Efficacy and safety of trastuzumab with or without a tyrosine kinase inhibitor for HER2-positive breast cancer: a systematic review and meta-analysis

Liji Li1, Di Zhang1,2, Yun Wu1, Jiayu Wang1, Fei Ma1*
1Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
2Department of Medical Oncology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, 250012, Shandong, China

*These authors contributed equally to this article.

Introduction

TKIs are a class of small-molecule inhibitors that target the intracellular region of HER2 and block tyrosine kinase activity. Trastuzumab and TKIs act on different targets with different mechanisms of action. Hence, dual HER2 blockade with trastuzumab and TKIs can theoretically achieve complementary therapeutic effects and overcome the insidious toxicity of these drugs.

Pharmacodynamic and pharmacokinetic parameters of different TKIs

- Revealed TKIs temporarily inhibit HER2, which may require frequent administration of higher doses to achieve the desired therapeutic effect. In contrast, irreversible TKIs form a covalent bond with the enzyme, leading to sustained target inhibition with lower doses typically sufficient for prolonged efficacy.
- Compared to reversible pan-HER2 receptor TKIs (such as lapatinib), irreversible pan-HER2 receptor TKIs exhibited greater anti-HER2 activity, as inferred from the efficacy data in clinical trials and their broader range of approved indications.
- Pharmacodynamics data in Table 1 showed that the IC50 of pyrotinib and neratinib against HER2 was significantly lower than that of lapatinib.
- Despite differences in structure and pharmacodynamics, the corresponding TKIs, pyrotinib, and neratinib, have been shown to be more potent in preclinical in vitro and/or in vivo preclinical and clinical applications.

Results

- Different TKIs are the principle of action and the biological mechanism of the TKIs combined with trastuzumab is synergistic. Whether the toxicity of dual-blocked HER2 will increase significantly may have affected their efficacy in combination with trastuzumab.

Search strategy and study selection

The PubMed, Embase, and Web of Science databases were systematically searched for relevant articles from inception until Nov 2022. Finally, 54 studies were included in this meta-analysis after another round of screening (Figure 1). The primary outcomes were overall survival (OS) and progression-free survival (PFS). Subgroup analyses were performed based on disease status, TKI type, and hormone receptor status. Figure 1. Flow diagram

Table 1. The comparison of features and properties between different TKIs

<table>
<thead>
<tr>
<th>TKI</th>
<th>Small Molecule</th>
<th>Inhibitory Constant (IC50)</th>
<th>Clinical Use</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>Yes</td>
<td>0.33 µM</td>
<td>Breast cancer</td>
<td>GI, fatality</td>
</tr>
<tr>
<td>Pyrotinib</td>
<td>Yes</td>
<td>0.03 µM</td>
<td>Breast cancer</td>
<td>GI, skin rash</td>
</tr>
<tr>
<td>Neratinib</td>
<td>Yes</td>
<td>0.02 µM</td>
<td>Breast cancer</td>
<td>GI, skin rash</td>
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Table 3. The comparison of features and properties between different TKIs

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Figure 2. Forest plot of the HR for the OS (A) and DFS (B)

Figure 3. Subgroup analysis for the OS and PFS

Figure 4. Forest plot of the HR for the pcr (A), ORR (B), and DFS (C)

Conclusions

In summary, combining TKIs with trastuzumab confers significant improvement in clinical outcomes with tolerable toxicity for individuals with HER2-positive breast cancer, especially in advanced settings.

- The incidence of AEs, including diarrhea, gastritis, and vomiting, may increase when administering trastuzumab plus TKI; however, the overall safety of this treatment is controllable.

- Different TKIs combined with trastuzumab have different efficiencies and AEs varying in their differences in their mechanisms and pharmacological properties.

- The irreversible pan-HER2 receptor inhibitor pyrotinib demonstrates superior anti-tumor activity when combined with trastuzumab.

References


Statistical analysis

Time-to-event and dichotomous outcomes were estimated by using HR and OR, respectively. A random-effects model was applied in the present study. Cochrane Q statistic was used to test the heterogeneity of each study, and I² statistic was used to quantify, where I² represented significant heterogeneity. Publication bias was evaluated using funnel plots, Egger’s test, and Begg’s test. All analyses were performed using STATA software (version 16.1, StataCorp, USA).

Figure 5. Forest plot of the HR for all-grade AEs (A), grade ≥3 AEs (B), discontinuation due to AEs (C), and death due to AEs (D)