Chapter 2: Treatment-related Adverse Events

Introduction:

In the past few years, several new targeted therapies have been added to the treatment landscape for HER2+ breast cancer.[1] While effective, these therapies can have significant toxicities that need to be closely managed. In this activity, participants will examine solutions for monitoring and managing treatment-related adverse events in patients with HER2+ breast cancer who are receiving novel targeted therapies.

Q1: Which of the following is TRUE regarding adverse events associated with trastuzumab deruxtecan?

a) Low emetogenic potential
b) Associated with peripheral neuropathy
c) Associated with hepatotoxicity
d) Associated with interstitial lung disease

Commentary
Trastuzumab deruxtecan is moderately emetogenic and not associated with peripheral neuropathy or hepatotoxicity. In the DESTINY trial, 13.6% of patients treated with trastuzumab deruxtecan reported interstitial lung disease (ILD).[2]

SH Patient Case
SH is a 53-year-old female with ER/PR-, HER2+ metastatic breast cancer. She is s/p 9 cycles of docetaxel/pertuzumab/trastuzumab and 6 cycles of trastuzumab emtansine. Recent scans indicate progressive bone disease and a new, small lesion in the liver. A brain MRI was performed and was negative for any brain involvement. The medical oncologist orders the next line of therapy to be trastuzumab deruxtecan. After 4 cycles, her CT scan demonstrates partial response in her liver. After cycle 5, the patient develops moderate dyspnea upon walking from her bedroom to the kitchen. She is due for cycle 6 next week. Her ECHO, performed prior to cycle 5, shows an LVEF of 60%.

Challenge Question
What are symptoms of ILD?
a) Cough
b) Dyspnea
c) Fever
d) New or worsening respiratory symptoms
e) All of the above

Commentary
The symptoms of ILD include cough, dyspnea, fever, and other new or worsening respiratory symptoms. Patients should be instructed to immediately report these symptoms.

Ask your patient the following questions to determine if she should be worked up for ILD.

- Have you been coughing recently? Is it a dry cough?
- Have you had any shortness of breath, especially during or after physical activity?
- Have you experienced any new breathing or respiratory problems?
- If you already have respiratory problems, have they gotten worse?
- Have you had a fever?
- Have you been feeling tired?
- Have you lost weight?

Q3: Challenge Question
If ILD is suspected, which test(s) should be ordered?

a) High-resolution CT
b) Pulmonologist consultation (infectious disease consultation as clinically indicated)
c) Blood culture and CBC
d) Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
e) Pulmonary function tests and pulse oximetry
f) All of the above

Commentary
If a patient demonstrates radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms (dyspnea, cough, or fever), it is necessary to rule out ILD/pneumonitis by conducting a thorough workup. Providers should obtain a high-resolution CT, blood cultures, CBC panel, pulmonary function tests, and pulse oximetry. A pulmonology consultation should be obtained, as well as an infectious disease consultation if clinically indicated. Bronchoscopy and bronchoalveolar lavage can be considered if clinically indicated and feasible.[1]

Severity	Description (NCI-CTCAE Grading)
Grade 1	Asymptomatic, clinical, or diagnostic observations only
Grade 2	Symptomatic, limiting instrumental activities of daily living
Grade 3	Severe symptoms, limiting self-care activities of daily living; oxygen indicated
Grade 4	Life-threatening respiratory compromise
Grade 5	Death

Reference

Q4: Challenge Question

What is the incidence and severity of ILD reported with trastuzumab deruxtecan?

a) 3.7% of patients had ILD, which was predominantly grade 1 or 2
b) 6.3% of patients had ILD, which was predominantly grade 1 or 2
c) 13.6% of patients had ILD, which was predominantly grade 1 or 2
d) 36.3% of patients had ILD, which was predominantly grade 1 or 2
e)

Commentary

In the DESTINY-Breast01 trial, 13.6% of patients had ILD, which was predominantly grade 1 or 2. Therapy discontinuation due to AEs was primarily related to pneumonitis and ILD.[2]

Q5: Challenge Question

What is the median onset of ILD from trastuzumab deruxtecan?

a) 4 days
b) 2 weeks
c) 4 months
d) 4 weeks

Commentary

In the DESTINY-Breast01 trial, the median time to onset of ILD was 4 months.[2]

Q6: What is the most appropriate management of ILD in the case of SH?

