

Impact of Clinical Oral Chemotherapy Program on Wastage and Hospitalizations

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Several oral chemotherapies and biologic therapies have been introduced in the last decade for use alone, in conjunction with intravenous therapy, or with other oral chemotherapies. The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium,¹ one of the approved compendiums used as the basis for coverage and reimbursement policies by Centers for Medicare and Medicaid Services and many commercial payers, identifies several oral chemotherapies as preferred or first-line treatment modalities for particular tumor types. A significant adherence risk exists with oral chemotherapy, particularly in the first 30 days of therapy.² In addition, some oral chemotherapy agents involve frequent and significant toxicities, which must be monitored.

A study conducted in 2007 showed that approximately 16.6% of patients with cancer in the United States receiving chemotherapy (oral chemotherapy, infused chemotherapy, and/or hormonal therapy) were prescribed oral chemotherapy alone or in combination with infused chemotherapy.³ Patients have expressed a preference for oral administration. In a 1997 study, Liu et al⁴ found that 9 of 10 patients surveyed preferred oral chemotherapy, provided it was equally efficacious. Patients prefer oral chemotherapy for 2 reasons: oral agents are perceived to be safer than parenteral agents, and self-administration of oral agents is more convenient than parenteral administration. However, the NCCN Task Force Report on Oral Chemotherapy addresses these as common misperceptions, both because patients receiving oral chemotherapeutic agents are at risk for severe adverse events, and because self-administration results in the transfer of responsibility to the patient for identifying, monitoring, and managing toxicity.⁵

Clinical trial results, reviewed in US Food and Drug Administration–approved package inserts, provide detail with respect to the toxicity potential of oral chemotherapy agents. More than 90% of patients administered sorafenib (Nexavar; Bayer HealthCare, Morristown, NJ)⁶ or sunitinib (Sutent; Pfizer, New York, NY)⁷ suffer adverse events, of which at least one-third are grade 3 to 4 (grade 3, severe and undesirable; grade 4, life threatening or disabling).⁸ For patients receiving single-agent erlotinib (Tarceva; Genentech, South San Francisco, CA),⁹ grade 3 to 4 rash

and diarrhea have been reported in 6% and 1.8% of patients, respectively. Dose reductions and interruptions as well as outright discontinuation of therapy are

Objective: The oral chemotherapy cycle management program (CMP) provides clinical management support to patients receiving certain oral chemotherapies. The CMP includes a dose-monitoring (ie, split-fill) plan for early identification and management of adverse effects. If serious adverse effects are identified mid cycle, the remainder of the monthly supply is withheld, thus avoiding potential waste associated with early therapy discontinuation. This study investigated medication wastage and estimated potential cost savings for patients who were enrolled in the CMP, as compared with those who were not enrolled in the program.

Study Design: Retrospective test-control study.

Patients and Methods: Patients whose oral chemotherapy was initiated between June 2008 and February 2010 and who were enrolled in the CMP were included as the test group. Patients whose oral chemotherapy was initiated between June 2007 and May 2008 and who were not part of the CMP were included as the control group.

Results: Medication wastage associated with early therapy discontinuation was found to be lower in the CMP group. Approximately 34% of patients in the CMP group could have avoided medication wastage if split-fill plans had been available, potentially realizing savings of approximately \$934.20 per patient. Linear probability regression models showed that the CMP group had a 2.9% probability for reduction in hospital admissions ($P < .05$), resulting in additional savings of approximately \$440.00 per patient. Combined savings resulting from reduced wastage and hospital admissions was approximately \$1374 per patient.

Conclusion: Dose-monitoring programs such as the CMP effectively reduce wastage and serious adverse effects associated with oral chemotherapeutic agents, realizing potential cost savings for both payers and patients.

