JOP. J Pancreas (Online) 2008; 9(6):739-743.

LETTER

Interaction between Capecitabine and Gemcitabine with Warfarin in a Patient with Pancreatic Cancer

Muhammad Wasif Saif, Nawal Wasif

Yale Cancer Center, Yale University School of Medicine. New Haven, CT, USA

Summary

Gemcitabine is the only chemotherapeutic agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced pancreatic cancer. 5-fluorouracil or its oral pro-drug, capecitabine is the second most commonly used agent in this malignancy. Capecitabine or 5-fluorouracil is the second most common agent used either in second-line or as a radiosensitizer. Thromboembolism requiring anticoagulation is a common paraneoplastic complication in these patients. We report a patient with pancreatic cancer, challenged with maintaining the international normalized ratio (INR) with gemcitabine-capecitabine combination, and later with gemcitabine monotherapy with concomitant warfarin, as well as, a brief review of the literature. Patients with pancreatic cancer who receive warfarin and gemcitabine should be monitored for any potential drug interactions. Frequent prothrombin time and INR evaluations are suggested for anticoagulated patients receiving gemcitabine, especially when combined with capecitabine.

Dear Sir:

Gemcitabine 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 addition, due to aging and common risk factors, cardiac ailments such as atrial fibrillation are also common in this group. In such cases, warfarin 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] Moreover, the U.S. Food and Drug Administration and Roche have added a "Black Box" warning and strengthened the "Precautions" section on the label of capecitabine, which is indicated for the treatment of colorectal and breast cancer [4, 5]. We present the seventh case of a patient with pancreatic cancer complicated by an elevated INR following treatment with concomitant gemcitabine-capecitabine-warfarin first and then gemcitabine-warfarin later.

Case Report

A 70-year-old female with a past medical history of atrial fibrillation who reports being

in her usual state of health until May of 2006 when she presented with history of fatigue, nausea, darkening of her urine, anorexia, and occasional diarrhea. She subsequently developed jaundice and underwent an abdominal ultrasound which revealed stones and sludge filling the gallbladder, dilated intrahepatic ducts and a 15 mm dilated common bile duct without evidence of stone. The pancreatic duct was dilated to nearly 1 cm in diameter. A CT scan failed to reveal any definite pancreatic mass, and MRI also did not reveal a discreet mass although an "abrupt truncation of the pancreatic and common bile ducts" suggesting a mass. An MRCP failed to identify any stones within the dilated duct system. Finally, she underwent endoscopic ultrasound which revealed a 20x17 mm intrapancreatic mass was seen obstructing the distal bile duct and pancreatic duct, abutting the portal vein and superior mesenteric vein over a 12 mm length with the loss of the echo plane. No liver masses were noted and a fine needle aspirate was performed with pathology revealing malignant cells consistent with pancreatic adenocarcinoma. Subsequently, she underwent ERCP at which time a metallic stent was deployed in the common bile duct.

Her medical history was notable for atrial fibrillation for which she was taking warfarin at a weekly dose of 7.5 mg and 5 mg. Her international normalized ratio (INR) was stable at 1.94.

She came to the Yale Cancer Center and was started on GTX (gemcitabine, taxotere, and xeloda) regimen. However, her treatment required cessation of capecitabine related to elevation of INR as shown in Table 1. Gemcitabine and docetaxol were continued but maintaining the INR in the required range remained a challenge as shown in the Table 1. Docetaxol was also discontinued after cycle 9 due to edema and fatigue. Gemcitabine was continued every 2 weeks with close monitoring of PT/INR suggesting an interaction between the two agents. Patient continued gemcitabine till February 2008 when CT scan showed progressive disease evidenced by development of new ascites and findings consistent with carcinomatosis. In addition an implant on the gallbladder fundus was also noticed. Patient was offered second-line chemotherapy but was not administered due to clinical deterioration.

Table 1. Association between capecitabine and gemcitabine with increase in PT/INR.

