A REVIEW ON CAPACETABINE

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ABSTRACT
Capecitabine, an oral drug used to treat breast and colorectal cancers, has been associated with potentially fatal cutaneous reactions. The drug's manufacturer, Hoffmann-La Roche, reported in an advisory from Health Canada that severe skin reactions have been observed in patients using capecitabine. In a letter to healthcare professionals, Health Canada noted that "very rare cases of severe cutaneous reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in some cases with fatal outcome, have been reported during treatment with [capecitabine]." Associated signs and symptoms of severe skin reactions can include flu-like symptoms, fever, skin itching, and a painful red or purplish skin rash that spreads and blisters and eventually causes the skin to shed. Other possible symptoms include mouth sores, eye burning, itching, and discharge.[1]

KEYWORDS: Capacetabine, cancer.

INTRODUCTION
Capecitabine is an oral medication for treating advanced breast cancer that is resistant to combination therapy with the drugs of choice, paclitaxel (Taxol) and a drug from the anthracycline family of drugs, for example, doxorubicin (Adriamycin). Capecitabine is converted by the body to 5-fluorouracil (5-FU), a drug which has been given intravenously for many years to treat various types of cancer. It is not surprising, therefore, that capecitabine also is effective in the treatment of colorectal cancer, a type of cancer that is treated frequently with 5-FU. 5-FU inhibits the production by the cancerous cells of both DNA and protein that are necessary for the cells to divide and the cancer to grow in size. Capecitabine was approved by the FDA in 1998 for the treatment of breast cancer and in 2005 for the treatment of colorectal cancer.[2] Capecitabine is approved in the United States.
for the treatment of metastatic colorectal and breast cancer. A generic Capecitabine received approval from the US Food and Drug Administration (FDA) in September. That product currently carries a boxed warning about a potential drug interaction; levels of warfarin in the blood can increase, leading to serious adverse effects. Adverse effects reported with capecitabine include diarrhea, vomiting, nausea, mouth sores, hand–foot syndrome, fever, and infection, according to the FDA.

Capecitabine is a cancer medication that interferes with the growth of cancer cells and slows their spread in the body. Capecitabine is used to treat breast cancer and colon or rectum cancer that has spread to other parts of the body. Capecitabine is often used in combination with other cancer medications and/or radiation treatments. Capecitabine may also be used for purposes not listed in this medication guide. Serious side effect of Capecitabine, such as:

- nausea, loss of appetite, eating much less than usual, vomiting (more than once in 24 hours);
- severe diarrhea (more than 4 times per day, or during the night);
- bloody, black, or tarry stools;
- coughing up blood or vomit that looks like coffee grounds;
- fever, chills, body aches, flu symptoms, easy bruising or bleeding, white patches or sores inside your mouth or on your lips;
- pale skin, feeling light-headed or short of breath, rapid heart rate, trouble concentrating;
- pain, tenderness, redness, swelling, blistering, or peeling skin on your hands or feet;
- swelling, rapid weight gain; or
- jaundice (yellowing of the skin or eyes).

Other common side effects may include:

- stomach pain or upset, constipation;
- tired feeling;
- mild skin rash; or
- numbness or tingling in your hands or feet.

PATIENT INFORMATION FOR CAPECITABINE. FDA pregnancy category D. Do not use capecitabine if you are pregnant. It could harm the unborn baby. Use birth control to prevent pregnancy while you are taking capecitabine, whether you are a man or a woman. Tell your doctor if a pregnancy occurs during treatment. It is not known whether capecitabine passes into breast milk or if it could harm a nursing
baby. You should not breast-feed while you are taking capecitabine. To make sure capecitabine is safe, doctor if you have any of these conditions:

- kidney disease;
- liver disease;
- a history of coronary artery disease; or
- if you take a blood thinner (warfarin, Coumadin, Jantoven).

During the weeks when you take capecitabine, take the medication once in the morning and once in the evening, unless your doctor tells you otherwise. You may also be given other medications as part of a combination cancer treatment. Capecitabine should be taken with food or within 30 minutes after eating a meal. Take this medication with a full glass (8 ounces) of water.[4]

**DRUG INTERACTION**

Capacetabine causes drug interactions with following drugs:

- leucovorin (Wellcovorin);
- phenytoin (Dilantin);
- heart or blood pressure medication;
- oral diabetes medication; or
- NSAIDs (non-steroidal anti-inflammatory drugs) such as ibuprofen (Advil, Motrin), naproxen (Aleve, Naprosyn, Naprelan, Treximet), celecoxib (Celebrex), diclofenac (Arthrotec, Cambia, Cataflam, Voltaren, Flector Patch, Pennsaid, Solareze), indomethacin (Indocin), meloxicam (Mobic), and others.[5]

