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ORIGINAL ARTICLE

Muhammad Wasif Saif · Glenda Black · Martin Johnson
Suzanne Russo · Robert Diasio

Radiation recall phenomenon secondary to capecitabine: possible role of thymidine phosphorylase

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Abstract *Background*: The first reported case of radiation (XRT) recall related to capecitabine described dermatitis in a previously radiated field in a breast cancer patient (Ortman; JCO). We previously reported the first case of recall syndrome manifesting as diffuse gastritis and duodenitis related to capecitabine with prior XRT with 5-FU in a pancreatic cancer patient (Saif; JARCET). We report here another pancreatic cancer patient with a radiation recall receiving capecitabine following capecitabine-XRT. *Patients and methods*: From April 2004 to June 2005, 20 patients with locally advanced pancreatic adenocarcinoma were treated with capecitabine 1,600 mg/m^2 daily with concomitant radiation (5040cGy) Monday–Friday (weekends off) for a total of 6 weeks, followed by capecitabine 2,000 mg/m^2 daily for 14 days every 3 weeks. One male patient with tumor in the neck and body of pancreas and not infiltrating the duodenum dropped hemoglobin to 7.3 g/dl at the end of the ninth week, and melena on rectal examination. Specimen of primary pancreatic ductal adenocarcinoma was obtained via EUS-guided biopsy before starting XRT on day 1 and utilized for RNA extraction. TP mRNA level was determined by real-time quantitative PCR (RT-Q-PCR). *Results*: Upper endoscopy revealed gastritis consistent with radiation toxicity. Colonoscopy was negative. Transfusion of three units of packed red blood cells (PRBCs) was given. The dose of capecitabine was reduced by 25%. His anemia continued to progress, a CT scan revealed 39% decrease in the tumor size (PR). Analysis of tumor specimen prior to the start of capecitabine-XRT showed TP expression of 183.16 (high). In addition to TP, DPD was 7.40, and TNF-alpha 4,114.56. *Conclusion*: We believe this case to be the second case of radiation recall presenting as diffuse gastritis in a patient receiving capecitabine after previous treatment with XRT. Further studies, including the role of TP are warranted into the pathogenesis of this unique phenomenon.

Keywords Capecitabine · Xeloda · Thymidine phosphorylase (TP) · Dihydropyrimidine dehydrogenase (DPD) · Radiation recall phenomenon · Pancreatic cancer · Fluorouracil (5-FU)

Abbreviations 5-FU: 5-Fluorouracil · XRT: External radiation therapy · GI bleeding: Gastrointestinal bleeding · TP: Thymidine phosphorylase · DPD: Dihydropyrimidine dehydrogenase

Introduction

Standard treatment for locally advanced pancreatic cancer for several decades has been 5-fluorouracil (5-FU) delivered in conjunction with radiation (XRT) [1]. Both abdominal XRT and 5-FU treatment are associated with gastrointestinal symptoms including diarrhea, nausea, vomiting, and intestinal fibrosis, sometimes leading to bowel obstruction. The preferred delivery of 5-FU, whether infusional or bolus, however, has not been well established [2]. Although, gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN, USA) has been offered as an alternative to 5-FU treatment, significant dose limiting toxicity has been reported when gemcitabine was administered concurrently with radiotherapy [3]. Capecitabine (Xeloda; Roche Laboratories, Nutley, NJ, USA) is an orally administered fluropyrimidine carbamate, preferentially converted to 5-FU in tumor cells [4]. Treatment with capecitabine therefore, offers the possibility of continuous tumor exposure to 5-FU with minimal toxicity to normal tissue [5]. Response rates to capecitabine as a single agent in the metastatic and locally advanced disease is similar to that of gemcitabine, and better than that of 5-FU [6, 7]. Capecitabine is generally well tolerated with nausea and hand–foot syndrome being the

M. W. Saif (✉)
Section of Medical Oncology, Yale University School of Medicine,
333 Cedar Street, FMP 116, New Haven, CT 06520, USA
E-mail: wasif.saif@yale.edu

G. Black · M. Johnson · S. Russo · R. Diasio
University of Alabama at Birmingham, Birmingham, AL, USA

most commonly reported adverse events. The ease of administration and toxicity profile makes capecitabine an ideal therapeutic option in this setting to be utilized as a radio-sensitizer.

