



Florida
CHAPTER



5-FU and Capecitabine

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CANCER BACKGROUND

Fluorouracil (5-FU) is a key agent in the treatment of many GI tract adenocarcinomas. It is a fluoropyrimidine antimetabolite agent. Combined with surgical resection, 5-FU offers an impressive absolute risk reduction of 5-year mortality in gastric cancer. However, it can result in a significant number of systemic and cardiac toxicities. It is generally used in combination regimens (FOLFOX, FOLFIRI), and in combination with other agents. Capecitabine, an oral agent that is metabolized to 5 FU is also widely utilized in colo-rectal, gastric and breast cancer. The incidence of cardio-toxicity of 5 FU varies: 2-3% in patients without coronary artery disease (CAD) and 10-15 % in patients with CAD.

ADVERSE EFFECTS

Mechanism of action in cardio-toxicity involves vasoconstriction of vascular smooth muscle cells via activation of protein kinase C. Coronary vasospasm, endothelial dysfunction and thrombosis can result in silent ischemia, angina, ST-T abnormalities and wall motion abnormalities. Acute coronary syndrome with positive troponin is also possible. QT prolongation, torsades, bradycardia and ventricular arrhythmias can also be present. Holter monitors during infusions show ST depression in > 50 % of patients. Cardio-toxicity is present in 7-18 %

with continuous infusions and only in 1.6 to 3 % of patients receiving shorter bolus treatments.

RECOMMENDATIONS

Cardio toxicity more commonly occurs during the first cycle, with mean time to symptoms of 12 hours after initiation of infusion although it can occur as late as after 48 hours post infusion. Consider risk stratification prior to initiation of treatment (CAD, prior chest radiation and renal failure are risk factors for 5-FU cardio-toxicity). In 50-90 % of patients treatment with calcium channel blockers and nitrates is quite effective, and high-risk patients should be pretreated (MSKCC algorithm). Treatment with short bolus as opposed to infusion also reduces the risk of cardio-toxicity. High risk patients with previous non-life threatening cardio-toxicity can be considered for pre-treatment and monitoring on telemetry as inpatients. Those with life-threatening episodes should not be re-challenged.

DATA TO SUPPORT

Sorrentino, M., Kim J., Foderaro A., Truesdell A. 5-FU induced cardio-toxicity. Review of the literature. *Cardiol Journal* 2012; 19: 453-458
Jensen S, Sorensen J. Risk factors and prevention of cardio-toxicity induced by 5 FU and capecitabine. *Cancer Chemother Pharmacol*, 200;58:487-493

INDICATIONS

Colorectal cancer either neo-adjuvant, adjuvant therapy, also for metastatic disease.

Gastric cancer as first- and second-line therapy.

Pancreatic cancer in different stages
Advanced breast cancer in HER2 negative LN positive patients, also in metastatic cancer and in CMF regimen (cyclophosphamide, methotrexate, fluorouracil)

ONCOLOGY COMMENTS

5 FU most common toxicities include diarrhea, mucositis, esophagitis, proctitis, alopecia, myelosuppression (neutropenia and thrombocytopenia) and immunosuppression, all of them with an incidence of 10 % or more. Thrombophlebitis is less than 10% but needs to be considered given increased thromboembolic risk in this population.

