

Safety of Capecitabine Use in Patients With Liver Dysfunction

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The issues of chemotherapy use and dosing in the setting of liver insufficiency are constantly debated in medical oncology clinics. Many chemotherapeutic agents are metabolized by the liver, and it is also relatively common for advanced cancer patients to have liver dysfunction secondary to metastatic disease. Some literature reviews the use of specific cytotoxic drugs in such patients,^{1,2} but data are still lacking for most agents. Hence, there are no formal dosing recommendations. Furthermore, most patients with hepatic insufficiency are excluded from clinical trials and case review series, perpetuating the lack of such information.

Capecitabine (Xeloda, Roche) is an oral, tumor-selective fluoropyrimidine carbamate that is preferentially converted to active 5-fluorouracil (5-FU) within the tumor by a three-step enzymatic conversion.^{3,4,5} Due to ease of administration and lower systemic 5-FU levels (ie, less toxicity), intermittent capecitabine (administered orally twice daily for 2 weeks followed by 1 week off) is being used with increasing frequency as an alternative to intravenous 5-FU therapy for metastatic gastrointestinal malignancies.⁶ It is well known that capecitabine is extensively metabolized by the liver. It is therefore important to know if hepatic dysfunction will alter its pharmacokinetics and whether dose adjustments are necessary in this setting. In this clinical case study, we report our experience with three patients suffering from gastrointestinal malignancies and associated mild to moderate liver insufficiency who received capecitabine for their metastatic disease.

Patients

Case 1

The first patient was a 59-year-old woman with hepatocellular carcinoma. Her past medical history was noncon-

tributary. Imaging revealed a large hyperdense area that had replaced most of the left lobe and part of the right lobe of the liver. There was another low-density mass in the right lobe measuring 1.6 cm. Laboratory data revealed moderate hepatic insufficiency based on standard liver biochemistry tests (Table 1), normal renal function, and an alpha-fetoprotein (AFP) level of 2,282 ng/mL.

Based on tumor size, location, and presence of other lesions, surgical resection or radiofrequency ablation was not deemed feasible. The patient was started on cycle 1 of intermittent (2 weeks on and 1 week off) oral capecitabine at 1,500 mg/m² twice daily.⁷ She tolerated this extremely well. In addition, the patient's liver profile actually normalized (Table 1) and her AFP dropped to 2,030 ng/mL. The patient's Eastern Cooperative Oncology Group (ECOG) performance status improved from 2 to 1.

For cycle 2, the patient's oral dose was increased to 1,800 mg/m² twice daily. She tolerated this higher dose well except for grade 1 hand-foot syndrome. Her liver profile remained normal and AFP dropped further, to 1,285 ng/mL.

The patient was continued on the same dose for cycle 3. On day 7 of this cycle, she presented with sudden-onset severe nausea, vomiting, and diarrhea. Imaging revealed a decrease in the size of her liver mass but marked dilation of her small bowel and colon, along with substantial wall thickening and mucosal enhancement. Infectious work-up was entirely negative. In the intensive care unit, the patient was intubated secondary to respiratory distress and developed multiorgan failure. She died 7 days later (day 14 of cycle 3). Of note, peripheral blood analysis during this time revealed low dihydropyrimidine dehydrogenase (DPD) activity levels, at 0.064 nmol/min/mg protein (normal range, 0.182–0.688), which likely led to elevated 5-FU levels and ensuing toxicity.⁸

Case 2

The second patient was a 64-year-old man with stage IV pancreatic cancer with liver metastasis. After progression of his disease on 6 months of gemcitabine (1,000 mg/m²),

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Table 1. Liver Profile and Response of Tumor Markers in Three Gastrointestinal Cancer Patients With hepatic dysfunction Treated With Capecitabine

	Case 1		Case 2		Case 3	
	Pre-chemotherapy	Post-chemotherapy (2 cycles)	Pre-chemotherapy	Post-chemotherapy (2 cycles)	Pre-chemotherapy	Post-chemotherapy (2 cycles)
AST (u/L)	449	33	117	46	81	18
ALT (u/L)	115	22	121	37	84	17
Alkaline phosphatase (u/L)	154	40	317	288	229	176
Total bilirubin (mg/dL)	1.2	0.7	4.63	1.0	3.96	0.69
Tumor marker	(AFP)	Decreased	(CA 19-9)	Stable	(CA 19-9)	Decreased

AFP=alpha-fetoprotein; ALT = alanine transaminase; AST= aspartate transaminase; CA=carbohydrate antigen.

he was started on intermittent (2 weeks on and 1 week off) capecitabine at a reduced dose of 750 mg/m² daily based on his abnormal liver biochemical profile (Table 1).⁹ The patient tolerated this dose extremely well and his liver profile showed good improvement. He was continued on this regimen and gradually titrated up to 1,000 mg/m² twice daily of intermittent capecitabine.

