CONTEMPORARY SUBJECT

Pharmacy Benefit Spending on Oral Chemotherapy Drugs

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ABSTRACT

BACKGROUND: Pharmacy benefits have historically excluded injectable drugs, resulting in coverage of injectable drugs under the medical benefit. High-cost biologics and other new drug therapies are often injectables and therefore have not presented cost threats to pharmacy benefits. The U.S. Food and Drug Administration approval of capecitabine, an oral form of fluorouracil, in 1998, and imatinib mesylate in oral dose form for chronic myeloid leukemia, in 2001, signaled a new period in budget forecasting for pharmacy benefits, particularly for small, self-insured employers for whom a drug with a cost of $25,000 per year of therapy for 1 patient could increase total pharmacy benefit costs by 10% or more.

OBJECTIVE: To quantify the actual relative costs of the oral chemotherapy drugs in pharmacy benefits in 2006 and identify the history of spending on oral chemotherapy drugs relative to total pharmacy benefit spending for small, self-insured employers over the 4.5 years through May 2006.

METHODS: Administrative pharmacy claims from the database of a pharmacy benefits manager (PBM) for approximately 500,000 members of small, self-insured employer plans were used to calculate the net plan cost of oral chemotherapy drugs relative to total drug benefit costs for the period January 1, 2002, through May 31, 2006. Current costs for oral chemotherapy drugs for small employers were compared with an insured health plan of approximately the same number of members for dates of service January 1, 2006, through May 31, 2006.

RESULTS: This descriptive analysis found that oral chemotherapy drugs represented 0.27% of total drug benefit costs, or approximately $0.08 per member per month (PMPM) for small, self-insured employers in 2002, rising linearly to 0.73%, or approximately $0.24 PMPM in the first 5 months of 2006. Members in pharmacy benefit plans sponsored by small employers paid an average 6.9% cost share for oral chemotherapy drugs in 2006, nearly identical to the average 8.5% paid by members of an insured health plan of similar size in total membership, versus 26.9% average cost share for all drugs. Imatinib mesylate accounted for 45% of total spending on oral chemotherapy agents in 2002 versus 40% in 2006.

CONCLUSION: Spending on oral chemotherapy drugs as a proportion of total pharmacy benefit costs has more than doubled, from about 0.3% in 2002 to 0.7% in 2006. For small, self-insured employers, this represents a nearly 3-fold increase in spending, from about $0.08 PMPM in 2002 to about $0.24 PMPM in 2006.

KEYWORDS: Pharmacy benefits, Budget forecasting, Chemotherapy drugs, Drug costs

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The U.S. Food and Drug Administration (FDA) approved lenalidomide (Revlimid), an analogue or derivative of thalidomide, on June 29, 2006, for use in combination with dexamethasone in patients with multiple myeloma who have received 1 prior therapy.[1] Its manufacturer immediately made headline news by announcing that it would price the chemotherapy agent at $6,195 per month, which extrapolates to a drug cost in excess of $74,000 per patient per year of therapy.[2] This was not lenalidomide's first approval, however. The FDA had approved it on December 27, 2005, for the treatment of transfusion-dependent anemia due to myelodysplastic syndrome (MDS); for that indication, it was dosed at 10 mg per day with downward dose adjustment for patients experiencing thrombocytopenia.[3] The manufacturer's pricing structure appeared different for the 2 indications.

When the FDA approved the second indication, lenalidomide's average price per patient per year increased by about 35%, from $55,000 for 12 months of therapy for anemia associated with MDS to $74,000 per patient per year for the second, more common indication, multiple myeloma. While the dose for multiple myeloma is 25 mg per day (two-and-one-half times higher than the starting MDS dose), some Wall Street analysts criticized the pricing of lenalidomide for multiple myeloma because (a) its annual cost far exceeds that of other antineoplastic agents, (b) its production costs should be lower since it is not a biologic agent and is an oral as opposed to an injectable dosage form, and (c) excessive pricing would likely invoke Congressional scrutiny due to its potential financial impact on Medicare and Medicaid programs.[1]

Capecitabine Marks New Era of Oral Antineoplastics

A few oral antineoplastics have been available for decades; most of these have been relatively inexpensive. The new world of high-cost oral chemotherapy began in the United States when the FDA approved capecitabine (Xeloda), an oral form of fluorouracil, on April 30, 1998, for the treatment of advanced breast cancer resistant to paclitaxel in combination with an anthracycline such as doxorubicin[4] (Table 1). Three years later, and despite the fact that "cancer" is a collection of diverse diseases, results from clinical trials of imatinib mesylate triggered hopes that not only was a cure for cancer possible but also that the treatment could be administered by mouth.

