Final Progress Report

**1.0 TITLE PAGE**

# Oral Chemotherapy Safety in Ambulatory Oncology:

# A Proactive Risk Assessment

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## 2.0 ABSTRACT

**Purpose:** We sought to assess the risks associated with the oral chemotherapy medication use process in adult and pediatric ambulatory oncology and to develop improvement strategies. **Scope:** We examined high-risk vulnerabilities in the medication use process for oral chemotherapies, a process that includes prescribing, dispensing, administering, as well as monitoring and follow up. Subjects included adult and pediatric patients at a Boston comprehensive cancer center. **Methods:** We analyzed oral chemotherapy-related medication errors from disparate sources, conducted patient and caregiver focus groups, and facilitated failure modes and effects analyses (FMEAs) for five oral chemotherapeutic agents to identify potential hazards and improvement strategies associated with the drugs. We developed an improvement plan to address high-risk hazards. **Results:** Each stage of the medication use process poses risks to oral chemotherapy safety. Key vulnerabilities include patient education about drug handling and adverse effects; safe prescription writing; patient administration and adherence difficulties; and failure to monitor and manage toxicities. In conclusion**,** oral chemotherapies are potentially high-risk treatments. Risk assessment analyses may identify opportunities to mitigate patient harm. **Key Words:** failure modes and effects analysis, oral medication, antineoplastic drug, medication error

## 3.0 PURPOSE

The objectives of this study were to assess the risks associated with the oral chemotherapy medication use process in adult and pediatric ambulatory oncology and to develop an improvement plan to address those risks. The project had four specific aims:

***Specific Aim #1***: **To characterize oral chemotherapy-related medication errors and the quality of information about oral chemotherapy errors from various sources.** We proposed to collect data about oral chemotherapy-related medication errors by using literature and web searches; by reviewing media reports; by searching summaries and analyses of sentinel events reported by organizations such as the Food and Drug Administration (FDA) and Institute for Safe Medication Practices (ISMP); by eliciting de-identified incidents, pharmacy interventions, and root cause analyses from 14 US comprehensive cancer centers; by using prompted physician reporting at a Boston cancer center; and by conducting patient focus groups. We planned to categorize reports by drug, disease, type and severity of injury, and error type.

***Specific Aim #2***: **To develop detailed process maps for five oral chemotherapies used by ambulatory oncology patients.** We proposed to convene interdisciplinary teams of patients and clinicians at a Boston-based comprehensive cancer center who will develop detailed process maps for five oral chemotherapies with significant potential toxicities, including 6-mercaptopurine (pediatric leukemia), temozolomide (brain cancer and melanoma), capecitabine (advanced GI and breast), imatinib (chronic myelogenous leukemia and GI stromal tumors), and an investigational oral agent (to be determined).

***Specific Aim #3***: **To identify, analyze, and prioritize failure modes associated with five oral chemotherapies used by ambulatory oncology patients.** We proposed to convene an interdisciplinary team to identify, analyze, and prioritize failure modes in the medication use process for the five oral chemotherapies used at the Boston-based comprehensive cancer center described in Aim #2, drawing in part on expert opinion and on the hazards identified in Aim #1.

***Specific Aim #4*: To develop a plan for improving the safety of oral chemotherapy.** We proposed to develop an improvement plan that includes a portfolio of interventions to address the high-priority failure modes identified in Aim #3, convening an interdisciplinary conference that included patients, frontline clinicians, clinical administrative leaders, board members, medication safety experts, and other key organizational stakeholders.

## 4.0 SCOPE

### 4.1 Background

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 have 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 cancer patients, the disproportionate representation of cancer among young children and the elderly, the toxicity of treatments, and the 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 FDA pipeline are oral agents.[3]

### 4.2 Setting

This study was conducted in the ambulatory adult and pediatric practice at Dana-Farber Cancer Institute (DFCI), a National Cancer Institute-designated comprehensive cancer center in Boston, Massachusetts. In 2005, DFCI clinicians examined 11,935 new patients, 7,035 for one-time consultations, and 4,900 for evaluation, continuing treatment, and follow up. Clinicians also completed 96,944 patient office visits for 17,744 established patients. In 2006, 65% of Dana-Farber patients were women. Ninety percent identified themselves as White, 3.2% as Black, 2.5% as Hispanic, and 1.6% as Asian. Although most patients had commercial insurance, 26% were covered by Medicare and 4% by Medicaid; 3% were uninsured. Eighteen percent of patients were age 70 or older.

