

Research Paper

Adverse Event Profiles of 5-Fluorouracil and Capecitabine: Data Mining of the Public Version of the FDA Adverse Event Reporting System, AERS, and Reproducibility of Clinical Observations

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Abstract

Objective: The safety profiles of oral fluoropyrimidines were compared with 5-fluorouracil (5-FU) using adverse event reports (AERs) submitted to the Adverse Event Reporting System, AERS, of the US Food and Drug Administration (FDA).

Methods: After a revision of arbitrary drug names and the deletion of duplicated submissions, AERs involving 5-FU and oral fluoropyrimidines were analyzed. Standardized official pharmacovigilance tools were used for the quantitative detection of signals, i.e., drug-associated adverse events, including the proportional reporting ratio, the reporting odds ratio, the information component given by a Bayesian confidence propagation neural network, and the empirical Bayes geometric mean.

Results: Based on 22,017,956 co-occurrences, i.e., drug-adverse event pairs, found in 1,644,220 AERs from 2004 to 2009, it was suggested that leukopenia, neutropenia, and thrombocytopenia were more frequently accompanied by the use of 5-FU than capecitabine, whereas diarrhea, nausea, vomiting, and hand-foot syndrome were more frequently associated with capecitabine. The total number of co-occurrences was not large enough to compare tegafur, tegafur-uracil (UFT), tegafur-gimeracil-oteracil potassium (S-1), or doxifluridine to 5-FU.

Conclusion: The results obtained herein were consistent with clinical observations, suggesting the usefulness of the FDA's AERS database and data mining methods used, but the number of co-occurrences is an important factor in signal detection.

Key words: adverse events, AERS, 5-fluorouracil, capecitabine, pharmacovigilance.

Introduction

5-Fluorouracil (5-FU) exerts its anticancer effects through the inhibition of thymidylate synthase and

incorporation of its metabolites into RNA and DNA, and has been widely used for the treatment of solid

tumors for nearly 50 years [1]. In the early 1990s, a repetitive injection of 5-FU with a biomodulating agent, leucovorin (LV) was the standard treatment for metastatic colorectal cancer [2, 3]. However, preclinical evidence that increased exposure to 5-FU improves the cytotoxic activity, and the fact that 5-FU has a short plasma half-life [4] resulted in the inclusion of continuous infusion in the regimens. Currently, the FOLFIRI or FOLFOX regimen, with or without a targeted monoclonal antibody, is the standard treatment, consisting of a bolus of 5-FU, the infusion of 5-FU/LV, and irinotecan or oxaliplatin, respectively [5-8]. One of the most important factors complicating the clinical use of 5-FU is difficulties for patients, because of the potential for infection, bleeding and thromboembolism [9, 10], and/or higher treatment costs [11-13], resulting in the development of oral fluoropyrimidines, e.g., capecitabine, tegafur, tegafur-uracil (UFT), tegafur-gimeracil-oteracil potassium (S-1), and doxifluridine [14-16].

Immediately after oral fluoropyrimidine development, replacement of the 5-FU/LV infusion with oral fluoropyrimidines was investigated, especially for capecitabine; with preferable clinical outcomes, oral fluoropyrimidines now hold great promise and they are named the XELIRI or XELOX regimens [17-21]. The FOLFOX regimen was associated with neutropenia more than the XELOX regimen, whereas XELOX was more frequently associated with diarrhea and hand-foot syndrome (HFS) [17-20]. However, no conclusions were obtained for adverse events with relatively low frequencies, including nausea, vomiting, and stomatitis [17-20], and the comparison between the FOLFIRI and XELIRI regimens failed to clarify a difference in safety profiles, presumably due to the low number of participants [21]. A recently published pooled-analysis of randomized trials with a total of 6571 participants demonstrated that the use of capecitabine instead of 5-FU resulted in significantly less toxicity in terms of neutropenia and stomatitis [22]. In contrast, HFS was more frequently observed for capecitabine, but the analysis could not elucidate the effect of the replacement on susceptibility to diarrhea, nausea and vomiting, due to extensive variation in the results of trials used for pooled-analysis [22].

