acceptable than one occurring within 24 hours of a patient's receipt of a prescription.

Third, publishing sensitive material such as chemotherapy near-miss rates can be viewed as a negative endeavor. However, sentinel events are now reported and available to the lay public.^{5,6} Moreover, a respected item in the literature on transparent reporting shows that such practices invite creative and collaborative solutions that enhance patient safety and represent an ethically sound approach for sustaining rigorous quality assurance.^{7,8} Thus, this report is put forth in the spirit of such collaboration and quality assurance.

Finally, we acknowledge that this project addresses only a small aspect of oral chemotherapy safety. Walsh et al⁹ reviewed 1,262 adult patient visits involving 10,995 medications and observed a 7.1% error rate with chemotherapy and other drugs. These errors included premedication mistakes, neglectful responses to adverse effects, and adherence to chemotherapy doses when intercurrent circumstances necessitated dose reductions. In addition, checking that prescriptions are filled correctly, making sure that pharmacies have information on patient height and weight, educating patients

on taking medications, discussing food-drug interactions, ensuring that out-of-pocket medication costs are affordable, educating patients on how to respond to extreme adverse events when correct doses have been prescribed, checking other laboratory parameters such as creatinine when appropriate, and maintaining other standards such as documentation of diagnosis and treatment goals are other issues that were not addressed here but nonetheless merit additional discussion and safety interventions.^{2,10}

Accepted for publication on April 21, 2010.

Acknowledgment

We thank the reviewers for all their helpful comments. A.J. and E.L.S. contributed equally to this work, which was partially funded by Grant No. K24CA131099 from the National Institutes of Health, Bethesda, MD. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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DOI: 10.1200/JOP.200031; posted online ahead of print at <http://jop.ascopubs.org> on June 22, 2010.

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