Imatinib Mesylate

At the annual meeting of the American Society of Hematology in early 2001, the results from three phase 3 clinical trials were presented for STI571, a tyrosine kinase inhibitor. One clinical

TABLE 1 Selected Oral Chemotherapy Drugs* Used in Outpatient Pharmacy Benefits in 2006

Generic Name	Brand Name	FDA Approval	Indication
Mercaptopurine	Purinethol	September 11, 1953	Multiple neoplasms
Thioguanine	Tabloid	January 18, 1966	Multiple neoplasms
Capecitabine	Xeloda	April 30, 1998	Breast cancer; colorectal cancer
Imatinib mesylate	Gleevec	May 10, 2001	Chronic myeloid leukemia
Gefitinib	Iressa	May 5, 2003	Advanced non-small cell lung cancer (NSCLC)
Erlotinib	Tarceva	November 18, 2004	Non-small cell lung cancer (NSCLC); pancreatic cancer (approved November 2, 2005)
Sorafenib	Nexavar	December 20, 2005	Advanced renal cell carcinoma
Sunitinib malate	Sutent	January 26, 2006	GI stromal tumor; advanced renal cell carcinoma
Thalidomide	Thalomid	May 26, 2006†	Multiple myeloma—in combination with dexamethasone, for the treatment of patients with newly diagnosed multiple myeloma
Dasatinib	Sprycel	June 28, 2006	Chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia; Philadelphia chromosome-positive acute lymphoblastic leukemia
Lenalidomide	Revlimid	June 29, 2006‡	In combination with dexamethasone for the treatment of multiple myeloma patients who have received at least 1 prior therapy

** These drugs are identified by Medi-Span Generic Product Indicator (GPI) beginning with 2153, or 9939 or 2130 (except not GPI beginning with 213000501 [methotrexate], which is standard treatment for several indications, including rheumatoid arthritis and psoriasis, in addition to use as an antineoplastic agent).*

† Thalidomide previously approved by the FDA on July 16, 1998, for acute and maintenance therapy for erythema nodosum leprosum.

‡ Lenalidomide previously approved by the FDA on December 27, 2005, for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 risk MDS associated with a del 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

FDA = U.S. Food and Drug Administration; GI = gastrointestinal; MDS = myelodysplastic syndrome.

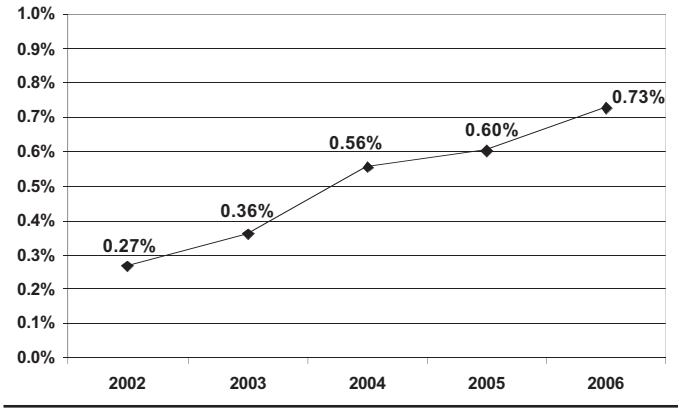
trial involved 500 chronic phase patients with chronic myelogenous leukemia (CML) who had failed to respond to interferon therapy. CML is characterized by translocation of chromosome material from chromosome 9 to chromosome 22 with formation of the so-called Philadelphia chromosome. After 6 months, greater than 90% of STI571-treated patients had white cell counts return to normal range and half had a significant reduction of Philadelphia chromosome-positive cells.[5] In a second study of 154 CML patients who had received STI571 for at least 1 month, 78% had a hematology response and 14% (22 patients) experienced disease remission. A third trial involving 94 patients in blast crisis (end-stage CML) showed a 47% response rate after 2 months of therapy with STI571. The researchers speculated that the combination of STI571 and cytosine arabinoside (Ara-C) or interferon could one day produce a cure for CML. Stem cell (bone marrow) transplant remains the only known cure for CML.[6]

