

Infused Chemotherapy Use in the Elderly After Patent Expiration

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The increasing use of drugs in the specialty medical care setting is an important determinant of national prescription drug spending trends.^{1,2} Cancer is the second-leading cause of death in the United States, and Medicare is the largest insurer of cancer-related treatment.³ The use of physician-administered specialty drugs is central to contemporary cancer treatment among the elderly (aged ≥65 years).^{1,4-6} For the elderly insured under Medicare, physician-administered and some oral anticancer drugs (chemotherapies) are covered and reimbursed under the Part B program; in contrast, most oral drugs used in primary care are covered under Part D. Physicians purchase Part B drugs from wholesalers, paying wholesale acquisition costs (WACs), and are reimbursed by Medicare, paying average sales price (ASP) plus 6%.

The generic entry of patent-protected drugs is considered to be an important cost-containment policy in the United States.⁷ The loss of patent protection for drugs increases competition among manufacturers and consequently decreases prices.⁸ In practice, physician reimbursement declines for the use of Part B drugs in the care of Medicare-insured patients after generic entry (the Centers for Medicare & Medicaid Services [CMS] rely upon US Food and Drug Administration [FDA] approval and authoritative compendia, like the National Comprehensive Cancer Network [NCCN], to determine what uses of physician-administered anticancer drugs to cover and reimburse).⁹ Several federal policies aim to accelerate access to generic drugs and consequently reduce spending by Medicare.¹⁰ A 2009 report released by the Office of the Inspector General (OIG) recommends CMS consider reducing the 6-month lag between generic entry and CMS reimbursement declines for Part B drugs, thus generating significant savings.¹¹ Others have suggested the adoption by CMS of other policies to encourage guideline-consistent and cost-conscious specialty treatment choices.^{12,13}

The anticipated cost savings to CMS of policies that would accelerate access to generic drugs and/or close the physician reimbursement lag for the use of Part B drugs to treat the elderly are predicated on the assumption that the use of the drug undergoing patent expiration would remain constant after generic entry.¹⁴⁻¹⁶ Also, challenges to the so-called Paragraph IV section of the Hatch-Waxman Act, providing 180-day marketing exclusivity for generic manufacturers first to file an abbreviated new drug applications to the

FDA, are active areas of litigation. Court decisions commonly

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Purpose: The use of anticancer drugs (chemotherapies) is an important determinant of national spending trends. Recent policies have aimed to accelerate generic entry among chemotherapies to generate cost savings.

Methods: We examined the effects of generic entry on the choice of chemotherapy for the treatment of metastatic colorectal cancer (MCRC) between 2006 and 2009 using autoregressive-moving average modeling with case control. A nationally representative sample of oncologists and patients with cancer (aged ≥65 years) was employed to estimate the magnitude and significance of the impact of the generic entry of irinotecan in February 2008 on the number of administrations of irinotecan compared with oxaliplatin.

Results: The generic entry of irinotecan resulted in a 17% to 19% decrease ($P < .001$) in use among elderly patients with MCRC compared with oxaliplatin. The results were robust to multiple sensitivity checks.

Conclusions: This study provides novel and robust estimates of the decline in use of a chemotherapy to treat a common cancer in the elderly after patent expiration. The results suggest estimates from a previous Office of the Inspector General report of the potential savings derived from the generic entry of irinotecan for public payers are an overestimate, likely confounded by oncologists' response to financial incentives, changes in scientific evidence, and promotional activities. As calls for improving the quality and cost efficiency of oncology increase, future empirical work is needed to examine the responsiveness of oncologists' treatment decision making to incentives among patients of all ages and insurance types.

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hinge upon whether use of the molecule in question is constant before and after generic entry occurs in the US market. Previous research has examined whether this assumption is justified in practice, focusing exclusively on observed changes in treatment patterns associated with the generic entry of Part D drugs.¹⁷⁻²⁰ Lackdawalla et al,¹⁷ Berndt et al,¹⁸ Huskamp et al,¹⁹ and Huckfeldt et al²⁰ found that Part D drug patent expirations coincided with stabilization or declines in use of the drugs across branded and generic formulations up to 12 months after patent expiration. We are aware of no empirical research examining whether the generic entry of Part B-covered chemotherapies is associated with changes in use.²¹

We examined the effects of patent expiration on the use of chemotherapies for the treatment of metastatic colorectal cancer (MCRC) among the elderly between 2006 and 2009 using interrupted cross-sectional time series methods with case control. MCRC is a good cancer with which to examine the potential impact of generic entry on treatment use among the elderly, because colorectal cancer is the third-most prevalent cancer in the United States, and the average age at MCRC diagnosis is 70 years.³