Refer to the table below for guidance on specific management recommendations for Grade 2 or greater ILD, along with other pertinent details for patients receiving fam-trastuzumab deruxtecan-nxki.[3]

CTCAE Grading for ILD
Asymptomatic ILD (Grade 1)
▪ Consider corticosteroid treatment (>/= 0.5mg/kg prednisolone or equivalent)
▪ Interrupt trastuzumab deruxtecan until ILD resolves to grade 0 ▪ If resolved in 28 days or less from date of onset, maintain the same dose ▪ If resolved in more than 28 days from date of onset, reduce dose one dose level
Symptomatic ILD (Grade 2 or greater)
▪ Promptly initiate corticosteroid treatment (>/= 1mg/kg prednisolone or equivalent) ▪ Upon improvement, follow by gradual taper of steroids (4 weeks) ▪ Permanently discontinue trastuzumab deruxtecan

Most common any grade AEs	Nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough, thrombocytopenia	
Most common grade 3/4 AEs	Neutropenia, anemia, nausea, leukopenia, fatigue, vomiting, hypokalemia, thrombocytopenia, interstitial lung disease, diarrhea	
Warnings/ Precautions	▪ ILD: Monitor closely for respiratory symptoms; discontinue therapy for grade >/= 2 ILD/pneumonitis ▪ Neutropenia: Monitor CBC prior to each dose; hold therapy or reduce dose as needed ▪ LVEF dysfunction: Assess LVEF regularly; hold therapy or discontinue based on severity; permanently discontinue for symptomatic CHF	
Dose modifications for general AEs	Starting dose: 5.4 mg/kg 1st reduction: 4.4 mg/kg 2nd reduction: 3.2 mg/kg Requirement for further dose reduction: Discontinue therapy	
Dose modifications for ILD/ pneumonitis	Asymptomatic ILD/ pneumonitis	▪ Consider corticosteroid treatment ▪ Interrupt therapy until resolved to grade 0, then: o If resolved in </= 28 d, maintain dose o If resolved in > 28 d, reduce dose
	Symptomatic ILD/ pneumonitis	▪ Initiate corticosteroid treatment ▪ Discontinue therapy
Dose modifications for neutropenia	Grade 3 neutropenia	▪ Interrupt therapy until resolved to </= grade 2, then maintain dose
	Grade 4 neutropenia	▪ Interrupt therapy until resolved to </= grade 2, then reduce dose
	LVEF > 45% and absolute decrease from baseline of	▪ Continue treatment

Dose modifications for left ventricular dysfunction	10%-20%	
	LVEF 40%-45% and absolute decrease from baseline < 10%	▪ Continue treatment ▪ Repeat LVEF assessment within 3 weeks
	LVEF 40%-45% and absolute decrease from baseline 10%-20%	▪ Interrupt therapy ▪ Repeat LVEF assessment within 3 weeks ▪ If LVEF does not recover to within 10% from baseline, discontinue therapy ▪ If LVEF recovers to within 10% from baseline, resume at same dose
	LVEF < 40% or absolute decrease from baseline > 20%	▪ Interrupt therapy ▪ Repeat LVEF assessment within 3 weeks ▪ If LVEF of < 40% or absolute decrease from baseline > 20%, discontinue therapy
	Symptomatic CHF	▪ Discontinue therapy

SH continued: Neratinib and Diarrhea
The medical oncologist discontinues trastuzumab deruxtecan secondary to toxicity and orders neratinib/capecitabine for SH's next line of therapy.

Which additional supportive care drug would you recommend SH to start concurrently with neratinib/capecitabine?

