Management of Breast Cancer Patients on Targeted Therapy

LAURA QUINTAL, PHARM.D., BCOP

PHARMACIST – ONCOLOGY | INVESTIGATIONAL DRUGS SERVICES

UCSF HELEN DILLER COMPREHENSIVE CANCER CENTER

Breast Case – Her-2 directed therapy

CS is a 59 yo postmenopausal patient with *de novo* HR-/HER2+ MBC involving liver, lung, bone, back in 2015

- Initial treatment: T (docetaxel) HP (trastuzumab, pertuzumab) x 7 cycles, followed by maintenance HP for 15 months
- Subsequent: ado-trastuzumab-emtansine (TDM-1) for 6 months

Developed CNS metastasis:

- Subsequent: clinical trial involving capecitabine, and tucatinib or placebo

After progression, started on:

- Current regimen: capecitabine, neratinib*, and trastuzumab

CS is presents to clinic today with complaints about diarrhea while on neratinib

- She is experiencing 5 bowel movements per day but otherwise feels fine

* Neratinib currently only FDA-approved for use as adjuvant treatment in early stage HER2 positive breast cancer, following trastuzumab-based therapy

Neratinib – Diarrhea management

- Happens early on when starting – educate patients to recognize it
- Studied prophylaxis regimens:

Medication	Administration
Loperamide Anti-diarrheal	- 4mg initial dose - 4mg TID on days 1-14 - 4mg BID on days 15-56, then prn
Budesonide Anti-inflammatory	- 9mg daily (extended release) - Administer in combination with loperamide
Colestipol Bile acid sequestrant	- 2g BID for 28 days - Taken either 4 hours before or 2 hours after neratinib - Administer in combination with loperamide per above schedule or prn

- Dose escalation for prophylaxis

Neratinib – Diarrhea management

Severity of Diarrhea*	Action
• Grade 1 diarrhea [increase of < 4 stools per day over baseline] **• Grade 2 diarrhea [increase of 4-6 stools per day over baseline] lasting <5 days** **• Grade 3 diarrhea [increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting ≤2 days**	• Adjust antidiarrheal treatment • Diet modifications • Fluid intake of ~2 L should be maintained to avoid dehydration • Once event resolves to ≤Grade 1 or baseline, start loperamide 4 mg with each subsequent neratinib administration
• Any grade with complicated features† **• Grade 2 diarrhea lasting 5 days or longer‡** **• Grade 3 diarrhea lasting longer than 2 days‡**	• Interrupt neratinib treatment • Diet modifications • Fluid intake of ~2 L should be maintained to avoid dehydration • If diarrhea resolves to Grade 0-1 in one week or less, then resume neratinib treatment at the same dose. • If diarrhea resolves to Grade 0-1 in longer than one week, then resume neratinib treatment at reduced dose • Once event resolves to ≤Grade 1 or baseline, start loperamide 4 mg with each subsequent neratinib administration
• Grade 4 diarrhea [life-threatening consequences; urgent intervention indicated]	• Permanently discontinue neratinib treatment
• Diarrhea recurs to Grade 2 or higher at 120 mg per day	• Permanently discontinue neratinib treatment

* Per CTCAE v4.0 ; † Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia ; ‡ Despite being treated with optimal medical therapy

- Keypoints:
  1. Diet modifications and maintain fluid intake
  2. Hold neratinib for complications
  3. Stop permanently for life threatening conditions

Barcenas et al: *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 548-548
Nerlynx [package insert]. Los Angeles, CA: Puma Technology, 2019.

Breast Case – Her-2 directed therapy

What is a therapy option for CS if she progresses?

- fam - trastuzumab deruxtecan - nxki (Enhertu®)
- Antibody drug conjugate: Her2 monoclonal antibody linked to topoisomerase inhibitor (DxD)
- DESTINY-01 Breast trial: improved tumor response rate and duration of tumor response

- What are some counseling points you want to discuss with her?
  - Nausea
  - Diarrhea
  - Neutropenia
  - Cardiac effects
  - Interstitial lung disease (ILD)

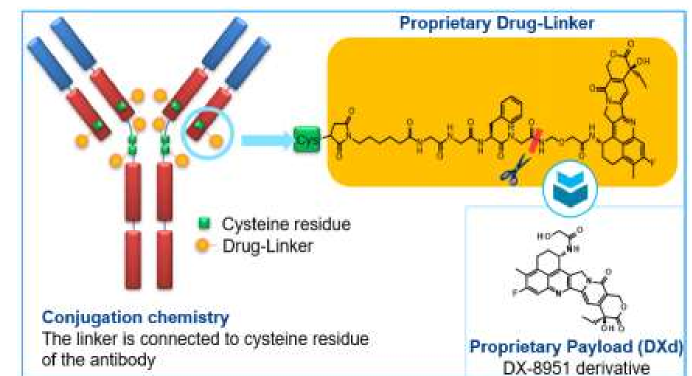

Image: https://www.astrazeneca.com/content/dam/az/PDF/2019/Strategic%20Collaboration%20Trastuzumab%20Deruxtecan%20DS-8201.pdf

