Medication Safety of Five Oral Chemotherapies: A Proactive Risk Assessment

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Abstract

Purpose: Oral chemotherapies represent an emerging risk area in ambulatory oncology practice. To examine the hazards associated with five oral chemotherapies, we performed a proactive risk assessment.

Methods: We convened interdisciplinary teams and conducted failure mode and effects analyses (FMEAs) for five oral chemotherapy agents: capecitabine, imatinib, temozolomide, 6-mercaptopurine, and an investigational agent. This involved the creation of process maps for each medication, identification of failure modes, selection of high-risk failure modes, and development of recommendations to mitigate these risks. We analyzed the number of steps and types of failure modes and compared this information across the study drugs.

Results: Key vulnerabilities include patient education about drug handling and adverse effects, prescription writing, patient self-administration and medication adherence, and failure to monitor and manage toxicities. Many of these failure modes were common across the five oral chemotherapies, suggesting the presence of common targets for improvement. Streamlining the FMEA itself may promote the dissemination of this method.

Conclusion: Each stage of the medication process poses risks to the safe use of oral chemotherapies. FMEAs may identify opportunities to improve medication safety and reduce the risk of patient harm.

Introduction

Oral chemotherapy in ambulatory oncology poses a new and emerging area of risk. In a survey of US cancer centers, pharmacy directors reported serious oral chemotherapy–related adverse drug events at one quarter of the centers and serious near-miss errors at one third. The survey found that few of these centers had safety precautions in place for monitoring or managing the risks of oral chemotherapies.[1]

Additional risks associated with oral chemotherapy use in ambulatory oncology derive from several factors including the severity of illness of many patients with cancer, disproportionate representation of cancer among young children and the elderly, toxicity of treatments, and complexity of cancer treatment.[2] According to the National Cancer Institute, 90% of cancer care is delivered in ambulatory settings, and more than 25% of the 400 antineoplastic agents in the US Food and Drug Administration pipeline are oral agents.[3]

In the most comprehensive review to date, Partridge et al[2] concluded that adherence to oral chemotherapies was highly variable depending on disease setting, population, and measurement method. Although adherence was generally satisfactory, most patients were enrolled onto clinical trials and therefore highly selected, motivated, and monitored. Certain patient subgroups—notably adolescent patients and possibly those with poor health literacy—were less likely to adhere. There remains significant concern about patients who are not enrolled onto clinical trials and their adherence to recommended oral chemotherapy treatment. Indeed, a study by Taylor et al[4] highlighted possible problems with oral chemotherapy adherence in general oncology care. In a study of parents of children with acute lymphoblastic leukemia, Taylor et al found that parents were often unable to prepare or dose the oral chemotherapy medications they provided to their children. Lastly, a chart review study of adult and pediatric outpatients with cancer conducted by Walsh et al[5] found higher numbers of medication errors than previously reported. In this study, medication errors involving drug administration were most common in the clinic setting for adults and in the home for pediatric patients.

To understand the risks associated with oral chemotherapy, we conducted five failure mode and effects analyses (FMEAs), a form of proactive risk assessment. Working with interdisciplinary clinical teams, we created detailed process maps for five oral chemotherapies used by ambulatory oncology patients. We then identified, analyzed, and prioritized failure modes associated with these five agents to identify opportunities for improvement.

Methods

Setting

This study was conducted in the ambulatory adult and pediatric practice at the Dana-Farber Cancer Institute (DFCI), a National Cancer Institute–designated comprehensive cancer center in Boston, Massachusetts. In 2009, DFCI clinicians examined and treated 299,202 adult and pediatric patients. Sixty-five percent of DFCI patients were women. Eighty-five percent identified themselves as white, 3.7% as black, 2.5% as Hispanic, and 1.8% as Asian. Nineteen percent of patients were age 70 years or older.

Care at DFCI is organized into disease-specific clinical groups working in interdisciplinary teams. Most medications are prescribed using electronic order-entry systems. However, handwritten prescriptions for investigational oral agents and patients on pediatric protocols were used at the time of this project. Oral chemotherapy for home use is dispensed from an

onsite ambulatory pharmacy but may also be obtained from retail or specialty pharmacies in the community or by mail order (depending on a patient's preference and insurance).

Overview of FMEA

FMEA is an analytic method for understanding potential process failures (ie, failure modes) in a system or organization.[6,7] Used originally in the military and aerospace industries, FMEA is now widely employed in a variety of manufacturing and service industries, including health care. It is performed by mapping the steps in a complex process and then identifying failure modes for each step. Because process steps may be vulnerable to multiple failure modes, it is important to identify the failure modes that pose the greatest risk of harm. This work is performed by a team of frontline staff who are familiar with the process. Once teams identify the failure modes, they examine the main causes and effects of each. Each failure mode is rated on the basis of its severity, frequency of occurrence, and detectability and then prioritized. Participants individually and then as a group rate the expected severity, frequency, and detectability of each failure mode, assigning a score to each element from a five-point Likert scale. The results are then multiplied to identify the highest risk failure modes.