The manufacturer sought fast-track approval in Europe and the United States, describing STI571 as a "smart" drug that disables only the abnormal protein that causes CML without affecting normal cells. In March 2001, STI571 was expected to be approved by the FDA as early as fall 2001.[7] In fact, the FDA approved STI571 (imatinib mesylate) in May 2001, just 3 months after the fast-track approval request, with a proprietary name change from the already-approved European name Glivec to Gleevec.[8]

The manufacturer marketed imatinib mesylate in June 2001 at an initial $19.68 average wholesale price (AWP) per 100 mg capsule, resulting in an annual cost in the range of $29,000 to $57,500 per patient when dosed in the recommended range of 400 mg to 800 mg per day. Nine months later, the FDA approved imatinib mesylate for the additional indication of inoperable or metastatic malignant gastrointestinal stromal tumors (GIST).[9] The GIST indication represented a significant advance in pharmacological treatment: until then, GIST had responded extremely poorly to polychemotherapy, and patients with inoperable GIST had extremely poor prognoses. Imatinib mesylate became the first effective treatment for GIST.[10]

Imatinib mesylate is now approved for the treatment of patients with all 3 stages of CML—myeloid blast crisis, accelerated phase, and chronic phase—either before or after other therapy, and GIST.[11] Its dosage form has been redesigned for patient convenience, and it is now available as 100 mg scored tablets and 400 mg tablets.

FIGURE 1 Proportion of Total Pharmacy Benefit Spending for Oral Chemotherapy Drugs



Thalidomide is excluded from these data since the drug was not approved for a cancer indication until May 26, 2006; summary data for claims with dates of service from January 1, 2002, through May 31, 2006, for more than 2,000 small, self-insured employers.

Gefitinib

On May 5, 2003, the FDA approved gefitinib (Iressa) for treatment of non-small cell lung cancer (NSCLC), dosed as a 250 mg tablet with or without food; higher doses do not improve response but do increase toxicity.[12] Two large trials involving 2,130 chemotherapy-naïve patients with stage III and IV NSCLC showed that gefitinib failed to improve tumor response rates, time to progression, or overall survival, when dosed at either 250 mg or 500 mg per day in combination with platinum-based chemotherapy regimens. The chemotherapies given in these first-line trials were gemcitabine and cisplatin (n = 1,093) or carboplatin and paclitaxel (n=1,037). Subsequent to the release of the findings from these 2 large clinical trials, the FDA asked the manufacturer to relabel gefitinib to restrict it to monotherapy for treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies.[13] On June 17, 2005, the FDA approved new labeling for gefitinib for use only in patients who have demonstrated benefit from receipt of the drug.[14] As part of the new labeling, distribution of gefitinib is restricted under a risk management plan called the Iressa Access Program. Gefitinib's effectiveness had been determined from objective response rates, and no controlled trials have demonstrated clinical benefit (e.g., improved disease-related symptoms or increased survival). Off-label use of gefitinib includes treatment of squamous cell head and neck cancer.

Erlotinib

Erlotinib (Tarceva) was first approved by the FDA on November 18, 2004. Erlotinib inhibits intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR), and further work is under way to completely characterize its mechanism of action.[15] Like gefitinib, erlotinib is approved as monotherapy for patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen. It is not approved, however, for first-line therapy, since 2 multicenter, placebo-controlled, randomized, phase 3 trials showed no clinical benefit when erlotinib was combined with platinum-based chemotherapy (carboplatin and paclitaxel, or gemcitabine and cisplatin) as first-line treatment of patients with locally advanced or metastatic NSCLC.[16] On November 2, 2005, the FDA approved the second indication for locally advanced, unresectable, or metastatic pancreatic cancer in combination with gemcitabine.[17] Unlike gefitinib, erlotinib's effectiveness has been proven in randomized, controlled trials.[18]

