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Analysis of data on capecitabine-related adverse drug reactions from the Korean adverse event reporting system database

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ABSTRACT

Purpose: The purpose of this study was to evaluate the adverse drug reactions (ADRs) and serious adverse events associated with capecitabine use in Korean patients by analyzing data from a comprehensive national database of adverse events.

Method: Data from all reports concerning capecitabine (Anatomical Therapeutic Chemical code: L01BC06) generated between January 2011 and December 2014 were collected from the Korean Adverse Event Reporting System database (KAERS).

Results: A total of 676 reports and 1069 capecitabine-related ADRs were identified. Ninety-nine cases (14.6%) were classified as serious adverse events. The most commonly reported capecitabine-related ADRs involved gastrointestinal system disorders (324, 30.3%), including diarrhea, nausea, vomiting, and stomatitis, followed by skin and appendage reactions (220, 20.6%), which included symptoms such as skin discoloration/disorder/dryness, itching, and rash.

Conclusions: Patients need to be educated about the common ADRs associated with capecitabine intake in a clinical setting. Patient characteristics must be considered when determining the capecitabine dosage and risk of ADRs, and nursing intervention is critical for preventing exacerbation of these ADRs.

1. Introduction

Since early 2000, there has been an increase in the development and use of oral chemotherapeutic agents (Ahn, 2007; Yap et al., 2010), which play an important role in cancer treatment. As intravenous therapy requires invasive medical procedures, it tends to cause discomfort and interfere with the patients' daily life because of the need for hospitalization or frequent outpatient visits for treatment. Both medical staff and patients prefer oral chemotherapy, which improves the quality of life of cancer patients, as long as it provides similar treatment outcomes (Lee et al., 2011; Lee and Jeong, 2013).

Capecitabine, an antimetabolic chemotherapeutic agent, inhibits the ability of cancer cells to produce the materials required for their growth (Saif et al., 2008). Diverse large-scale clinical trials conducted in the 2000s have demonstrated the anti-cancer effects of capecitabine, specifically against colorectal and breast cancer (Hoff et al., 2001; Talbot et al., 2002; Van Cutsem et al., 2001). In addition to being used as monotherapy for palliative chemotherapy in inoperable patients, capecitabine is currently being used, in combination with preoperative radiotherapy, as postoperative adjuvant therapy, or in combination with other chemotherapeutic agents that are effective against certain types of cancer (Lee et al., 2011; Saif et al., 2008; Yarbro et al., 2013).

Intravenous administration of 5-fluorouracil (5-FU), another antimetabolite chemotherapeutic agent, may require hospitalization for the delivery of continuous injections through a peripheral catheter, or if the vein condition is poor, a central venous catheter. In contrast, oral capecitabine chemotherapy circumvents any such discomfort or inconvenience to the patient and is safer because of the lower incidence of leukopenia. Thus, capecitabine is considered as efficacious as 5-FU, and its use is gradually increasing (Lee et al., 2011). Generally, when used for monotherapy, capecitabine is administered at a daily dose of 2500 mg/m^2 of body surface area in 21-day cycles where the patients receive the drug for 14 of the 21 days and rest for the remaining 7 days (Saif et al., 2008). Capecitabine has several notable adverse effects involving the hands and feet, such as hand and skin pain, tenderness on pressure, edema, blisters, and peeling (Abushullaih et al., 2002; Park, 2014; Park et al., 2009), which occur in 54–60% of patients receiving the drug. Because oral chemotherapy decreases the number of required hospital visits, it decreases the number of opportunities for patient interaction with medical staff. Therefore, medical staff may be unable to immediately identify any adverse effects or drug interactions, and may not be able to accurately evaluate the effectiveness of the treatment (Gerbrecht and Kangas, 2004; Choi and Oh, 2005). Therefore, hospitals emphasize the need for patient education to improve self-care

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competency, which allows outpatients taking capecitabine at home to evaluate any adverse effects and control their dosages accordingly (Moore, 2007; Park et al., 2009).

Adverse drug reactions (ADRs) are defined as negative and unintended reactions to normal dosages of drugs. ADRs to anti-cancer drugs are as significant as the effectiveness of these drugs because they may lead to physical and mental damage to patients and increase medical costs by extending the duration of hospitalization for treatment (Choi et al., 2012; Rhew and Lee, 2011). With the increasing use of drugs, these ADRs to chemotherapy may appear even years after taking the drug, and as such, continuous monitoring is required. The United States presently operates a spontaneous adverse event reporting system, which was established in the early 1960s. In Korea, the regulations on drug safety information management were enacted in 1985, marking the beginning of adverse event monitoring, and the monitoring institution was designated in 1988, enabling patients to report adverse events spontaneously (Choi et al., 2012). In addition, regional pharmacovigilance centers have been established since 2006, and Regional Drug Monitoring Project Teams began operations in 2009 under the Ministry of Food and Drug Safety, thereby establishing specialized ADR reporting policies and systems. Cases of adverse events can be reported to the Korea Institute of Drug Safety and Risk Management (KIDS) or the regional drug safety center by medical professionals, manufacturers, and consumers through a website or by email, fax, mail, or telephone. The cases are comprehensively managed by the Korean Adverse Event Reporting System (KAERS), leading to a rapidly increasing number of reports (Choi et al., 2012; Rhew and Lee, 2011). Since capecitabine was made available commercially to patients, no large-scale analyses of capecitabine-related ADRs have been performed using data from various institutions. Therefore, the aim of this study was to evaluate the ADRs and serious adverse events associated with capecitabine use in Korean patients by analyzing data from a comprehensive national database of adverse events. The findings of this study may provide useful basic data for the development of effective patient education materials.

