Editorial

Pyrotinib as a therapeutic for HER2-positive breast cancer

Ivelina Kioutchoukova[1], Brandon P. Lucke-Wold[2]

[1]College of Medicine, University of Florida, Gainesville, Florida, USA; [2]Department of Neurosurgery, University of Florida, Gainesville, Florida, USA

Correspondence to: Ivelina Kioutchoukova, BS. College of Medicine, University of Florida, 1600 SW Archer Rd., Gainesville, Florida 32610, USA. Email: ikioutchoukova@ufl.edu.

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Approximately 20% of breast cancers overexpress or amplify the expression of human epidermal growth factor receptor 2 (HER2), resulting in an aggressive tumor (1,2). Cancers that overexpress HER2 result in an abnormally high level of malignant cells and women diagnosed with this form of breast cancer experience significantly shortened survival (3). Previous studies have provided laboratory evidence that HER2 amplification and overexpression serve a direct role in the tumorigenesis and pathogenesis of these breast cancers (4). This presents an opportunity for the use of targeted therapeutics to be applied in the treatment of HER2-positive metastatic breast cancers (2).

Approximately 50% of patients with HER2-positive metastatic breast cancer also exhibit brain metastases, with the incidence increasing over the years (5). However, despite treatment advances, brain metastases still correlate to a poor prognosis, with a median overall survival of about 24 months in patients with HER2-positive metastatic breast cancers (6). Due to the tight junctions of the blood-brain barrier limiting the ability of effective drugs to diffuse through, targeting the central nervous system poses a challenge (7). This especially poses a challenge for monoclonal antibodies, like trastuzumab and pertuzumab (5). Due to this reason, small molecules which target HER2 are currently being investigated for the treatment of patients with brain metastases and HER2-positive metastatic breast cancer (5). Tyrosine kinase inhibitors that target HER2 are currently a drug class being investigated (8).

Currently, the first-line therapy includes a combination of trastuzumab, pertuzumab, and taxane, which specifically target HER2 (9). However, resistance can be developed to these agents and Hu *et al.* argue that the development of new anti-HER2 therapeutics is crucial (10). In their systematic review and meta-analysis, the authors investigated the efficacy of pyrotinib, an irreversible ErbB receptor tyrosine kinase inhibitor, for the treatment of HER2-positive metastatic breast cancers (10).

pyrotinib received approval to be used in China in 2018 as a second-line therapy in combination with capecitabine for the treatment of HER2-positive metastatic breast cancers (10). Hu *et al.* also state that the use of pyrotinib is critical in countries that lack access to antibody-drug conjugates (ADCs) (10). Their study focuses on evaluating the efficacy of pyrotinib in treating HER2-positive metastatic breast cancers through a meta-analysis and systematic review (10).

Hu *et al.* develop a strong argument for the use of pyrotinib as a second-line therapy in the treatment of HER2-positive metastatic breast cancers (10). ADCs are inaccessible in developing countries as a second-line therapy and presenting another option, such as pyrotinib, offers patients an opportunity to receive treatment for their cancers (10). Pyrotinib is an inexpensive option, while also being safe and effective (10). Pyrotinib also presents an option to patients with brain metastases due to HER2-positive metastatic breast cancers, with an overall response rate (ORR) of 0.52 (10). This presents a favorable treatment option for brain metastases in HER2-positive breast cancers as the current treatment options include surgery, radiation therapy, and systemic therapy (11). Continuous use of anti-HER2 therapies, such as pyrotinib, has been shown to significantly decrease mortality (12).

Monoclonal antibodies like trastuzumab, have a limited effect in treating brain metastases due to the permeability of the blood-brain barrier (13). Additionally, cancers in a significant number of patients can develop resistance against trastuzumab, requiring additional therapies (14). Hu *et al.* argue that the incidence of resistance against trastuzumab is rising, warranting a need for additional therapeutic agents against brain metastases in HER2-positive metastatic brain cancer patients. Exploration of other chemotherapies for patients with brain metastases is crucial in managing their care and within their study, Hu *et al.* explore the efficacy of pyrotinib as a possible solution (10). This study performed a systematic review and meta-analysis of pyrotinib's efficacy in treating HER2-positive metastatic breast cancers (10). Furthermore, the authors compared the use of pyrotinib to standard therapies in treating HER2-positive breast cancers, such as trastuzumab (10). The authors also addressed any adverse effects of the drug while reporting the progression-survival rates of patients treated with different therapies (10).