Sorafenib and Sunitib Malate

The FDA approved 2 additional oral agents, sorafenib (Nexavar) on December 20, 2005,[19] and sunitinib malate (Sutent) on January 26, 2006.[20] Sorafenib, a multikinase inhibitor that decreases tumor cell proliferation, was approved for advanced renal cell carcinoma (RCC). Dose instructions include expected skin toxicity and consequent dose reductions to 50% or 25% of the initial recommended dose of 400 mg (two 200 mg tablets) twice daily.[21] Sunitinib malate, which inhibits multiple receptor tyrosine kinases, was approved for GIST after disease progression or imatinib mesylate intolerance. Concurrent FDA approval for the indication RCC was based on partial response rates and duration of responses since there are no randomized trials of sunitinib malate demonstrating clinical benefit, such as increased survival or improvement in disease-related symptoms in RCC.[22]

Thalidomide

On May 26, 2006, the FDA approved thalidomide (Thalomid) under expedited review for the indication of newly diagnosed multiple myeloma patients in combination with dexamethasone.[23] Despite a preapproval, U.S. market withdrawal decades earlier for teratogenicity identified in postapproval European markets, thalidomide had been reintroduced to the U.S. market on July 16, 1998, when the FDA approved an indication for erythema nodosum leprosum (ENL; a complication of leprosy).[24] Thalidomide's wide range of off-label uses include treatment of graft-versus-host disease after bone marrow transplantation, refractory multiple myeloma, primary brain tumors, appetite stimulant for cachexia in advanced cancer or human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDs), aphthous ulcers, and prostate cancer in combination with docetaxel.[25]

Dasatinib

The FDA approved dasatinib (Sprycel) on June 28, 2006, for use in the treatment of adults with chronic phase, accelerated

phase, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy, including imatinib mesylate.[26] The expedited approval requires additional follow-up data to be converted to regular approval by the FDA. The FDA granted regular approval to dasatinib for use in the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

Lenalidomide

The first FDA approval of lenalidomide was on December 27, 2005, for myelodysplastic syndrome (MDS), characterized by hyperactive bone marrow but low blood cell counts.[27] While the colony-stimulating factors such as filgrastim are used off-label for MDS, lenalidomide is the only oral drug approved by the FDA for MDS. Other drugs for MDS are injectables such as azacitidine (Vidaza), approved by the FDA on May 19, 2004.[28] The Myelodysplastic Syndromes Foundation, sponsored by the manufacturers of drugs for MDS, includes on its Web site patient information for Medicare Part D and a Web link to find drug formulary coverage for MDS chemotherapy.[29]

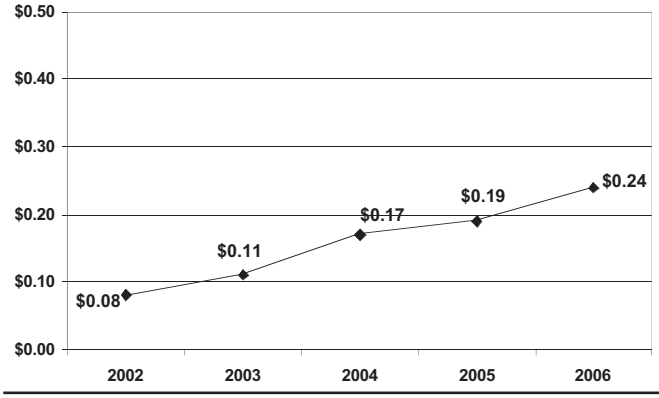
Methods

The present study was precipitated in part by the pharmacoeconomic work by Ramsey et al. who earlier this year found a seemingly small budget impact from the coverage of erlotinib as a formulary drug, for 1 indication, NSCLC.[30] The estimated budget impact of $0.01 per member per month in a hypothetical health plan of 500,000 members could be consequential in a small employer health plan of 500 members, particularly if the pharmacy benefit is self-insured. Second, 5 new FDA approvals for high-cost oral chemotherapy drugs in 7 months through June 30, 2006, creates the need for descriptive, benchmark analysis of the actual direct pharmacy benefit costs for oral chemotherapy drugs.

