Original Work

Evaluation of a Focused Intervention on Patient Reported Outcomes in Patients Taking Capecitabine in a Specialty Pharmacy Setting

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Abstract

Objective: To evaluate the effect of patient support kits, including loperamide and an emollient cream, on incidences of diarrhea, hand-foot syndrome (HFS), and therapy satisfaction scores among patients prescribed capecitabine through an outpatient specialty pharmacy.

Methods: This retrospective cohort study included patients who were prescribed capecitabine during the designated study period between August and November of 2022. The two study arms were the intervention group, including patients who received a capecitabine support kit, and the control group, including patients who did not. Outcomes, including incidences of diarrhea and/or HFS and average patient therapy satisfaction scores, were compared between both groups.

Results: Chi-squared analyses indicated no differences ($\chi 2 = 2.84$, p=0.09) in the incidences of diarrhea between the intervention and control groups. However, a significant difference in the incidences of HFS was detected ($\chi 2 = 7.70$, p=0.01) between the intervention (20.6%) and control (40.7%) groups. There were no differences in patient therapy satisfaction scores between the two groups.

Conclusions: Pharmacy-provided capecitabine patient support kits, including adverse drug events (ADEs) management tools, may serve as an effective method for patients to recognize and manage serious toxicities, avoiding ADEs-related sequelae. Further prospective studies are in progress to better understand the impact of this intervention.

Capecitabine is a widely prescribed oral cytotoxic chemotherapy agent, which has shown promising results either as monotherapy or in combination with other chemotherapeutic agents in the curative and palliative management of several metastatic solid tumors.[1-2] This medication is also an efficient and safe treatment option in all line settings in patients with advanced gastric cancer and locally advanced or metastatic breast cancer. In addition to the well-established efficacy of capecitabine, it fulfills the need for a convenient and cost-effective oral anticancer therapy for patients who prefer oral medication with proven clinical efficacy.[3-5] While capecitabine continues to be a mainstay in clinical practice, the frequent side effects associated with its use may impair patients' quality of life and treatment retention, and consequently deteriorate disease-related outcomes.[6]

The most frequently reported side effect of capecitabine is palmar-plantar erythrodysesthesia, commonly known as hand-foot syndrome (HFS), which has been reported in 53-77% of patients treated with capecitabine.[7] The first presentation of this skin reaction, in most of the patients, is dysesthesia, often accompanied with a tingling sensation in the palms and soles of the hands and feet, with the hands being more commonly affected. The median onset of symptoms is estimated to be around 21 days (13.0–42.0) days.[8] Symptoms can progress in 3-4 days to sharply demarcated erythema with or without edema, cracking, or desquamation.[9] In advanced stages, painful blistering and ulceration may occur. While mild HFS, in early stages, can be managed with topical emollients[10-12], if ignored it can contribute to poor patient compliance and significantly impair normal daily living activities, thereby resulting in dose reduction and, in some cases, early discontinuation of therapy.[8]

Diarrhea is another common dose-limiting systemic toxicity associated with capecitabine. In patients undergoing treatment for metastatic breast cancer with capecitabine monotherapy, diarrhea was reported in 53% of the patients.[13] Capecitabine-associated diarrhea has been reported to negatively impact patients' self-care and is a major cause for perioperative treatment interruption or cessation. Furthermore, agents used in combination with capecitabine and concomitant radiation therapy can both increase the risk of severe and potentially life-threatening dehydration from diarrhea.[14] Historically, mild to moderate cases of chemotherapy-induced diarrhea have been managed using loperamide, an anti-diarrheal agent, sparing the need for dosage reductions or interruptions in most patients.[15]

Many patients receive their prescribed capecitabine therapy from an outpatient specialty pharmacy setting. This point of contact provides an opportunity to introduce interventions to mitigate the side effects associated with capecitabine use. Although several studies have documented

capecitabine-associated patient-reported side effects, there are limited studies addressing the impact of approaches in the prophylaxis and treatment of capecitabine-associated HFS and diarrhea.