Date	Regimen	PT (sec) /INR	ALT/AST (U/L)
September 11th, 2006	GTX	23.2/2.5	33/18
October 1st, 2006	GTX	52.1/6.0	27/19
November 1st, 2006	GT	19.9/2.1	22/16
December 7th, 2006	GT	19.9/2.1	23/16
December 27th, 2006	GT	25.6/2.8	27/13
January 10th, 2007	GT	25.1/2.7	38/20
January 30th, 2007	GT	13.7/1.4	24/15
February 20th, 2007	GT	25.9/2.8	34/14
March 7th, 2007	GT	54.8/6.3	26/23
April 6th, 2007	G	28.8/3.2	28/12
April 21st, 2007	G	32.4/3.6	27/16
May 6th, 2007	G	28.0/3.1	20/15
June 3rd, 2007	G	25.4/2.8	21/11
July 2nd, 2007	G	19.0/2.0	19/12
July 30th, 2007	G	15.6/1.4	22/414
August 3rd, 2007	G	23.0/2.5	21/16
September 17th, 2007	G	24.5/2.7	25/14
October 15th, 2007	G	34.4/1.5	26/23
November 9th, 2007	G	18.0/1.8	22/12
November 27th, 2007	G	26.0/2.7	53/26
December 7th, 2007	G	26.2/4.8	21/13
January 7th, 2008	G	38.6/4.1	21/9
February 4th, 2008	G	20.8/3.0	22/12
February 12th, 2008	G	18.9/2.5	20/8

Reference ranges: PT, 0-14.0 sec; INR, 0.9-1.4; ALT, 0-37 U/L; AST, 0-37 U/L
Standard desired range of INR for patients with atrial fibrillation: 2.0-3.0
GTX: gemcitabine + taxotere + capecitabine
GT: gemcitabine + taxotere
G: gemcitabine

Discussion

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 poor 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.

In this patient, an interaction between warfarin and gemcitabine-capecitabine and then with gemcitabine monotherapy resulted in an elevated INR and a drop in hematocrit requiring upper and lower endoscopy. However, no evidence of gastrointestinal bleeding was found.

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 31st, 2000, regarding interactions between gemcitabine and anticoagulants. This search included published literature, spontaneous reports, and serious reports from clinical trials involving gemcitabine. The results 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 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 anti-coagulation 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 5l-monophosphate form (dFdCMP) by deoxycytidine kinase (dCK). The drug is subsequently phosphorylated by nucleotide monophosphate kinase and nucleotide diphosphate kinase to the 5l-diphosphate (dFdCDP) and 5l-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 metabolite ranges from 1.7 to19.4 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 she received gemcitabine. Neither changes in diet nor any severe episodes of vomiting were observed in this patient. She 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 gemcitabine either by:

1) decreasing the metabolic function of the CYP enzymes, resulting in decreased warfarin metabolism, or
2) decreased synthesis of clotting factors, resulting in reduced warfarin requirements. The exact mechanism of this interaction is still not clear.

Fluoropyrimidines, including intravenous 5-FU and capecitabine have been reported to cause clinically significant increase in partial thromboplastin time (PTT) and INR in patients on concomitant use with anticoagulants [8, 9]. These alterations in coagulation parameters occurred within several days and for as long several months after initiation of capecitabine or 5-FU therapy and, in a few cases, within a month after stopping capecitabine or 5-FU therapy. These events occurred in patients with and without liver metastases. The inhibition of hepatic metabolism of warfarin by 5-FU was postulated to explain this drug interaction, but the true mechanism and how to monitor it remain under investigation [8, 9]. The U.S. Food and Drug Administration and Roche have added a "Black Box" warning and strengthened the "Precautions" section on the label of capecitabine, which is indicated for the treatment of colorectal and breast cancer [8, 9]. Patients should have their anticoagulant response (INR or PTT) monitored frequently in order to adjust the anticoagulant dose accordingly.

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.

This issue gains more significance when a combination chemotherapy regimen, such as GTX is administered in a patient already anticoagulated with warfarin, akin to our patient. Fine *et al*. retrospectively studied 35 patients who received GTX and showed grade 3-4 leukopenia in 14%, thrombocytopenia in 14%, and anemia in 9% [10]. However, no data regarding interaction with anticoagulants were given, probably due to the small sample size.