The patient went on to tolerate 16 more such cycles, with an improvement in ECOG performance status from 2 to 1. Imaging and serial carbohydrate antigen (CA) 19-9 levels showed stable disease. Eventually, chemotherapy was discontinued due to failure to thrive, and he was transferred to hospice care.

Case 3

This patient was a 60-year-old man with locally advanced pancreatic cancer. Due to tumor encasement of the portal vein and celiac axis, the patient was deemed not to be a surgical candidate. Of note, he had an external biliary drain placed by interventional radiology at the time of presentation for his obstructive jaundice (total bilirubin 17.6 mg/dL). Due to persistent hyperbilirubinemia, he was placed on a low dose of oral capecitabine at 1,000 mg/m² twice daily for 1 week on and 1 week off (Table 1). Following the first cycle, his bilirubin and the rest of his liver functions improved. He tolerated capecitabine very well without any toxicity.

Therefore, intravenous gemcitabine at a dose of 1,000 mg/m² over 30 minutes on days 1 and 8 and oral capecitabine at a dose of 1,000 mg/m² twice daily on days 1–14, in 21-day cycles, were administered.¹⁰ His liver profile continued to improve and finally became normal.

At cycle 4, the oral dose of capecitabine was escalated to 1,500 mg/m² twice daily, which he also tolerated very well except for grade 1 hand-foot syndrome at the end of cycle 6. His CA 19-9 prior to therapy was 10,200, and the most recent marker at cycle 19 was 29 (normal). His mass in the head of the pancreas has decreased from 6.0 cm to 2.4 cm, although he remains unresectable due to vascular encasement. He continues to enjoy an excellent performance status and has no known distant metastases as of today. The plan is to continue to maintain the patient on this current combination.

Discussion

Our three case reports highlight the safety of capecitabine in such patients. Two earlier reports^{11,12} of breast cancer patients with liver dysfunction also suggest that capecitabine can be safely administered and can benefit the patients. Treatment-related toxicity can be unpredictable due to altered drug clearance, and bilirubin exceeding 5.0 mg/dL is generally considered an absolute contraindication for the administration of cytotoxic agents. Generally, the pharmacokinetics of capecitabine are not affected in patients with mild to moderate hepatic dysfunction, but there are no data available for patients with severe hyperbilirubinemia. Our clinical experience also corresponds to the findings of Twelves and colleagues¹³ who reported that impaired hepatic function had no clinically significant influence on the pharmacokinetics of capecitabine and its metabolites.

Akin to cases of breast cancer, our patients in this series also showed significant clinical response in their dis-

ease (hepatocellular cancer for Case 1 and pancreatic cancer for Cases 2 and 3) at reduced doses of capecitabine.¹⁴ This finding is particularly interesting, as it shows that the efficacy of capecitabine was not necessarily compromised at the reduced doses chosen for our patients. Of note, the patients in each case tolerated a higher dose of capecitabine without difficulty. Such an observation was also found to be true in the study by Twelves et al,¹³ which actually concluded that no dose adjustment of capecitabine was necessary in patients with mild to moderate hepatic dysfunction secondary to liver metastases.

One interesting observation in this series comes from the patient in Case 1, who was found to be DPD-deficient and likely died secondary to 5-FU toxicity after tolerating two cycles of capecitabine extremely well. Even though such toxicity is less common than previously seen with infusional 5-FU, it is still important to suspect and test for DPD deficiency in patients on capecitabine with any manifestation of toxicity.^{8,15} It is unclear what role the patient's hepatic insufficiency played in precipitating her clinical deterioration.