In this study, the safety profiles of oral fluoropyrimidines were compared with 5-FU using more than a million case reports on adverse events (AERs) submitted to the US Food and Drug Administration (FDA) database. This database relies on reports of spontaneous adverse events submitted to the FDA generated by health professionals, consumers, and manufacturers; the system is referred to as the Ad-

verse Event Reporting System (AERS). A statistically significant association with an adverse event was detected as a signal by applying standardized official pharmacovigilance methods [23-29]. Here, the adverse events focused on included myelosuppression (leucopenia, neutropenia, and thrombocytopenia), gastrointestinal toxicity (diarrhea, nausea, and vomiting), stomatitis, and HFS.

Methods

Data sources

Input data for this study were taken from the public release of the FDA's AERS database, which covers the period from the first quarter of 2004 through the end of 2009. The data structure of AERS is in compliance with international safety reporting guidance ICH E2B, consisting of 7 data sets: patient demographic and administrative information (DEMO), drug/biologic information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), drug therapy start and end dates (THER), and indications for use/diagnosis (INDI). The adverse events in REAC are coded using preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Here, MedDRA ver. 13.0 was used.

Prior to analysis, all drug names were unified into generic names by a text-mining approach, because AERS permits the registering of arbitrary drug names, including trade names and abbreviations. Spelling errors were detected by GNU Aspell and carefully confirmed by working pharmacists. Foods, beverages, treatments (e.g. X-ray radiation), and unspecified names (e.g. beta-blockers) were omitted for this study. Duplicated reports were deleted according to the FDA's recommendation of adopting the most recent CASE number, resulting in the reduction of the number of AERs from 2,231,029 to 1,644,220. The total number of co-occurrences, i.e., drug-adverse event pairs, in 1,644,220 AERs was 22,017,956.

Definition of adverse events

According to the MedDRA ver. 13.0, leucopenia, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, stomatitis and HFS are coded as preferred term identifiers PT10024384, PT10029354, PT10043554, PT10012735, PT10028813, PT10047700, PT10042128 and PT10033553, respectively.

Data mining

In pharmacovigilance analyses, data mining algorithms have been developed to identify drug-associated adverse events as signals that are

reported more frequently than expected by estimating expected reporting frequencies on the basis of information on all drugs and all events in a database [23-25]. For example, the proportional reporting ratio (PRR) [26], the reporting odds ratio (ROR) [27], the information component (IC) [28], and the empirical Bayes geometric mean (EBGM) [29] are widely used, and indeed, the PRR is currently used by the UK Medicines and Healthcare products Regulatory Agency (MHRA), the ROR by the Netherlands Pharmacovigilance Centre, the IC by the World Health Organization (WHO), and the EBGM by the FDA.

All of these algorithms extract decision rules for signal detection and/or calculate scores to measure the associations between drugs and adverse events from a two-by-two frequency table of counts that involve the presence or absence of a particular drug and a particular event occurring in case reports. These algorithms, however, differ from one another in that the PRR and ROR are frequentist (non-Bayesian), whereas the IC and EBGM are Bayesian. In this section, only the scoring thresholds used in the present study are given, and the reader is referred to review articles for more extensive details of each statistical test [23-25].

Here, we define how a drug and associated adverse event is classified as a signal, when using each statistical test. Using the PRR, a signal is detected, if the count of co-occurrences is 3 or more, and the PRR is 2 or more with an associated χ^2 value of 4 or more [26]. For the ROR, a signal is detected, if the lower bound of the 95% two-sided confidence interval of ROR exceeds 1 [27]. Signal detection using the IC is done using the IC025 metric, a criterion indicating the lower bound of the 95% two-sided confidence interval of the IC, and a signal is detected with the IC025 value exceeds 0 [28]. Finally, the EB05 metric, a lower one-sided 95% confidence limit of EBGM [29], is used and a signal is detected when EB05 is greater than or equal to the threshold value 2. In this study, the adverse events were extracted when at least 1 of 4 indices met the criteria indicated above.

