Interaction between Gemcitabine and Warfarin Causing Gastrointestinal Bleeding in a Patient with Pancreatic Cancer

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KEY WORDS: pancreatic cancer, gemcitabine (Gemzar), warfarin (Coumadin), gastrointestinal toxicity, gastrointestinal bleeding

ABSTRACT

Gemcitabine (Gemzar) is the only chemotherapeutic agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced pancreatic cancer. Thromboembolism requiring anticoagulation is a common paraneoplastic complication in these patients. We report a case of patient with pancreatic cancer, complicated by gastrointestinal bleeding following therapy with concomitant gemcitabine-warfarin (Coumadin).

The patient was a 65-year-old male with medical history notable for atrial fibrillation for which he was taking warfarin 57.5 mg/week (international normalized ratio [INR] 1.94). He received capecitabine-radiotherapy for locally advanced pancreatic cancer. Later, he developed multiple liver metastases. The patient was started on gemcitabine. At the end of first cycle, he experienced bright red blood per rectum. His platelet count was normal, but his INR was noted to be significantly elevated at 8.00. Esophagogastroduodenoscopy (EGD) revealed 2 antral ulcers and a duodenal ulcer. The patient was stabilized and recovered without further incident.

Patients with pancreatic cancer who receive warfarin and gemcitabine should be monitored for any potential drug interactions. Weekly prothrombin time (PT)/INRs for anticoagulated patients receiving gemcitabine is suggested.

INTRODUCTION

Gemcitabine (Gemzar) is the only chemotherapeutic agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with pancreatic cancer.[1] It is also indicated for use in non-small-cell lung cancer, bladder cancer, and is commonly used in other gastrointestinal malignancies. Patients with cancer, specifically pancreatic carcinoma, are at increased risk for thrombosis requiring anticoagulation. In such cases, warfarin (Coumadin) is generally the agent of choice. In 1999, a potential interaction between gemcitabine and warfarin was reported.[2] In 2002, the manufacturer of gemcitabine, Eli Lilly, reported four

similar cases, indicating an incidence of 0.04% suspected drug interaction between gemcitabine and an anticoagulant.[3] They also reported that overall 5.4% of patients undergoing gemcitabine therapy received concomitant anticoagulants.[3] We report a sixth case; that of a patient with pancreatic cancer complicated by gastrointestinal bleeding with an elevated INR following treatment with concomitant gemcitabine-warfarin.

CASE REPORT

The patient was a 65-year-old male who presented with obstructive jaundice and a 20-lb weight loss. He was initially staged as having T4N0M0 disease. His medical history was notable for atrial fibrillation for which he was taking warfarin at a weekly dose of 57.5 mg. His international normalized ratio (INR) was stable at 1.94. He received 6 weeks of concomitant capecitabine-radiotherapy from May 27 to July 7. Computed tomography (CT) scan following capecitabine-radiotherapy revealed a decrease in the size of the pancreatic mass (2.3 cm versus 2.9 cm in maximum dimension prior to treatment), but new multiple liver metastases were noted at that time. The patient was therefore started on gemcitabine (1,000 mg/m^2) on August 8 to be given weekly for 3 out of every 4 weeks. His liver function tests at the start of gemcitabine therapy included total bilirubin, 1.2 mg/dL; aspartate aminotransferase (AST), 32 U/L; alanine aminotranferease (ALT), 20 U/L; and alkaline phosphotase, 312 U/L. His INR was 1.50. After the first two doses of gemcitabine, he presented with elevated liver function tests revealing total bilirubin, 2 mg/dL; AST, 194 U/L; ALT, 130 U/L; and alkaline phosphotase, 780 U/L. His INR was 1.8. No chemotherapy was given that day.

Seven days later, he presented to the emergency department with bleeding per rectum described as fresh, bright red blood per rectum for 2 days. No cardiac or pulmonary symptoms were present. No diarrhea or abdominal pain was accompanied. His platelet count was normal (130,000/cmm), but his INR was noted to be significantly elevated at 8.00.

Esophagogastroduodenoscopy (EGD) was performed without difficulty to the second portion of the duodenum. The esophagus was normal in its entirety. The stomach revealed two antral ulcers with exudate. One of these was approximately 1 cm and one was approximately 0.5 cm. The duodenal bulb was normal. The second portion of the duodenum revealed a 7-mm ulcer. Also noted was a stent that had been placed previously for the pancreatic cancer. Retroflexion revealed a normal angularis and proximal stomach. Air was withdrawn from the stomach and the endoscope was withdrawn confirming the above findings. Antral biopsies were taken for clotest (Urease enzyme). Flexible sigmoidoscopy to 30 cm was normal with no source of bleeding identified.

The patient was stabilized with transfusion of fresh frozen plasma and vitamin K and recovered without further incident. Unfortunately, his disease progressed and no further chemotherapy was administered.

DISCUSSION

In this patient, an interaction between warfarin and gemcitabine resulted in an elevated INR and gastrointestinal bleeding. After the publication of the first case report in 1999,[2] the Eli Lilly safety database was searched for any information reported up to December 31, 2000, regarding interactions between gemcitabine and anticoagulants. This search included published

literature, spontaneous reports, and serious reports from clinical trials involving gemcitabine. The results were used to determine if the safety concern was justified. Six cases of a suspected interaction between gemcitabine and anticoagulants were found. Four cases reported a suspected interaction with warfarin, one with phenprocoumon, and one with heparin.[3] The latter patient experienced palpitations but no bleeding.

