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Exceptional disease control with neratinib monotherapy in HER2-positive advanced breast cancer: A case report

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ABSTRACT

Human epidermal growth factor receptor 2 (HER2) represents a crucial drug target in breast cancer treatment. Currently, several agents that target HER2 are available, including monoclonal antibodies, antibody-drug conjugates, and tyrosine kinase inhibitors (TKIs). Despite major research efforts, no validated biomarker exists to identify patients who respond to anti-HER2 therapy alone and could be spared the toxicity of chemotherapy. Here we report the case of a 45-years-old patient with recurrent, hormone receptor-positive, and HER2-positive advanced breast cancer who had progressed various lines of treatment but showed an exceptional and prolonged response to neratinib monotherapy. A next-generation sequencing (NGS) analysis on her tumor showed a CDK12-PLXDC1 truncation and amplification of several genes, including CDK12. This case illustrates the activity of neratinib monotherapy and suggests its clinical potential without chemotherapy in a certain subtype of HER2-positive breast cancer, that may possess distinct molecular features, such as CDK12 expression.

BMI	body mass index
CNS	central nervous system
CT	computed tomography
EAP	expanded Access Program
ER	estrogen receptor
HER2	human epidermal growth factor receptor 2
NGS	next-generation sequencing
PFS	progression-free survival
PR	progesterone receptor
T-DM1	ado-trastuzumab emtansine
TKI	tyrosine kinase inhibitor

Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for approximately 15–20% of breast cancers and is associated with worse survival outcomes as compared to their negative counterpart (Loibl and Gianni, 2017; Cesca et al., 2020). The development of HER2 directed therapies has revolutionized the treatment paradigm of patients with HER2-positive breast cancer and several agents have been approved, including monoclonal antibodies (trastuzumab, pertuzumab), antibody-drug conjugates (ado-trastuzumab emtansine and fam-trastuzumab deruxtecan) and small molecules, such as oral tyrosine kinase inhibitors (TKIs) which act intracellularly (Cesca et al., 2020; le Du et al., 2021).

In particular, the TKIs lapatinib, neratinib and tucatinib showed good clinical outcomes in phase III trials in combination with chemotherapy for patients who progressed on previous anti-HER2 treatment (Geyer et al., 2006; Saura et al., 2020; Murthy et al., 2020). By targeting the intracellular domain, they could potentially circumvent any modification of the extracellular domain and could cross the blood-brain barrier to target central nervous system (CNS) disease, which remains a worrisome risk in patients with HER2-postive breast cancer.

Neratinib is an irreversible, oral, pan-HER TKI, which targets EGFR, HER2 and HER4 receptors: this broad inhibitory profile can potentially explain its high burden of toxicity (Rabindran et al., 2004). The randomized phase 3 NALA trial evaluated the combination of capecitabine and neratinib compared to capecitabine and lapatinib, showing an improvement in progression-free survival (PFS) (8.8 vs 6.6 months,

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respectively), but with a higher prevalence of diarrhea (all-grade 83.2%, of which grade 3–4 24.4% vs 66.2%, of which grade 3–4 12.5% respectively) (Saura et al., 2020). The phase II CONTROL study found that the addition of budesonide or colestipol to regular prophylactic loperamide reduce the incidence of grade 3 diarrhea and risk of treatment discontinuation with neratinib (Barcenas et al., 2020).

In this report we would like to describe the clinical course and outcomes of a hormone receptor-positive and HER2-positive advanced breast cancer patient, who achieved an exceptional disease control after receiving neratinib monotherapy treatment.

Case report

In October 2012 a 45-years-old healthy woman underwent right radical mastectomy and ipsilateral axillary node dissection. The patient had no family history for breast cancer or other neoplasms. The pathological diagnosis was triple-positive, grade 2 breast cancer (estrogen receptor [ER] 80%, progesterone receptor [PR] 70%, Ki67 35%, and HER2 immunohistochemistry score 3+). Eight of eighteen nodes examined tested positive for carcinoma, resulting in TNM classification pT2 pN2a (AJCC 7th edition) and a pathological stage IIIA. At that time, the patient was treated in a different Center, hence no information regarding the proposal of neoadjuvant treatment is available. Post-surgery staging, including abdominal ultrasound, chest X-ray, and bone scan, was negative.

The patient subsequently began adjuvant chemotherapy with doxorubicin and cyclophosphamide: however, after the completion of the fourth cycle, she reported intense and localized dorsal back pain. A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed the presence of bone (sternum and from 6th to 9th thoracic vertebrae) and bilateral lung metastases.