## 5.0 METHODS

### 5.1 Specific Aim #1 (*To characterize oral chemotherapy-related medication errors and the quality of information about oral chemotherapy errors from various sources)*

#### *5.1.1 Incident Report Substudy*

In order to identify oral chemotherapy-related incident reports, we searched academic and professional literature sources, news sources, government agencies, and the websites of organizations such as the Institute for Safe Medication Practices (ISMP), the Food and Drug Administration (FDA), and USP. We obtained a report of all oral chemotherapy errors reported to the USP for capecitabine, imatinib, 6-mercaptopurine, and temozolomide between November 1, 1999, and November 3, 2007.

Additionally, we sought oral chemotherapy-associated error reports from 14 organizations in the Comprehensive Cancer Center Consortium for Quality Improvement (C4QI). C4QI is a national group of cancer centers that collaborate on quality improvement initiatives, including a recent survey of oral chemotherapy best practices. We requested de-identified reports from 2004 to 2008 for oral chemotherapy-related medication errors, adverse events, and near misses involving patients who received care at a C4QI organization. We also requested the root cause analyses of the events, if available.

DFCI pharmacy staff members reviewed each DFCI safety report and pharmacy intervention – including reports submitted through DFCI's online reporting system, an earlier paper-based system, and an electronic pharmacy system – and identified oral chemotherapy-related errors reported from January 2004 through June 2008. Relevant reports were de-identified.

In addition, we collected oral chemotherapy-associated incident reports by recruiting 18 oncologists and oncology nurse practitioners who prescribe oral chemotherapy at DFCI. We elicited confidential reports from these clinicians via 12 weekly email reminders.

A summary of the various sources of data is shown below in Table 1. A physician and oncology nurse classified the type of incident, severity, stage in medication use process, and type of medication error. We examined the yield of the various reporting methods used to identify oral chemotherapy-related medication errors.

**Table 1. Sources of oral chemotherapy event reports**

| Source | Dates of Search | Source Detail | Number of Incidents N (%) | Ex-clusions N (%) | Available for Analysis N (%) |
|---|---|---|---|---|---|
| Literature Search | Through 12/31/07 | • PubMed | 0 | 0 | 0 |
| Web Search and Use of Selected Websites | Through 12/31/07 | • Google/LexisNexis<br>• US VA<br>• Pennsylvania Patient Safety Authority<br>• The Joint Commission<br>• US FDA<br>• Drug Topics<br>• ISMP<br>• USP website | 28 (4.0) | 2 (1.0) | 26 (5.1) |
| USP Reports | 11/1/99 – 11/3/07 | USP's MedMarx and MERP | 413 (58.9) | 122 (63.2) | 291 (57.3) |
| Cancer Centers | 1/1/04 – 3/1/08 | C4QI | 46 (6.6) | 7 (3.6) | 39 (7.7) |
| Pharmacy Interventions | 1/12/04 – 4/29/08 | Pharmacy interventions reported at cancer center | 177 (25.2) | 50 (25.9) | 127 (25.0) |
| Incident Reports | 12/3/03 – 3/25/08 | Staff-reported incidents at cancer center | 20 (2.9) | 3 (1.6) | 17 (3.4) |
| Elicited Clinician Reports | 4/21/08 – 8/14/08 | Prompted reports from 14 physicians and four nurse practitioners at cancer center | 17 (2.4) | 9 (4.7) | 8 (1.6) |
| Total | | | 701 | 193 | 508 |

***5.1.2 Focus Group Substudy***

In addition, we conducted two focus groups composed of a convenience sample of current and former users of oral chemotherapy as well as caregivers who administered the medications to a child. We identified potential subjects by asking oncologists at Dana-Farber to recommend suitable patients and caregivers. In addition, we requested that the hospital's Patient Family Advisory Council, a patient advisory body, publicize the project and forward the investigators' contact information to any interested parties. Candidate subjects were then mailed a letter that outlined the project and assessed their availability for one of two focus group dates, and an investigator made a maximum of two follow-up calls to nonresponders. In return for their participation, we offered participants parking, dinner, and $100 compensation.

Each of the 2-hour sessions was highly interactive, and the facilitator used both formatted and spontaneous probes to explore participants' perceptions of and experiences with oral chemotherapy, together covering all stages of the medication use process. In the focus group discussions, patients were asked open-ended questions about their experiences and knowledge of oral chemotherapy; factors that affected their decision to use an oral chemotherapy; how they were educated about administering oral chemotherapy; pharmacy experiences or prescription issues; issues with administering oral chemotherapy; monitoring side effects; adherence problems; and medication errors.