Radiation recall phenomenon is defined as the recalling of an effect, which is similar to an acute radiation reaction in an area of previous irradiation. This recall effect is seen in patients who have received previous radiation followed by a "recall" medication, typically an antineoplastic agent [8]. Multiple drugs have been described as potential recall-triggering medications including doxorubicin [9], paclitaxel [10], etoposide [11], gemcitabine [12], 5-FU [13], and more recently capecitabine [14, 15]. We are reporting here the second case of gastrointestinal (GI) bleeding, what we believe to be radiation recall presenting as diffuse gastritis in a patient receiving capecitabine alone following capecitabine-XRT.

Patients and methods

Study design

From April 2004 to June 2005, 20 patients received capecitabine 800 mg/m^2 orally twice daily Monday through Friday concurrently XRT (50.4–54.0 Gy delivered in 28–30 fractions 5 days per week over 6 weeks) followed by a 4-week rest at the University of Alabama at Birmingham on a clinical study approved by the institutional review board. Patients with stable or responding disease then received 3-weekly cycle of capecitabine (1,000 mg/m^2 orally twice daily for 14 days every 3 weeks) till progression. Computed tomography (CT) image-based three dimensional treatment planning was utilized to optimize radiation treatment planning by facilitating identification of the target volume and surrounding normal structures. Attempts were made to minimize XRT dose to surrounding normal tissues while ensuring adequate dose to the target volume. CT simulation was performed with intravenous and oral contrast material to assist in localizing the kidneys, liver, stomach, and intestines. The gross tumor volume (GTV) was defined as the maximum extent of the tumor and involved nodal areas or tumor bed after surgical resection (marked with clips placed at the time of surgery). The clinical target volume (CTV) was then defined as the GTV plus adjacent loco-regional nodes (celiac, peri-pancreatic, and portal) and para-aortic nodal areas at risk for residual microscopic disease. Anatomical structures were contoured for dose–volume histogram (DVH) analysis. The intestines were defined as the contents within the peritoneal cavity, excluding the stomach, spleen, liver, kidneys, aorta, CTV, and GTV.

Patients were assessed weekly during capecitabine-XRT and every 3 weeks during capecitabine monotherapy. Acute side effects (within 90 days from the start of XRT) were documented using the NCI common toxicity criteria (CTC) version 2.0. Late side effects (after 90 days from the start of XRT) were evaluated and graded according to the radiation therapy oncology group (RTOG) late radiation morbidity scoring scale.

Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 declaration of Helsinki as revised in 2000, as reflected in a priori approval by the University of Alabama Institutional Review Board.

Tissue collection, preparation, and determination of TP

Specimens of primary pancreatic ductal adenocarcinoma were obtained via EUS-guided biopsy before starting XRT on day 1 and during week 2 following chemo-radiation. Tissues to be utilized for RNA extraction were snap frozen in liquid nitrogen and stored at −80°C. Total RNA was isolated using the Qiagen RNA purification kit following manufacturer's instruction (Qiagen, Valencia, CA, USA). All sample concentrations were calculated spectrophotometrically at A_{260} and diluted to a final concentration of 20 ng/μl in RNAse-free water containing 12.5 ng/μl of total yeast RNA (Ambion, Austin, TX, USA) as a carrier.

Real-time quantitative PCR (RT-Q-PCR)

Expression levels were determined using an ABI 7,900 sequence detection system as previously described by our laboratory [16, 17, 18]. The real-time quantitative PCR (RT-Q-PCR) primers were as follows: human TP forward (5′-TCC TGC GGA CGG AAT CC-3′), reverse (5′-TGA GAA TGG AGG CTG TGA TGA G-3′) and fluorophore-labeled probe (FAM-CAG CCA GAG ATG TGA CAG CCA CCG T-TAMRA); TNF-alpha forward (5′-GGA GAA GGG TGA CCG ACT CA-3′), reverse (5′-TGC CCA GAC TCG GCA AAG-3′), and probe (FAM-CGC TGA GAT CAA TCG GCC CGA CTA T-TAMRA). The sequence for the primers and probes for human DPD, and S9 ribosomal have been previously described [17, 18]. Expression levels were calculated using the relative standard curve method [17, 18]. All reactions were run in triplicate and standard curves with correlation coefficients falling below 0.98 were repeated. Control reactions confirmed that no amplification occurred when yeast total RNA was used as a template or when no-template-control reactions were performed.

