

Cost of Drug Wastage From Dose Modification and Discontinuation of Oral Anticancer Drugs

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IMPORTANCE Oral chemotherapy is often dispensed to patients as a 1-month supply, with pill dose and package size predetermined by the drug manufacturer; thus, changing the patient dosage may waste the remaining initial drug supply. The cost of pills wasted due to dose modification and discontinuation is often unreported.

OBJECTIVE To estimate the cost of pill wastage due to dose modification and discontinuation for oral anticancer drugs that were recently approved by the US Food and Drug Administration (FDA) or that are commonly prescribed.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cross-sectional economic evaluation initially identified 26 oral anticancer drugs newly approved between January 1, 2020, and August 31, 2022, from the FDA website and the top 50 best-selling pharmaceuticals in 2021 abstracted from the Drug Discovery Trends website managed by Drug Discovery and Development. The monthly costs of each agent were extracted from the Micromedex RED BOOK database. The FDA package insert, and in some cases PubMed, of each identified drug and indication was searched (matching on trial registration number) for information on registration trials. Information extracted for each drug included the name of the drug approved, drug target, cost of the drug, number of pills per bottle, available strengths, indication, name of the trial, number of patients exposed to treatment drug, number of dose level reductions, median duration of treatment, percentage of patients who received dose reduction, and percentage of dose discontinuation. All variables included in calculations were derived from the package insert or original trial publication.

MAIN OUTCOMES AND MEASURES The cost of wastage for selected oral anticancer drugs due to dose reduction or discontinuation and the percentage of wastage in comparison with the total cost of treatment.

RESULTS After removing duplicates, 22 oral anticancer medications were included in the study. Because some drugs had more than 1 indication, data from 35 clinical trials were analyzed. Eight of the medications (covering 9 indications) had pill strengths divisible at each dose-reduction level; thus the cost of reduction for these pills was assumed to be zero. Two medications did not allow for dose reduction. The median cost of wastage from dose reduction and discontinuation was \$1750 (range, \$43-\$27 200), with a mean cost of \$4290 (SD, \$5720) per patient. The median percentage of wastage from the total cost of treatment was 1.04% (range, 0.04%-10.80%) with a mean of 1.78% (SD, 2.21%).

CONCLUSIONS AND RELEVANCE This economic evaluation found that due to both the high cost per pill and limited pill strength availability, the mean cost of wastage associated with dose reduction or discontinuation was \$4290 per patient. These results suggest that to reduce the financial burden for patients with cancer, regulatory bodies should enforce availability of pill strengths that will limit pill wastage during dose modification or recommend that drug manufacturers issue credit for unused pills.

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 Editorial

 Supplemental content

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Oral anticancer drugs are a convenient form of cancer treatment for patients and have achieved widespread popularity.¹ In a report published in 2022,² oral anticancer medications had the highest rate of increase in use in the last 13 years among all cancer drugs. This trend will likely continue, as pharmaceutical companies have a vested interest in developing oral medications. Oral chemotherapies, similar to other forms of cancer treatment, are extremely costly at more than \$150 000 per patient per year.^{3,4} Oral cancer drugs are often dispensed as a monthly supply, with pill strength and quantity per bottle predetermined by the manufacturer. In terms of pricing, 56% of oral anticancer drugs have a single fixed price for each tablet regardless of dose strength.⁵

It has been reported that the limited vial size of single-dose intravenous cancer drugs leads to costly drugs being discarded.⁶ Similar to the limited vial sizes for intravenous cancer drugs, oral cancer drugs also have a limited availability of pills per bottle, which may lead to costly medication wastage. A study from 2016 estimated that as much as \$1.8 billion of intravenous chemotherapy drugs were discarded due to the oversized single-dose vials.⁷

Similar to intravenous chemotherapy, dose modification is often needed for tolerance for oral medications.⁸ There is a possibility that pills are wasted whenever patients develop adverse effects that lead to dose reductions. This wastage is due to patients discarding pills with strengths that are unusable at the next reduced dose level. The cost of wastage from oral chemotherapy dose modification is often unreported. Our objective was to quantify the cost of wasted oral anticancer pills for commonly prescribed and newly approved drugs.

