

CASE REPORT

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Concurrent use of fam-trastuzumab-deruxtecan-nxki and larotrectinib in metastatic breast cancer: A case report

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ABSTRACT

A 60-year-old female presented in 2010 with left breast invasive lobular carcinoma, estrogen receptor (ER)+ (98%), progesterone receptor (PR)+ (98%), Her2 (2+), Ki67 (8%), Stage IIIC, T2 N3. She had lumpectomy, adjuvant chemo and radiation, took anastrozole until July 2019 when she had metastasis to bone. She started on palbociclib and fulvestrant. Imaging showed minimal improvement. In March 2022, her bone pain worsened and blood counts dropped and became transfusion dependent, bone marrow biopsy showed breast cancer metastases, ER+ (35%), PR–, Her2 (2+). PDL1 was negative, NTRK 1 was positive. She started on larotrectinib for her NTRK1 mutation, which showed some improvement and added fam-trastuzumab-deruxtecan-nxki for her Her2neu weekly positive, resulting in normalization of her blood counts. She has been on this combination which has never been reported, for over a year and has remained in remission with no significant toxicity. Targeting these two mutations simultaneously with possible additive effect can open some new trial ideas.

Keywords: Breast cancer leukemia, Breast cancer metastasis, Fam-trastuzumab-deruxtecan-nxki, Larotrectinib, Neurotrophic tyrosine receptor kinase (NTRK), Next-generation sequencing (NGS), Targetable mutations

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INTRODUCTION

Metastatic breast cancer poses significant challenges, particularly in cases with multiple mutations that require targeted therapy. Next-generation sequencing (NGS) has revolutionized the identification of genomic alterations, and more new targetable mutations are being identified, but questions remain on how to use these targeted therapies, which mutation combination to target at a time, in what order, and whether these should be targeted up front or later in treatment upon progression? Multitargeted therapy has been favored in oncology, for example, entrectinib (FDA approved for ROS1-positive metastatic non-small cell lung cancer in 2019) has been used in a study by De Braud et al. and Chen et al. to target TRK, ROS1, and ALK [1, 2]. In locally advanced or metastatic solid tumors with NTRK1/2/3, ROS1, and ALK gene fusion mutations, targeted therapy has shown unequivocal and durable response with minimal toxicity. This holds true even with the added benefit of blood brain barrier permeability allowing brain metastasis to be targeted.

Our case report presents a unique case of concurrent treatment with fam-trastuzumab-deruxtecan-nxki and larotrectinib in a patient with metastatic breast cancer who was weakly positive for both Her2neu and neurotrophic tyrosine receptor kinase 3 (NTRK) mutations. There are no current clinical trials on this combination. Case reports

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like this can initiate clinical trials to identify the efficacy and tolerability of combination therapy and even bring such therapies to an earlier stage of treatment—part of first line therapy.

The objective of this report is to show that concurrent use of fam-trastuzumab-deruxtecan-nxki and larotrectinib in a patient with metastatic breast cancer presenting with both Her2neu and NTRK mutations is tolerable, durable, and may have additive effects.

CASE REPORT

A 60-year-old female presented in 2010 with left breast invasive lobular carcinoma estrogen receptor (ER)+ (98%), progesterone receptor (PR)+ (98%), Her2 (2+), Ki67 (8%), positive for lymphovascular invasion and extranodal extensions, stage IIIC, T2 (4.5 cm), N3 (14/16 nodes positive). She had a lumpectomy with adjuvant chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel followed by radiation. After completion, she started and stayed on anastrozole until July 2019, when she had metastasis to bone (T11).

Bone biopsy showed metastatic breast cancer ER+ (10%), PR–, and Her2 (1+). Mismatch repair and PIK3CA testing could not be performed. She was most likely not responding to endocrine therapy due to the ER lobular cancer status becoming negative since the original biopsy in 2010, as patient pathology can change over time with gaining, or in her case, losing tumor expression. This is why every time there is a progression in cancer, a repeat biopsy is recommended.

Her treatment regimen was changed to palbociclib and fulvestrant. Imaging showed minimal improvement. Magnetic resonance imaging (MRI) in 2020 showed bilateral hip avascular necrosis with stress type reaction changes to the femoral head without evidence of metastasis. However, her metastatic disease precluded her from undergoing surgery.

In March 2022, her bone pain worsened and blood counts dropped (Figure 1), requiring multiple blood and platelet transfusions. She received an average of 1–3 units weekly, between March 10 and June 7 in 2022. A bone marrow biopsy showed 60% tumor infiltration consistent with primary breast cancer, ER+ (35%), PR–, and Her2 (2+). PDL1 was negative and NTRK1 was positive. PIK3 and remaining NGS could not be performed.

Her treatment regimen was changed to larotrectinib in April 2022, resulting in a decrease in the frequency of blood and platelet transfusions. In June 2022, fam-trastuzumab-deruxtecan-nxki was added resulting in normalization of her blood counts.