Results

The total number of co-occurrences with 5-FU was 40,284, and 34,928 for capecitabine, 320 for tegafur, 1,215 for UFT, 1,422 for S-1, and 495 for doxifluridine, representing 0.183%, 0.159%, 0.001%, 0.006%, 0.006% and 0.002% of all co-occurrences in the database, respectively. In total, 864, 802, 110, 227, 246 and 168 adverse events were extracted as 5-FU- or oral fluoropyrimidine-associated adverse events with 23,690, 20,290, 200, 773, 861 and 305 co-occurrences, respectively. For each of tegafur, UFT, S-1 and doxi-

fluridine, the total number of co-occurrences was not large enough to compare with 5-FU.

The 5-FU-associated adverse events are listed in Table 1, which are ranked according to the number of co-occurrences, and the data for capecitabine is listed in Table 2. The adverse events commonly found in the worst 20 included neutropenia, diarrhea, nausea, vomiting, pyrexia, pulmonary embolism, mucosal inflammation, asthenia, a decrease of haemoglobin level, and sepsis.

In Tables 3-6, the data on capecitabine was compared with 5-FU in terms of susceptibility to myelosuppression, gastrointestinal toxicity, stomatitis, and HFS, respectively. The statistical metrics suggested 5-FU- and capecitabine-associated leukopenia, neutropenia and thrombocytopenia, but the association was weaker for capecitabine than 5-FU (Table 3). The associations with diarrhea, nausea and vomiting were also suggested for both, but it was more noteworthy for capecitabine than 5-FU (Table 4). The signals were also detected for stomatitis, but there were no statistical differences between 5-FU and capecitabine (Table 5). The analysis suggested that HFS occurred more extensively for capecitabine (Table 6).

Table 1. Adverse events more frequently associated with the use of 5-FU.

N	Adverse event
1076	Diarrhoea
774	Vomiting
715	Nausea
708	Dehydration
658	Neutropenia
631	Pyrexia
494	Febrile neutropenia
415	Abdominal pain
345	Pulmonary embolism
344	Mucosal inflammation
342	Asthenia
328	Thrombocytopenia
316	Anaemia
312	Haemoglobin decreased
306	Hypotension
277	Leukopenia
277	Sepsis
256	Decreased appetite
252	Pneumonia
251	White blood cell count decreased

N: the number of co-occurrences.

Official PT terms of MedDRA ver. 13.0 are listed.

The total number of co-occurrences with 5-FU was 40,284, and 864 adverse events were extracted as 5-FU-associated adverse events with 23,690 co-occurrences in total.

The adverse events were extracted when at least 1 of 4 indices met the criteria: the proportional reporting ratio (PRR), the reporting odds ratio (ROR), the information component (IC), and the empirical Bayes geometric mean (EBGM).

Table 2. Adverse events more frequently associated with the use of capecitabine.

N	Adverse event
1790	Diarrhoea
843	Vomiting
842	Nausea
694	Dehydration
626	Death
500	Disease progression
490	Pyrexia
456	Palmar-plantar erythrodysesthesia syndrome
386	Fatigue
385	Asthenia
325	Mucosal inflammation
305	Abdominal pain
288	Osteonecrosis
284	Decreased appetite
276	Neutropenia
244	Sepsis
242	Malignant neoplasm progression
219	General physical health deterioration
198	Pulmonary embolism
191	Haemoglobin decreased

N: the number of co-occurrences.

Official PT terms of MedDRA ver. 13.0 are listed.

The total number of co-occurrences with capecitabine was 34,928, and 802 adverse events were extracted as capecitabine-associated adverse events with 20,290 co-occurrences in total.