Data for this study were obtained from 2 sources: the administrative pharmacy claims in the database of a pharmacy benefits manager (PBM) for approximately 500,000 members from more than 2,000 small, self-insured employers (2 to 5,000 members each) and an insured health plan with approximately 520,000 members. The PBM serves members nationwide, and the insured health plan is located in the southern United States. The net plan cost of oral chemotherapy drugs relative to total drug benefit costs was calculated for the period from January 1, 2002, through May 31, 2006, for the small employer drug plans. Current costs in 2006 for oral chemotherapy drugs for small employers were compared with the insured health plan for dates of service from January 1, 2006, through May 31, 2006. These oral chemotherapy drugs were identified by Medi-Span Generic Product Indicator (GPI) starts with 2153 or 9939 or 2130 (except not GPI starts with 213000501 [methotrexate, which has indications such as rheumatoid arthritis and psoriasis in addition to use as a antineoplastic agent]), and all but oral dose forms were excluded.

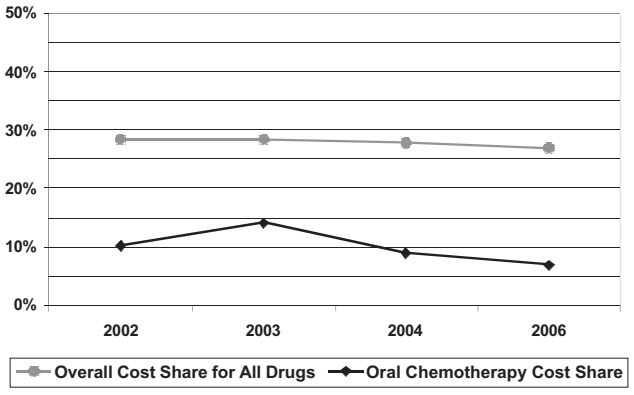
Drug cost is defined from the payer perspective as the allowed charge less the member cost share (sum of deductibles, copayments, and coinsurance); hence, unless otherwise noted, drug cost is the net plan cost after subtraction of member cost share. Allowed charge is the sum of the allowed (discounted) drug ingredient cost plus the allowed pharmacy professional fee. Days of drug therapy is the sum of the days supply submitted

FIGURE 2 Small Employer Cost Per Member Per Month for Oral Chemotherapy Drugs



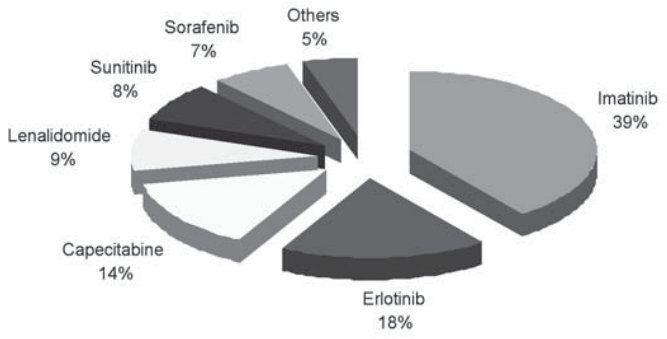
Thalidomide is excluded from these data since the drug was not approved for a cancer indication until May 26, 2006; summary data for claims with dates of service from January 1, 2002, through May 31, 2006 for more than 2,000 small, self-insured employers.

FIGURE 3 Average Member Cost Share* Over 5 Years for Beneficiaries of Small Employers Pharmacy Benefit Plans for Oral Chemotherapy Drugs Versus All Drugs



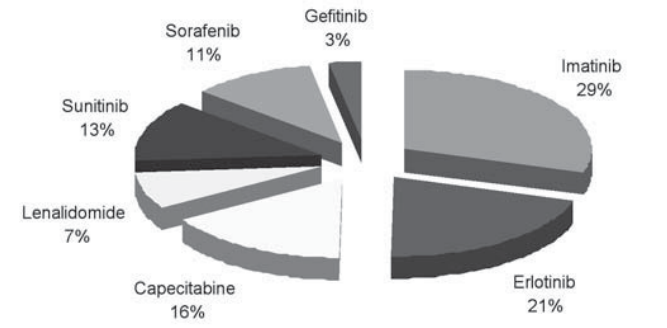
** Member cost share is the sum of all out-of-pocket costs at the point of service, including pharmacy benefit deductibles, benefit maximums, copayments, and coinsurance.*