Methods

Study Design and Search Strategy

This retrospective, cross-sectional economic evaluation sought to identify oral anticancer drugs approved between January 1, 2020, and August 31, 2022, and oral anticancer drugs on the top 50 best-selling pharmaceuticals list in 2021. The combination of these 2 research strategies aimed to capture recent patterns in oral anticancer drugs through approvals as well as highly prescribed drugs based on approvals that occurred prior to 2020. We identified the medications by extracting all of the newly approved oral chemotherapy medications from the US Food and Drug Administration (FDA) website (January 1, 2020, to August 31, 2022) and the 2021 top 50 best-selling pharmaceuticals list.⁹

For the selected drugs, indication-specific trial data were identified through the FDA package insert. Prices for each drug were obtained from the Micromedex RED BOOK database of drug pricing information (based on US dollars from the wholesale acquisition cost). This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline for economic evaluations. Because we used publicly available data, and this study is not considered human

Key Points

Question What is the cost of oral chemotherapy pill wastage due to dose modification or discontinuation?

Findings In this economic evaluation of the 22 best-selling oral anticancer drugs in 2021 and US Food and Drug Administration–approved oral anticancer drugs prescribed between January 2020 and August 2022, the median cost of wastage from dose reduction plus discontinuation was \$1750, with a mean of \$4290 per patient.

Meaning These results suggest that oral anticancer drugs have considerable cost in wastage from pills that are not usable after a dose reduction or that are wasted due to discontinuation.

participants research in accordance with 45 CFR §46.102(f), we did not submit this study to an institutional review board for approval and were not required to obtain informed consent.

Inclusion and Exclusion Criteria

Website and drug list searches were performed in August 2022. To be included, drugs needed to be orally administered and be an anticancer agent. Supportive medications were excluded, as were medications that had variations in their treatment duration, starting dose, and dose modification. Medications withdrawn from the market or medications only indicated for pediatric use were also excluded.

Data Abstraction and End Point Calculations

For each drug, we extracted the price, strength availability, number of pills per bottle, indication, tumor type, and registration trial information. The dose reduction levels and the percentage of patients who received dose reduction and discontinuation were obtained from the latest version of the FDA package insert. Data were extracted from published clinical studies if the information needed was not provided in the “Clinical Studies” section of the package insert. For those studies, we searched PubMed by using the trial registration number. For drugs with multiple indications, each indication was analyzed separately, based on the different clinical studies given in the package insert.

We made several assumptions in our cost estimates. For the cost of discontinuation, we assumed that each patient who experienced adverse reactions leading to treatment discontinuation wasted half of the bottle prescribed. The cost of discontinuation was the number of patients with dose discontinuation, multiplied by the cost of half a bottle. We also assumed that medications were dispensed as a 1-month supply because this has been the most common way for drugs to be dispensed.¹⁰

For the cost of dose reduction, we assumed that pills were not wasted if the pill strength could be reused at the next reduced dose level. For example, sotorasib is available only as a 120-mg tablet, with 240 tablets per bottle. The dose level reduction is from 960 mg to 480 mg, then to 240 mg once daily, and the same pill strength can be used at each reduction level.

For medications with only 1 dose reduction level, the number of patients who received a dose reduction was assumed to

have wasted half of the bottle prescribed. The cost of dose reduction was the number of patients with dose reduction, multiplied by the cost of half a bottle. eTable 3 in Supplement 1 gives a calculation template.

For medications with 2 dose reduction levels, patients were separated into 2 groups: a group who received 2 levels of dose reduction, and a group who received only 1 level of dose reduction. We used the number of patients with dose discontinuation for this calculation. We assumed that the number of patients who experienced dose discontinuation received 2 levels of reductions and wasted 1 whole bottle of a drug. The number of patients who received only 1 dose reduction level were the remaining patients (those who experienced any dose reduction minus the number of patients who received dose discontinuation). Patients who received only 1 dose reduction level were assumed to have wasted half a bottle of a drug. The sum of the 2 groups was the total cost of drug wastage for 2 dose reduction levels. eTable 4 in Supplement 1 gives a calculation template.