The adverse events were extracted when at least 1 of 4 indices met the criteria: the proportional reporting ratio (PRR), the reporting odds ratio (ROR), the information component (IC), and the empirical Bayes geometric mean (EBGM).

Discussion

The efficacy of each regimen is one of the most influential factors when the method of cancer chemotherapy is chosen from patients; however, there is increasing emphasis on assessment of quality of life, convenience for and preference of the patients. Some questionnaire-based studies have shown that oral treatment is more preferred, provided that it is not at the expense of efficacy [30-32]. Another study suggested that patients prefer the regimen with less toxicity and that it is of minor importance whether the medication is administered orally at home or intravenously at a hospital [33]. The AERS database covers several million case reports on adverse events, and is characterized by spontaneity. Despite some limitations inherent to spontaneous reporting, the AERS database is a rich resource and the data mining tools provide a powerful means of identifying potential associations between drugs and adverse events. Pharmacovigilance aims to search for previously unknown patterns and automatically detect important signals, i.e., drug-associated adverse events, from such a large database. Recently developed data mining tools, i.e., the PRR, ROR, IC, and EBGM, have been successful at detecting signals that could not be found by individual case reviews and that warrant further investigation together with continuous surveillance [23-29]. These tools are now used routinely for pharmacovigilance, supporting signal detection and decision-making at companies, regulatory agencies, and pharmacovigilance centers.

Table 3. Signal detection for 5-FU- and capecitabine-associated myelosuppression.

	N	PRR (χ^2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Leukopenia					
5-FU	277	5.282 * (952.334)	5.323 * (4.727, 5.919)	2.368 * (2.197, 2.540)	5.224 * (4.720)
Capecitabine	115	2.520 * (103.730)	2.526 * (2.103, 2.949)	1.306 * (1.041, 1.570)	2.432 * (2.081)
Neutropenia					
5-FU	658	6.912 * (3272.836)	6.986 * (6.465, 7.507)	2.755 * (2.643, 2.867)	6.808 * (6.382)
Capecitabine	276	3.315 * (441.127)	3.327 * (2.955, 3.700)	1.707 * (1.535, 1.878)	3.241 * (2.931)
Thrombocytopenia					
5-FU	328	2.749 * (360.868)	2.758 * (2.473, 3.042)	1.442 * (1.284, 1.599)	2.699 * (2.463)
Capecitabine	180	1.735 (55.060)	1.737 * (1.500, 1.974)	0.782 * (0.570, 0.993)	1.708 (1.509)

N: the number of co-occurrences.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Leukopenia, neutropenia, and thrombocytopenia were coded as PT10024384, PT10029354, and PT10043554, respectively.

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean.

Table 4. Signal detection for 5-FU- and capecitabine-associated gastrointestinal toxicity.

	N	PRR (χ^2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Diarrhea					
5-FU	1076	3.243 * (1625.228)	3.256 * (3.064, 3.448)	1.667 * (1.579, 1.754)	3.169 * (3.013)
Capecitabine	1790	6.383 * (7716.174)	6.435 * (6.135, 6.736)	2.606 * (2.537, 2.675)	6.104 * (5.870)
Nausea					
5-FU	715	1.364 (68.113)	1.365 * (1.268, 1.463)	0.440 * (0.333, 0.547)	1.355 (1.274)
Capecitabine	842	1.865 (329.449)	1.868 * (1.744, 1.991)	0.881 * (0.782, 0.980)	1.839 (1.737)
Vomiting					
5-FU	774	2.174 * (481.110)	2.179 * (2.029, 2.329)	1.102 * (1.000, 1.205)	2.143 * (2.019)
Capecitabine	843	2.745 * (912.239)	2.752 * (2.570, 2.935)	1.431 * (1.332, 1.530)	2.689 * (2.540)

Column headings are identical to Table 3.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Diarrhea, nausea, and vomiting were coded as PT10012735 (diarrhoea), PT10028813, and PT10047700, respectively.