Diarrhea is an important consideration for patients taking neratinib. The majority of patients (83.2%) had diarrhea. Based on data from the phase 2 CONTROL study, prophylactic antidiarrheal therapy is now recommended for all patients treated with neratinib.[6] In the NALA study, prophylactic loperamide was given during cycle 1 and 24% of patients receiving neratinib/capecitabine reported grade 3 diarrhea, with a median time to onset of 11 days and duration of 4 days.[4] Patients should be counseled to initiate antidiarrheal prophylaxis with loperamide when starting neratinib and to continue loperamide for at least 8 weeks, then titrate the loperamide to maintain 1 to 2 bowel movements per day.[5] Patients also need to be educated regarding the risk of diarrhea and the importance of reporting any changes in the frequency of bowel movements to their healthcare team.

Q7: Challenge Question

At her 2-week telemedicine follow-up visit, SH complains of 5-7 loose stools per day for 6 days. She states she is taking loperamide as prescribed. What is the most appropriate management strategy for SH's diarrhea?

a) Assess need for hydration and electrolyte replacement
b) Interrupt therapy (neratinib/capecitabine)
c) Add either budesonide or colestipol to loperamide therapy
d) If diarrhea resolves in <7 days, may restart both agents w/o dose modification; if >7 days, restart neratinib at reduce dose and continue capecitabine
e) All of the above

Commentary

The most appropriate management strategy for SH's diarrhea is to assess the need for hydration and electrolyte replacement, interrupt neratinib/capecitabine therapy, and add either budesonide or colestipol to loperamide therapy.[6] If the diarrhea resolves in <7 days, both agents may be restarted without dose modification, but if the diarrhea persists >7 days, then restart neratinib at a reduced dose and continue capecitabine.

Neratinib + Capecitabine[5]	
Most common any grade AEs	Diarrhea, nausea, vomiting, decreased appetite, constipation, fatigue/asthenia, decreased appetite, weight decreased, dizziness
Most common grade 3/4 AEs	Diarrhea, fatigue/asthenia, nausea, vomiting, decreased appetite, renal impairment, constipation
Warnings/ Precautions	**Diarrhea**: administer loperamide prophylaxis; aggressively manage diarrhea with antidiarrheals, fluids, and electrolytes; hold for persistent or severe diarrhea; reduce dose or discontinue based on severity. **Hepatotoxicity**: monitor LFTs monthly for first 3 months, then every 3 months; hold for grade 3 and discontinue for grade 4 liver abnormalities.
Dose modifications for general AEs	▪ Hold for grade 3, then resume at next lower dose upon recovery to </= grade 1 ▪ Discontinue for grade 4 **Starting dose: 240 mg daily** **1st reduction: 160 mg daily** **2nd reduction: 120 mg daily**

Antidiarrheal prophylaxis with loperamide	**Weeks 1-2:** 4 mg 3 times daily **Weeks 3-8:** 4 mg 2 times daily **Weeks 9-52:** 4 mg as needed; titrate dosing to achieve 1-2 bowel movements/day	
Dose modifications for diarrhea	**Diarrhea grade** Grade 1; Grade 2 lasting </= 5 d; Grade 3 lasting </= 2 d	▪ Adjust antidiarrheal therapy, diet modifications, and increased fluid intake ▪ Continue therapy at same dose After resolution to </= grade 1, give loperamide 4 mg with each dose
	Diarrhea grade Grade 2 lasting > 5 d; Grade 3 lasting > 2 d Grade 4	▪ Interrupt therapy ▪ Diet modifications and increased fluid intake ▪ If diarrhea resolves in </= 1 week, resume at same dose ▪ If it resolves in 1-3 weeks, reduce neratinib dose and maintain capecitabine dose ▪ For subsequent events, alternate reducing the dose of neratinib or capecitabine Give loperamide 4 mg with each dose
Dose modifications for hepatotoxicity	**Grade 3 ALT, AST, or bilirubin:** ▪ Hold until recovery to </= grade 1 and evaluate alternative causes ▪ Resume neratinib at the next-lower dose if recovery occurs within 3 weeks. If grade 3 ALT or bilirubin recurs, permanently discontinue therapy. **Grade 4 ALT, AST, or bilirubin:** ▪ Permanently discontinue neratinib and evaluate alternative causes	

SH continued: Tucatinib and Hepatoxicity and Diarrhea

After 4 cycles of neratinib/capecitabine, SH has progression of disease in the CNS as well as new liver lesions. Her ECOG performance status is 1. The medical oncologist orders tucatinib/capecitabine/trastuzumab therapy. Her repeat ECHO shows an LVEF of 60%. She has LFT abnormalities with a total bilirubin of 2.5 mg/dL, elevated ALT of 75 U/L and AST of 100 U/L, and an Alk Phos of 150 U/L. The patient has a Child Pugh score of B. Her calculated creatinine clearance is 45ml/min.