In our specialty pharmacy setting, capecitabine patient support kits were introduced at no additional cost to patients, which included loperamide and an emollient cream as potential effective measures for prevention and management of diarrhea and HFS, respectively. An educational handout, lip balm, a thermometer, and a pill box were also included in the kits. As a part of our patient management program, all patients are provided with individualized therapy education on side effects at the initial fill, subsequent first three refills, and at regular intervals thereafter, discussing potential benefits of the effective and timely use of kit contents. Utilizing a standardized scripting, patients were each offered a capecitabine therapy kit at the initiation of therapy.

To our knowledge, no study has yet examined the effect of providing patient care kits curated with items to support patients receiving capecitabine therapy on the incidence of diarrhea, HFS, and patient therapy satisfaction scores. Therefore, the aim of this study was to evaluate the pharmacist-led interventions for the management of capecitabine-associated diarrhea and HFS in an outpatient-based specialty pharmacy model.

TABLE 1. Patients Baseline Characteristics (N=215)

Characteristic	*Intervention Group (n= 63)*	*Control Group (n= 152)*
Gender (n, %)		
Female patients	37 (59%)	99 (65%)
Male patients	26 (41%)	53 (35%)
Average age (years) ± SD*		
Female patients	59± 11.4	59± 11.89
Male patients	56± 11.1	59± 10.73
Indication (n, %)		
Breast cancer	15 (23.8%)	53 (34.9%)
Hepatobiliary cancers	3 (4.8%)	6 (3.9%)
Lower gastrointestinal tract cancers *1. Colon cancer* *2. Colorectal* *3. Rectal cancer*	35 (55.6%) *17 (48.5.%)* *5 (14.3%)* *13 (37.1%)*	66 (43.4%) *43 (65.2%)* *2 (3.0%)* *21 (31.8%)*
Pancreatic cancer	5 (7.9%)	6 (3.9%)
Upper gastrointestinal tract cancers*	4 (6.3%)	4 (2.6%)
Other	1 (1.6%)	17 (11.2%)
Treatment Regimen (n, %)		
Capecitabine monotherapy	24 (38.1%)	126 (82.9%)
Combination systemic therapy	27 (42.9%)	20 (13.2%)
Radiotherapy	10 (15.9%)	6 (3.9%)
Radiation + combination systemic therapy	2 (3.2%)	-

**SD: standard deviation*

Methods

Study Design

A retrospective chart review was initially conducted on 215 patient records (aged ≥ 18 years) who had received capecitabine over a two-month period of August to November 2022 across a multisite, integrated delivery network specialty pharmacy. Patients who had a capecitabine prescription filled at least twice during this timeframe, whether they were initiating or continuing therapy, were eligible for inclusion in the study. Capecitabine patient support kits were created by the clinical services team in August 2022 and included an emollient and loperamide to help patients manage the capecitabine-associated HFS and diarrhea, respectively. Since the inception of the kits, they have been offered universally to all patients at no out-of-pocket cost as a standard part of the capecitabine patient management program.

Of the 215 patients, 198 (92.1%) had all outcome variables documented on their charts and thereby were included in the final analysis with 63 (31.8%) patients being given the patient support kits with their filled prescription of capecitabine; these patients were defined as the intervention group. The remaining 135 (68.2%) patients did not receive the support kit and were considered the control group.

In addition to identifying patients who were eligible for the study, baseline patient characteristics, including age, gender, international classification of diseases (ICD-10) diagnosis codes, and adjunct therapy were either collected using internal analytic tools linked to the pharmacy software or pulled from patients' profiles and then de-identified. Study outcomes, including the percentage of patients who experienced diarrhea and/or HFS in both groups based on patient-reported outcomes during the last patient-clinician encounter in the study period, were documented for all patients. Additionally, average scores of patient satisfaction with therapy (on a scale of 1-10, with 10 representing the highest satisfaction), as reported by patients during the study period, were collected. These collected patient-reported outcomes are routinely discussed and assessed with patients as part of our in-house patient management program. As a standard expectation for all patients participating in the pharmacy patient management program, clinicians are advised to probe patients further for additional information about barriers or challenges with their medication therapy when responding with a satisfaction score of equal to or less than 6 to determine if additional intervention should be made. This study received an IRB review exemption.