Hu *et al.'s* study analyzes the data from other studies to offer support for the use of pyrotinib as a therapeutic agent in the treatment of HER2-positive metastatic breast cancers (10). The authors establish the efficacy of pyrotinib and advocate for its use in developing nations without access to ADCs (10). Additionally, the authors also address the difficulties in the treatment of brain metastases due to the permeability of the blood-brain barrier and the limited agents that can diffuse through (10,13). This highlights the importance of pyrotinib being an effective agent in the treatment of brain metastases, as there are a limited number of drugs able to act on this site of the body. Additionally, Hu *et al.* address how there is improved efficacy of the drug when whole-brain radiotherapy or local radiotherapy is conducted alongside, allowing for the disruption of the blood-brain barrier and improving the diffusion of pyrotinib to reach the brain metastases (10).

This study undoubtedly organizes and presents the argument for the use of pyrotinib in the treatment of HER2-positive metastatic breast cancers (10). However, some other important points can be addressed in the paper. Surgical interventions, whole-brain radiotherapy, and stereotactic radiotherapy are the traditional approaches to treating brain metastases, however, recurrences typically occur within 6 to 12 months of intervention, and it poses a risk for neurocognitive impairments (15,16). However, systemic therapy provides an advantage in that it accounts for both intracranial and extracranial lesions through the use of effective drugs (15). Results from a previous study demonstrated that the addition of small-molecule tyrosine kinase inhibitors along with trastuzumab and capecitabine improved survival by 5–7 months in comparison to the other agents without the addition of a small-molecule tyrosine kinase inhibitor (17).

Hu *et al.* briefly mentioned the common adverse effects of pyrotinib in their study, but further discussion on the management of these effects is needed (10). For instance, diarrhea was the most common adverse reaction reported by Hu *et al.* (10). This adverse event is reversible by adjusting dosage and directly treating diarrhea through montmorillonite powder or loperamide (15). It's also important to note that this grade 3 adverse event did not result in discontinuation of the treatment in previous studies investigating the efficacy of pyrotinib (15). Additionally, diarrhea primarily occurred in the 400 mg dose group of another study (18). Another common adverse effect of pyrotinib reported by Hu *et al.* was palmoplantar erythema (10) which can be addressed by being aware of the possibility and addressing it early to ensure timely treatment (19). Being aware of this adverse event helps reduce the risk of reducing the dose or discontinuing treatment overall (19). Neutropenia was another adverse effect reported by Hu *et al.* (10). One study addressed this event by prophylactically prescribing 6 mg of mecapegfilgrastim or using other granulocyte-colony stimulating factors (20). The same study also found no significant difference between neutropenia in the pyrotinib group versus the placebo group (20).

One recently published article explores another potential adverse effect of pyrotinib in patients, cardiotoxicity (21). Despite advances in treatments for breast cancers, adverse drug reactions, such as cardiotoxicity, can offset the survival outcomes of patients (21). Cancer therapy-related cardiac dysfunction, arrhythmias, and myocarditis are possible adverse outcomes of cardiotoxicity (22). Additionally, there is a high need for cancer therapeutics with less cardiotoxicity as cardiotoxicity can occur at any stage of cancer, in patients of different ages, and even low-risk individuals (23). This study found that pyrotinib used with trastuzumab was non-inferior with regards to cardiac safety in comparison to trastuzumab and pertuzumab (21).

Although Hu *et al.* address the efficacy of pyrotinib in patients and acknowledge that pyrotinib was developed in China, the study didn't expand upon what type of patients were included in the studies investigating the efficacy of pyrotinib (10). It's important to note that out of the 23 studies included in Hu *et al.'s* study, 21 studies specifically conducted their studies on Chinese patients (10). Pyrotinib

has not yet been approved for marketing in the European Union or the United States, but additional studies which evaluate its efficacy in a more diverse patient set are needed to confer therapeutic benefits applied to all HER2-positive metastatic breast cancer patients (24).

One study conducted a cost-effectiveness analysis of pyrotinib in combination with capecitabine in the treatment of HER2-positive metastatic breast cancers after previous treatment with trastuzumab (24). Pyrotinib in combination with capecitabine is a more cost-effective second-line therapy than lapatinib and capecitabine (24). However, because data is lacking on pyrotinib use in other countries, economic benefits require further verification and analysis (24).