Case

One of the twenty patients in this study presented with GI bleeding. He was a 66-year-old Caucasian male with locally advanced pancreatic adenocarcinoma, who initially presented with abdominal pain and weight loss. CT of the abdomen revealed an infiltrative low-density mass involving the pancreatic neck and body. The mass measured 6.8×3.6 cm on image 18 with encasement of the celiac, common hepatic, and SMA arteries. The SMV and portal vein were thrombosed by the mass. The

pancreatic tail was not visualized and thought to be atrophied. No involvement of duodenum was seen. The liver, spleen, gallbladder, adrenals, and kidneys had a normal appearance except for parapelvic cysts and simple renal cysts. Shotty retroperitoneal nodes were not pathologically enlarged. No retroperitoneal adenopathy or free fluid was present.

The patient received capecitabine 1,600 mg/m^2 daily with concomitant XRT (5040cGy) Monday–Friday (weekends off) for a total of 6 weeks. (Monday through Friday) from March 8 till April 23. The patient tolerated the treatment well without any complications, except for Grade 2 nausea and vomiting, which he responded to anti-emetic therapy.

A CT scan following capecitabine-XRT on May 24 showed stable disease. He was started on capecitabine 2,000 mg/m^2 daily in two divided doses for 14 days every 3 weeks. On July 26, he was hospitalized in a local hospital due to a drop in hemoglobin to 7.3 g/dl. His only medications included fentanyl patch, oxycodone, zofran, and prilosec. He was not taking aspirin. He was found to have melena on rectal examination.

Results

An upper endoscopic examination revealed gastritis consistent with radiation toxicity nearly 12 weeks after XRT (Fig. 1). Colonoscopy was negative. Transfusion of three units of packed red blood cells (PRBCs) was given and the patient was discharged on proton pump inhibitor. The dose of capecitabine was reduced by 25%. On August 23, he developed a second episode of anemia with hemoglobin of 9.3 g/dl. One unit of PRBCs was infused.

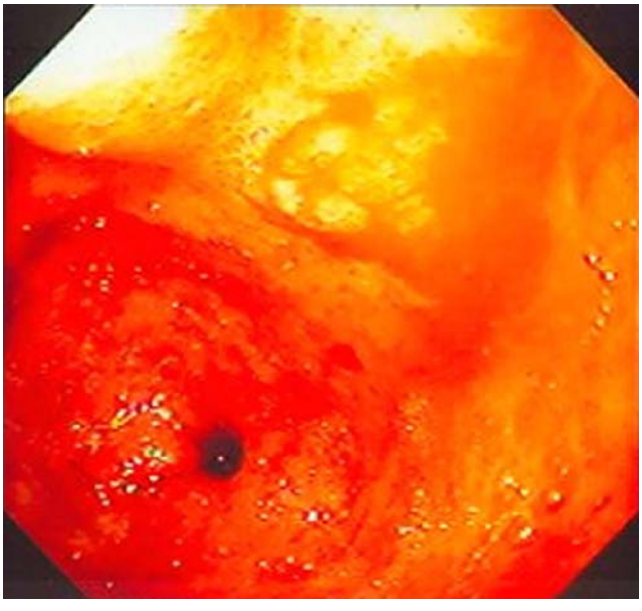

Fig. 1 Endoscopic findings are consistent with the radiation recall syndrome

On October 19, he was found to have another drop in hemoglobin to 6.8 g/dl. Further transfusion or PRBCs was administered. Capecitabine was not resumed. A CT scan was performed which revealed 39% decrease in the tumor from baseline (PR). However, due to decline in the performance status, he was placed on hospice. The patient expired on November 24.

Analysis of the tumor specimen prior to the start of capecitabine-XRT showed the expression of TP 183.16, DPD 7.40, and TNF-alpha 4,114.56.

