Positive Quality Intervention: Capecitabine (Xeloda®): A New Approach to Dosing and Side Effect Management

Description: The purpose of this PQI is to compare different dosing regimens of capecitabine to assess efficacy and tolerability in patients with metastatic breast cancer. Patients are living longer as more effective agents become available and will be on therapy for longer periods of time. As these agents prolong overall survival, it is equally important to balance patients' quality of life since goals of treatment are focused on palliative care.

Background: Capecitabine (Xeloda) is the prodrug of fluorouracil and undergoes hydrolysis in the liver and tissues to form the active pyrimidine antimetabolite. Capecitabine is indicated for multiple indications such as metastatic breast cancer, colorectal cancer, gastric, esophageal, or gastroesophageal junction cancer, and pancreatic cancer. In metastatic breast cancer, capecitabine is prescribed at the FDA approved dose of 1250mg/m^2 orally twice daily, for 14 days followed by 7 days off (Standard Dose – SD).[1-2] This dosing regimen is associated with a high discontinuation rate due to poor tolerance. The X-7/7 trial suggests using a fixed dose (FD – 1500mg twice daily), dose dense (7 days on, 7 days off) schedule may be optimal for maintaining efficacy while decreasing the need for dose reductions and discontinuation due to toxicity.[1] While there was no significant difference in progression free survival when comparing FD and SD, the data did show statistically significantly less diarrhea, hand-and-foot syndrome, and mucositis, including Grade 2-4 toxicities in the FD group.[1]

Hand-and-foot syndrome (HFS) is a common dose-dependent toxicity of capecitabine which often leads to dose reductions or discontinuation and impairment of quality of life. HFS is characterized by painful erythema and edema of the hands and feet and varying degrees of dysesthesia followed by skin desquamation.[3-4] A hypothesized mechanism of capecitabine-induced HFS is the upregulation of COX-2 expression. Celecoxib (a COX-2 inhibitor) may be an option for the prevention of HFS, but its practical use is limited due to associated cardiotoxicity.[3-4] Topical 1% diclofenac gel, a localized COX-2 inhibitor, has been studied in the D-TORCH clinical trial to determine its efficacy in preventing capecitabine-induced HFS without causing systemic toxicity as shown with celecoxib. When applied prophylactically twice a day, 1% diclofenac gel was associated with significantly less HFS, of any grade, when compared to placebo. This finding was observed across all subgroups (breast and GI cancers; males and females) and capecitabine dose reductions were less frequent in the diclofenac arm compared to placebo.[3-4] The D-TORCH trial established topical diclofenac as the new standard of care to prevent capecitabine-induced HFS.

PQI Process:

- **Capecitabine 7/7 Fixed Dosing**
  - Educate providers and appropriate clinical staff on new dosing schedule
  - Ensure EMR to include both regimens for capecitabine: fixed dose and standard dose
  - Implementation of clinical interventions on appropriate reassessments
    - Potential to change from standard dosing to fixed dosing as a new standard of care given the lack of tolerance to the standard dose regimen
- **Topical 1% Diclofenac Gel**
  - Identify patients on capecitabine
    - Provide new education to patients who are already on treatment with capecitabine
  - Implement the addition of 1% diclofenac gel in the supportive care kit or recommend patients to purchase over the counter equivalent

Capecitabine Dose Modifications due to Hand-and-Foot Syndrome (HFS)[2]

	Characterization	Impact on therapy
Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling, or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities	Continue current therapy
Grade 2	Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living	Capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1 Following grade 3 hand-and-foot syndrome, subsequent doses of capecitabine should be decreased
Grade 3	Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living	

Patient Centered Activities:

- Provide Treatment Support Kit (TSK)
- **Capecitabine 7/7 Fixed Dosing**
    - Review patient tolerability at least every 21 days through reassessment nurses/adherence team
    - Cross reference patient tolerability with medical record for documented side effects or dose reductions
    - Implement pharmacists intervention/triage clinics to discuss possible change in capecitabine schedule due to tolerance
- **Topical 1% Diclofenac Gel**[5]
    - A dosing card is supplied by the manufacturer and should be used for each application
        - Apply 2g of gel to both hands twice a day[4] – gently massage into the skin ensuring application to the entire hand
    - Counseling Pearls
        - Avoid washing hands for at least 1 hour after application
        - Do not apply to open wounds, do not apply external heat or occlusive dressings, do not put gloves on for at least 10 minutes after applying
        - Should not be used with sunscreen, cosmetics, lotions, moisturizers, insect repellants or other topical medications on the hands concomitantly
        - Should not be administered in patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs
    - Counsel patients on how to obtain topical diclofenac over the counter if they do not already have on hand
    - Counsel patients on the importance of preventing HFS from the beginning and how to avoid additional triggers
    - Recommend that patients immediately report any new or worsening of symptoms

References:

1. Khan, Q., Bohnenkamp, C., Monson, T., et al. (2023). Randomized trial of fixed dose capecitabine compared to standard dose capecitabine in metastatic breast cancer: The X-7/7 trial. Journal of Clinical Oncology, 41(16_suppl), 1007–1007. https://doi.org/10.1200/jco.2023.41.16_suppl.1007.
2. Capecitabine [Package Insert] Revised 2022.
3. Santhosh, A., Batra, A., Kumar, A., et al. (2023). Randomized double-blind, placebo-controlled study of topical diclofenac in prevention of hand-foot syndrome in patients receiving capecitabine. Journal of Clinical Oncology, 41(16_suppl), 12005–12005. https://doi.org/10.1200/jco.2023.41.16_suppl.12005.
4. Santhosh, A., Kumar, A., Pramanik, R., et al. (2022). Randomized double-blind, placebo-controlled study of topical diclofenac in the prevention of hand-foot syndrome in patients receiving capecitabine (the D-TORCH study). Trials, 23(1), 420. https://doi.org/10.1186/s13063-022-06353-2.
5. Diclofenac [Package Insert] Revised 2016.
6. Active Clinical Trial - https://clinicaltrials.gov/study/NCT02595320.