Overall, Hu *et al.'s* study demonstrates the efficacy of pyrotinib for the treatment of HER2-positive metastatic breast cancers (10). With increasing resistance to the current standard therapy, more chemotherapeutic agents are needed to improve patient survival. Pyrotinib has proven to be an effective and safe agent for treating tumors, controlling disease, and has manageable adverse reactions. Hu *et al.'s* study confirms its efficacy for use, offering patients a new therapy for treatment (10).

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References

1. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-92.
2. Martínez-Sáez O, Prat A. Current and Future Management of HER2-Positive Metastatic Breast Cancer. JCO Oncol Pract 2021;17:594-604.
3. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177-82.
4. Hudziak RM, Schlessinger J, Ullrich A. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. Proc Natl Acad Sci U S A 1987;84:7159-63.
5. Masci G, Agostinetto E, Giordano L, et al. Prognostic factors and outcome of HER2+ breast cancer with CNS metastases. Future Oncol 2020;16:269-79.
6. Nader-Marta G, Martins-Branco D, Agostinetto E, et al. Efficacy of tyrosine kinase inhibitors for the treatment of patients with HER2-positive breast cancer with brain metastases: a systematic review and meta-analysis. ESMO Open 2022;7:100501.
7. Conrad CA. Chemotherapy for metastatic tumors to the central nervous system. Curr Oncol Rep 2001;3:490-4.
8. Saura C, Oliveira M, Feng YH, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol 2020;38:3138-49.
9. Nader-Marta G, Martins-Branco D, de Azambuja E. How we treat patients with metastatic HER2-positive breast cancer. ESMO Open 2022;7:100343.
10. Hu W, Yang J, Zhang Z, et al. Pyrotinib for HER2-positive metastatic breast cancer: a systematic review and meta-analysis. Transl Cancer Res 2023;12:247-56.
11. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31:1623-49.
12. Olson EM, Abdel-Rasoul M, Maly J, et al. Incidence and risk of central nervous system metastases as site of

first recurrence in patients with HER2-positive breast cancer treated with adjuvant trastuzumab. Ann Oncol 2013;24:1526-33.
13. Montemurro F, Delaloge S, Barrios CH, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial☆. Ann Oncol 2020;31:1350-8.
14. Pohlmann PR, Mayer IA, Mernaugh R. Resistance to Trastuzumab in Breast Cancer. Clin Cancer Res 2009;15:7479-91.
15. Yan M, Ouyang Q, Sun T, et al. Pyrotinib plus capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases (PERMEATE): a multicentre, single-arm, two-cohort, phase 2 trial. Lancet Oncol 2022;23:353-61.
16. Hughes RT, Masters AH, McTyre ER, et al. Initial SRS for Patients With 5 to 15 Brain Metastases: Results of a Multi-Institutional Experience. Int J Radiat Oncol Biol Phys 2019;104:1091-8.
17. Lin NU, Borges V, Anders C, et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. J Clin Oncol 2020;38:2610-9.
18. Liu Y, Zhang Q, Lu C, et al. Multiple Administrations of Itraconazole Increase Plasma Exposure to Pyrotinib in Chinese Healthy Adults. Drug Des Devel Ther 2021;15:2485-93.
19. Kwakman JJM, Elshot YS, Punt CJA, et al. Management of cytotoxic chemotherapy-induced hand-foot syndrome. Oncol Rev 2020;14:442.
20. Wu J, Jiang Z, Liu Z, et al. Neoadjuvant pyrotinib, trastuzumab, and docetaxel for HER2-positive breast cancer (PHEDRA): a double-blind, randomized phase 3 trial. BMC Med 2022;20:498.
21. Chai Y, Jiang M, Wang Y, et al. Protocol for pyrotinib cardiac safety in patients with HER2-positive early or locally advanced breast cancer-The EARLY-MYO-BC study. Front Cardiovasc Med 2023;10:1021937.
22. Herrmann J, Lenihan D, Armenian S, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. Eur Heart J 2022;43:280-99.
23. Riihimäki M, Thomsen H, Brandt A, et al. Death causes in breast cancer patients. Ann Oncol 2012;23:604-10.
24. Bao Y, Zhang Z, He X, et al. Cost-Effectiveness of Pyrotinib Plus Capecitabine versus Lapatinib Plus Capecitabine for the Treatment of HER2-Positive Metastatic Breast Cancer in China: A Scenario Analysis of Health Insurance Coverage. Curr Oncol 2022;29:6053-67.

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