Self-Study Chapter 3: Strategies to Improve Treatment Adherence

Introduction

In this activity, participants will review strategies to improve treatment adherence in patients with HER2+ metastatic breast cancer.

Q1: Pretest Question

Tucatinib/capecitabine/trastuzumab combination therapy requires patient education to minimize the dose-limiting potential of which most common side effect?

a) **Diarrhea**
b) Neutropenia
c) Rash
d) Fever

Commentary

Diarrhea is the most common side effect of the tucatinib/capecitabine/trastuzumab combination and can be dose-limiting.[1] Patient education can help mitigate the diarrhea and reduce the need for dose reduction.

Meet ML, a 59-year-old woman

ML is a 59-year-old woman. In 2014, she was diagnosed with stage IIA left breast invasive ductal carcinoma that was estrogen receptor negative, progesterone receptor negative, HER2+. She received neoadjuvant docetaxel/carboplatin/trastuzumab/pertuzumab. She underwent a bilateral total mastectomy and completed one year of trastuzumab. In 2019, she was found to have lung and liver metastases. Liver biopsy confirmed estrogen receptor negative, progesterone receptor negative, HER2+ invasive ductal carcinoma. She received first line docetaxel/trastuzumab/pertuzumab followed by trastuzumab/pertuzumab. She was on trastuzumab/pertuzumab for 12 months before disease progression in the liver. She was subsequently started on 2nd line ado-trastuzumab emtansine. After 3 months, she developed brain metastases and underwent stereotactic radiation. She continued ado-trastuzumab emtansine for 5 more months and then experienced further liver progression. She has been recommended to start treatment with tucatinib, capecitabine, and trastuzumab. She is 68 inches tall and weighs 50 kg, with a BSA of 1.55 m^2.

What now?

Logistically, the first step would be to submit the orders for tucatinib and capecitabine to specialty pharmacy and submit authorization to insurance. The specialty pharmacy would then contact the patient to discuss delivery and co-pay.[2] The patient should be instructed that this process happens every month and that they should answer phone numbers they don't recognize, as it could be from specialty pharmacy.

If the medication co-pay is too high, then specialty pharmacy will refer the patient to a foundation for assistance.[3] If no foundation money is available, then specialty pharmacy can help the patient apply for free drugs through the manufacturer. Of note, the manufacturer will always want the patient to apply for foundation assistance first, prior to applying for free drugs. If free drugs are approved, the drug will likely ship straight from the manufacturer, and it may take up to 1-2 weeks for the patient to receive delivery.

What, when, how

The starting dose for tucatinib is 300 mg BID, administered as 150 mg or 50 mg tablets. Tucatinib doses should be taken 12 hours apart, with or without food.[4] In regard to capecitabine, tucatinib should be taken with or without capecitabine and the patient should continue to take tucatinib during the week off capecitabine.

This patient's capecitabine dose is 1500 mg BID, administered as 500 mg tabs. It should be taken twice daily with food for 14 days, then off for 7 days while tucatinib continues.

Trastuzumab is given every 21 days at 6 mg/kg after an initial loading dose of 8 mg/kg. This should fall on the patient's first day back on capecitabine; the patient would receive all 3 drugs on that day.

Tucatinib should be stored in its original packaging rather than a pill case. This is due to the desiccant in the packaging, with the secondary benefit of keeping the drugs separate in the patient's mind, as they do look similar.

Patients should be instructed not to chew, crush, or split the tablets. Do not take the medication if the package or tablets are broken or cracked.[4] If the patient vomits or misses a dose of either oral medication, he/she should wait until the next scheduled dose to take another dose.[4]

If ML has diarrhea, what instructions should you provide?

If the patient develops diarrhea, have them take an over-the-counter anti-diarrheal. Diarrhea usually occurs about 12 days after starting therapy. With an anti-diarrheal, symptoms typically resolve in 3-8 days. Providers can consider adding prescription anti-diarrheals such as diphenoxylate/atropine or colestipol, which is a bile acid sequestrant that can help manage diarrhea without the potential resultant constipation associated with Lomotil. Dietary modifications for diarrhea include avoiding spicy, fatty or greasy, and high-fiber foods.[3] If diarrhea persists and the patient continues having >4 stools/day over baseline, consider dose reduction.

