The Diffusion of Docetaxel in Patients With Metastatic Prostate Cancer

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Abstract

Background: Diffusion of new cancer treatments can be both inefficient and incomplete. The uptake of new treatments over time (diffusion) has not been well studied. We analyzed the diffusion of docetaxel in metastatic prostate cancer.

Methods: We identified metastatic prostate cancer patients diagnosed from 1995 to 2007 using the Surveillance, Epidemiology, and End Results Program (SEER)–Medicare database. Medicare claims through 2008 were analyzed. We assessed cumulative incidence of docetaxel by socioeconomic, demographic, and comorbidity variables, and compared diffusion patterns to landmark events including release of phase III results and FDA approval dates. We compared docetaxel diffusion patterns in prostate cancer to those in metastatic breast, lung, ovarian, and gastric cancers. To model docetaxel use over time, we used the classic “mixed influence” deterministic diffusion model. All statistical tests were two-sided.

Results: We identified 6561 metastatic prostate cancer patients; 1350 subsequently received chemotherapy. Among patients who received chemotherapy, docetaxel use was 95% by 2008. Docetaxel uptake was statistically significantly slower (P < .01) for patients older than 65 years, blacks, patients in lower income areas, and those who experienced poverty. Eighty percent of docetaxel diffusion occurred prior to the May, 2004 release of phase III results showing superiority of docetaxel over standard-of-care. The maximum increase in the rate of use of docetaxel occurred nearly simultaneously for prostate cancer as for all other cancers combined (in 2000).

Conclusion: Efforts to increase the diffusion of treatments with proven survival benefits among disadvantaged populations could lead to cancer population survival gains. Docetaxel diffusion mostly preceded phase III evidence for its efficacy in castration-resistant prostate cancer, and appeared to be a cancer-wide—rather than a disease-specific—phenomenon. Diffusion prior to definitive evidence indicates the prevalence of off-label chemotherapy use.
Diffusion is the transmission of a new innovation over time within a social system and is driven by perceptions of the innovation, characteristics of adopters, and contextual factors (6,7). Perceptions of an innovation pertain to (often qualitative) assessments of the risks and benefits of the new innovation. Presentation of efficacy findings for a new drug at a scientific conference or in a journal may influence the perception of new treatment benefits (8). Drugs with clearly positive benefit/risk ratios may be taken up immediately into clinical practice. One question is whether adoption follows definitive evidence of a new treatment in a phase III study. Patient characteristics may also influence patterns of chemotherapy use. For instance, older lymphoma and ovarian cancer patients are less likely to receive chemotherapy (2,9).

Patients with metastatic prostate cancer typically receive androgen deprivation therapy (ADT) (10), with response durations of 18 to 24 months (11,12). For patients with castration-resistant prostate cancer (CRPC), standard therapy was mitoxantrone combined with prednisone following positive clinical trials in the 1990s, showing that mitoxantrone provided palliative relief but no survival benefit (13,14). Docetaxel (Taxotere, Sanofi-Aventis) received US Food and Drug Administration (FDA) approval for treatment of advanced breast and lung cancers in the late 1990s. Thereafter in 2004, docetaxel was shown to provide both pain relief and improved survival in CRPC, reducing the risk of death by about 20%, and, with concurrent FDA approval, became new standard care (15,16). In this analysis, we hypothesized that docetaxel uptake followed definitive evidence of docetaxel efficacy in a phase III trial, and that diffusion was slower for disadvantaged patient populations.

Methods

We used the linked Surveillance, Epidemiology, and End Results Program (SEER)—Medicare database, a vital resource combining national cancer registry data (SEER) with medical claims data (Medicare) (17). The primary analysis included men older than 65 years diagnosed with metastatic prostate cancer from 1995 to 2007 (inclusive). Medicare claims through 2008 were analyzed. To avoid attributing receipt of chemotherapy to another cancer, men must have had no other prior or subsequent cancers. To ensure that patients had a minimum amount of Medicare claims coverage to provide an opportunity to receive treatment, we required patients to have had continuous Medicare Parts A and B, with no HMO participation, for one or more years after diagnosis.