**PHARMACOGENOMICS.**[6]

Dihydropyrimidine dehydrogenase (DPD), an enzyme encoded by the DPYD gene, is the rate-limiting step in pyrimidine catabolism and deactivates >80% of 5FU standard doses and the 5FU prodrug capecitabine

Contraindicated in patients with DPD deficiency; causes severe toxicity with conventional doses (ie, grade III/IV toxicity and potentially fatal neutropenia, mucositis, and diarrhea)

Because true DPD deficiency is rare and because the clinical implications of partial deficiency are still unclear, screening for mutations prior to initiating therapy is not warranted.
PRECAUTIONS.[7]  
Before taking capecitabine, tell your doctor or pharmacist if you are allergic to it; or to 5-fluourouracil; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: a certain enzyme deficiency (dihydropyrimidine dehydrogenase deficiency), blood disorders (e.g., bone marrow suppression), heart problems (e.g., coronary artery disease, heart failure), kidney disease, liver problems.

Wash your hands well to prevent the spread of infections. Do not have immunizations/vaccinations without the consent of your doctor, and avoid contact with people who have recently received oral polio vaccine. Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products). This medication may make you more sensitive to the sun. Avoid prolonged sun exposure, tanning booths, and sunlamps. Use an effective sunscreen and wear protective clothing when outdoors. This will also help protect you from problems related to heat (hand/foot syndrome). To lower the chance of getting cut, bruised or injured, use caution with sharp objects like safety razors and nail cutters, and avoid activities such as contact sports. Use a soft-bristle toothbrush to lower the risk of bleeding gums. Caution is advised when this drug is used in the elderly because they may be more sensitive to the side effects of this medication, especially nausea, vomiting, and diarrhea. This medication is not recommended for use during pregnancy. It may harm an unborn baby. It is not known if this drug passes into breast milk. Because of possible harm to the nursing infant, breast-feeding while using this drug is not recommended. Consult your doctor before breast-feeding.

CLINICAL STUDIES.[8]  
CM Walko et al shows that Capecitabine is an oral prodrug that is converted to its only active metabolite, FU, by thymidine phosphorylase. Higher levels of this enzyme are found in several tumors and the liver, compared with normal healthy tissue. In adults, capecitabine has a bioavailability of ~100% with a C_max of 3.9 mg/L, T_max of 1.5 to 2 hr, and AUC of 5.96 mg·h/L. The predominant route of elimination is renal, and dosage reduction of 75% is recommended in patients with creatinine clearance (CrCl) of 30 to 50 mL/min. The drug is contraindicated if CrCl is <30 mL/min. Capecitabine has shown varying degrees of efficacy
with acceptable tolerability in numerous cancers including prostate, renal cell, ovarian, and pancreatic, with the largest amount of evidence in metastatic breast and colorectal cancer. Single-agent capecitabine was compared with IV FU/leucovorin (LV) using the bolus Mayo Clinic regimen in 2 Phase III trials as firstline treatment for patients with metastatic colorectal cancer. Overall response rate (RR) favored the capecitabine arm (26% vs 17%, \( P < 0.001 \)); however, this did not translate into a difference in time to progression (TTP) (4.6 months vs 4.7 months) or overall survival (OS) (12.9 months vs 12.8 months). In Phase II noncomparative trials, combinations of capecitabine with oxaliplatin or irinotecan have produced results similar to regimens combining FU/LV with the same agents in patients with colorectal cancer. In metastatic breast cancer patients who had received prior treatment with an anthracycline-based regimen, a Phase III trial comparing the combination of capecitabine with docetaxel versus docetaxel alone demonstrated superior objective tumor RR (42% vs 30%, \( P = 0.006 \)), median TTP (6.1 months vs 4.2 months, \( P < 0.001 \)), and median OS (14.5 months vs 11.5 months, \( P = 0.013 \)) with the combination treatment. Noncomparative Phase II studies have also supported efficacy in patients with metastatic breast cancer pretreated with both anthracyclines and taxanes, yielding an overall RR of 15% to 29% and median OS of 9.4 to 15.2 months. The most common dose-limiting adverse effects associated with capecitabine monotherapy are hyperbilirubinemia, diarrhea, and hand-foot syndrome. Myelosuppression, fatigue and weakness, abdominal pain, and nausea have also been reported. Compared with bolus FU/LV, capecitabine was associated with more hand-foot syndrome but less stomatitis, alopecia, neutropenia requiring medical management, diarrhea, and nausea. Capecitabine has been reported to increase serum phenytoin levels and the international normalized ratio in patients receiving concomitant phenytoin and warfarin, respectively. The dose of capecitabine approved by the US Food and Drug Administration (FDA) for both metastatic colorectal and breast cancer is 1250 Mg/M\(^2\) given orally twice per day, usually separated by 12 hours for the first 2 weeks of every 3-week cycle.

REFERENCES