The analysis exploits the presence of 2 close therapeutic substitutes for MCRC: one underwent generic entry in February 2008 (irinotecan), whereas the other (oxaliplatin) was available only in branded formulation during this period. According to the NCCN Drugs and Biologics Compendium, contemporary treatment for MCRC involves multiple drugs; the gold standard for first- and second-line MCRC treatments is either irinotecan, fluorouracil, and leucovorin (FOLFIRI), first approved in 1996, or oxaliplatin, fluorouracil, and leucovorin (FOLFOX), first approved in 2002. Randomized controlled trials released in 2005 suggested FOLFIRI and FOLFOX produce equivalent mortality and morbidity gains among patients with MCRC.²² In practice, FOLFOX is the preferred therapy over FOLFIRI for elderly patients because of the perceived relative adverse effect profile of FOLFIRI, mainly involving diarrhea. In 2007, guideline-recommended therapy for first-line treatment of MCRC was altered to include FOLFIRI and FOLFOX as well as bevacizumab plus FOLFOX, bevacizumab plus FOLFIRI, and combinations including capecitabine. Between February and March 2008, generic entry into the irinotecan market was significant; 6 biopharmaceutical firms received FDA approval.¹¹ Concurrent with generic entry, clinical evidence supporting irinotecan and oxaliplatin use in MCRC changed. In April 2008, a randomized controlled trial supported the use of FOLFOX in combination with bevacizumab as a potential first-line therapy.²³ At the American Society of Clinical Oncology (ASCO) meetings in 2007 and 2008, Van Cutsem et al^{24,25} presented results of the CRYSTAL (Cetuximab Combined With Irino-

tecan in First-Line Therapy for Metastatic Colorectal Cancer) trial, supporting the use of FOLFIRI with cetuximab therapy as first-line therapy.²⁶ New evidence supporting the use of irinotecan in combination with cetuximab in second-line therapy (EPIC trial [Eribitux Plus Irinotecan for Metastatic Colorectal Cancer]) was also released.²⁷ We are unaware of any other changes in guideline-recommended treatment for MCRC based on a search of the ASCO annual meeting proceedings (accepted abstracts searched from 2005 to 2010), NCCN guidelines, and the FDA approvals website.

Consequently, the example allows us to study potential changes in the use of 1 chemotherapy (irinotecan) after generic entry, holding constant the impact of treatment choice on likely patient benefit and unaffected by coincident changes in patient composition or available therapeutic substitutes. The potential biases introduced into the analyses resulting from concurrent changes in multidrug recommended regimens are addressed under Discussion.

METHODS

The IntrinsicQ Intellidose data system (IntrinsicQ, Waltham, Massachusetts) provided data on a population-based cohort of US oncologists to measure aggregate prescribing behavior and patient usage of selected oncologic therapies from 2006 to 2009.²⁸ IntrinsicQ data are collected via the Intellidose software system, a pharmacy tracking system intended to improve chemotherapy dosing and enhance administrative billing. IntrinsicQ captures clinical data from all patients treated by participating physicians, including administration and dose of chemotherapy, duration and date of treatment, stage of cancer diagnosis, and line of therapy. Monthly data volume includes 570 reporting physicians, 19,500 patients, 47,000 office visits, and 135,000 drug administrations. The drug administrations, patient counts, and clinical rationales reported by participating physicians are monitored in real time for record completeness by a team of cancer nurses and weighted by IntrinsicQ to be nationally representative of oncologists practicing in the United States using the American Medical Association master file, monthly tumor and patient prevalence estimates, and monthly sales for each agent from the National Sales Perspectives of IMS Health (Danbury, Connecticut). For this study, we obtained from IntrinsicQ nationally weighted drug administrations and patient counts for MCRC overall, by drug, and by line of therapy among patients aged ≥ 65 years.

We employed standard interrupted cross-sectional time series analysis to examine the relationship between physician choice of treatment (irinotecan- or oxaliplatin-based therapy) and the generic entry of irinotecan for elderly patients with MCRC. The main outcome of interest was administra-

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tions of irinotecan and oxaliplatin before and after the generic entry of irinotecan in February 2008; the secondary outcome was patient counts.