Since her cancer was well controlled, we referred her for hip replacement surgery which she underwent on March 24, 2023. Fam-trastuzumab-deruxtecan-nxki was stopped from February 23 to April 10, 2023, to avoid any surgery complication. Despite continuing with larotrectinib, her hemoglobin count showed a

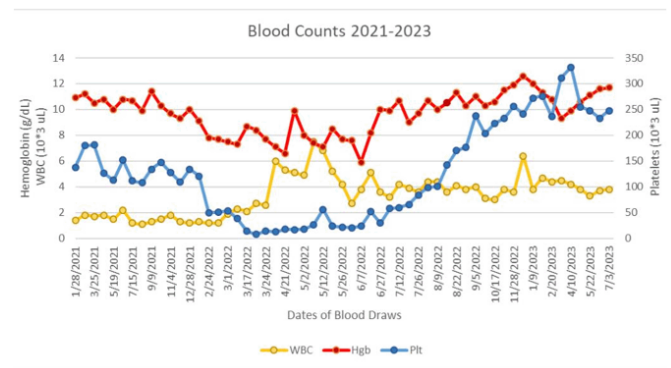


Figure 1: The trend of blood counts before and after the change in medications. Larotrectinib was started at the beginning of April 2022 and fam-trastuzumab deruxtecan-nxki was started in mid-June 2022 after which the counts consistently trend upward.

drop during the two months, reaching a nadir of 9.3 g/dL. This value rapidly rebounded after resuming fam-trastuzumab-deruxtecan-nxki postoperatively in April, showing additive effect of these two drugs combination.

DISCUSSION

This case is unique and brings up multiple area of discussion. First, her lobular, strongly positive ER cancer, after 10 years, became negative on repeat biopsy. This showed how important is to repeat biopsy upon progression as a liquid biopsy conducted in April 2023, failed to detect any variants, including ESR1.

Second, from diagnosis she was Her2neu 2+ and remained so, which brings up the question: if she would have had anti-Her2 and anti-NTRK inhibitor therapy at diagnosis, would the cancer not have metastasized? In general, the more tested markers that we can target early on in disease results in less likely recurrent, especially when these targeted treatments are very tolerable and reliable in comparison to standard chemotherapies.

Third, her cancer metastasized to the bone marrow (breast cancer leukemia) making chemotherapy treatment impossible. These targeted therapies have saved her life since they are tolerable and not associated with any bone marrow toxicity.

Fourth, the patient had a partial response to larotrectinib but better response with combination of fam-trastuzumab-deruxtecan-nxki and larotrectinib. This was seen 2 times, once at beginning of treatment from April 2022 to June 2022, when she took only larotrectinib and another time when she had hip surgery and was on larotrectinib only from February 2023 to April 2023. Both times her blood count improved some with larotrectinib alone, but did better with combination therapy, showing additive effect.

Fifth, at this time, she has no clinical symptoms or toxicity reported, except for mild nausea and fatigue with fam-trastuzumab-deruxtecan-nxki for few days. Great tolerance is noted and no concern for toxicity in her case. As she continues combination therapy, signs of tropomyosin receptor kinase (TRK) inhibition such as weight gain, dizziness, and withdrawal pain are being carefully monitored in the clinic [3].

Sixth, durability of response is seen as she is now approaching 1.5 years of treatment with targeted therapy and continues to be in remission. Although it is known through the findings of DESTINY-Breast04 that trastuzumab deruxtecan doubles progression-free survival compared to chemotherapy alone in patients with hormone receptor-positive, HER2-low breast cancer, the use of larotrectinib in combination has also demonstrated durability of response [4].

Seventh, no dose adjustment was done for either of the drugs, despite a shared pharmacokinetics. The importance of the efficacy and durability of concurrent treatment is better understood when considering the pharmacokinetics and mechanisms of action of the two drugs. Larotrectinib is an inhibitor of the 3-TRK proteins, which are encoded by NTRK genes, NTRK1, NTRK2, and NTRK3 [5]. Larotrectinib is primarily metabolized in the liver by CYP3A4. Similarly, fam-trastuzumab deruxtecan that targets HER2 is a topoisomerase I inhibitor metabolized by CYP3A4 in the liver [6]. As both drugs act as substrates for CYP3A4 metabolism in the liver, combination therapy may increase drug level and related toxicity. However, we were able to use full doses with no apparent clinical or lab-recognized toxicity.

CONCLUSION

This case report highlights the successful concurrent use of fam-trastuzumab-deruxtecan-nxki and larotrectinib in a patient with metastatic breast cancer harboring both Her2neu and NTRK mutations. The combination therapy demonstrated great response with durability even after a period of one year and without significant toxicity. The concurrent use of fam-trastuzumab-deruxtecan-nxki and larotrectinib in this patient holds implications for future research in the field of metastatic breast cancer treatment or use of combinations therapies even earlier on adjuvant setting. Larger clinical trials are needed to validate the efficacy and safety of combination therapies targeting multiple mutations. Future treatment should use advanced diagnostic technology and molecular markers to select the most suitable combination targets and prescribe precise drugs, instead of treatment based on the location of the tumor.

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Author Contributions

Hrishita Tiwari – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Aryana Pourmotamed – Conception of the work, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Caroline Crocker – Design of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Elham Abbasi – Design of the work, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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