For drugs with 3 dose reduction levels, we used the same principle in calculating drug wastage from dose reductions. A detailed explanation is provided in eTable 5 and eTable 6 in Supplement 1.

The cost of wastage per patient was calculated as the sum of the medication wastage cost (from dose reduction and discontinuation) in the trial divided by the total number of patients who were exposed to the treatment drug in the clinical trial. Additionally, we calculated the total percentage of wastage as the total cost of wastage divided by the total treatment cost of the trial. The total treatment cost was the sum of medication cost for the median duration of treatment rounded up to the nearest month, multiplied by the number of patients who were exposed to the treatment drug in the trial. The total cost of wastage was the sum of wastage from dose reduction and dose discontinuation.

Finally, we performed sensitivity analyses to determine more conservative and less conservative scenarios of wastage from dose reduction and discontinuation by assuming one-third bottle and two-third bottle wastage.

Statistical Analysis

Descriptive statistics were performed and reported throughout. Prices were rounded to the nearest dollar. All analyses were performed in Microsoft Excel, and figures were developed using R statistical software, version 4.1.2 (R Project for Statistical Computing). A univariate linear regression analysis was performed to model the correlation between the percentage of patients who received dose reduction and the corresponding cost of wastage per patient.

Results

A total of 26 unique oral chemotherapy medications were extracted from the 2020 to 2022 FDA Novel Drug Approvals and the 2021 top 50 best-selling pharmaceuticals lists. Four medications were excluded. Lenalidomide and pomalidomide were excluded because of the variability in starting dose and dose

Table. Descriptive Characteristics of 22 Oral Anticancer Drugs Analyzed for Drug Wastage

Characteristic	Drugs analyzed, No. (%)
Total No. of clinical trials analyzed	35
Drug target	
KIT plus PDGFRA	3 (9)
EGFR	4 (12)
FGFR	3 (9)
PARP	7 (21)
Other	17 (50)
Indication	
Breast cancer	4 (12)
NSCLC	9 (26)
Ovarian cancer	3 (9)
Prostate cancer	3 (9)
Other	15 (44)
Patients exposed to drug, median (IQR), No.	204 (106-320)
Level of dose reduction	
None, not allowed	2 (5.9)
1	9 (28)
2	19 (59)
3	4 (12)
Drugs divisible at each dose level	8 (24)
Duration of treatment, median (IQR), mo	9 (6-19)
Dose modification	
Received dose reduction, median (IQR), %	24 (11-32)
Permanently discontinued drug, median (IQR), %	10 (7-16)
Cost	
Dose reduction, median (IQR), \$	654 291 (231 486-1 403 392)
Permanent discontinuation, median (IQR), \$	184 452 (121 840-281 407)
Wastage per patient, median (IQR), \$	1751 (1096-5195)
Drug wastage in trial, median (IQR), %	1.04 (0.55-1.89)