To examine risks associated with oral chemotherapy, we conducted five FMEAs by convening interdisciplinary teams with expertise and experience in all aspects of the medication-use process for the study drugs. The teams developed detailed process maps for five oral chemotherapies with significant potential toxicities, including 6-mercaptopurine (6-MP; pediatric leukemia), temozolomide (brain cancer and melanoma), capecitabine (advanced colorectal and breast cancers), imatinib (chronic myelogenous leukemia and GI stromal tumors [GIST]), and a phase II investigational agent used for treatment of GIST. The analyses included an evaluation of electronic and paper-based prescription writing, preparation and dispensing of medications on site and at community-based pharmacies, administration (largely at home by the patient or caregiver), and follow-up and symptom monitoring.

Each group was facilitated by quality improvement specialists from the Department of Quality Improvement and Risk Management at the hospital. The participants included physicians, nurses and nurse practitioners, pharmacists and pharmacy technicians, information technology analysts, patients and family members, patient safety and risk management experts, and research nurses and clinical research coordinators (for the investigational agent). We retained the services of a consultant with extensive experience in proactive risk assessment to provide training to the staff and periodic advice and guidance. We briefed each team about the FMEA process in stages, orienting team members to the work for each day. The first meeting included an overview of FMEA and example of a process map. Subsequent sessions included examples of failure mode analyses and guidelines for rating the failure modes.

To expedite the FMEAs, we searched the scholarly literature and Internet for references pertinent to patient safety risks of oral chemotherapies. We also conducted 10 preliminary interviews with individuals who were integrally involved in the medication-use process. On the basis of this information, we constructed process maps for each of the oral chemotherapies. Again, to expedite the analyses, we asked teams to verify and modify, rather than create, these maps.

Variation Across FMEAs

The scope of each FMEA varied slightly as a result of the customary use of each drug in clinical practice. For capecitabine, temozolomide, and imatinib, the scope began with the physician's writing of the prescription (ie, after deciding that the drug was clinically appropriate) through 6 months of treatment and follow-up. For the investigational agent, FMEA began at the time the patient was informed of the investigational drug through 3 months of follow-up. For 6-MP, FMEA began at the patient's first outpatient clinic visit after initial inpatient hospitalization through 2 years of treatment and follow-up.

We performed traditional, detailed FMEAs for capecitabine, the investigational agent, and 6-MP. FMEAs for temozolomide and imatinib were abbreviated when we discovered significant overlap and redundancy with the capecitabine FMEA. These teams reviewed the capecitabine FMEA and identified similarities and differences in the medication-use process between temozolomide or imatinib and capecitabine. The processes and failure modes for capecitabine and imatinib were nearly identical, whereas differences in the temozolomide analysis reflected risks resulting from the vulnerabilities of the patient population that most commonly used this medication and their particular needs and challenges.

Analyses

Analyses were descriptive. We tabulated the number of major and minor steps in the medication-use process for each of the five study drugs and the number of failure modes identified for each. We defined high-risk failure modes as those with the highest severity and frequency scores and lowest likelihood of detection, selecting the top one third of failure modes from each analysis. We then calculated the number of high-risk failure modes and calculated the ratio of high-risk failure modes to the total. We identified the high-risk failure modes that were common among multiple FMEAs and the stage in the medication process to which they applied. Finally, we examined team recommendations for improving the safety of these medications.

Results

Oral Chemotherapy Medication Process

The complexity of the oral chemotherapy medication-use process is represented in Table 1. The teams identified 15 to 40 major steps per drug, divided among the prescribing, dispensing, administering, and monitoring stages of the medication-use process. A more granular analysis identified 23 major and minor steps for 6-MP; 48 for capecitabine, imatinib, and temozolomide; and 67 for the investigational agent. The dispensing stage had the greatest number of steps in the process maps of capecitabine, imatinib, and temozolomide, whereas prescribing and moni-

Table 1. No. of Process Steps and Failure Modes Identified in Oral Chemotherapy FMEAs