In summary, we have described three cases in which capecitabine was safely used to treat advanced cases of hepatocellular and pancreatic cancer with associated hepatic insufficiency. The patients with pancreatic cancer had a particularly striking clinical response despite reduced doses of capecitabine. These results suggest that low-dose capecitabine may be a safe and efficacious treatment for patients with hepatic dysfunction. Clinical trials of low-dose capecitabine in such patients are therefore warranted. It is important to remember that the liver dysfunction in all of these patients was secondary to their malignancy. More work needs to be done to define the safety and efficacy of capecitabine in the setting of pre-existing liver disease such as that secondary to alcohol or viral hepatitis.

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(Clinical Case Study, continued from page 732)

Review

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Saif and Tejani¹ describe three cases highlighting the use of capecitabine in patients with gastrointestinal malignancy and malignancy-induced hepatic dysfunction.

In Case 1, the authors describe a patient with unresectable hepatocellular carcinoma and elevated transaminases who was treated with intermittent-dose oral capecitabine (2 weeks on and 1 week off) at the dose of 1,500 mg twice daily. The regimen was initially well tolerated, with subsequent normalization of liver profile, decline in alpha-fetoprotein, and improvement in performance status. The oral capecitabine dose was then increased to 1,800 mg twice daily. On day 7 of cycle 3, the patient developed complications clinically consistent with dihydropyrimidine dehydrogenase deficiency, which was confirmed by a peripheral blood sample collected hours before her death.

In the next two cases, the authors describe two patients with advanced pancreatic cancer with significant hyperbilirubinemia who underwent therapy with reduced-dose capecitabine. Both patients achieved normalization of liver function after two cycles, which allowed for further titration of capecitabine; in one, though, the drop in bilirubin may be related to relief of obstructive jaundice in the presence of an external biliary catheter.

The administration of chemotherapy in a patient with hepatic dysfunction remains a challenge and is not well studied. It is understood that hepatic impairment can alter drug clearance and therefore increase the toxicity profile of the agent used. There are very few data currently available regarding the necessity and degree of dose modification and its effect on efficacy. As most clinical trials exclude patients with hepatic dysfunction, there is a lack of prospective clinical information regarding dosing and efficacy data in this patient population. The majority of experience in treating cancer patients with malignancy-induced hepatic dysfunction comes from retrospective reports. Eklund and colleagues have described the dosing of various chemotherapy agents in the setting of liver dysfunction.² Liver dysfunction affects the pharmacokinetics of chemotherapy agents and therefore affects hepatic clearance, hepatic metabolism, and biliary excretion of drug. Hypoalbuminemia can result in increased fractions of free

drug, and portal hypertension can affect drug absorption. Serum bilirubin is the most commonly used measurement to determine if chemotherapy dose modification is needed. A bilirubin level greater than 5 mg/dL is generally accepted as a contraindication for systemic chemotherapy. There is no formal system to define the degree of hepatic dysfunction in cancer patients. As capecitabine is a commonly used drug in many cancers and is extensively metabolized by the liver, knowledge regarding its use in patients with hepatic dysfunction is critical for optimal patient care.

Capecitabine is an oral prodrug that is absorbed intact via the gastrointestinal tract and metabolized to the active drug, 5-fluorouracil (5-FU), in the liver and target tumor tissue through a series of three enzymatic reactions.^{3,4} First, capecitabine is converted to 5'-deoxy-5-fluorocytidine (5'-DFCR) by carboxylesterase in the liver. 5'DFCR is then converted to doxifluridine (5'DFUR) by cytidine deaminase, which is present in high concentrations in healthy liver and tumor tissues. Finally, 5'DFUR is converted to 5-FU by thymidine phosphorylase. Thymidine phosphorylase is a tumor-associated angiogenic factor primarily expressed in abundance in tumor cells and lacking in normal tissue, which allows higher intratumoral 5-FU concentrations (than with systemic intravenous 5-FU) and reduced exposure of normal tissue to the toxic side effects of 5-FU.

Twelves and colleagues evaluated the effect of hepatic dysfunction due to liver metastasis on the pharmacokinetics of capecitabine and its metabolites.⁵ This study showed that mild to moderate hepatic dysfunction had no clinically significant influence on the pharmacokinetic properties of capecitabine. The authors suggest that no dose adjustment is required strictly on the basis of hepatic dysfunction; however, caution is strongly advised when treating such patients.

Prospective trials can help us evaluate the safety, dose range, and efficacy of capecitabine in patients with pre-existing or malignancy-induced hepatic dysfunction. In the interim, if it is in the patient's best interest to receive chemotherapy, clinicians should proceed with caution. Close monitoring is essential.

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