Sessions were audio recorded and transcribed for analysis. Investigators analyzed facilitator notes and written transcripts from the sessions using standard qualitative methods. We grouped quotations from the transcripts based on the study objectives to which they referred. Next, we reviewed the transcripts and notes from study team observers, identifying major and minor themes within each study objective until thematic saturation was reached (i.e., no new themes emerged).

### 5.2 Specific Aim #2 (*To develop detailed process maps for five oral chemotherapies used by ambulatory oncology patients*) and #3 (*To identify, analyze, and prioritize failure modes associated with five oral chemotherapies used by ambulatory oncology patients*)

We conducted five failure modes and effects analyses (FMEAs) by convening interdisciplinary teams of patients and clinicians to develop detailed process maps for five oral chemotherapies with significant potential toxicities, including 6-mercaptopurine (pediatric leukemia), temozolomide (brain cancer and melanoma), capecitabine (advanced GI and breast), imatinib (chronic myelogenous leukemia and GI stromal tumors), and a phase II investigational agent named XL820 (advanced gastrointestinal stromal tumors). The analyses included an evaluation of electronic and paper-based prescription writing; preparation and dispensing of medications onsite and at community-based pharmacies; administration (largely at home by the patient or caregiver); and symptom monitoring.

We convened interdisciplinary teams with expertise and experience in all aspects of the medication use process for the study drugs. Each group was facilitated by quality improvement specialists from the DFCI Department of Quality Improvement/Risk Management. The participants included physicians, nurses and nurse practitioners, pharmacists and pharmacy technicians, information technology analysts, patients or family members, patient safety and risk management experts, as well as research nurses and clinical research coordinators (for the FMEA with investigational agents).

Each interdisciplinary team identified, analyzed, and prioritized failure modes in the medication use process for the five oral chemotherapies, drawing in part on expert opinion and identified hazards. We asked the same interdisciplinary teams to identify vulnerabilities in the medication use process. The teams considered the identified failure modes and, using weighted voting techniques, identified high-priority targets based on their likelihood of failure, severity, and detectability.

In order to expedite the FMEAs, we conducted 10 preliminary interviews with individuals who were integrally involved in the medication use process. Based on this information, we constructed process maps for each of the oral chemotherapies. These process maps included a comprehensive list of steps involved in prescribing, dispensing, administering, and monitoring. In order to expedite the group meeting, the FMEA teams were asked to verify and modify, rather than create, these maps.

The scope of each FMEA varied slightly due to 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 (i.e., after deciding that the drug was clinically appropriate) through 6 months of treatment and follow up. For XL820, in contrast, the FMEA began at the time the patient was informed about the investigational drug through 3 months of follow up. For 6-mercaptopurine, the FMEA began at the patient's first outpatient clinic visit after the initial inpatient hospitalization through 2 years of treatment and follow up.

### *5.2.1 Capecitabine FMEA*
The capecitabine FMEA required 9 hours of face-to-face meeting time, in which study team members explained the purpose of the study and the FMEA process. The FMEA team reviewed the capecitabine process map and identified potential failures at each step in the medication use process. They identified the causes and effects of each failure mode and ranked each failure mode based on its severity, frequency of occurrence, and detectability. Each failure mode was prioritized by using a weighted voting technique. The group focused on improvement strategies for the failure modes deemed to pose the greatest risk to patients and most likely to have a significant impact on care.

### *5.2.2 Temozolomide and Imatinib Gap Analyses*
In order to address the risks associated with temozolomide and imatinib, we conducted a modified FMEA that focused on similarities and differences between capecitabine and these two agents. For temozolomide, we held a single meeting in which a clinical team of temozolomide expert users (two oncologists, a physician assistant, and two pharmacists) was presented with the results of the capecitabine FMEA. They identified risks associated with temozolomide that were not identified by the capecitabine FMEA team. The imatinib analysis was conducted in a similar fashion, although the review was conducted asynchronously by telephone and email communication. Participants felt that the imatinib FMEA could largely be subsumed under the capecitabine analysis, given similar hazards and patients at risk.

### *5.2.3 Investigational Drug (XL820) FMEA*
A team of clinicians who were closely involved with XL820, an investigational sarcoma drug, participated in a full FMEA. The scope of the analysis spanned from informing the patient about the XL820 protocol to 3 months of monitoring and follow up.

### *5.2.4 Pediatric (6-mercaptopurine) FMEA*
Because most pediatric patients begin their 6-mercaptopurine regimen in an inpatient setting, the scope of the 6-mercaptopurine FMEA began with the patient's first follow-up visit to Dana-Farber's outpatient clinic, which generally occurs within 1 week after hospital discharge. Because most patients on 6-mercaptopurine at Dana-Farber are on a 2-year protocol, the scope of the pediatric FMEA concluded after 2 years of monitoring.