Receipt of chemotherapy was identified at any time after diagnosis using Medicare claims according to ICD-9 Healthcare Common Procedure Coding System (HCPCS) J-codes from hospital outpatient and physician reimbursement records. Hospital inpatient records were used to identify diagnostic and surgical procedures for establishing comorbidity status (18,19). Docetaxel use was defined based on HCPCS J-code J9170 (first implemented on January 1, 1998), and mitoxantrone use was based on HCPCS J-code J9293 (first implemented on January 1, 1990) (20). Other potential chemotherapy types are shown in Supplementary Table 1 (available online). Although docetaxel did not receive a J-code until 1998, we included metastatic prostate cancer patients diagnosed from 1995 onward to allow up to three years of follow-up time, such that a set of patients would already be at risk of becoming castration-resistant (identified through receipt of chemotherapy) beginning in 1998, when the docetaxel J-code was first available, in order to better characterize docetaxel use early in the period. Unspecified J-codes (J8999, J9999) were not used because they may identify unanticipated procedures (21).

Dependent Variable

A challenge for this analysis was that prostate cancer patients who became castration resistant were the candidate population for chemotherapy. However, CRPC cases are not explicitly identifiable using SEER data. Rather, SEER patients are indexed according to the stage of their presenting diagnosis (local, regional, or distant metastatic). Thus the denominator of patients with CRPC was not explicitly identifiable.

Therefore, we first analyzed the five-year cumulative incidence of first docetaxel use from diagnosis of metastatic prostate cancer. Following a closed cohort over time using cumulative incidence accounts for competing events (ie, death) and is useful for assessing factors associated with use of docetaxel (22). However, the estimates represent docetaxel use among all patients diagnosed with metastatic prostate cancer, not those with CRPC.

Secondly, we analyzed the subset of metastatic prostate cancer patients who received chemotherapy from 1998 to 2008. This subset represents CRPC cases, because chemotherapy would typically not be used in prostate cancer prior to castration resistance. Within each yearly interval, among those who received their first chemotherapy, we calculated the rate of docetaxel use. This approach mimics a series of cross-sectional yearly cohorts (23) and has the advantage of assessing docetaxel usage rates over calendar time. First receipt of chemotherapy was used because it is consistent with the cumulative incidence analysis and in the real world represents the chemotherapy of first choice.

The Model

In diffusion analyses, cumulative adoption over time typically adheres to an S-shaped or sigmoid curve, representing a pattern of bounded geometric growth in which adoption occurs infrequently at first, accelerates as more individuals adopt, then slows as adoption reaches a natural ceiling (7,24–26). To model yearly docetaxel use rates, we used the classic “mixed influence” deterministic diffusion model, which describes the instantaneous change in the shape of the diffusion curve by the differential equation:

\[
d\frac{dF(t)}{dt} = (k_f + k_s F(t)) \cdot (F - F(t))
\]

where \(F(t)\) is the cumulative number of adopters at time \(t\), \(F\) is the total potential number of adopters, and \(k_f\) and \(k_s\) are coefficients representing a mix of influences both external to the social system (\(k_s\)) and internal to the social system (\(k_f\)) (24,27). Conceptually, the behavior of this function indicates the influence of social dynamics on diffusion, because, if the magnitude of \(k_s\) is nontrivial, then the instantaneous rate of change of diffusion with respect to time is proportional to the interaction between prior adopters (\(k_s F(t)\)) and potential adopters (\(F - F(t)\)) (28). Thus, the magnitude of \(k_s\), relative to \(k_f\), suggests the extent to which an underlying social process influences diffusion.

Independent Variables

Socioeconomic Status, Demographic, Comorbidity, and Geographic Variables

We analyzed the five-year cumulative incidence of docetaxel use by demographic variables including age (split at 75 years) and race (black vs other). Socioeconomic (SES) factors were income and education, based on whether the patient’s Year 2000 Census tract median income and percentage with some
college education were, respectively, higher or lower than the study sample median. Poverty status was based on individual-level data reflecting prior Medicaid participation (yes vs no) (29). Differences by baseline comorbidity index within one year prior to diagnosis were analyzed using the Charlson index, modified as per Klabunde (18,19,30). Binary indicator variables were used for consistency across variables and to aid interpretation, with the exception of geographic region, which was analyzed by SEER registry area (East vs Midwest vs West). Univariate associations were tested using Gray’s test (31) and multivariable associations using Cox regression (32). All statistical tests were two-sided.