The patient had good performance status and her body mass index (BMI) was within the normal range. She initially received palliative radiation therapy on three thoracic vertebrae (30 Gy in 10 fractions). Thereafter, given the presence of metastatic disease, the patient underwent several lines of chemotherapy combined with anti-HER2 treatment:

At first, she received 12 cycles of paclitaxel and trastuzumab, followed by maintenance therapy with trastuzumab, anastrozole and triptorelin. Moreover, denosumab was administered every 4 weeks due to bone involvement for two years. Serial CT scan studies documented a radiological complete response of both bone and lung lesions, owing a total PFS of 56 months.

Due to lung, nodal (bilateral hilar lymph nodes) and bone progression, the patient was switched to capecitabine and lapatinib treatment. However, this combination regimen was poorly tolerated because of Grade 2 hand-foot syndrome and recurrent Grade 2 paronychia, which both required treatment interruptions and dose reductions. The total PFS was 6 months.

Radiological pulmonary progression was showed and treatment with ado-trastuzumab emtansine (T-DM1) was started. The treatment was well tolerated, and a radiological partial response was achieved as best response. The total PFS was 14 months.

Due to further pulmonary progression, rechallenge with trastuzumab in association to vinorelbine as part of a clinical trial was chosen. However, the PFS was only 6 months.

In January 2020 a CT scan documented further lung progression. Since the patient had already received all anti-HER2 treatment available at that time, a formal request for neratinib in the Expanded Access Program (EAP) was done.

Furthermore, a next-generation sequencing (NGS) analysis, detecting substitutions, insertions, deletions, and copy number alterations of her primary tumor was carried out: as well as confirming HER2-amplification, it showed a KEL alteration (R192*), a CDK12-PLXDC1 truncation and amplification of several genes (including IGF1R, RAD21, MAPK1, and CDK12).

Treatment with neratinib was approved by the local ethics committee (Comitato Etico Brianza) and the patient provided written informed consent prior to initiation of treatment. Neratinib 240 mg monotherapy was started in February 2020; antidiarrheal prophylaxis with loperamide (12 mg/die on days 1–14, then 8 mg/die on days 15–56) and budesonide (9 mg/die on days 1–28) was given, as this combination strategy was suggested in the CONTROL trial (Barcenas et al., 2020). The treatment was well tolerated and there was no need of either interruption or dose reduction of neratinib, since only Grade 1 diarrhea occurred. The CT scan of the brain, chest, abdomen, and pelvis performed after 3 months of treatment showed a radiological partial response of the lung lesions, which was maintained over time. Since the treatment did not include any chemotherapy drug, the quality of life of our patient was well preserved and she was able to work and fully perform her daily activities.

Neratinib treatment continued at starting dose until October 2021, when progressive disease according to RECIST criteria of a single lung lesion was revealed by a CT scan: therefore, the total PFS was 20 months.

Our patient's timeline diagram is reported in Fig. 1.

The patient is currently receiving trastuzumab deruxtecan, available for compassionate use, given the results of the recent DESTINY-Breast03 trial (Cortés et al., 2022).

Discussion

The efficacy of neratinib in combination with chemotherapy for HER2-positive breast cancer is well established, as was showed in the NALA and NEfERT-T trials (Saura et al., 2020; Awada et al., 2016). However, neratinib monotherapy was less explored within a clinical trial setting, as only in the phase II trial by Martin et al. (NCT00777101) (Martin et al., 2013) and in the SUMMIT trial (Hyman et al., 2018) this treatment regimen was adopted.

Our patient progressed during adjuvant anthracycline treatment, but subsequently responded to trastuzumab and paclitaxel therapy. The tumor did not progress for more than 4 years, but thereafter was not or poorly responsive to subsequent anti-HER2 treatments.

The NGS carried out on the primary tumor revealed, among other alterations, a CDK12-PLXDC1 truncation, which resulted in CDK12-amplification. The CDK12 gene is commonly co-expressed with HER2 (Kauraniemi and Kallioniemi, 2006; Choi et al., 2020), because it is usually contained in the HER2 amplicon. The role of CDK12 in cancer pathogenesis is currently being evaluated (Tien et al., 2017) and its inhibition could resensitise breast cancer cells to anti-HER2 blockade (Li et al., 2021). A recent study has also suggested that CDK12 expression is correlated with response to TKI, among which neratinib, rather than trastuzumab and might be a biomarker of response to these small molecules (Conlon et al., 2021).

Our patient showed an exceptional disease control during fifth line neratinib monotherapy for over one year and we hypothesize that CDK12 amplification might partially explain this outcome: in fact, we speculate that there might be a subgroup of HER2-positive breast cancer patients who could benefit from TKIs monotherapy, without needing their association with chemotherapy that could heavily impair their quality of life. As such, CDK12 amplification could potentially be one of the markers of these disease subgroup.