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Take-Away Points

Patients receiving oral oncology medications are likely to experience adverse effects if not managed appropriately. Trained clinicians in the oral chemotherapy cycle management program (CMP) offer clinical support to patients and provide dose monitoring and early identification of adverse effects. CMP adds value by:

- reducing medication wastage resulting from discontinuation.
- reducing hospitalizations associated with untimely management of adverse effects, resulting in potential indirect savings. There is great potential for health plans and payers to improve quality and patient satisfaction and achieve significant cost savings by participating in programs like the CMP, which provide active management for patients receiving oral chemotherapy.

common responses to severe adverse events related to these agents.

Unlike chemotherapy that is infused by a professional in a controlled setting, oral chemotherapy is subject to a number of additional risk factors, including:

- diffusion of patient care from the oncologist to a variety of professionals as well as to the patient.
- inability to read and understand complex instructions. For example, a study by Wolf et al¹⁰ found that 46% of patients misunderstood 1 or more of the dosage instructions on a sample drug label.
- compliance risk, which may reflect inadequate adherence, overadherence, or reduced persistency. According to Ergolin,¹¹ poor adherence leads to low or uneven drug concentration. Chronic exposure of cancer cells within a tumor to noncytotoxic drug concentrations may allow for selection of cells resistant to the drug.
- inadequate identification and reporting of and response to adverse events related to oral chemotherapy. The recent NCCN Task Force Report on Oral Chemotherapy states that “fewer controls are built in for oral chemotherapy . . . For example standard order forms do not exist for oral chemotherapy.”^{5(p.56)}
- unanticipated drug interactions with food and other medications.
- apparent nonresponsiveness to the drug regimen, which may be the result of chemotherapy resistance or patient nonadherence.

Given that approximately 25% of antineoplastic agents in the research pipeline are being studied in oral formulations, it is certain that the role of oral agents in cancer therapeutics will increase in future years.¹²

Oral Chemotherapy Cycle Management Program

Since June 1, 2008, the Walgreens Specialty Pharmacy Oral Chemotherapy Cycle Management Program (CMP) has provided pharmacist- and nurse-facilitated clinical management and support to patients for whom sorafenib, sunitinib, or erlotinib medications were initiated as part of their oral oncology

therapy management. Before CMP implementation, patients new to therapy, after completion of patient assessment surveys, often received general oncology care from Walgreens Specialty Pharmacy as part of the clinical management program. The CMP was primarily designed and implemented to better manage patient health and address concerns regarding potential adverse effects from using oral chemotherapy. Through the CMP, patients receive superior and intensive oncology care from trained clinicians, including education,

close supervision, and patient counseling at predetermined intervals. Patients are contacted at days 10 and 20 during their first month of therapy and monthly thereafter to provide education about their medications and potential adverse effects and assess compliance and adverse events. To minimize medication waste, plan sponsors may instruct the pharmacy to dispense part-month supplies of oral chemotherapy, followed by the balance of the monthly supply if the patient demonstrates adherence and lack of serious adverse effects. Additionally, the prescriber is faxed a patient adherence report suitable for inclusion in the patient medical record.

The objectives of the CMP are to address factors that lead to patient nonadherence, minimize drug wastage, improve quality of care, and maximize satisfaction of the patient, payer, and provider. The CMP does so by:

- increasing patient understanding of the treatment regimen and importance of compliance and communication.
- identifying earlier any adverse effects from the medication, leading to timely changes in dose, frequency, and/or medication.
- regularly communicating with both patients and providers, reducing toxicity and adverse events; advising payers of the opportunity to reduce medication wastage resulting from mid-cycle changes in dosage and discontinuation of therapy.

Study Hypotheses

The present study evaluates the impact of the CMP on 2 key outcomes: quality and cost of care. We evaluated these outcomes by assessing opportunities to minimize medication wastage and by assessing reduction in hospital admissions as a surrogate for early identification and effective management of severe adverse effects. The 2 hypotheses tested in this study follow:

Hypothesis 1.

Participation in the CMP program results in lower wastage of medications.