Discussion

The first reported case of radiation recall dermatitis after administration of capecitabine described a breast cancer patient receiving capecitabine for progressive disease [14]. The patient developed a painful dermatitis in a previously irradiated field. We reported the first case of GI bleeding, manifested as diffuse gastritis and duodenitis in a patient receiving capecitabine after previous treatment with 5-FU-XRT [15]. The present patient is the second case of radiation recall complication in GI bleeding.

The exact pathogenesis for radiation recall phenomenon remains unclear. Some investigators have suggested that it may be the result of vascular damage, epithelial stem cell sensitivity, or drug hypersensitivity [14, 15]. One proposed mechanism suggests a lowering of the inflammatory threshold in radiated tissue, which leads to a non-immune inflammatory reaction upon exposure to certain drugs. Ortmann et al. [14] postulated that this phenomenon might be the result of up-regulation of TP in radiated tissues, leading to local pro-drug activation. This seems a reasonable hypothesis supporting a direct toxic effect of capecitabine in tissues previously treated with XRT.

Thymidine phosphorylase, also known as platelet-derived endothelial cell growth factor, is a potent angiogenic factor [19]. The expression of TP correlates with poor prognosis in a range of tumor types. 2-Deoxy-D-ribose-1-phosphate, a product of thymidine catabolism by TP, is a strongly reducing sugar that generates oxygen radical species during the early stages of protein glycation. It is suggested that thymidine induces oxidative stress in TP-over expressing carcinoma cells, promoting secretion of the stress-induced angiogenic factors vascular endothelial growth factor and interleukin-8, and inducing matrix metalloproteinase-1, which underline the mechanism for TP-induced angiogenesis. [19]. Sawada et al. [20] previously showed that XRT induces TP and enhances the efficacy of capecitabine in human cancer xenografts. Since this patient received XRT, it is probable that up-regulation of TP may have a role in inducing angiogenesis in the radiated area, leading to bleeding. This hypothesis is further supported by the fact that palmar-plantar erythrodysthesisa (Hand–foot syndrome), the most common adverse reaction related to capecitabine is also thought to be related to hypervascular anat-

omy [21]. Analysis of tumor specimen prior to the start of capecitabine-XRT showed the expression of TP 183.16 (high). Other marker of interest, i.e. DPD 7.40 was normal. Unfortunately, follow-up EUS was not performed during week 2 in this patient due to the risk associated with it. It is possible that the up-regulation of TP, increased angiogenesis in an area of previous vascular injury, and local pro-drug activation (capecitabine → 5-FU) are the underlying explanations of this phenomenon. This is a crucial issue as a potential increase in TP levels by XRT (which should translate into increased activation of capecitabine) [20] also provides a potential target for therapeutic intervention, suggesting that the combination of capecitabine and XRT would be a rational one.

In our recent study, presented at the annual meeting of ASCO 2003, we quantified TP mRNA by real-time quantitative PCR (RT-Q-PCR) in pancreatic tumor and uninvolved (normal) tissues [22]. TP expression was approximately 7.5-fold higher in pancreatic tumor tissue (mean 41.7; SE 8) as compared to normal pancreatic tissue (mean 5.5; SE 1.5) with a mean difference of 36.16. These differences were statistically significant ($P=0.01$). Similarly, in this patient who developed GI bleeding while on capecitabine baseline TP mRNA was comparatively higher (183.16) than the normal pancreatic tissue (mean 5.5) and also the pancreatic tumor specimens (mean 41.7). Of particular interest, XRT has been shown to result in increased TP levels when used with concurrent capecitabine as previously described [20, 23]. Also, in a prospective phase I study, we treated 15 patients with locally advanced pancreatic cancer with the same regimen (three-dimensional conformal XRT to a dose of 50.4 Gy with capecitabine at escalating doses from 600 to 1,250 mg/m^2 bid M-F) [23]. Tumor specimens were procured with an endoscopic ultrasound-guided fine-needle aspiration 1 week before and 2 weeks after chemo-XRT to evaluate TP, DPD, and TNF-alpha mRNA levels (Table 1). Pre-XRT mRNA TP levels were lower than the current case who developed GI bleeding and findings consistent with radiation recall (median 21.83; range 2.31–141.90) as well as the post-XRT mRNA TP levels (median 79.62; range 15.25–137.76) [23]. Unfortunately, post-XRT level is not available in this patient but higher level of baseline TP in this patient incites new thoughts that future research is to explore the role of TP in patients who develop GI bleeding following chemo-XRT, especially when capecitabine is used as a radiosensitizer. The role of TP in bleeding is further complemented by similar findings in non-malignant conditions, which support the role of TP in causing bleeding (petecheal), such as interstitisal nephritis. Glomerulation has been one of the requisite criteria for the diagnosis of interstitial cystitis. Tamaki et al. [24] investigated the relationship between the cystoscopic findings of vascular events and the expression of angiogenic growth factors in 45 patients. The investigators found that the expression of TP (measured by enzyme-linked immunosorbent assay) was significantly higher in patients with glomerulation (97.4%) than in symptomatic patients (0) without glomerulation or asymptomatic patients ($P<0.001$) [24], further complementing the hypothesis that neovascularization is likely promoted by angiogenic growth factors, including TP.