To identify the timing of price declines of irinotecan for the elderly, we examined trends in the difference between the Medicare reimbursement limit (ASP plus 6%) and the WAC per milligram of irinotecan and oxaliplatin between 2006 and 2009. The Medicare reimbursement limit for these drugs was obtained from the CMS reimbursement rate database.²⁹ The WAC for each drug over time was obtained from First Data Bank.³⁰ The difference between ASP plus 6% and WAC for irinotecan increased on its generic entry in February 2008 and then declined by approximately 85% in September 2008, coincident with Medicare reimbursement declines. The difference between ASP plus 6% and WAC for oxaliplatin was constant between 2006 and June 2009. In August 2009, this difference was observed to decline substantially after a district court decision allowed the generic entry of oxaliplatin under a Paragraph IV challenge (Paragraph IV of the Federal Food, Drug, and Cosmetic Act allows 180-day exclusivity to companies that are the first to file abbreviated new drug applications against holders of patents for branded counterparts). Consequently, the analysis time frame is limited to 24 months before and 15 months after February 2008 (January 2006 to June 2009).

Ordinary least squares was used to estimate the relationship between the outcome variables and chemotherapy choice, the timing of the generic entry of irinotecan, the timing of the Medicare payment change for irinotecan, and interactions between chemotherapy and entry and chemotherapy and payment.^{31,32} Dickey-Fuller generalized least squares tests for autocorrelation in the outcome variables were calculated.^{31,32} Because of the skewed distribution of administrations and patients, counts were transformed to logs, and the ordinary least squares models were rerun. Breusch-Pagan tests on the log-transformed models suggested the null hypothesis of no heteroskedasticity for outcome variables could not be rejected.^{31,32}

The main results reported are derived using autoregressive moving average (ARMA) analysis. ARMA is a method for modeling time-series data and allows the analyst to identify, test, and correct for autoregressive and moving average processes. We employed a second-order autoregressive structure and no moving average process (ARMA 2.0) to model log (drug administrations) and log (patient counts) based on an examination of the correlation, partial correlation, variance, and covariance data structures. The models were estimated using maximum likelihood. Estimated coefficients were transformed into percent changes using the exponential method.^{31,32} We report average percent changes in irinotecan administrations and patients compared with oxaliplatin after

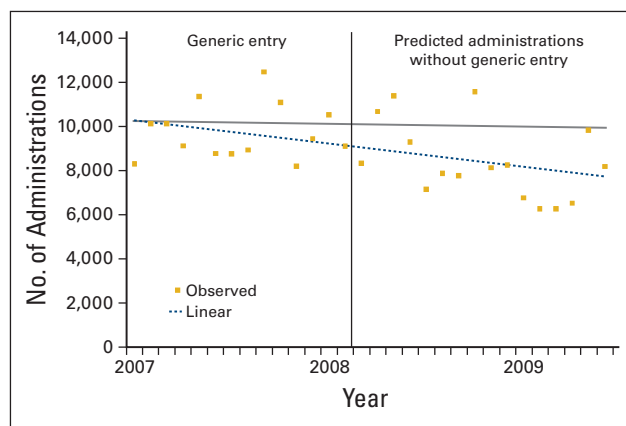
the generic entry of irinotecan and the Medicare payment limit declines. Changes were considered statistically significant if estimated *P* values were $\leq .05$. Sensitivity analyses were performed to assess the robustness of the result to choice of autocorrelation structure, to the outcome variable log transformations, to the inclusion of 2006 data, to the inclusion of third- and fourth-line therapy administrations and patients, and to the inclusion of total monthly elderly patients with MCRC. We examined raw trends in drug administrations to discern trends. The raw data suggested the number of elderly patients receiving treatment for MCRC irrespective of treatment choice declined between 2006 and 2009. Consequently, we reran the ARMA model including monthly estimates of total elderly patients with MCRC to control for the trend in disease incidence over time.

All analyses were performed using STATA version 11 (STATA, College Station, Texas). The University of Chicago Institutional Review Board approved the study.