This analysis was performed last, and it was the most efficient of the project, in part because of the experience of the facilitation staff and lessons learned in earlier analyses. The team quickly narrowed its focus to the areas of highest risk.

### 5.3 Specific Aim #4 *(To develop a plan for improving the safety of oral chemotherapy)*
In this section of the study, we proposed to develop an improvement plan that included a portfolio of interventions to address the high-priority failure modes identified in Aim #3, convening an interdisciplinary conference that included patients, frontline clinicians, clinical administrative leaders, board members, medication safety experts, and other key organizational stakeholders.

## 6.0 RESULTS

### 6.1 Specific Aim #1
In the incident reporting substudy, we identified 99 adverse drug events (ADEs), 322 near misses, and 87 medical errors with low risk of harm.

Of the 99 ADEs, 20 were serious or life threatening, 52 were significant, and 25 were minor. The most common medication errors involved wrong dose (38.8%), wrong drug (13.6%), wrong number of days supplied (11.0%), and missed dose (10.0%). The majority of errors resulted in a near miss; however, 39.3% of reports involving the wrong number of days supplied resulted in ADEs. The distribution of error types across the stages of the medication use process is shown in Table 2. Incidents derived from the literature search and hospital incident reporting system included a larger percentage of ADEs (73.1% and 58.8%, respectively) compared with other sources.

**Table 2. Medication errors, by stage of medication process**

| Medication Error | Ordering | | Dispensing | | Administration | | Monitoring and Follow Up | |
|---|---|---|---|---|---|---|---|---|
| | N | (Row %) | N | (Row %) | N | (Row %) | N | (Row %) |
| Wrong or extra dose | 117 | (59.4) | 26 | (13.2 | 54 | (27.4) | 0 | (0.0) |
| Wrong drug | 14 | (20.3) | 2 | (2.9) | 53 | (76.8) | 0 | (0.0) |
| Wrong no. of days supplied | 23 | (41.1) | 18 | (32.1) | 15 | (26.8) | 0 | (0.0) |
| Missed dose or nonadherence | 3 | (5.9) | 39 | (76.5) | 9 | (17.6) | 0 | (0.0) |
| Failure to check treatment parameters | 22 | (68.8) | 0 | (0.0) | 0 | (0.0) | 10 | (31.3) |
| Wrong instructions | 13 | (76.5) | 2 | (100.0) | 2 | (11.8) | 0 | (0.0) |
| Wrong frequency | 12 | (92.3) | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) |
| Incomplete prescription | 13 | (100.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Wrong time/delay | 2 | (16.7) | 6 | (50.0) | 4 | (33.3) | 0 | (0.0) |
| Protocol breach | 12 | (100.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Wrong patient | 4 | (36.4) | 1 | (16.7) | 6 | (54.5) | 0 | (0.0) |
| Order system error | 3 | (30.0) | 2 | (40.0) | 5 | (50.0) | 0 | (0.0) |
| Dispensing error | 0 | (0.0) | 0 | (0.0) | 9 | (100.0) | 0 | (0.0) |
| Other* | 2 | (33.3) | 4 | (66.7) | 0 | (0.0) | 0 | (0.0) |

*Other=wrong administration, failure to recognize drug interaction, don't know/need more information

In the focus group substudy, we convened two focus groups in June 2008 for adult patients and caregivers of pediatric patients. Each focus group consisted of seven or eight participants (N=15 total). Fourteen participants were receiving treatment with an oral chemotherapeutic agent, and one was a caregiver of a pediatric patient who had previously received treatment with an oral chemotherapy. Two reported using an investigational oral chemotherapy, 10 reported using an approved oral chemotherapy, and one did not know if their therapy was investigational or FDA approved (13 of the 15 participants responded to this question). Participants had various types of cancers and used a variety of oral chemotherapies.

The average participant age was 56 years (range: 32 to 77 years), and the group included 11 women and four men. All focus group members were non-Hispanic, and 14 were White. The average length of time as a patient (or as the caregiver of a patient) at DFCI was 6 years (range: 1 to 21 years); the average length of time using oral chemotherapy was 1 year and 10 months (range: 2 months to 6 years).

Participants were largely satisfied with oral chemotherapy. They appreciated its ease of use and convenience, and they described the ability to self-administer it as “empowering.” Some participants struggled, however, with the idea of being on oral chemotherapy indefinitely. Others described feeling “terrified” by the magnitude of their responsibility. Many participants reported feeling unprepared for the severity of side effects they experienced and unaware, at least initially, of the possibility of dose modifications to mitigate drug toxicity. Participants also described difficulties obtaining medications though retail pharmacies.