**Landmark Events**

We estimated the proportion of total diffusion occurring prior to October, 1999, the period prior to the first early phase (phase I and II) study reports regarding docetaxel efficacy (33–37); the proportion of diffusion occurring between October 1999 and May 2004, the period between the first early phase study reports and phase III reports/FDA approval (which occurred nearly simultaneously) (38–40); and after May, 2004.

**Docetaxel Use over Time in Prostate Cancer Compared With Other Cancers**

To evaluate whether docetaxel diffusion patterns for prostate cancer were unique among cancers, we compared them with those in advanced breast, gastric, ovarian, and non–small cell lung cancer (NSCLC), which served as controls. For these other cancers, docetaxel is often indicated after failure of initial chemotherapy. Therefore, rather than using first chemotherapy, within each year a patient received chemotherapy, we coded patients as “1” if docetaxel was received, “0” if other chemotherapy was received, and “0.5” if both were received. We compared patterns across all cancers with FDA approval times.

**Results**

**Cohort Characteristics**

We identified 6561 patients with metastatic prostate cancer meeting the inclusion criteria (Table 1). The majority of patients (58%) were age 75 years or older, 14% were black, and 7% were Hispanic. Poverty was reported in 21% of patients. Median Census tract income was $42,654, higher than the median US year 2000 income for this age cohort (41). Thirty percent had evidence of prior comorbidity.

We identified 1350 patients who subsequently received chemotherapy. Compared with the 5211 patients without subsequent chemotherapy, chemotherapy patients were younger, less likely to be black, had higher income, and had less comorbidity.

**Cumulative Incidence by Year of Diagnosis**

Five-year cumulative incidence of docetaxel use after diagnosis of metastatic prostate cancer increased from 2% for patients diagnosed in 1996 or 1997 to 33% for patients diagnosed in 2004 or 2005 (Figure 1). The use of mitoxantrone decreased in conjunction with the increased use of docetaxel, although five-year cumulative incidence of mitoxantrone use never exceeded 7%.

**Cumulative Incidence by Factors**

Figure 2 shows five-year cumulative incidence of docetaxel use combined over all years of diagnosis (1995–2007) by SES, demographic, comorbidity, and geographic factors. The cumulative incidence was slower for older patients, black patients, patients experiencing poverty, lower-income patients, and patients from Western and Midwestern SEER regions (all P < .01), in both univariate and multivariable settings.

**Association of Landmark Events With Docetaxel Use Over Time**

As shown in Figure 3, among metastatic prostate cancer patients who received chemotherapy, the observed proportion whose first chemotherapy was docetaxel was 95% by 2008. Docetaxel uptake in this patient population began well before the results for the phase III trials were reported. Thirteen percent of total (maximum) diffusion occurred prior to initial phase I and II journal reports, 67% between phase I and II journal reports and

<table>
<thead>
<tr>
<th>Factor</th>
<th>Metastatic prostate cancer (n = 6561)</th>
<th>Subsequently received chemotherapy?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (i.e., castration-resistant prostate cancer) (n = 1350)</td>
<td>No (n = 5211)</td>
</tr>
<tr>
<td>Age, ≥75 y, %</td>
<td>58</td>
<td>41</td>
</tr>
<tr>
<td>Black, %</td>
<td>14</td>
<td>10</td>
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<tr>
<td>Asian/Pacific Islander, %</td>
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<td>8</td>
</tr>
<tr>
<td>Income, %</td>
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<tr>
<td>≥$50 000/year, %</td>
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<td>46*</td>
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<tr>
<td>Poverty, %</td>
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</tr>
<tr>
<td>Median, $</td>
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<td>47,344*</td>
</tr>
<tr>
<td>Median proportion with some college, %</td>
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<td>28</td>
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<tr>
<td>Site‡</td>
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<td></td>
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<tr>
<td>East, %</td>
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<td>20†</td>
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<td>35</td>
</tr>
<tr>
<td>West, %</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>Comorbidity index ≥1, %</td>
<td>30</td>
<td>25</td>
</tr>
</tbody>
</table>

* Statistically significantly higher, P < .001.
† Statistically significantly higher, .01 ≤ P ≤ .05.
‡ Surveillance, Epidemiology, and End Results Program registry areas were categorized according to geographic location as follows: “East” included Connecticut and New Jersey; “Midwest” included Atlanta, Detroit, Iowa, Kentucky, Louisiana, Rural Georgia, and Utah; and “West” included California, Hawaii, New Mexico, and Seattle.
Studies of cancer treatment use by patient SES, demographic levels, and health status have frequently shown lower usage for disadvantaged patients (8,9,42–54). Differences by geographic region have also been found (55). Diffusion, which tracks patterns of usage over time, has been explicitly studied in some instances. Slower diffusion for older patients, minorities, and patients with lower SES were identified (22,56,57). In this study, docetaxel diffusion was slower for socioeconomically and demographically disadvantaged patients. The absence of differences in cumulative incidence by comorbidity status is surprising, but may be because of sicker patients becoming castration resistant more quickly, hastening receipt of chemotherapy.