FIGURE 4 Distribution of Cost by Oral Chemotherapy Drug for Small Self-Insured Employers in 2006*



Thalidomide is excluded from these data since the drug was not approved for a cancer indication until May 26, 2006; summary data for claims with dates of service from January 1, 2002, through May 31, 2006 for more than 2,000 small, self-insured employers.

FIGURE 5 Distribution of the Costs for Oral Chemotherapy Drugs for an Insured Health Plan in 2006*



** Pharmacy claims with dates of service from January 1, 2006, through May 31, 2006.*

on pharmacy claims. The PBM database includes mail-service and community pharmacy claims. During the time period of this study, from January 1, 2002, through May 31, 2006, mail-service pharmacy accounted for 5% to 7% of all pharmacy claims and 15% to 23% of total net plan (payer) cost. Pharmacy claims are aggregated by date of service, and all resource utilization and costs are reported net of claim reversals and adjustments.

Results

Oral chemotherapy drugs represented approximately 0.27% of total drug benefit costs in 2002, rising in a nearly linear manner over a 5-year period to 0.73% in 2006 (Figure 1). Net plan cost PMPM, after subtraction of member cost share, was approximately $0.08 in 2002 and approximately $0.24 PMPM in the first 5 months of 2006 (Figure 2). Due to dollar copayments as the predominant structure for member cost sharing in pharmacy benefit plans of small, self-insured employers during this time period and the relatively high cost for oral chemotherapy drugs, the average member cost share for oral chemotherapy drugs was about one third that for all drugs over this 4.5-year period Figure 3). In the first 5 months of 2006, the average member cost share for oral chemotherapy drugs was 6.9% for beneficiaries in pharmacy benefit plans sponsored by small employers versus an average 8.5% for the comparison insured health plan of similar total membership (data not shown).

Imatinib mesylate accounted for 45% of total spending on oral chemotherapy agents for small employers in 2002 versus 40% in 2006 (Figure 4). Despite market availability for only a few months in 2006, erlotinib accounted for 18% of the net cost of oral chemotherapy drugs, followed by capecitabine at 14%; among the other oral chemotherapy drugs, each accounted for less than 10% of total spending. The distribution of spending among the oral chemotherapy agents was similar for the insured health plan, with the exception of gefitinib which, unlike the small employers, had some utilization at 3% of total spending (Figure 5), accounting for approximately $0.01 PMPM (Table 2).

The actual price of the oral chemotherapy drugs in the first 5 months of 2006 is derived from the average allowed charge per day of therapy multiplied by 30 to obtain a standardized price per 30-day supply, prior to subtraction of the member cost share. Lenalidomide and sunitinib malate had the highest average allowed charge per 30-day supply, approximately $7,000 for each (Figure 6). The average allowed charge per 30-day supply for the 3 highest-expenditure oral chemotherapy drugs was $3,015 for imatinib mesylate, representing approximately 40% of total spending; $2,864 for erlotinib (18% of total spending); and $2,127 for capecitabine (14% of total spending).

Discussion

Prior to the market introduction of capecitabine and imatinib, chemotherapy agents were either relatively low-cost oral drugs or injectable drugs. The relatively low-cost oral chemotherapy drugs included mercaptopurine (6-MP, Purinethol), and thioguanine, both approved before 1967. High-cost chemotherapy drugs such as trastuzumab (Herceptin; initially approved by the FDA on September 25, 1997[31]), bevacizumab (Avastin; approved for metastatic colon cancer February 26, 2004), and cetuximab (Erbitux; approved for metastatic colon cancer, February 12, 2004) are available as injectable dosage forms only. All of these have had either indications added to their approved package labeling or will have in the near future.

While the present impact on outpatient pharmacy budgets is still relatively small, oral antineoplastic agents are associated

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