Fam- trastuzumab deruxtecan-nxki – Interstitial Lung Disease

After 3 cycles, CS presents to clinic with complaints of a dry cough she has had for a week

Experiences SOB when she walks up a flight of stairs

No reports of fever, runny nose, congestion or other symptoms

- What is the next approach?
  - Rule out infectious process
  - Imaging: Chest X-ray, CT scan
- What to do with her therapy?
  - Continue or hold?
  - HOLD
- Treatment for ILD: corticosteroid treatment (≥ 1 mg/kg prednisone or equivalent)
  - Rechallenge?
  - Grade 2 – permanently discontinue
  - Grade 1 (asymptomatic) – if resolved in ≤ 28 days, maintain dose; if >28 days reduce one dose level

Image: https://www.astrazeneca.com/content/dam/az/PDF/2019/Strategic%20Collaboration%20Trastuzumab%20Deruxtecan%20DS-8201.pdf

Breast Case – PI3K Inhibitor Therapy

YY is a 44 yo postmenopausal (chemically) female with history of invasive ductal carcinoma

- s/p right mastectomy of 6.3 cm tumor and SLND found to be strongly ER+ / Her2-

- Received ddAC x 4, followed by dd-paclitaxel x 4 followed by radiation and tamoxifen

- 4 years later presented with back pain found to have biopsy proven ER+ / Her2-

- started on letrozole, palbociclib and denosumab for 2 years

After progression, found to have PI3KCA mutation (Guardant 360)

- Started on alpelisib, fulvestrant

Image: https://www.fiercepharma.com/pharma/novartis-double-good-news-day-saw-fda-nod-for-blockbuster-cancer-prospect-piqray

Alpelisib - Rash

- Often presents as pruritic, erythematous maculopapular
- Usually occurs within first 2 weeks of treatment
- High dose antihistamines shown to help reduce rates of rash in trials
  - Can consider using non-sedating antihistamine prophylactically
  - i.e. day before starting alpelisib and continue for at least one month of treatment
  - Can double the dose of antihistamine if develops a rash from daily to BID
- Steroids can be considered – topical, oral and even IV if severe enough
- Dose modifications if appropriate
- Tips for patients
  - Use alcohol- and perfume-free skin products
  - Use tepid water for bathing/showering
  - Use mild, unscented detergent to wash clothes and bedding
  - Wear loose clothing

Mayer IA et al, Clin Cancer Res. 2017 Jan 1;23(1):26-34.
Andre F et al, NEJM 2019 May; Mar, 380:1929-1940 (SOLAR-1)
Ando Y, et al. Cancer Sci. 2019 Mar; 110(3): 1021-1031

Alpelisib - Hyperglycemia

- Result of decreased glucose utilization and dysregulation of insulin activity
- Screen: Baseline fasting glucose (FBG) and hemoglobin A1C (HbA1c) before starting
  - FBG weekly for first two weeks then once every 4 weeks
  - HgbA1C every 3 months
- Patients with borderline glucose control appear at higher risk for developing
  - Home glucose monitoring
- Treat aggressively:
  - Initially start with metformin
  - Counsel on lifestyle changes: low carbohydrate diet, increased physical activity
- Consider co-management with a diabetes specialist for persistent hyperglycemia
- Alpelisib should only be interrupted if AE management is unsuccessful

Busaidy NL, et al. J Clin Oncol 2012;30:2919-28

Alpelisib - Diarrhea

- Occurs usually between cycle 1 & 2
- Proactive management at first sign of loose stool:
  - Rule out infectious or viral causes
  - Loperamide can be offered and used with typical dosing
- If severe enough consider dose interruption, reduction or discontinuation
- Tips for the patient:
  - Maintain hydration – do not want to progressing to acute kidney injury
  - Eat low-fiber foods and foods easy to digest (i.e. banana, rice, applesauce, toast)
  - Frequent and small meals
  - Clean the anal area with mild soap/ wipes after bowel movements and apply water-repellant ointment

Busaidy NL, et al. J Clin Oncol 2012;30:2919-28

UCSF Bakar Precision Cancer Medicine Building