The observation that disadvantaged patients have slower diffusion presents opportunities to improve uptake of proven new therapies in subpopulations. For instance, direct-to-consumer advertising (DTCA) has recently been shown to improve the appropriate use of aromatase inhibitors (58). Since oncology patients are frequently aware of DTCA, DTCA could be a useful tool to promote the use of proven new therapies in certain target populations (59). Even if patient out-of-pocket costs for newer treatments are similar, anxiety about how to pay may exist (60–61), in which case improved communication between physicians and patients is crucial for clarifying treatment costs (62).

Evidence of a sigmoid shape for use of docetaxel over time is consistent with prior observations that social dynamics, especially among physicians, accelerate new innovation diffusion (7,25). Thus, enhancing communication channels among physicians, especially between key opinion leaders and their colleagues, may encourage more rapid adoption of treatments. One factor that has been repeatedly identified to increase adoption rates is attendance at scientific symposia (8,63), which serve as forums for disseminating information about new treatments. Unfortunately, the nature of the relationships among physicians was not analyzable in this study because of lack of data on their social links.

The rapid uptake of docetaxel in CRPC prior to definitive evidence from a phase III trial is a concern. Considerations that may have led to early adoption of docetaxel include prior FDA indications in other solid tumors and the fact that conventional treatment, mitoxantrone, provided only palliative relief.
The evidence in Figure 5 indicates that docetaxel diffusion occurred across different cancers approximately simultaneously, in most cases prior to FDA approval. This suggests that once oncologists begin to use a drug for a given cancer, they may be more likely to do so for other cancers; the mechanism that allows this is off-label drug use. Off-label use is considered appropriate in many instances, with 25% to 50% of cancer drug prescriptions delivered off label (70–73). Reimbursement for off-label drug use is facilitated by inclusion in medical compendia. For instance, Medicare contractors are required by Congress to pay for cancer drug prescriptions if their use is supported by selected standard medical compendia (74,75). Importantly, taxane-based therapy, including docetaxel, was itself included in standard medical compendia for treatment of CRPC prior to publication of phase III evidence (76,77). Reliance on compendia to facilitate treatment reimbursement represents an attempt to balance tradeoffs. On the one hand, the requirement that every variation in target population for a drug require a separate FDA indication would overwhelm available resources. On the other hand, reliance on compendia of potentially questionable quality may lead to inappropriate use. And, in fact, questions about the quality of the medical compendia have been raised. A recent review found that compendia “lack transparency, cite little current evidence, and lack systematic methods to review or update evidence” (78). The evaluation of evidence for docetaxel...
in particular was found to be problematic (79). The questionable quality of medical compendia is astonishing in light of the role compendia play in determining reimbursement. The American Society of Clinical Oncology has stated that the “system for identifying medically appropriate cancer therapies, including those that involve off-label uses... requires attention” (70).

One limitation in this study is the inability to identify the true denominator of patients who become castration resistant, a key eligibility criterion for receiving docetaxel. Identifying CRPC cases based on receipt of chemotherapy does not capture patients with CRPC who received no chemotherapy. Such patients may be too sick to receive chemotherapy. Thus, diffusion estimates for CRPC are likely biased high. In this context, performance status would be an informative descriptive factor, but it was not available. The necessity of using Medicare claims to identify relapse or recurrence is often problematic (21), but especially when treatment is itself the endpoint, because it raises the question of whether patients not identified as relapse/recurrent by Medicare claims (i.e., HMO patients) may be different, limiting generalizability of the findings. Also, the use of Medicare data limits the analysis to patients age 65 years or older. However, prostate cancer occurs primarily in patients age 65 years or older (~70% of cases) (80), and older patients may receive suboptimal care, representing a critical target population (81,82). Physician-level data were not available; therefore, the extent to which physicians were exposed to marketing