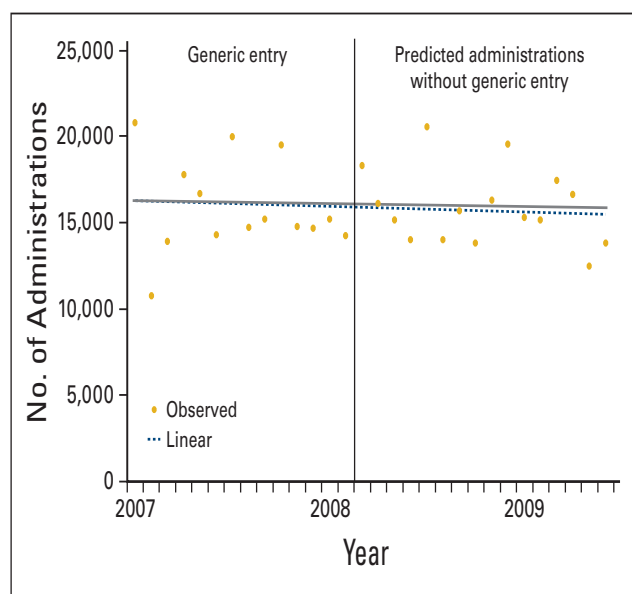
RESULTS

Figures 1 and 2 display observed and extrapolated trends in the administration of irinotecan and oxaliplatin in the elderly. In all years, the number of administrations of oxaliplatin (Figure 2) outnumbers the number of administrations of irinotecan (Figure 1), consistent with reported practice patterns and the emerging consensus on guideline-consistent treatment choice.³³ These observations provide some confidence in the external validity of the data employed. In Figure 1, the observed linear trend in the number of administrations of irinotecan seems to decrease sharply after the irinotecan patent expiration. Trends in administrations of irinotecan extrapolated from trends observed in the pregeneric entry period

■ **Figure 1.** Trends in the Number of Irinotecan Administrations to Elderly Patients for the Treatment of Metastatic Colorectal Cancer from 2007 to 2009



■ **Figure 2.** Trends in the Number of Oxaliplatin Administrations to Elderly Patients for the Treatment of Metastatic Colorectal Cancer From 2007 to 2009



alone suggest that there would be a small decline in the number of administrations of irinotecan. Although it is possible this pattern is related to the release of evidence supporting the use of FOLFOX in combination with bevacizumab as first-line therapy, in Figure 2, the number of observed administrations of oxaliplatin also seems to slightly decline. Trends in the predicted number of administrations of oxaliplatin extrapolated from the preirinotecan generic entry trends suggest the use of oxaliplatin would remain largely unchanged.

The **Table** lists the estimated percent changes in administrations and patients for irinotecan compared with oxaliplatin after the generic entry of irinotecan based on ARMA estimation. After the generic entry of irinotecan, the number of irinotecan administrations compared with oxaliplatin administrations decreased by 17% ($P < .001$), and the number of patients administered irinotecan compared with the number of patients administered oxaliplatin decreased by 16.5% ($P < .001$). The Table also lists the estimated percent changes in administrations and patients for irinotecan compared with oxaliplatin after the generic entry of irinotecan and Medicare payment declines. After the generic entry of irinotecan and Medicare payment declines, we found that the number of irinotecan administrations compared with oxaliplatin administrations declined by approximately 19% ($P < .001$), and the number of patients administered irinotecan compared with the number of patients administered oxaliplatin declined by 18% ($P < .001$), holding all else constant. The results were robust to other alternative model specifications and sensitivity

checks. The estimated decline in the administration of irinotecan relative to oxaliplatin in first- and second-line MCRC treatment after generic entry and Medicare reimbursement decline was 10% ($P < .001$) and 13% ($P < .001$), respectively, suggesting the main results may have been driven in part by changes in third- and fourth-line treatment choice.

DISCUSSION

The generic entry of irinotecan in February 2008 resulted in a substantial decrease in use among the elderly in comparison with a close therapeutic substitute: oxaliplatin. Results of the preferred ARMA model suggest after the generic entry of irinotecan, the use of irinotecan compared with oxaliplatin administrations decreased by approximately 17% to 19% ($P < .001$). The results were robust to multiple sensitivity checks.

A focus on changes in the use of irinotecan after generic entry in the treatment of MCRC among the elderly is an important empirical question in its own right.^{11,34,35} The OIG estimated that the generic entry of irinotecan could save Medicare on behalf of its beneficiaries \$6.5 million in the first month after generic entry if use of the drug remained at pregeneric entry levels, and Medicare reduced the 2-quarter lag between patent expiration and reimbursement declines. Our results suggest the estimate by the OIG of the potential monthly cost savings derived from the generic entry of irinotecan was an overestimate; anticipated savings to the Medicare program would likely be offset by documented declines in the use of irinotecan after patent expiration.

Furthermore, our estimates are consistent with the direction and magnitude of use declines among nonspecialty molecules reported in previous studies.¹⁷⁻¹⁹ The empirical setup allows us to say that the estimated declines in the use of irinotecan compared with oxaliplatin were not the result of the introduction of branded substitute therapies commonly observed to be coincident in previous empirical work.^{19,36} Assessments should also have accounted for potential price increases of branded versions of generic drugs.