Table 1. Potential Savings From Split-Fill Versus Full Monthly Supply

Discontinuation Month	No. of Patients	Patients With Wastage		Potential Savings (\$)	Average Savings per Patient With Wastage (\$) ^a
		No.	%		
1	261	20	7.7	53,167	2658.34
2	219	103	47.0	288,387	2799.87
3	134	62	46.3	169,758	2738.04
4 or later	209	93	44.5	257,538	2769.23
Subtotal	823	278	33.8	768,850	2765.65

^aBased on average wholesale price.

Hypothesis 2.

CMP participants, when grouped by disease and treatment regimen, have a lower incidence of hospital admissions.

PATIENTS AND METHODS

The intervention group (CMP group) consisted of patients who were part of the CMP program between June 1, 2008, and June 30, 2010. All patients who received oral chemotherapy drugs such as sorafenib, sunitinib, or erlotinib anytime after June 1, 2008, were automatically included in the CMP. The study was restricted to 1069 patients who met the following criteria:

- Patients who received 1 of the oral chemotherapy drugs (sorafenib, sunitinib, or erlotinib) from Walgreens Specialty Pharmacy Services;
- Patients whose first fill date for the study drugs was between June 1, 2008, and February 28, 2010 (to allow a minimum of 4 months' follow-up);
- Patients who were new to therapy (with no prescription history of the study drugs in the prior 6 months); and
- Patients for whom survey assessment data were available.

The control group (non-CMP group) consisted of patients who received 1 of the oral chemotherapy drugs from Walgreens Specialty Pharmacy Services between January 1, 2007, and May 31, 2008 (before the inception of the CMP program) and who also completed a patient assessment survey. A total of 351 patients met these criteria.

To test the first hypothesis, we used information from both prescription claims and survey assessment data for the CMP group members. Many patients with cancer conditions may die or discontinue therapy without completing full treatment cycles (typically 5 to 7 cycles of 28 to 30 days each, depending on the medication). The split-fill program reduces wastage when therapy is discontinued during the first half of the month. To determine the relationship between treatment end date and last medication fill date across

3 oral chemotherapy drugs, we linked assessment data to prescription data.

The split-fill medication program, which is an optional program, is only offered through the CMP. Thus, only patients who are in the CMP were able to do the split fill. Payers may elect to participate in the dose-monitoring or split-fill program. Payers who participated in the split-fill program agreed to split the entire monthly supply of medication into 16-day and 14-day batches. We assessed potential for savings in a split-fill program, assuming that 100% of payers participate in the program. For the purpose of this study, we defined medication wastage as follows for prescriptions filled in 30-day quantities:

- 14-day supply (when discontinuation occurred between days 1 and 16 of the monthly cycle); or
- Zero-day supply (when discontinuation occurred between days 17 and 30 of the monthly cycle).

To test the second hypothesis, we compared hospital admission rates between the intervention (CMP) and control (non-CMP) groups. Recognizing that patient attributes could be different across the CMP and non-CMP groups, we adjusted patient attributes between the 2 groups using a propensity score matching method. We used a linear probability model on monthly cycle data to compare the matched intervention and control groups, controlling for confounding factors such as age, sex, drug type, clinical attributes (ie, cancer type), adverse events, treatment time, and an intervention variable representing test versus control group.

RESULTS

Hypothesis 1

Table 1 summarizes potential wastage reduction across the 3 drugs by discontinuation month for those CMP patients who discontinued therapy. In the first month, a total of 261 patients discontinued, and 20 patients (7.7%) could have saved at least one-half of 1 cycle (14 days) had the payer used the split-fill program. Over the entire study period, 278

■ **Table 2.** Wastage Savings by Discontinuation Reason

Discontinuation Month	No. of Patients	Potential Savings (\$)	Patients With Wastage		Average Savings per Patient With Wastage (\$)ª
			No.	%	
Death	172	161,114	61	21.9	2641.22
Physician decision	80	73,598	28	10.1	2628.49
Therapy ineffective	85	66,621	27	9.7	2467.46
Switched medication	53	94,404	25	9.0	3776.15
Adverse effects	94	48,413	20	7.2	2420.66
Unable to contact	65	33,625	11	4.0	3056.79
Unknown	130	151,633	54	19.4	2808.01
Other	178	139,442	52	18.7	2681.58
Total	823	768,850	278	100.0	934.20

ªBased on average wholesale price.