Participants identified a number of improvement opportunities. They desired more comprehensive education at the initial prescribing encounter, particularly concerning side effects and handling of the medications by nonpatients, as well as more frequent, provider-initiated follow up. Participants with previous experience as research subjects emphasized the need for resources and support systems equivalent to those provided as part of clinical trials.

**6.2 Specific Aim #2 and Aim #3**

Table 3 illustrates the complexity of each process. Whereas the FMEA analyses of capecitabine and XL820 examined 63 and 82 process steps and identified 77 and 199 failure modes,

**Table 3. Oral chemotherapy processes**

| | Major Steps | Substeps | Possible Failures | Causes of Failures | Highest-Risk Failures |
|---|---|---|---|---|---|
| **Capecitabine/Imatinib** | | | | | |
| Prescribing | 5 | 11 | 21 | 54 | 3 |
| Dispensing | 6 | 22 | 33 | 101 | 6 |
| Administration | 3 | 5 | 7 | 23 | 2 |
| Monitoring | 1 | 10 | 16 | 47 | 4 |
| **Total** | **15** | **48** | **77** | **225** | **15** |
| **XL820*** | | | | | |
| Prescribing | 8 | 14 | 51 | -- | 8 |
| Dispensing | 16 | 4 | 50 | -- | 2 |
| Administration | 9 | 7 | 34 | -- | 1 |
| Monitoring | 7 | 17 | 64 | -- | 7 |
| **Total** | **40** | **42** | **199** | **--** | **18** |
| **6-mercaptopurine** | | | | | |
| Prescribing | **4** | **10** | **14** | **42** | **3** |
| Dispensing | **3** | **0** | **6** | **16** | **3** |
| Administration | **3** | **3** | **12** | **6** | **1** |
| Monitoring | **6** | **1** | **17** | **9** | **3** |
| **Total** | **16** | **14** | **49** | **73** | **10** |

*The total number of failure causes was not collected for XL820 in the streamlined process, which focused only on the highest-risk failure modes.

respectively, we examined only 30 key process steps and identified 49 failure modes during the 6-mercaptopurine FMEA. Note that high-risk failure modes were identified at each stage of the medication use process (Figure 1).

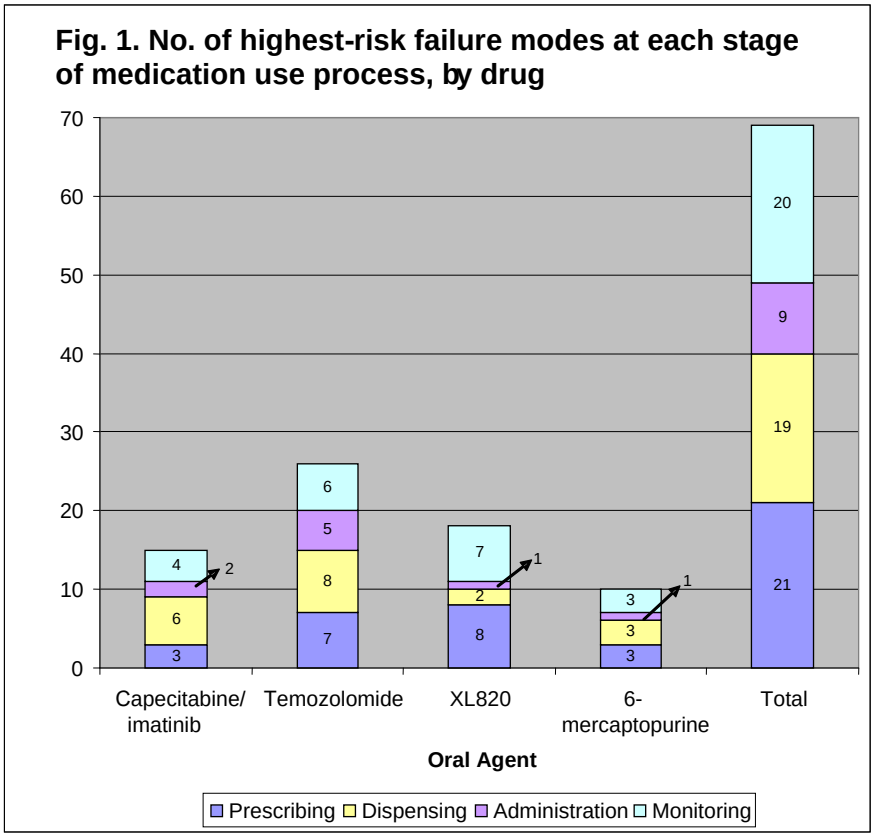


Table 4 shows the most commonly identified high-risk failure modes, by oral agent. These hazards are common to most of the agents and span the medication use process.