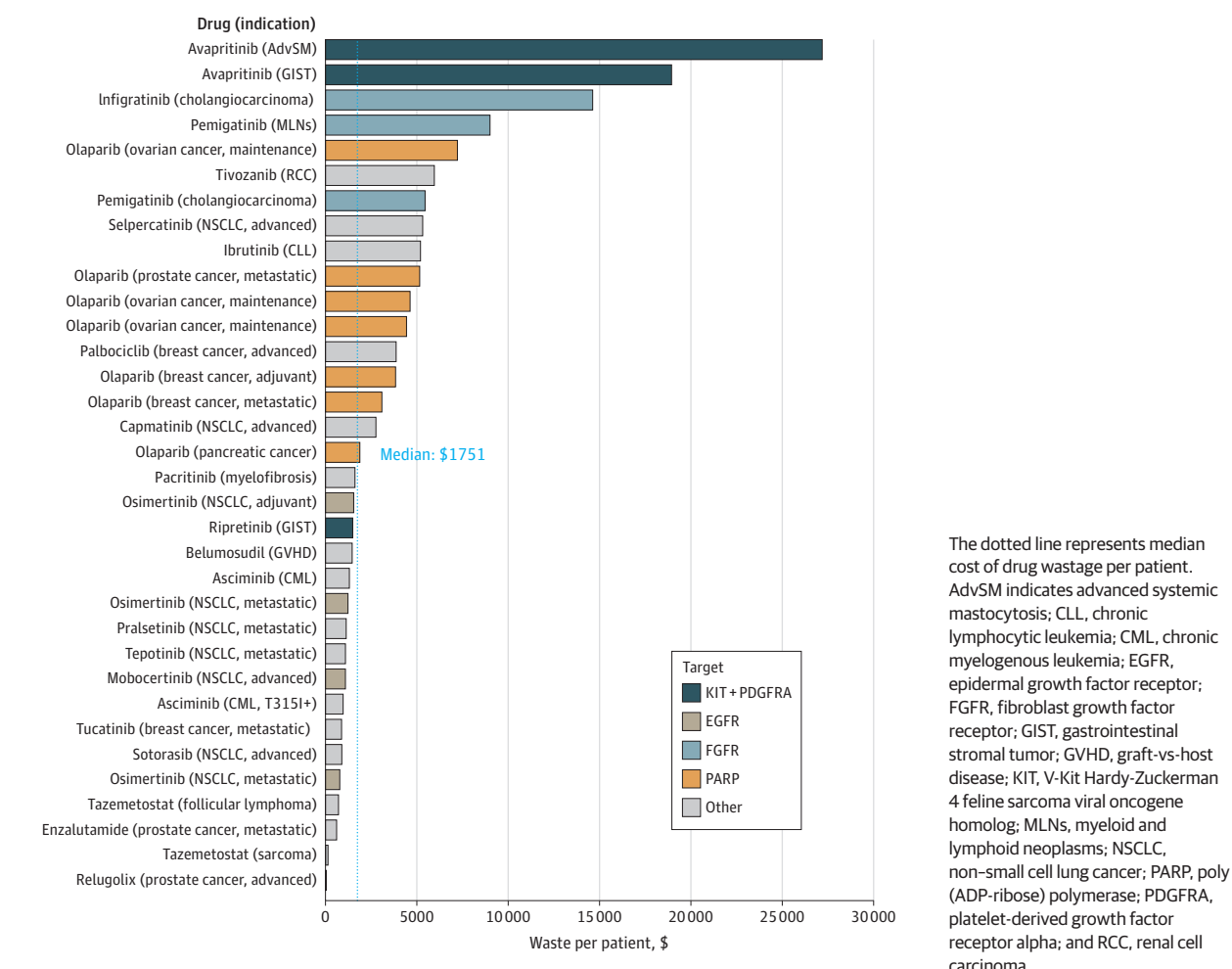
Abbreviations: EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; KIT, V-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; PARP, poly (ADP-ribose) polymerase; PDGFRA, platelet-derived growth factor receptor alpha.

adjustments. Umbralisib was excluded because it has been withdrawn from the market. Selumetinib was excluded because it is indicated for pediatric use only.

A final total of 22 oral chemotherapy medications with data from 35 clinical trials were analyzed in this study.¹¹⁻⁴⁵ The Table describes the characteristics of the medications, such as the drug target, indications, dose modification, and cost. eTable 1 in Supplement 1 gives the drug name, clinical trial, number of patients, levels of dose reduction, percentage of patients who received dose reduction and dose discontinuation, total cost of dose reduction and dose discontinuation, and cost of wastage per patient. eTable 7 in Supplement 1 provides price information for the 22 medications, including the price per pill.

Eight of the medications (covering 9 indications) had zero cost of dose reduction because the available pill strength could be reused at each reduced dose level. Two medications did not allow for dose reductions (eTable 1 in Supplement 1).