Interestingly, some investigators evaluated the effects of low-dose warfarin and regional chemotherapy on survival in patients with pancreatic carcinoma [11]. A retrospective analysis was performed on 180 patients with pancreatic carcinoma. Patients received one of seven regimens of chemotherapy. Unrelated to the type of chemotherapy, some patients received 1.25 mg warfarin daily. The primary end-point was median survival. The results showed that treatment with warfarin resulted in improved median survival from the start of regional therapy (warfarin *versus* no warfarin: 5.0 *versus* 2.3 months; 111 *versus* 69 patients; $P<0.0001$). This effect was not dependent on the type of chemotherapy used. Among the seven regimens examined, the one consisting of regional gemcitabine and mitomycin-C with systemic gemcitabine was associated with the longest median survival of 5.1 months from the start of regional therapy ($P=0.006$) and 12.7 months from diagnosis. This regimen combined with warfarin was associated with improved median survival (7.1 months; 32 patients). However, no such data exist based on a prospective randomized study.

It is also important to bear in mind that acetaminophen is an underrecognized cause of overanticoagulation in the outpatient setting [12]. Increased monitoring of INR values when such risk factors are present or modification of the risk factors themselves should reduce the frequency of dangerously high levels of anticoagulation.

Conclusion

In oncology clinics, INR is 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.

Received July 25th, 2008 - Accepted September 24th, 2008

Keywords capecitabine; gemcitabine; Hemorrhage; Pancreatic Neoplasms; Warfarin

Abbreviations CYP: cytochrome P450; G: gemcitabine; GT: gemcitabine + taxotere; GTX: gemcitabine + taxotere + capecitabine; INR: international normalized ratio

Conflict of interest The authors have no potential conflict of interest

Correspondence
Muhammad Wasif Saif
Division of Medical Oncology
333 Cedar Street, FMP 116
New Haven, CT 06520
USA
Phone: +1-203.737.1875
Fax: +1-203.785.3788
E-mail: wasif.saif@yale.edu

Document URL: http://www.joplink.net/prev/200811/10.html

References

1. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15:2403-13. [PMID 9196156]

2. Kinikar SA, Kolesar JM. Identification of a gemcitabine-warfarin interaction. Pharmacotherapy 1999; 9:1331-3. [PMID 10555940]

3. Kilgour-Christie J, Czarnecki A. Gemcitabine and the interaction with anticoagulants. Lancet Oncol 2002; 3:460. [PMID 12147431]

4. Holford NHG. Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. Clin Pharmacokinet 1986; 11:483-504. [PMID 3542339]

5. Hui YF, Reitz J. Gemcitabine: a cytidine analogue active against solid tumors. Am J Health Syst Pharm 1997; 54:162-70. [PMID 9117804]

6. Gandhi V, Plunkett W, Du M, Ayres M, Estey EH. Prolonged infusion of gemcitabine: clinical and pharmacodynamic studies during a phase I trial in relapsed acute myelogenous leukemia. J Clin Oncol 2002; 20:665-73. [PMID 11821446]

7. Sessa C, Aamdal S, Wolff I, Eppelbaum R, Smyth JF, Sulkes A, et al. Gemcitabine in patients with advancedmalignant melanoma or gastric cancer: Phase II studies of the EORTC EarlyClinical Trials group. Ann Oncol 1994; 5:471-2. [PMID 8075055]

8. Shah HR, Ledbetter L, Diasio R, Saif MW. A retrospective study of coagulation abnormalities in patients receiving concomitant capecitabine and warfarin. Clin Colorectal Cancer 2006; 5:354-8. [PMID 16512995]

9. Saif MW. An adverse interaction between warfarin and fluoropyrimidines revisited. Clin Colorectal Cancer 2005; 5:175-80. [PMID 16197620]

10. Fine RL, Fogelman DR, Schreibman SM, Desai M, Sherman W, Strauss J, et al. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. Cancer Chemother Pharmacol 2008; 61:167-75. [PMID 17440727]

11. Nakchbandi W, Müller H, Singer MV, Löhr M, Nakchbandi IA. Effects of low-dose warfarin and regional chemotherapy on survival in patients with pancreatic carcinoma. Scand J Gastroenterol 2006; 41:1095-104. [PMID 16938724]

12. Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. JAMA 1998; 279:657-62. [PMID 9496982]