**Table 4. High-risk hazards identified across multiple oral chemotherapy FMEAs**

| Hazard | Stage | Cape-citabine/ imatinib | Temo-zolo-mide | XL820 | 6-MP | No. of FMEAs |
|---|---|---|---|---|---|---|
| Prescription writing error due to shortcuts, miscalculations, or illegible handwriting | P | X | X | X | X | 4 |
| Inadequate education (provider rushed, language barriers, assumptions that education has already occurred, etc.) | P | X | X | | X | 3 |
| Errors when transmitting Rx to pharmacy | P | X | X | | X | 3 |
| Wrong tabs, wrong liquid, wrong dose, or wrong # of tabs dispensed | D | X | X | X | X | 4 |
| Data entry/keystroke errors | D | X | X | | X | 3 |
| Pharmacist fails to thoroughly verify Rx | D | X | X | X | | 3 |
| Patient does not correctly adhere to regimen (takes wrong drug, self-modifies, forgetfulness, stress, etc.) | A | X | X | X | X | 4 |
| Patient fails to report side effects or incompletely reports side effects | M | X | X | X | X | 4 |
| Provider inaccurately modifies dose | M | X | X | | X | 3 |
| Provider inaccurately modifies dose if previous dose was verbally modified and the information was not noted in the patient's chart | M | X | X | X | | 3 |

Stage: P=Prescribing/Education, D=Dispensing, A=Administration, M=Monitoring

Drawing on the results of each FMEA, each team next identified remediation strategies to mitigate the risk associated with the key hazards. Some of the remediation strategies suggested by each team were common across all five of the study drugs. For example, each group recommended prohibiting handwritten prescriptions and "called in" prescriptions in favor of electronic prescribing only. All groups also recommended making improvements in patient education and by requiring the use of written, informed consent for all oral chemotherapy.

### *6.2.1 Risk Reduction Strategies for Capecitabine, Imatinib, and Temozolomide*

The teams identified a variety of strategies to mitigate the risk associated with oral chemotherapy agents. Strategies for capecitabine and imatinib included creating a standardized oral chemotherapy checklist for clinicians of educational topics that should be presented to patients who are new to the medication. Dispensing strategies included the use of pharmacy barcode scanning systems; installing visual cues in pharmacy to remind pharmacists to verify each element of each prescription; providing patients with a picture of the pill they should be taking; and modifying the electronic prescribing system so that patients' allergies are automatically written on each prescription for the pharmacists to review.

Improving medication administration should include techniques that support the ability of patients and their families to use oral chemotherapy at home. For example, patients could be given dosing calendars similar to those distributed in clinical trials; encouraged to use automated reminder systems (including web-based, e-mail, text message, and telephone call approaches); and provided with prefilled pill boxes. Additional strategies include increased opportunities for education and follow-up support; telephone or online support to help answer questions about side effects; and simplifying clinicians' entry of dose modifications in the patient's chart.

Temozolomide risk reduction strategies should address the potential cognitive limitations of patients on temozolomide, given that many are treated for brain cancer. Participants felt that a formal assessment of the suitability of the patient and their family for use of this medication was appropriate. Additional measures included efforts by the physicians' offices to confirm with the mail-order or other pharmacy that the prescription had been received and would be filled without delays in therapy. The vulnerabilities of this patient population made it especially important to deliver explicit directions for home administration, to encourage family participation, and to support safe home use through nurse practitioner follow-up calls.

### *6.2.2 Risk Reduction Strategies for Investigational Agent XL820*

XL820 is a phase II trial drug with which patients are treated according to a clearly defined protocol. Patients must provide written informed consent before they begin treatment on a clinical trial. Several suggested risk improvement strategies included providing patients with an educational CD/DVD with protocol information so that patients and family members could review the material at home; developing a call-in number that patients could use for asking questions about the protocol and/or consent; creating a "mini protocol guide" or roadmap to simplify the protocol for patients; having a research nurse call a patient or family member a few days after the start of treatment to review the protocol and consent and to answer any questions; verifying dose changes with patient or patient's designee that are made by telephone and ensuring that dose changes are documented reliably in the medical record. Risk reduction opportunities for dispensing include instituting a triple-check system before activation of orders when the drug is administered in the clinic and providing patients with a picture of the correct pill when they pick up their medication (for verification).