2. Methods

2.1. Study design

This study was a secondary data analysis study using the Korean Database of Spontaneously Reported Adverse Drug Reactions to confirm ADRs to capecitabine.

2.2. Subjects

This study used the KIDS KAERS Database (KIDS-KD), comprising data from KAERS, a system collecting data on adverse events through KIDS, compiled over 48 months from January 2011 to December 2014. This study included all ADRs relating to the use of capecitabine, coded “L01BC06” in the Anatomical Therapeutic Chemical (ATC) code, and excluded “unlikely,” “unclassified,” and “unassessable” adverse event cases. Overall, this study analyzed data from a total of 1069 cases with a causal relationship between ADRs and capecitabine use, including 41 “certain” cases (3.8%), 325 “probable” cases (30.4%), 376 “possible” cases (35.2%), and 327 cases (30.6%) with no assessment.

2.3. Study parameters

1) General information: These data included reporting year, presence of serious adverse events, patient sex, and patient age.
2) Drug information: The drug contents in the reports were classified using ATC codes, which are managed by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. The data collected included the ingredient name, administration purpose, administration date, and drug-related action taken after the manifestation of ADRs, such as “drug cessation,” “dose maintenance” and “dose reduction.”
3) Adverse drug reaction information: Adverse drug reactions were classified using WHO-Adverse Reaction Terminology, which was developed by the WHO Uppsala Monitoring Center (Lim et al., 2007); system-organ classes were used to classify the side effects.
4) Serious adverse event information: Serious adverse events were classified as life-threatening, temporary or permanent disabilities, and prolonged hospitalization.
5) Reporter information: This included information regarding the original reporter, defined as the person who first identified the side effect, as well as the person(s) who filed the actual report. These data were classified as doctor, pharmacist, nurse, consumer, and others.
6) Causality evaluation information: ADRs were classified, in accordance with the causality evaluation criteria of the WHO Uppsala Monitoring Centre, into “certain,” “probable,” “possible,” “unlikely,” “unclassified,” and “unassessable.”
7) Medical history: Korean Standard Classification of Diseases codes were used.

2.4. Data collection and ethical considerations

This study received an approval exemption permit from the Institutional Review Board (No. 1040968-E-2015-003). We also obtained approval from KIDS for the use of the KIDS-KD by submitting a request and pledge for KIDS-KD in October 2015.

2.5. Statistical analyses

All statistical analyses were performed using Windows SPSS version 22.0 (IBM SPSS Statistics, Chicago, IL, USA). Descriptive statistics were used to summarize data regarding the capecitabine-related ADRs and severe events. General characteristics were compared between the serious adverse events and non-serious adverse events groups by using the independent *t*-test and the chi-square test. A *P* value of 0.01 was considered statistically significant.

3. Results

3.1. General features of spontaneously reported data on capecitabine-related ADRs

The general features of capecitabine-related ADR reports are listed in Table 1. There were 676 reports: 44 cases (6.5%) in 2011, 125 cases (18.5%) in 2012, 277 cases (41.0%) in 2013, and 230 cases (34.0%) in 2014. Pharmacists were the largest group of reporters at 224 cases (33.1%), followed by 183 cases (27.1%) reported by nurses, and 106 cases (15.7%) by doctors. In terms of location of reporting, 548 cases were reported at the regional drug safety center (81.1%), followed by 78 cases (11.5%) at manufacturer/importers, 30 cases (4.4%) at pharmacies, and 20 cases (3.0%) at hospitals. An average of 1.58 ADRs were included in each report, with 212 reported cases (31.4%) consisting of two or more ADRs. Serious adverse events were recorded in 99 cases (14.6%), with 1 case of permanent disability (0.2%), 4 cases of death (0.6%), and 46 cases of hospitalization/prolongation of hospital stay (6.6%). In terms of drug-related action after the manifestation of ADRs, the drug dose was maintained in 155 cases (22.9%) and reduced in 53 cases (7.8%), and drug treatment was terminated in 42 cases (6.2%); for 368 cases (54.4%), no records were available.

3.2. General characteristics of patients

The demographic and clinical characteristics of patients with capecitabine-related ADRs are listed in Table 2. The reported cases comprised 339 male (50.1%) and 312 female (46.2%) patients, with