We believe declines in the use of irinotecan after generic entry among elderly patients with MCRC may in part be the result of how oncologists are reimbursed for the administration of infused chemotherapies. Traditionally, outpatient oncology practice revenues have been tied to cost recovery.^{11,37,38} Recent work has suggested oncologists act on variations and alterations in cost recovery derived from the use of Part B drugs to treat elderly patients with cancer, given that Medicare has not pursued the enactment of mandatory generic substitution policies or other Part B drug access restrictions targeting patient or provider behavior.^{37,38} However, if physicians were solely acting on the CMS reimbursement policy in this setting, we-

Table. Estimated Percent Changes in Use of Irinotecan and Oxaliplatin After Irinotecan Generic Entry Among Medicare-Eligible and All Patients

Variable	Change in Administration of Irinotecan Compared With Oxaliplatin		Change in No. of Patients Compared With Oxaliplatin	
	Estimated Change (%)	SE	Estimated Change (%)	SE
Generic entry (February 2008)	-17	0.07	-16.50	0.0033
Generic entry and Medicare reimbursement decline (August 2008)	-19	0.05	-18	0.02

SE indicates standard error.

would expect to see declines in irinotecan use only after Medicare reimbursement declines (6 months after generic entry). The fact that we did not observe this pattern suggests aggregate observed physician behavior may be related to the mix of insurance that elderly patients with MCRC may have and/or the mix of insured patients whom oncology practices treat. CMS estimates >80% of Medicare beneficiaries have supplemental insurance coverage,³⁹ which may produce financial and nonfinancial incentives among oncologists to prescribe specific chemotherapies. Furthermore, oncology practices treating MCRC will commonly treat a mix of patients insured by Medicare, Medicaid, and commercial insurance. Consequently, our results are consistent with the following: reimbursement by commercial insurers declines immediately on the generic entry of chemotherapies; and whereas the average incident age of MCRC is 70 years in the US population, reported revenue of Pfizer from sales of Camptosar (irinotecan; Pfizer, New York, NY) reimbursed by Medicare was \$147 million in 2006, 27% of total sales.⁴⁰ Data limitations prevented us from examining the presence and nature of supplemental insurance coverage among the elderly and the insurance mix and treatment decision making at the physician practice level. Understanding the correlation between the existence and type of insurance and chemotherapy selection is an important direction for future work aiming to inform CMS policy making.

It is plausible that other factors contributed to these observations and introduced bias into the estimates. For example, declines in the use of irinotecan may be related to the coincident release of phase III randomized controlled trials supporting FOLFOX with bevacizumab in first-line therapy. This would produce upward bias in the estimates. The release of the EPIC and CRYSTAL studies and the coincident promotion of cetuximab would have biased the estimates in the opposite direction (holding coincident declines in the promotion of irinotecan and increases in the promotion of bevacizumab constant). Although results of 1 analysis are suggestive of compositional effects associated with generic entry by line of therapy, data limitations did not allow us to robustly distinguish between alternative mechanisms. We are aware of no empirical work examining the level and nature of promotion

among specialty molecules and how promotional activities among specialty molecules may be altered when generic entry occurs.

Our analyses have several other limitations. It is possible provider selection in the IntrinsicQ sampling frame could have biased the estimates toward capturing patterns of use from more concentrated, guideline-adherent oncology practices.^{2,13,37} It is possible these limitations biased our estimates downward, because more guideline-adherent practices would be less likely to alter practice patterns based on reimbursement changes alone. We were unable to examine other patient or provider correlates of treatment selection, including actual insurance coverage. Consequently, we inferred Medicare eligibility from patient age alone. It is likely this assumption biased our estimates downward because of type II misclassification error.

In summary, this study provides novel estimates of the direction and magnitude of the effects of patent expiration on the use of a physician-administered drug to treat a common cancer in the elderly using robust empirical estimation methods. We found that the generic entry of irinotecan resulted in a 17% to 19% decrease in use among elderly patients with MCRC compared with a close therapeutic substitute: oxaliplatin. Our results suggest the estimate by the OIG of the potential monthly cost savings derived from the generic entry of irinotecan was an overestimate, likely confounded by financial incentives implicit in insurance coverage, changes in scientific evidence, and drug promotion. Although our results are similar in direction and magnitude to previous empirical work examining changes in use associated with the generic entry of oral drugs, the mechanisms responsible for declines in use are different in part because of the unique financing and organizational features of specialty drugs. As calls for improving the quality and cost efficiency of oncology increase, future empirical work is needed to examine the responsiveness of oncologist decision making to financial and nonfinancial incentives among patients of all ages and insurance types.^{12,41}

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The authors indicated no potential conflicts of interest.

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