### *6.2.3 Risk Reduction Strategies for 6-Mercaptopurine*

Risk reduction strategies for 6-mercaptopurine prescribing included requiring a second clinician to verify each prescription (i.e., a double check); utilizing a specialized calculator for body surface area; reinforcing with patients the importance of avoiding certain foods (i.e., dairy) while taking 6-mercaptopurine; supporting nurse teaching of families and patients about using 6-mercaptopurine; and designating a staff member to verify that the pharmacy has received prescriptions so as to avoid delays in drug dispensing.

Risk reduction strategies for dispensing strategies include standardizing data entry methods at the onsite pharmacy for oral chemo prescriptions in order to avoid data entry errors; enhancing pharmacist oversight of drug preparation; eliminating the rarely used 4-mL concentration of 6-mercaptopurine from pharmacy stock to reduce the potential of dispensing the wrong concentration; and creating processes to ensure that pharmacists or pharmacy technicians reduce the risk of calculation errors in preparing liquid medications.

Administration risk reduction strategies mirror many of the recommendations outlined above, such as giving families a telephone number to call with questions about drug usage or side effects; scheduling appointment times that are dedicated to medication education; and providing family members with dosing calendars. Special attention was recommended for children whose parents are separated, such as providing a medication travel kit. Other recommendations included having patients/families bring in the medication bottle for clinicians to examine for adherence and administration errors (i.e., too much liquid left in bottle); implementing a standardized clinic discharge follow-up process; creating a dedicated staff member responsible for teaching and follow up; and enhancing availability of parent and patient support groups and programs.

## 6.3 Specific Aim #4

In order to develop an oral chemotherapy safety improvement plan, we had initially planned to use a modified Delphi approach to address uncertainties associated with the risks of oral chemotherapies. This approach would use repeated cycles of weighted voting to assign risk scores and to develop recommendations. However, given the relatively clear and consistent pattern of risks and recommendations that evolved from the FMEA groups, we decided to proceed directly to a board-level review of the project's results.

On July 14, 2008, we presented the preliminary results of our study to Dana-Farber's Joint Committee on Quality Improvement and Risk Management. The members of the Committee include all the key stakeholders in the organization (the same groups that were originally planned to participate in the Delphi groups), including frontline clinicians; senior administrative leaders, including the Chief Medical, Nursing, Operating, and Information officers (CMO, CNO, COO, and CIO) at Dana-Farber; members of the board-level quality committee; and representatives from the organization's Patient and Family Advisory Councils. We provided an overview of the study and shared our preliminary findings with regard to high-risk areas associated with oral chemotherapy. The board-level quality committee agreed that oral chemotherapy safety was a top priority for the organization and enthusiastically endorsed pursuing research and improvement strategies to address the risks associated with oral agents and adherence. The Committee offered specific emphasis on safe prescribing and the importance of ongoing patient support in the home. Other than the onsite outpatient pharmacy, the committee believed there was less leverage to influence dispensing practices in community pharmacies.

In the year following the Committee's endorsement, Dana-Farber staff, together with partners in the Dana-Farber Harvard Cancer Center, developed and deployed a series of enhancements to the ambulatory electronic order entry system for oral chemotherapy agents. The module includes a dose-limited warning for oral chemotherapy; 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 and are being advanced, including the incorporation of oral chemotherapy investigational agents into the enhanced ordering module as well as enhancements that would better integrate the chemotherapy order entry system (for research protocols and standard regimens) with the ambulatory electronic medical record. Another oral chemotherapy project – to provide oral chemotherapy-specific informed consent documents for standard regimens at the time of prescription – has been prioritized and is in development.

In the area of home administration, we have identified a team of clinical leaders and frontline nursing staff who are interested in developing better education materials for patients. We are collaborating with Dr. Kathleen Walsh from the University of Massachusetts Medical Center on an observational study of oral chemotherapy administration in the home of pediatric oncology patients. We have also partnered with Dr. Nate Rickles, a pharmacy professor at Northeastern University, to develop a research proposal to identify risk factors for oral chemotherapy nonadherence in our adult ambulatory population, and we plan to develop a tool that can be used to flag high-risk patients for targeted adherence interventions.

### 6.4 Outcomes

As a result of this study, we were able to characterize the types of risk associated with oral chemotherapies in ambulatory care across a variety of organizations, vulnerabilities in the medication use process for these drugs in our own cancer center, and promising opportunities for improvement. This work has led to safe prescribing interventions in the electronic order entry system and improvements in our approach to obtaining written informed consent. It has also generated additional research about risks associated with safe administration in the home. We expect that this latter work will soon lead to improvements that support medication adherence and safe handling of these medications in the home. Importantly, the project has helped establish oral chemotherapy as area of priority for leadership and governance, in turn helping advance the development and implementation of practice innovations.