Based on the above values, there are several dose adjustments recommended for this regimen. Capecitabine needs a dose adjustment due to the patient's reduced CrCl. Hepatic adjustments for tucatinib upon initiation of therapy would depend on the patient's Child Pugh score; if the Child Pugh score is C, then the dose of tucatinib should be reduced.[7] As this patient's Child Pugh score is B, her initial tucatinib dose does not need to be reduced. Since her ECHO is normal and has not changed over time, continuing trastuzumab is appropriate.

The most common AE reported in the HER2CLIMB trial was diarrhea, occurring in 81% of patients. The median time to onset of diarrhea was 12 days, and the median time to resolution was 8 days.[8]

SH is concerned with diarrhea and wants to take prophylactic loperamide; how do you respond?

In the HER2CLIMB study, antidiarrheal medication was not mandatory and the majority of diarrhea cases were low grade (43% grade 1 and 25% grade 2).[8] If diarrhea occurs, antidiarrheal therapy should be initiated, and tucatinib should be held; once diarrhea resolves, tucatinib should be dose reduced or discontinued based on the severity of diarrhea.

Tucatinib Safety[7]	
Most common any grade AEs	Diarrhea, PPE syndrome, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, rash
Most common grade 3/4 AEs	PPE syndrome, diarrhea, hepatotoxicity, fatigue, nausea, anemia, vomiting, stomatitis
Warnings/ Precautions	**Diarrhea**: Monitor closely, administer antidiarrheal treatment as indicated. Hold therapy for grade 3 diarrhea, reduce dose or discontinue based on severity. **Hepatotoxicity**: Monitor ALT, AST, and bilirubin; interrupt dose, then reduce dose or discontinue based on severity.
Dose modifications for	▪ Hold for grade 3 until recovery to </= grade 1, then resume at next-lower dose

general AEs	▪ Discontinue for grade 4 Starting dose: 300 mg twice daily 1st reduction: 250 mg twice daily 2nd reduction: 200 mg twice daily 3rd reduction: 150 mg twice daily	
Dose modifications for diarrhea	Diarrhea grade 3 without anti-diarrheal treatment	▪ Initiate or intensify appropriate medical therapy. ▪ Hold tucatinib until recovery to grade </= 1, then resume at same dose.
	Diarrhea grade 3 with anti-diarrheal treatment	▪ Initiate or intensify appropriate medical therapy. ▪ Hold tucatinib until recovery to grade </= 1, then resume at next lower dose.
	Diarrhea grade 4	▪ Permanently discontinue
Dose modifications for hepatotoxicity	Grade 2 bilirubin	▪ Hold tucatinib until recovery to grade </= 1, then resume at same dose.
	Grade 3 ALT, AST, or bilirubin	▪ Hold tucatinib until recovery to grade </= 1, then resume at next lower dose.
	Grade 4 ALT, AST, or bilirubin Or ALT or AST > 3 X ULN AND bilirubin > 2 X ULN	▪ Permanently discontinue

Summary

With the increasing number of novel HER2+ therapies for patients with breast cancer, it is becoming more important to monitor and manage treatment-related adverse events to ensure treatment adherence.

Q8: Post-test:
Which of the following is TRUE regarding adverse events associated with trastuzumab deruxtecan?

a) Low emetogenic potential
b) Associated with peripheral neuropathy
c) Associated with hepatotoxicity
d) Associated with interstitial lung disease

Trastuzumab deruxtecan is moderately emetogenic and not associated with peripheral neuropathy or hepatotoxicity. In the DESTINY trial, 13.6% of patients treated with trastuzumab deruxtecan reported interstitial lung disease (ILD).[1]

Thank you for completing this 2nd Self Study Chapter. You can now move on to Self-Study Chapter 3.

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