Table 1 mRNA Thymidine Phosphorylase (TP) levels in tumor collected at 1 week before and 2 weeks after chemo-XRT in a Phase I study capecitabine-XRT in patients with locally advanced pancreatic cancer versus the present case [23]

Sample	TP	
	Pre-XRT	Post-XRT
1	16.18	15.25
2	108.87	87.72
3	15.44	–
4	2.31	–
5	–	–
6	6.01	32.22
7	–	–
8	21.83	79.62
9	–	–
10	141.90	21.97
11	15.21	23.25
12	53.29	105.9
13	81.25	137.76
14	4.39	20.5
15	26.49	29.9
Present case	183.16	–

Additional factors, including local tumor invasion and but interestingly this patent had a PR (39% shrinkage) paralleling the bleeding episode. As noted above, capecitabine is believed to be a potent radiation sensitizer, but it was hoped that this effect would preferentially occur in the tumor. Our case suggests that normal tissues may also be adversely affected. It is also possible that an enhanced inflammatory response in the areas immediately adjacent to the tumor sites may have contributed to the observed toxicity. But another more probable explanation underlying this toxicity may be related to extensive fibrosis primarily at the tumor site following capecitabine-XRT, a finding we found in another cohort of 22 patients published elsewhere [25]. Among those patients, five patients underwent exploratory laparotomy 6–9 months after completion of CAP-XRT for possible resection of the tumor. Histology in these patients showed an extensive fibrosis and absence of tumor [25]. Although, we cannot define the exact mechanism of the observed GI bleeding, each case may likely be multi-factorial. Hematological toxicity did not appear to play a contributing role.

This toxicity related to combined capecitabine-XRT becomes more important when anti-angiogenesis agents, such as bevacizumab (Avastin; Genentech) are added. In a phase I study that combined bevacizumab with Concurrent XRT and capecitabine in patients with locally advanced pancreatic adenccarcinoma. Three patients had tumor-associated duodenal ulceration with bleeding, 3, 10 (fatal), and 20 weeks after XRT, and one had a contained duodenal perforation 10 weeks after XRT [26]. Of interest, our patient did not have duodenal involvement.

The time frame of the incidents of GI bleeding is instructive. The time since XRT was 3 months (12 weeks) in the current case. Vigilance in looking for this serious side effect must therefore continue long after the completion of XRT in patients receiving capecitabine. This is especially true if the patient is predisposed to bleeding for any reason. Therefore, we recommend that prolonged use of CAP after concurrent CAP-XRT be undertaken with caution.

In summary, this is the second case of gastrointestinal bleeding we believe is the radiation recall associated with capecitabine. We agree that there may be many other potential and plausible explanations for the bleed, such as bleeding related to tumor invasion and/or necrosis secondary to therapy. However, this issue is very important and relevant given the increase in use of capecitabine with concurrent XRT given outside the context of a clinical trial. The role of TP also seems intriguing and needs to be confirmed with more patient numbers and longer follow-up.

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