Statistical Methods

Statistical analysis took place in three steps. First, the data of all eligible patients

were transcribed from the patients' profiles to an SPSS v28.0 database. This database was spot checked for accuracy in transcription and found to be validly transcribed. The next step of the analysis involved calculating descriptive statistics of all the variables extracted to assess the assumptions of the statistical tests being employed to address the aim of the study. Independent t-tests were used to compare the continuous variables, and Chi Square analysis was used to compare the discrete patient characteristics between the two study groups. These descriptive statistics also provided a description of the sample to support external validity of the study and comparisons of the patient characteristics between the two study groups to support the internal validity of the study. Finally, the intervention and control groups were compared using Chi Square for whether they reported any adverse event, diarrhea, HFS, or both adverse events. Using the nonparametric Mann-Whitney U statistics, patient therapy satisfaction scores were compared between the study groups. G*Power analysis indicated that comparing groups of 63 and 135 individuals using the Mann-Whitney U statistic, anticipating a small effect size of 0.3016, at an alpha level of 0.05 would yield an acceptable level of statistical power (1-β >.80).[17]

Results

A total of 215 retrospective chart reviews were performed across a multisite integrated delivery network specialty pharmacy for adult patients who had received at least two capecitabine prescriptions between August and November 2022. A total of 198 patients had all outcome variables documented on their charts. Of these, 135 (68.2%) were in the control group and 63 (31.8%) were in the intervention group.

Table 1 compares the baseline characteristics of the 215 patients across the control and intervention groups. It was noted that there is no difference in gender distribution [2:1 ratio of females to males ($\chi 2 = 1.18$, $p = 0.278$)] or the mean age [59 years (SD± 11.4) for females, 56 years (SD± 11.1) for males in the intervention group; 59 years (SD± 11.89) for females, 59 years (SD± 10.73) for males in the control group] between the groups. However, the percentage of patients receiving adjunct therapy during the study was significantly higher in the intervention group (42.9%) than the control group (13.2%). As for capecitabine indications, lower gastrointestinal tract cancers (55.6% in the intervention group and 43.4% in the control group) and breast cancer (23.8% in the intervention group and 34.9% in the control group) were found to be the most prevalent in both groups (Table 1).

TABLE 2. Patient-reported Outcomes and Therapy Satisfaction Scores

*Patient-reported ADEs**		
	Intervention Group (n= 63, 31.8%)	***Control Group (n= 135, 68.2%)***
Diarrhea (n, %)	12 (19.0%)	14 (10.4%)
HFS* (n, %)	13 (20.6%)	55 (40.7%)
HFS+ Diarrhea	2 (3.2%)	6 (4.4%)
Patient-reported Therapy Satisfaction		
	Intervention Group (n= 63)	***Control Group (n= 134)***
Therapy satisfaction score = 10	18 (28.6%)	53 (39.6%)
Therapy satisfaction score = 6-9	25 (39.7%)	53 (39.6%)
Therapy satisfaction score < 6	3 (4.8%)	8 (5.9%)
Unknown therapy satisfaction	17 (26.9%)	20 (14.9%)

ADEs: Adverse Drug Events; HFS: Hand-foot Syndrome

Table 2 presents the comparison of the study outcomes for the 198 patients who had their outcome variables documented within their charts. The percentage of patients experiencing diarrhea was similar (p=0.09) in the intervention (12 patients, 19.0%) and control (14 patients, 10.4%) groups. The groups did report significant differences in HFS (p<0.01) with 17 patients (20.6%) of intervention group and 55 patients (40.7%) of the control group reporting this adverse event. The percentage of individuals who reported experiencing both diarrhea and HFS during the study were similar (p=0.67) among the intervention group (2 patients, 3.2%) and control group (6 patients, 4.4%), (Table 2).