Figure 1. Cost of Wastage in US Dollars PER Patient of Oral Anticancer Drugs Commonly Prescribed or Recently Approved and Their Indications and Targets



The dotted line represents median cost of drug wastage per patient. AdvSM indicates advanced systemic mastocytosis; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GIST, gastrointestinal stromal tumor; GVHD, graft-vs-host disease; KIT, V-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MLNs, myeloid and lymphoid neoplasms; NSCLC, non-small cell lung cancer; PARP, poly (ADP-ribose) polymerase; PDGFRA, platelet-derived growth factor receptor alpha; and RCC, renal cell carcinoma.

The median cost of wastage from dose reduction and discontinuation was \$1751 (range, \$43-\$27 200; **Figure 1**) with a mean of \$4290 (SD, \$5720) per patient. The top five 5 drugs with the highest wastage cost per patient were avapritinib, infigratinib, pemigatinib, olaparib, and tivozanib (**Figure 1**). Avapritinib for treatment of advanced systemic mastocytosis had the highest cost of wastage at \$27 200 per patient because it had a combination of a high cost per bottle, multiple dose reduction levels at different pill strengths, and a high rate of dose reduction. Relugolix had the lowest cost of wastage at \$43. Dose reduction was not allowed for relugolix, and the cost of wastage was from 3.5% of patients who received a dose discontinuation.

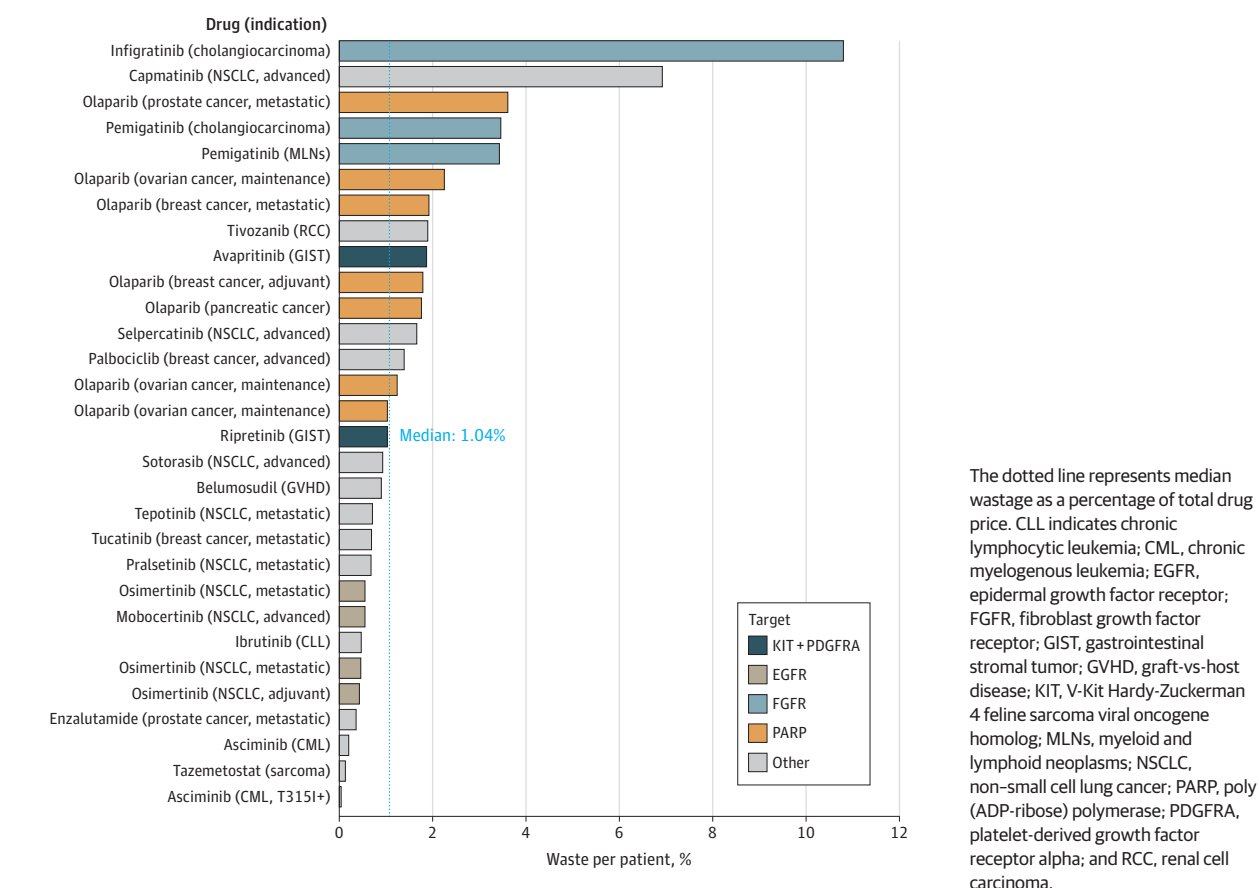
The median percentage of wastage from the total cost of treatment was 1.04% (range, 0.04%-10.80%) (**Figure 2**) with a mean of 1.78% (SD, 2.21%). Asciminib used for the treatment of chronic myeloid leukemia had the lowest percentage of wastage at 0.04%. Infigratinib used for the treatment of cholangiocarcinoma had the highest percentage of wastage at 10.08%. The percentage of wastage was not calculated for 4 of the medication indications because the median duration of treatment was not reported.