Medication and Stage of Medication-Use Process	Major Steps		Major and Minor Steps		Failure Modes		Failure Modes per Major and Minor Step
	No.	%	No.	%	No.	%	
Capecitabine/imatinib/temozolomide							
Prescribing	5	33	11	23	21	27	1.9
Dispensing	6	40	22	46	33	43	1.5
Administration	3	20	5	10	7	9	1.4
Monitoring	1	7	10	21	16	21	1.6
Total	15		48		77		1.6
Investigational agent							
Prescribing	8	20	17	25	51	26	3.0
Dispensing	16	40	19	28	50	25	2.6
Administration	9	23	12	18	34	17	2.8
Monitoring	7	18	19	28	64	32	3.4
Total	40		67		199		3.0
6-mercaptopurine							
Prescribing	4	25	10	43	14	29	1.4
Dispensing	3	19	3	13	6	12	2.0
Administration	3	19	4	17	12	24	3.0
Monitoring	6	38	6	26	17	35	2.8
Total	16		23		49		2.1

Abbreviation: FMEA, failure mode and effects analysis.

toring accounted for most of the steps involving 6-MP. The investigational agent had an elaborate process at each stage.

Failure Modes

Table 1 also shows that the number of failure modes per stage varied by drug. The investigational drug team identified an average of three failure modes per stage, about twice the rate of the capecitabine, imatinib, and temozolomide teams. The number of high-risk failure modes was between 10 (for 6-MP) and 18 (for the investigational agent). The number of high-risk failure modes relative to the total number of failure modes was greatest for the investigational agent, for which the team judged only 18 (9%) of 199 failure modes as high risk.

Table 2 displays the high-risk failure modes that teams identified in multiple FMEAs. Teams identified four high-risk failure modes in all five FMEAs:

- Prescription writing errors resulting from shortcuts, miscalculations, or illegible handwriting.
- Wrong tablets, liquid, dose, or number of tablets dispensed in the pharmacy.
- Patient did not correctly adhere to regimen.
- Patient failed to or incompletely reported adverse effects.

Teams identified six additional high-risk failure modes in at least four of the FMEAs, spanning the stages of the medication-use process.

The teams also identified high-risk failure modes specific to a single drug. For example, temozolomide poses special risks because of its use as first-line therapy in patients with brain tumors. These patients' potential for cognitive impairment may affect their ability to understand instructions and prepare daily doses composed of pills of various strengths. Temozolomide prescribers noted particular difficulty in arranging for uninterrupted therapy when dose changes required insurance approval and coordination with mail-order pharmacies. Similarly, high-risk failure modes particular to the investigational agent included problems with protocol enrollment, incomplete medication-adherence logbooks, protocol violations, and patient misunderstanding of informed consent documents.

Risk-Reduction Strategies

Drawing on the results of the FMEAs, teams proposed remediation strategies to address high-risk failure modes. Some remediation strategies were common to all five study drugs. For example, each group recommended prohibiting handwritten prescriptions and called-in prescriptions—especially if this involved leaving a message on the pharmacy answering machine—in favor of exclusive use of electronic prescribing. All groups recommended making improvements in patient education, including requiring use of written informed consent for all oral chemotherapy treatment. A representative set of additional recommendations, including those tailored to specific agents, is listed in Table 3.

Discussion

We performed FMEAs for five oral chemotherapies used at a comprehensive cancer center to understand potential vulnerabilities associated with these medications. We found that the medication-use processes were surprisingly complex, that processes varied significantly across different oral cancer drugs, and that these processes were vulnerable to many failure modes. High-risk failure modes spanned the medication-use process; these represent potential targets for improvement.

Table 2. High-Risk Failure Modes Identified Across Multiple Oral Chemotherapy FMEAs

Error	Medication-Use Stage	Capecitabine/Imatinib/ Temozolomide	Investigational Agent	6-Mercaptopurine	No. of FMEAs
Prescription writing error resulting from shortcuts, miscalculations, or illegible handwriting	Prescribing	●	●	●	5
Inadequate education (eg, provider rushed, language barrier, assumption that education had already occurred)	Prescribing	●		●	4
Error when transmitting prescription to pharmacy	Prescribing	●		●	4
Wrong tablets, liquid, dose, or number of tablets dispensed	Dispensing	●	●	●	5
Data entry/keystroke error	Dispensing	●		●	4
Pharmacist failed to thoroughly verify prescription	Dispensing	●	●		4
Patient did not correctly adhere to regimen (eg, took wrong drug, self-modified, forgot dose)	Administration	●	●	●	5
Patient did not report or incompletely reported adverse effects	Monitoring	●	●	●	5
Provider inaccurately modified dose on basis of laboratory or toxicity assessment	Monitoring	●		●	4
Provider inaccurately modified dose when previous dose was verbally modified, and information was not noted in record	Monitoring	●	●		4

NOTE. Solid circles indicate that a high-risk failure mode was associated with the drug.
Abbreviation: FMEA, failure mode and effects analysis.