Finally, the patient therapy satisfaction scores exhibited a ceiling effect and negative skew, and the data were not normally distributed in both study groups. These characteristics of the patient therapy satisfaction scores indicated that the groups should be compared on this variable using the nonparametric Mann-Whitney U. This statistic indicates no significant differences (p=0.28) between the intervention (8.46 + 1.85) and control (8.65 + 1.68) groups on their levels of patient therapy satisfaction (Figure 2). Further segmentation of therapy satisfaction ratings is noted in Table 2.

An additional factor not specifically noted in Table 2 was the prevalence of lower gastrointestinal (GI) cancer diagnosis among all reported diarrhea incidences in both groups. It was found that 67.0% and 57.0% of the patients had lower gastrointestinal cancer diagnosis in the intervention and control groups, respectively, regardless of HFS existence.

Discussion

In this study, patient-reported incidences of HFS and diarrhea, as well as therapy satisfaction scores, were compared among patients who received a capecitabine support kit (intervention group) and those who did not (control group). The results indicate that the incidences of HFS were lower among patients who received capecitabine patient support kits that included an emollient cream to manage HFS events. The incidences of HFS in the intervention group were clinically and statistically lower when compared to the control group. This observation aligns with a previous study that demonstrated the prophylactic benefits of urea-based cream in reducing chemotherapy-associated HFS rates and delaying onset of first episode.[18] Since HFS is the most common capecitabine dose-limiting toxicity, this demonstration of clinical benefit has important implications

for patients' ability to adhere to therapeutic dosing and potentially achieve better long-term outcomes in palliative and curative settings.[19-20]

Although the observed difference in diarrhea incidences between the two study groups does not represent a statistically meaningful difference, it is worth mentioning that diarrhea incidences might be confounded by the uneven distribution of concomitant systemic therapies and cancer type between the compared groups. A higher proportion of the diarrhea-reported cases were for patients suffering from lower GI cancers. Thus, it is hard to identify whether diarrhea is a treatment-related adverse drug events (ADE) from capecitabine or a consequence of the disease location and severity.

The study revealed no statistical differences in patient-reported therapy satisfaction scores between the two groups. In fact, oncology patients' satisfaction with therapy is usually based on their subjective experiences with treatment that entails multiple factors.[21-22] This limits the utility of the therapy satisfaction score alone to accurately represent the true benefit of capecitabine balanced against ADEs associated with therapy. Forthcoming quality of life outcomes from an ongoing prospective trial may better elucidate the benefits of this intervention.

Limitations

The findings of this study should be interpreted cautiously due to several limitations. First, the study has a retrospective design and is limited in duration. A second limitation was the disproportionality of some of the baseline characteristics across the two study groups, which might have impacted the patient-reported outcomes. For example, more patients in the intervention group were receiving additional systemic therapy (42.9%) compared to the control group (13.2%). This could partially explain the high incidences of diarrhea in the intervention group and may underestimate the overall benefit of patient support kits.

Third, patients who were initiating therapy and continuing therapy were both included in the study, which may have impacted the timing of developing ADEs and therapy satisfaction. Also, the duration of therapy and capecitabine doses were screened by clinical pharmacists to be appropriate for the patient's body surface area and treatment plan, but not included in baseline characteristics, which is a confounding variable contributing to ADE development.

Finally, utilization of the kits the effect of capecitabine therapy on quality of life, due to its adverse effects, was not examined in this analysis which is a crucial outcome to consider especially in the metastatic setting, when goals of therapy are not curative. Given these limitations, there is a need for future prospective studies to further investigate the impact of this intervention.

Conclusions

The introduction of capecitabine patient support kits in a specialty pharmacy setting that included loperamide and an emollient cream into the routine care of patients receiving capecitabine may confer a potential benefit in the management of capecitabine-associated HFS. Further prospective studies are in progress to support wider adoption of this intervention and its applicability to general pharmacy practice.

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