Capecitabine has about 57% incidence of diarrhea, while tucatinib has about 81% incidence of diarrhea; therefore, both drugs may have to be dose reduced. Depending on the severity of diarrhea, consider dose reducing one at a time or both concurrently. There is a higher risk of diarrhea in patients older than 65.

What should you consider if ML has nausea?

The question to consider is which drug is more likely to be causing the nausea. Tucatinib has a slightly higher incidence of nausea and vomiting. It is important to investigate the timing of the medications in relation to the onset of nausea.[3] You may also consider evaluating the patient's tolerance of food.

Dose reductions of tucatinib and capecitabine may be necessary. Depending on the severity of nausea, dose reduce one at a time or both concurrently.

These are patients who have been treated in the past and typically have insight into their symptoms.[5]

Below is a sample schedule of medications and symptom management:

	Upon Waking	Immediately post-breakfast	Lunch	Pre-dinner	Immediately post-dinner	Evening	Bedtime
Tucatinib		X					X
Capecitabine		X			X		
Ondansetron	X			X		X	
Loperamide		X	As Needed		X		X

Adapted by UPMC Hillman Cancer Center from TUKYSA_Treatment_Tracker.pdf (seagendocs.com)

What should you consider if ML has Palmar-plantar erythrodysesthesia (PPE) syndrome?

PPE with the tucatinib/capecitabine combination is worse than with capecitabine alone, but tucatinib does not have to be dose reduced if a dose reduction is required for PPE.[4]

PPE can prevent daily activities if patients are unable to use their hands and if their feet are in pain.

Certain topical medications can help prevent PPE, such as topical urea 10% or essential oils like Helichrysum that can help with skin repair. Other lifestyle modifications include aggressive moisturizing of extremities throughout the day and using ice baths for hands and feet after vigorous activity or strenuous use.[3]

The skin's appearance does not always equate to the severity of pain; therefore, providers need to assess the patient's tolerance of daily activities. In Black patients, PPE can present as thickening of the skin, keratoderma, instead of desquamation. There is an increased risk of severe PPE in patients with poor perfusion.

Dose reductions

The levels of dose reduction for tucatinib are as follows:[4]

- First dose reduction: 250 mg orally twice daily
- Second dose reduction: 200 mg orally twice daily
- Third dose reduction: 150 mg orally twice daily

Tucatinib should be permanently discontinued in patients unable to tolerate 150 mg orally twice daily.

Dose reductions for capecitabine are as follows:

- First dose reduction: 75% of initial dose
- Second dose reduction: 50% of initial dose

Summary

Patient education, along with care coordination and communication within the interprofessional team, can help to mitigate side effects and improve treatment adherence.[3,5]

Q2: Post-test

Tucatinib/capecitabine/trastuzumab combination therapy requires patient education to minimize the dose-limiting potential of which most common side effect?

a) **Diarrhea**
b) Neutropenia
c) Rash
d) Fever

Commentary

Diarrhea is the most common side effect of the tucatinib/capecitabine/trastuzumab combination and can be dose-limiting.[1] Diarrhea was the most common adverse event, and most events of diarrhea were of grade 1 (in 43.3% of the patients) or grade 2 (in 24.8%, respectively); diarrhea of grade 3 or higher occurred in 12.9%.[1] Patient education can help mitigate the diarrhea and reduce the need for dose reduction.

Thank you for completing this 3rd Self-Study chapter. You can now move on to the Final Assessment module.

References:

1. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med.* 2020;382:597-609.
2. Oral Oncolytics. Association of Community Cancer Centers. https://www.accc-cancer.org/Pages-from-Migration/ACCC-NEWER-Import/oral-oncolytics/implementation-tools/oral-oncolytics. Last accessed April 23, 2021.
3. Oral Adherence Toolkit. Oncology Nursing Society. https://www.ons.org/clinical-practice-resources/oral-adherence-toolkit. Last accessed April 23, 2021.
4. TUKYSA® (tucatinib) [prescribing information]. Bothell, WA: Seattle Genetics, Inc.; Approved 2020. Revised April 2020.
5. Shared Decision Making. National Patient Advocate Foundation. https://www.npaf.org/roadmap/shared-decision-making/. Last accessed April 23, 2021.