### 6.5 Limitations

This study has several limitations, including the use of incident reports in Aim #1. Underreporting is common, because clinicians may be reluctant to report their own errors. In addition, many systems are inconvenient to use, and physicians rarely participate. These data sources also overrepresent the experience of patients at large cancer centers. Given the telegraphic nature of many reports, we may have inadvertently misclassified some events. Similarly, we lack information about the number of doses dispensed or patients at risk; without this information, we lack denominators that permit estimates of event rates. The strengths of the study include the variety of sources used to identify oral chemotherapy-related incidents as well as the range of medications and practice settings. Rather than presenting epidemiologically valid prevalence estimates, these reports provide a descriptive account of a range of medication errors and facilitate the development of targeted interventions to address areas of risk.

The focus group portion of the study may also be limited in several ways. Participants were identified largely by their oncologists, and they likely were more knowledgeable and motivated than the average patient. We acknowledge a potential selection bias but believe that this approach elicited many of the concerns and experiences that are common among oral chemotherapy users. In addition, a limited number of oral chemotherapy drugs was represented in the focus groups. Finally, the subjects were all drawn from a single comprehensive cancer center. Therefore, these findings need to be replicated. Our confidence in the results, however, is supported by the congruence of our findings with issues identified by a previous review and an expert panel.[1]

The FMEA process has a respectable pedigree in industrial safety, though it is an approach that is less well established in healthcare. Although results of FMEAs have been reported in the scholarly literature, it has generally been used as a risk assessment tool rather than a research method, so its application has not been standardized. Although we took measures to ensure that the FMEA process was reliable – by use of an external consultant for training and advice, use of standard materials, and a single team of FMEA facilitators – this method was a challenging one to apply to an ambulatory oncology practice setting. The process itself is demanding on the participants, and the results reflect the particular views and experiences of the participants and their organization. Each of the FMEA teams and the conduct of each session evolved over the course of the project as we sought to streamline the process and reduce the burden on the participants. Recognizing the inherent variability of FMEAs is important if this approach is used more widely within healthcare settings.

**6.6 Significance and Implications**

This study is significant in that it characterizes the types of medication errors that may affect oral chemotherapies. Pharmaceutical manufacturers, clinical research organizations, healthcare delivery organizations, healthcare providers, informaticists, patient safety specialists, and patients and their families may find this information valuable for identifying risks and designing preventive strategies.

The study also demonstrates the use of FMEAs to analyze risks across drugs within a single cancer center. Although we found more similarities than differences in the failure modes, effects, and mitigation strategies, the differences were meaningful and could lead to targeted interventions for particular populations. For example, the cognitive impairments common among brain tumor patients made it important to engage family members in the use temozolomide. Similarly, the use of liquid formulations created measurement and dosing challenges for parents of pediatric 6-mercaptopurine users.

The hazard assessment process in our organization led, in turn, to the endorsement by key stakeholders of oral chemotherapy safety as a high priority. This alignment of stakeholders helped foster an environment in which additional targeted interventions could be developed.

At the same time, the process led to a healthy skepticism about the cookie-cutter application of FMEAs in healthcare. Members of the study team and many of the FMEA participants agreed that the FMEA process (as traditionally conceived, taught, and practiced) was not an effective

use of time. It was often redundant and unnecessarily detailed. Although it helped uncover areas of risk, it did not seem to help the FMEA teams identify high-priority hazards that were previously unknown to participants. We found that the modified FMEA process, consisting of two 2-hour meetings, was as effective as one that required four to five 2-hour meetings. Participants reported that identifying the effects of failure modes was a highly repetitive process that dulled critical thinking.

At the same time, participants reported that the systematic approach to risk assessment provided them with a more comprehensive understanding of the medication use process than normally provided by their usual perspective. Understanding the internal process involved in prescribing, dispensing, administering, and monitoring oral chemotherapy – as well as the interfaces between them – provided a novel perspective on the process and made the vulnerabilities more transparent and actionable.

## 7.0 List of Publications and Products

Simchowitz B, Shiman L, Spencer J, et al. Using oral chemotherapy: patients' perceptions and experiences. Unpublished manuscript. Center for Patient Safety, Dana-Farber Cancer Institute, Boston, MA, 2009.

Weingart SN, Toro J, Spencer J, et al. Medication errors involving oral chemotherapy. Unpublished manuscript. Center for Patient Safety, Dana-Farber Cancer Institute, Boston, MA, 2009.

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[3] Weingart SN, Brown E, Bach PB, et al. NCCN Task Force Report: Oral chemotherapy. *J Natl Compr Canc Netw*. 2008; 6 Suppl 3: S1-14.