In sensitivity analyses (eTable 2 in **Supplement 1**), with the assumption of one-third bottle of medication wasted, the median cost of wastage from dose reduction and discontinuation was \$1167 (range, \$29-\$21 304), with a mean of \$2951 (SD, \$4156). With the assumption of two-thirds bottle of medication wasted, the median cost from dose reduction and discontinuation was \$2335 (range, \$58-\$42 607), with a mean of \$5902 (SD, \$8312). Similar to that for the assumption of half a bottle of medication wastage, the sensitivity analysis found that avapritinib had the highest cost of wastage, and relugolix had the lowest cost of wastage.

Discussion

Our economic analysis of 22 oral anticancer drugs with data from 35 clinical trials found that the median cost of wastage from dose reduction plus discontinuation was \$1751 (mean, \$4290 per patient). This represents a mean of 1.78% of the cost of patients' expenses for the entire treatment. Although 1.78% of wastage may seem low, the cost of wastage should not be ignored given the high cost of cancer treatment.

Figure 2. Percentage of Wastage From Total Cost of Treatment for Oral Anticancer Drugs Commonly Prescribed or Recently Approved and Their Corresponding Indications and Targets



In addition, we calculated the wastage cost conservatively; therefore, it is likely that the cost of wastage may be even higher. First, we assumed that only half a bottle of pills was wasted at each dose reduction. Although dose reduction may occur at any time during treatment, it more commonly occurs soon after the patient starts treatment. Thus, even more pills may be wasted. Our upper bound sensitivity analysis assumed two-thirds of the bottle was wasted. Second, we assumed that no pills were wasted if the pill strength from the previous dosing level could be reused. This may not always occur in practice. Third, we assumed that no pills were wasted at the completion of therapy. It is possible that patients moved to the next line of treatment in the middle of a cycle due to progression; thus, pills may have been wasted. To our knowledge, this is the first study that analyzed costs related to the wastage of pills among patients with cancer.

Several factors contributed to the high cost of wastage. First, 5 medications had dose reduction levels that required new pill strengths at the next dose level. Second, likely due to intolerability, a high percentage of patients required dose reductions. Drugs with multiple levels of reductions contributed to more pills being wasted. Third, the costs of these drugs were the same price regardless of dose strength. By contrast, oral anticancer drugs that were dosed to allow for pills to be reused at the next dose reduction level had less wastage. We

found that only 8 of the 22 drugs (36%) had pills that could be used for dose reduction.