It may seem counterintuitive that previous lapatinib treatment, which is also a TKI, was not as effective as neratinib, as there is evidence of cross-resistance between these two TKIs (Breslin et al., 2017). The explanation we propose for this event is that lapatinib and capecitabine combination therapy was not well tolerated and several dose interruptions and reductions during the first three cycles were made, which have somewhat impaired dose-intensity maintenance and treatment response. As these adverse events were mostly ascribed to capecitabine treatment, this drug was not rechallenged in further lines. As a confirmation of this, neratinib monotherapy (in addition to antidiarrheal prophylaxis with loperamide and budesonide) was well tolerated,

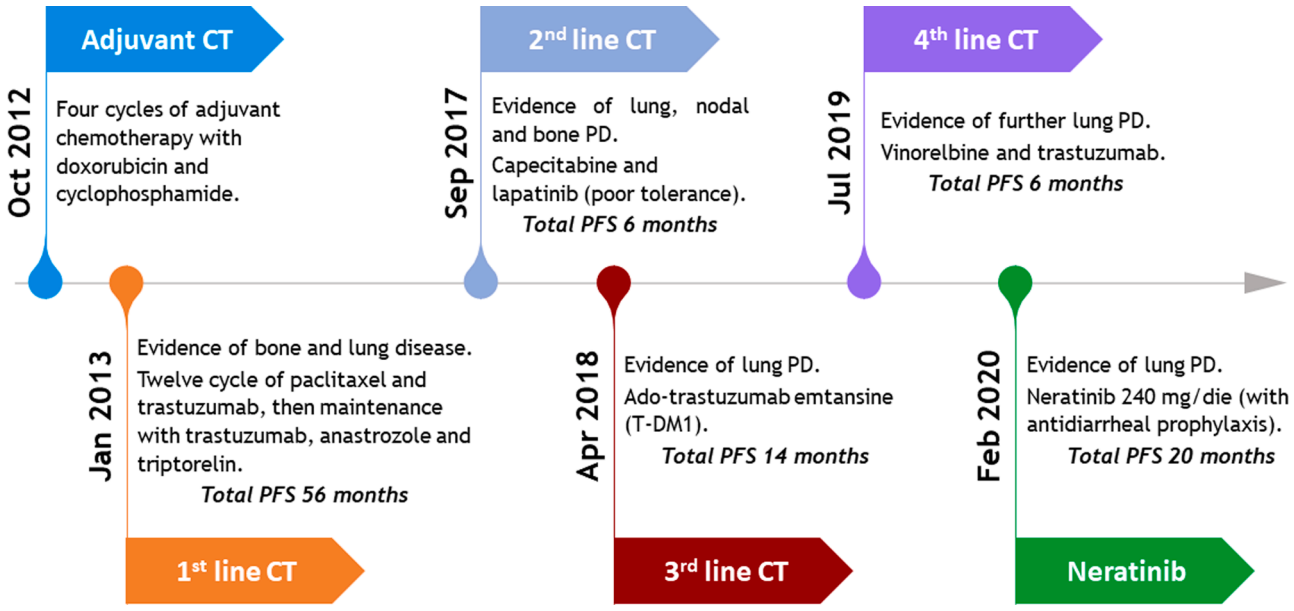

Fig. 1. Patient's timeline diagram. CT, chemotherapy; PFS, progression-free survival; PD, progressive disease.

no relevant adverse events were reported, and our patient maintained a good quality of life.

Another point to consider is the patient's BMI, which remained within the normal range during the consecutive therapies: this feature could explain the long-lasting response with T-DM1, as reported by Krasniqi et al. (Krasniqi et al., 2020), and possibly with other anti-HER2 treatments.

Finally, we speculate that neratinib monotherapy was effective due to the triple-positive profile of our patient's breast cancer: in fact, neratinib extended adjuvant therapy has improved outcomes in this cancers' subtype (Martin et al., 2017) and neratinib is currently being evaluated in the neoadjuvant setting (NCT04886531).

Taken together, these data suggest that neratinib monotherapy might represent a relevant strategy in a subgroup of patient with advanced HER2-positive breast cancer.

CRediT authorship contribution statement

Pierluigi di Mauro: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Serena Capici:** Methodology, Data curation. **Viola Cogliati:** Methodology, Data curation. **Francesca Fulvia Pepe:** Methodology, Data curation. **Claudia Maggioni:** Writing – review & editing. **Francesca Riva:** Writing – review & editing. **Federica Cicchiello:** Writing – review & editing. **Marina Elena Cazzaniga:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Patient Consent Statement

Treatment with neratinib was obtained within an expanded access program (EAP) and was subsequently approved by the local ethics committee (Comitato Etico Brianza) in the palliative setting. The patient provided written informed consent prior to initiation of treatment and consented the publication of the data in this case report.

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Ethical approval

Treatment with neratinib was obtained within an Expanded Access Program (EAP) and was subsequently approved by the local ethics committee (Comitato Etico Brianza) in the palliative setting. The patient provided written informed consent prior to initiation of treatment and consented the publication of the data in this case report.

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