Table 5. Signal detection for 5-FU- and capecitabine-associated stomatitis.

	N	PRR (χ^2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
5-FU	193	5.905 * (779.160)	5.959 * (5.169, 6.748)	2.517 * (2.312, 2.722)	5.853 * (5.184)
Capecitabine	174	6.141 * (741.267)	6.192 * (5.331, 7.053)	2.567 * (2.351, 2.782)	6.087 * (5.357)

Column headings are identical to Table 3.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Stomatitis was coded as PT10042128.

Table 6. Signal detection for 5-FU- and capecitabine-associated hand-foot syndrome.

	N	PRR (χ^2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
5-FU	64	6.059 * (265.364)	6.116 * (4.779, 7.452)	2.478 * (2.124, 2.832)	5.952 * (4.774)
Capecitabine	456	50.368 * (21762.799)	54.596 * (49.588, 59.604)	5.488 * (5.350, 5.626)	49.485 * (45.787)

Column headings are identical to Table 3.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Hand-foot syndrome was coded as PT10033553 (palmar-plantar erythrodysesthesia syndrome).

Here, AERs submitted to the FDA's AERS database were reviewed to compare the safety profiles of oral fluoropyrimidines with 5-FU, but the total numbers of co-occurrences with tegafur, UFT, S-1 and doxifluridine were not large enough for comparisons. Previously, the same database and data mining tools were used to confirm the adverse events accompanied with the use of the platinum agents, cisplatin, carboplatin, and oxaliplatin [34]. The analysis suggested that these agents possibly cause nausea, vomiting,

acute renal failure, neutropenia, thrombocytopenia, and peripheral sensory neuropathy [34]. In terms of susceptibility, their rank-order was consistent with clinical observations, suggesting the usefulness of the AERS database and the data mining method used [34]. Additionally, the National Cancer Institute Common Terminology Criteria for Adverse Events, NCI-CTCAE, version 4.0 was applied to evaluate the susceptibility of 14 anticancer agents to hypersensitivity reactions, and it was found that the number of

co-occurrences was an important factor in signal detection [35, 36]. Very recently, this system was applied for evaluation of muscular and renal adverse events induced by the administration of pravastatin, simvastatin, atorvastatin, or rosuvastatin, and their rank-order of susceptibility was quantitatively suggested [37].

Comparison of the FOLFOX regimen with the XELOX regimen has indicated 5-FU to be more highly associated with neutropenia compared to capecitabine [17-20]. This was proved by a pooled-analysis of randomized trials [22], and again confirmed here (Table 3). In contrast, clinical reports indicated that HFS was more frequently accompanied by the use of capecitabine than 5-FU [17-20, 22], and this was also consistent with the data shown here (Table 6). Although a pooled-analysis failed to clarify their difference in terms of susceptibility to diarrhea [22], the comparisons of two regimens have shown that diarrhea was more noteworthy for capecitabine [17-20]. This was confirmed in the present study, and additionally, the statistical metrics suggested that capecitabine possibly caused nausea and vomiting more frequently than 5-FU (Table 4). For stomatitis, a pooled-analysis suggested that it occurred more frequently with 5-FU than capecitabine, though the present study did not show the same difference (Table 5).

In conclusion, the safety profiles of oral fluoropyrimidines were compared with 5-FU using AERs submitted to the FDA's AERS. Based on 22,017,956 co-occurrences found in 1,644,220 AERs from 2004 to 2009, it was suggested that myelosuppression were more frequently accompanied by the use of 5-FU than capecitabine, whereas gastrointestinal toxicity and HFS were more frequently associated with capecitabine. The total number of co-occurrences was not large enough to be conclusive for tegafur, UFT, S-1 and doxifluridine. The results obtained herein were consistent with clinical observations, suggesting the usefulness of the FDA's AERS database and data mining methods used, but the number of co-occurrences is an important factor in signal detection.

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Conflict of Interest

The authors have declared that no conflict of interest exists.

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