Oral anticancer agents offer patients convenience and ease of administration. However, unlike intravenous chemotherapy, dose reduction of oral medication may lead to wastage of high-cost pills that must be discarded. The cost in wastage generated by oral anticancer pills is critical given rises in anticancer drug prices and the recognized burden of financial toxicity for patients with cancer. The cost of cancer treatment continues to rise rapidly while household income remains relatively flat.⁴⁶ This could result in a disproportionate burden for patients who are expected to pay for an increasing gap in coverage with no concomitant increase in wages.

One interesting observation resulting from our analysis is that of differences in drug wastage by indication. Some of the drugs in this study were approved for treatment of multiple cancer types. Two of the drugs we analyzed, olaparib and osimertinib, were initially approved in the metastatic setting and then later approved for treatment in the adjuvant setting. Our group previously reported that patients receiving medication in the adjuvant setting are more likely than patients in the metastatic setting to discontinue treatment regimens, which we have theorized to be due to lower tolerance in settings where the treatment is being used as more of a preventive measure, rather than a treatment measure.⁴⁷ These differences in wastage were

most notable for olaparib.⁴⁷ Focusing on settings where discontinuation is more likely is important when considering drug wastage. However, only 2 drugs in this analyses had approval for both adjuvant and metastatic treatment of the same tumor type.

The wastage from anticancer pills may be reduced if drug makers develop dose strengths that can be reused at each dosing level, or if packaging allows for a different number of doses, in case of discontinuation. Clinicians can help mitigate the cost of cancer pill wastage by ensuring that adverse effects are managed and by making the necessary dose reduction prior to the dispensing of medication. Clinicians may also consider giving patients treatment holidays instead of proceeding with a reduced dose to help reduce pill wastage. Clinicians may also consider integrating pharmacy dispensing within their clinic.⁴⁸ This would allow them to dispense a shorter pill supply early in the patient's treatment, when patients are often monitored more closely and have more visits to their physicians.

In addition to solutions for clinicians, there are several possible solutions for payers, such as pharmacy benefit managers. Payers may consider implementing plan designs that allow for a split-fill program that provides a 15-day supply with prorated copays for the first 3 months of treatment when the risk of drug wastage is highest. Payers may also create benefit designs that incentivize members to learn about the benefits and possible adverse effects of potential available options and to report drug treatment tolerance and wastage. Ultimately, real cost savings may occur through better stewardship of oral anticancer prescribing.

Strengths and Limitations

This study has strengths. The major strength of this study is that we identified an often unaccounted cost of oral chemotherapy medications. We also identified the factors that may contribute to wastage of oral anticancer pills, such as dose strength availability and levels of dose reduction.

This study also has limitations. The first is that the numbers of pills wasted were calculated based on assumptions due to patient-level data for time to dose reduction, the number of dose reductions not being available, and frequency of dispensing. In considering our assumptions, we made them based on the most likely scenarios presented in the literature. In addition, these assumptions may have resulted in estimates that were higher or lower than in reality; however, we selected a midpoint estimate to account for this. For our sensitivity analyses, we calculated less and more conservative estimates, based on bottle wastage of one-third and two-thirds. We encourage others to replicate our analysis with real-world data. The second limitation is that clinical study data were mainly extracted from the FDA package insert, and the duration of treatment and the percentage of dose reduction and dose discontinuation may change as more data emerge. The third limitation is that our estimates were based on clinical trial data, which often include data for patients who are younger and healthier than patients in the clinical practice. As a result, it is likely that our estimates were an underestimation of cost wastage.

Conclusions

Oral anticancer drugs offer many advantages and convenience compared with intravenous anticancer medications. However, this economic evaluation found that disadvantages of oral medication include prespecified and limited pill strengths, which when paired with dose reductions may result in wastage. Because of dose modification or discontinuation, the high cost per pill, the limited options for the number of doses per package, and pill strength availability, a mean of \$4290 per patient was wasted. Future research should evaluate the effect of pricing strategies and drug switching on drug wastage.

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