Table 3. Selected Recommendations to Address High-Risk Failure Modes Affecting Five Oral Chemotherapies

Recommendation	Source
Prescribing	
Create checklists to guide and remind clinicians about key elements required for patient education	Capecitabine/imatinib/temozolomide
Provide patients and families members with educational material about research protocol and call-in number for questions	Investigational agent
Provide patients and families with abbreviated protocol guide or roadmap	Investigational agent
Require study nurse to call patients and families shortly after starting protocol to review protocol and consent and ensure understanding	Investigational agent
Dedicate follow-up appointment specifically to medication education	6-mercaptopurine
Dispensing	
Implement barcode scanning for dispensed medications	Capecitabine/imatinib/temozolomide
Provide patients with images of pills	Capecitabine/imatinib/temozolomide/investigational agent
Standardize clinician documentation of dose modifications to facilitate pharmacy verification	Capecitabine/imatinib/temozolomide/investigational agent
Standardize data entry in ambulatory pharmacy to avoid data entry errors	6-mercaptopurine
Minimize number of dose forms and concentrations available in pharmacy	6-mercaptopurine
Institute triple-check system for dispensing oral chemotherapies	Investigational agent/6-mercaptopurine
Administration, monitoring, and follow-up	
Provide patients with dosing calendars similar to those provided in clinical trials	Capecitabine/imatinib/temozolomide/6-mercaptopurine
Encourage use of automated reminder systems and prefilled pill boxes	Capecitabine/imatinib/temozolomide
Offer online educational and management tools for addressing adverse effects	Capecitabine/imatinib/temozolomide
Support safe home administration by reaching out to patients and families through nurse practitioner follow-up calls	Temozolomide
Encourage patients to bring in medication bottles to monitor adherence	6-mercaptopurine
Identify specific clinic staff responsible for patient and family education about medications	6-mercaptopurine
Provide oral chemotherapy travel kits to children whose parents are separated	6-mercaptopurine

These results are consistent with the emerging literature addressing medication errors involving oral chemotherapy. Studies by Partridge et al,[2,8] Taylor et al,[4] and Walsh et al[5] identified home medication administration as a vulnerable care process in the use of oral chemotherapy. Supply of the wrong number of daily doses resulted in a high rate of adverse drug events (39%) in a study of

oral chemotherapy incident reports.[9] Investigators at St Louis Children's Hospital (St Louis, MO) reported a reduction in the oral chemotherapy prescribing error rate from 23% to 14% concomitant with an increase in the use of standardized order forms—an intervention that resulted from an FMEA project.[10]

Although the goal of our FMEA project was to identify vulnerabilities in the medication process for oral chemotherapies, this initiative also helped our organization to target improvement efforts. After presentation of the preliminary results of this study to the board-level quality committee of our hospital, the organization endorsed additional initiatives to support safe prescribing, dispensing, monitoring, and home administration of oral chemotherapies. We developed and deployed a series of enhancements to the ambulatory electronic-order entry system for oral chemotherapy, including dose-limit warnings, weight- and body surface area–based dosing, and fields for cancer diagnosis, cycle number, and protocol (if appropriate). Additional safe prescribing recommendations have been formulated, which include the incorporation of oral chemotherapy investigational agents into the enhanced ordering module and development of oral chemotherapy–specific informed consent documents that print at the time of prescription.

The FMEA process has a storied pedigree in industrial safety. It is less well established in health care. Despite its benefits, the process led to a healthy skepticism in our organization about the cookie-cutter application of FMEAs in health care. Members of the study team and many of the participants found that the traditional FMEA model was time consuming and inefficient. Although it promised a systematic and disciplined analysis, few teams identified high-risk hazards that were previously unknown to the participants. We found that an abbreviated FMEA of two 2-hour meetings was as effective as one requiring four to five 2-hour meetings.

This study has several limitations. As a single-institution study, the findings reflect the care delivery model at one comprehensive cancer center. Although many features of the medication-use system at our institution are common to many health care organizations, others reflect local arrangements. This limits the generalizability of the results to organizations with similar medication systems. In addition, we studied a limited number of medications. Although several high-risk failure modes were shared among the five study drugs, we do not propose that these failure modes apply to the universe of oral chemotherapies. Finally, the results of FMEA rely heavily on the style of the facilitator and composition of the team. It is possible that different teams could have identified and prioritized a different set of failure modes. Nevertheless, FMEA is a technique intended to be customized to particular practice settings.

In conclusion, we found FMEA to be a useful but resource-intensive tool for identifying vulnerabilities in the medication-use process for five oral chemotherapies used by ambulatory care patients at our comprehensive cancer center. The approach demonstrated the complexity of the medication-use process and identified potential opportunities for improvement.

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