The Eli Lilly safety database showed a total of 13,496 reported adverse events for gemcitabine during that period among an estimated 426,000 patients treated with the drug since its initial licensing. Seven hundred twenty-four patients taking gemcitabine were receiving concomitant anticoagulants as well, showing a proportion of 5.4% (724/13,496). The 6 identified cases that reported a suspected drug interaction accounted for an incidence of 0.8% (6/724).[3] This proportion is much higher than the number of patients in whom a suspected drug interaction between gemcitabine and an anticoagulant was reported (0.04%; 6/13,496).

Warfarin is the most commonly used oral anticoagulant for long-term anticoagulation for a variety of conditions including atrial fibrillation, deep venous thrombosis, and venous line patency. With rapid absorption by the gastrointestinal tract, warfarin is metabolized by the cytochrome P450 (CYP) enzyme system in the liver.[4] It is administered as a racemic mixture of both the S and R enantiomers. The more potent S enantiomer has a short half-life and is metabolized mainly by CYP2C9. The R enantiomer has a longer half life and is metabolized by CYP1A2, CYP3A4, and other isoenzymes. The drug is highly protein bound (99%). Pharmacokinetic and pharmacodynamic factors influence maintenance of anticoagulation and occurrence of toxicity.

Gemcitabine is a deoxycytidine analog similar to the pyrimidine antimetabolite cytarabine, with activity against solid tumors.[5] The pharmacokinetics of gemcitabine are different from warfarin. Gemcitabine enters cells by the facilitated nucleoside transport mechanism and undergoes phosphorylation in a stepwise fashion by the enzyme dC kinase, first to the 5^{l}-monophosphate form (dFdCMP) by deoxycytidine kinase (dCK). The drug is subsequently phosphorylated by nucleotide monophosphate kinase and nucleotide diphosphate kinase to the 5^{l}-diphosphate (dFdCDP) and 5^{l}-triphosphate derivatives (dFdCTP), respectively. dFdCDP is an inhibitor of ribonucleotide reductase, resulting in decreases in the four physiologic deoxyribonucleotide triphosphates: dATP, dCTP, dGTP, and dTTP. dFdCTP is incorporated into DNA by DNA polymerase and results in inhibition of DNA synthesis. The cytotoxicity of this compound is related to the di- and tri-phosphate forms.[6] When administered as a 30-minute infusion, the plasma half-life of gemcitabine ranges from 32 to 94 minutes. The intracellular half-life of the tri-phosphate metababolite ranges from 1.7 to 19.4 hours.

Based on the above description, a pharmacokinetic interaction between warfarin and gemcitabine appears unlikely. Our patient's warfarin dose and INRs were stable both before and after he received gemcitabine. Neither changes in diet nor any severe episodes of vomiting were observed in this patient. He did not start or discontinue any drugs during chemotherapy that could have had an interaction with gemcitabine. Gemcitabine can cause reversible elevations in hepatic transaminases in more than 50% of

patients, as happened in our patient.[7] The exact mechanism underlying liver dysfunction is not known but is probably related to cytotoxicity to hepatic cells. It is possible that the decreased warfarin requirement during gemcitabine therapy might be due to reversible hepatotoxicity caused by gemcitabine either by: (1) decreasing the metabolic function of the CYP enzymes, resulting in decreased warfarin metabolism, or (2) a decreased synthesis of clotting factors, resulting in reduced warfarin requirements. The exact mechanism of this interaction is still not clear.

However, despite the lack of data supporting the interaction between anticoagulants and gemcitabine, we still believe that it is important to be aware of the possible interaction between warfarin and gemcitabine that could manifest as a rise in INR. Such an interaction may require a weekly monitoring of INR and a reduction in warfarin dose accordingly. In oncology clinics, INRs are typically measured every 1 to 3 months in patients on chronic anticoagulation receiving chemotherapy, reducing the likelihood of identifying a drug interaction before an adverse event. In addition, more frequent monitoring of liver function is advised, as it may identify interactions earlier and help decrease the likelihood of adverse reactions associated with an elevated INR. This is an important issue as gemcitabine is indicated for pancreatic and breast cancers, the risk of which increased with age. Moreover, atrial fibrillation is also associated with increased age. As the average age of the population continues to increase, we expect to see more concomitant use of gemcitabine and warfarin in the future.

CONCLUSION

Gemcitabine is licensed for use in pancreatic cancer, and is also used for other gastrointestinal malignancies, as well as for bladder cancer, breast cancer, and non-small-cell lung cancer. Patients with cancer, specifically pancreatic carcinoma, are more prone to develop thrombosis. Such patients have long periods of immobility, often lack appetite, and experience nausea and vomiting with a subsequent decrease in vitamin K while receiving chemotherapy. As a consequence, the prothrombin time increases and the effect of warfarin increases. Despite these factors, the suspected interaction has been rarely reported.

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