(33.8%) of 823 patients could have been prevented from wasting oral chemotherapy medications through implementation of a split-fill program. On the basis of the prevailing average wholesale price of the drug at the time of dispensing, we estimated total potential savings at \$768,850, or \$2765.65 per patient eligible for split fill. Approximately 246 patients in the CMP group were on hold for medications. Because these patients could restart their medication later, and may use excess medications already in possession, they were excluded from this analysis.

Table 2 summarizes potential savings from wastage by reason for therapy discontinuation. Patient death was the most common of the top 5 discontinuation reasons, contributing approximately 21.9% of potential wastage reduction, followed by physician decision (10.1%), ineffective therapy (9.7%), medication switch (9.0%), and adverse effects (7.2%). A large number of discontinuations were recorded as reason unknown, preventing additional analysis. The average potential direct savings that could result from avoiding medication wastage was found to be \$934.20 per patient who discontinued use.

Hypothesis 2

Patients receiving cancer treatment often experience severe adverse effects from chemotherapeutic agents. CMP nurses seek to identify adverse effects early and take appropriate steps to minimize them and enable patients to continue therapy. At the direction of the physician, adverse effects may

be managed with a combination of support therapies/medications, drug titration, temporary withholding of medications, or alternative therapy. Adverse effects that are severe and remain unmanaged may result in emergency department visits or hospitalizations.

We hypothesize that CMP patients are less likely to experience severe and unmanaged adverse effects and will thus experience fewer hospital admissions. We tested this hypothesis by applying a linear mixed regression model, a generalized linear model that captures both fixed and random effects resulting from characteristics of the observations. **Table 3** summarizes the probability of hospital admission reductions together with potential savings per patient resulting from such reductions.

To obtain the average savings per patient, we estimated costs associated with various types of hospital admissions (hospitalization costs for the period of June 1, 2008, to August 31, 2010, were computed from the Solucia Consulting [Farmington, CT] national claims database) and then used a weighted average cost per hospitalization. Average savings was found to be \$439.87 per patient, which is the indirect savings resulting from the reduced probability of hospitalization.

DISCUSSION

In this study, we tested 2 hypotheses relating to medication wastage and avoidance of hospitalization due to severe and unmanaged adverse effects in patients using 3 oral chemother-

■ **Table 3.** Model Estimation for Reduced Hospital Admissions Across CMP and Non-CMP Groups

Linear Mixed Regression Model	Probability of Reduced Hospital Admission (%)	P	Average Savings per Patient (\$)
CMP versus non-CMP (matched)	-2.9	<.100	439.87

CMP indicates cycle management program.

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apy drugs. Due to a high drop-off rate for patients on these drugs, there is a significant likelihood of medication wastage. The split-fill program has the potential to reduce wastage in members who discontinue midcycle. Our analysis showed that of those patients that discontinued therapy, approximately 34% would have experienced reduced wastage had they been on a split-fill medication plan.

Additionally, we analyzed the impact of the CMP program on hospitalizations. We found that CMP patients that were monitored for early identification of serious adverse effects are more likely to avoid hospitalization. We tested linear regression models utilizing matched test and control group patients, and found about 2.9% reductions in likelihood of hospitalization for the CMP group as compared with the control group. The combination of reduced wastage and reduced hospital admissions, expressed on a per-patient basis, amounts to approximately \$1374 per patient.

Oral chemotherapy has gained popularity with patients over the last decade as an effective and convenient approach to treatment of certain cancers. Although oral chemotherapy may reduce visits to clinics or physicians, it also transfers monitoring responsibility to patients. This analysis has calculated potential savings resulting from a split-fill medication plan and fewer hospitalizations associated with the timely identification and management of severe adverse effects of 3 oral chemotherapy drugs. This suggests potential for health plans and other payers to improve quality and achieve significant cost savings by participating in programs that actively manage oral chemotherapy patients through monitoring programs such as the CMP.

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