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**Figure 3.** Proportion using docetaxel over time with landmark events. Thirteen percent of total (i.e., maximum) diffusion occurred prior to phase I and II journal reports, 67% between phase I and II journal reports and initial phase III conference reports and US Food and Drug Administration (FDA) approval, and 20% after the phase III reports/FDA approval. Importantly, taxane-based therapy was included in standard medical compendia (i.e., National Comprehensive Cancer Network) as a treatment for castration-resistant prostate cancer as early as 1997, with docetaxel in particular listed prior to publication of phase III evidence and FDA approval (76,77). CRPC = castration-resistant prostate cancer; FDA = US Food and Drug Administration.

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**Figure 4.** Mixed influence diffusion model fit of rate of docetaxel use over time by year. The model explained 99.2% of total observed variation. The coefficient for $k_2 (= 0.462)$, the measure of internal influence, was 7.2x the magnitude of the coefficient for $k_1 (= 0.064)$, consistent with the hypothesis that social dynamics played an important role in the diffusion of docetaxel.
efforts (which may have reinforced docetaxel uptake) was not identifiable in the data, nor were differences in diffusion according to facility type or degree of provider specialization. Finally, these results may not be generalizable to agents with different trial evidence profiles.

Currently, the FDA is reviewing whether to loosen constraints on the marketing of drugs prescribed off label (83). In contrast, our findings point to the potential risks of off-label use. By enabling the widespread diffusion of a new therapy prior to definitive phase III evidence, the off-label mechanism undermines the assumption that phase III comparative clinical trials necessarily determine which treatments become standard care. In this setting, inappropriate use is inevitable, with potential costs in increased morbidity and mortality if a different drug may have been more appropriate. Inappropriate use also places an unnecessary financial burden on health care payers. As declared by ASCO, medical compendia, which facilitate off-label reimbursement, require greater oversight (70), especially if they serve as the arbiters of reimbursement for Medicare, a federal program. Ultimately, greater levels of investment in clinical research are required to produce the highest levels of evidence—especially phase III trial evidence—for a given indication, in order to reduce the tendency for off-label use.

Funding
Funding for this work was provided to the SWOG cancer research cooperative group, Outcomes and Comparative Effectiveness Committee (Cancer Control and Prevention) by Public Health Service grant CA37429 awarded by the National Cancer Institute (NCI), Division of Cancer Prevention.

Figure 5. Rate of docetaxel use over time, by cancer type, with landmark events and model-fitted curves. A) The proportion using docetaxel over time for metastatic prostate cancer is compared with rates in advanced breast, lung, gastric, and ovarian cancers. US Food and Drug Administration (FDA) approval times for each cancer are shown. Docetaxel was approved for use in patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy in May, 1996; in patients with metastatic breast cancer who failed adjuvant therapy in June, 1998; in patients with non–small cell lung cancer who failed cisplatin-based treatment in December, 1999; and in patients with advanced gastric cancer (in combination with 5-FU and cisplatin) in March, 2006. Docetaxel has not received an FDA indication for use in ovarian cancer patients, but is included to convey the similarity of diffusion patterns of docetaxel for a cancer in which prescriptions are strictly off-label. B) The observed proportions using docetaxel over time for metastatic prostate cancer are compared with the combined rates from advanced breast, lung, gastric, and ovarian cancers. Fitted model-based estimates are superimposed. The inflection points for the fitted curves indicate the time of maximum increase in the rate of docetaxel use and are approximately the same (1.2 months or 37 days difference) between the two curves. NSCLC = non–small cell lung cancer.
None of the authors have any conflicts to declare with this manuscript. This study used the linked Surveillance, Epidemiology, and End Results Program (SEER)–Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program of the NCI, the Office of Research, Development and Information of the Centers for Medicare and Medicaid Services, Information Management Services (IMS), Inc., and the SEER Program tumor registries in the creation of the SEER-Medicare database.

Prior Presentations: The results of this study were previously presented at the Scientific Session of the SWOG Outcomes and Comparative Effectiveness Committee meeting on May 2, 2013. The results have not been previously published.

References


76. Center for Medicare and Medicaid Services regulations and guidance transmittal. Subject: “Compendia and Authoritative Sources for use in the Determination of a ‘Medically Accepted


