The Combination Therapy in Breast Cancer Treatment

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Abstract. Breast cancer (BC) is the cancer that most commonly diagnosed worldwide, which result in the cause of cancer-related deaths. The majority of BC diagnoses were HR+ and HER2- (71%) and HER2+BC accounts for 10-20% of all breast tumors. There is no magic drug for the treatment of breast cancer at present. Endocrine therapy is the preferable treatment for HR+/HER2- metastatic breast cancer. However, long-term use may produce certain drug resistance. Tucatinib, as a HER2 inhibitor, can be combined with chemotherapy to treat HER2+BC. Combination therapy can offer patients the opportunity to derive the maximum benefit from treatment, at the same time, it can minimize or eliminate relapse, drug resistance and toxic effects and thus the BC patients can have a good quality of life. This paper discussed the combination therapy of endocrine therapy or tucatinib with other drugs and compared their advantages and disadvantages in breast cancer therapy, providing better choice for clinical treatment of BC.

Keywords: Breast cancer, HR+/HER2-, HER2+, combination therapy.

1. Introduction

Breast cancer (BC) is a major worldwide issue, which effect the physical and mental health of patients. BC is the most prevalent cancer among women (11.7% of new cancer cases, more than lung cancer) [1]. Worldwide, nearly 685,000 women died of BC in 2020, according to epidemiological data [2]. BC is classified into six subtypes based on macromolecular and cellular biomarkers: luminal A, luminal B, HER2+, basal-like subtype, normal breast-like, claudin-low [3]. We classified the subtypes into the following models: the HR+/HER2-, the HER2+/HR+, the HER2+/HR- and ER-/PR-/HER2-. The subtype with the highest incidence (HR+/HER2-) accounts for 70% of all breast cancers, followed by the (HR-/HER2+) subtype with 15% of all breast cancers [4].

Endocrine therapy as the preferable choice to treat HR+/HER2- metastatic breast cancer (mBC) according to international HER2+ mBC guidelines and the Cochrane database analysis [5-7]. CDK 4/6 inhibitors can be combined with endocrine therapy as first- or second-line treatment for premenopausal women with HR+/HER2-mBC [8]. In order to treat HER2+ BC patients, three types of HER2 inhibitors have been developed: monoclonal antibodies, Antibody-drug combinations and inhibitors of tyrosine kinases (TKI) [9]. HER2 inhibitors are usually used to cure HER+ patients, however they have showed some promise in the treatment of HER2- and HER2-mutant BC patients [10].

Tucatinib is HER2-specific TKI that can oral, potent and reversible, nowadays is becoming a novel treatment to ERBB2/HER2-positive BC. Combination therapy has become the cornerstone of cancer treatment to enhance the therapeutic effect and overcome drug resistance and metastasis. This paper aims to explore the possibility of combining with tucatinib or other combination therapy for HR+/HER2- BC, HER2+ BC and compare the advantages and disadvantages of different drug combinations.
2. Combination therapy of Tucatinib

2.1. Tucatinib, combine with Capecitabine and Trastuzumab

A clinical trials to compare the effect of the double therapy of Capecitabine and Trastuzumab solely and combine with Tucatinib. By interpreting the final statistical analysis, asignificant decrease in tumor progression and the general survival rate was higher than treating without Tucatinib. The tucatinib-combination group showed a 33.1% rate for Progression-free survival at 1 year and the rate for the placebo-combination group was 12.3% [11]. Tucatinib had a low repel rate, and its safety profile was recorded in previous reports [13]. The benefit in Progression-Free-Survival was similarly maintained with longer follow-up, the Tucatinib group was followed up to 7.6 months compared to the 4.9 months of the placebo group. The total study has conducted for 29.6 months,27 percentage reduction in the death risk was observed in Tucatinib group, in median OS was 24 months, while the placebo is 19.2 months. Combination of Tucatinib, Trastuzumab and Cepecitabine had lowered 46% of death rate of heavily pretreated patients. In a year, the progression-free survival (PFS) rate of Tucatinib combination group was 33.1% and the control group received a PFS rate of 12.3%. The combination group had a 8.8 months median duration of PFS and the control group had a 5.6 months duration [12].

However, this combination of treatment showed higher risk of diarrhea, with 52% of severe GI effect, and the aminotransferase level was remarkably high in the test result, with 18% of significant Aspartate aminotransferase increased and 22% of significant Alanine aminotransferase increased. A high level of aminotransferase may indicate liver damage and increase the risk of getting liver cancer. Since cancer patients are required to take multiple drugs, their burden on liver is greater than normal individuals. Therefore, this treatment is not recommended to cancer patients who have liver impairment. It is recommended that patients should do a liver function test before being prescribed this treatment.

Overall, for patients in severe cancer statement, the combination of Capecitabine and Trastuzumab with Tucatinib is still considered as an effective treatment regardless of the potential GI effect in a cancer therapy [14].

2.2. Triple targeted combination therapy of tucatinib, palbociclib and fulvestrant

The initial line of treatment for HR+ breast cancer is endocrine therapy, which is a treatment for BC patients to prevents the combination of estrogen in the body and cancer cells, and it is required for the majority of patients. From the American Society of Clinical Oncology clinical practice guidelines, we can know that endocrine therapy with tamoxifen and meanwhile plus an aromatase inhibitor lowers recurrence and mortality in individuals with ER+ BC [15]. On the other hand, drug resistance is a serious issue in endocrine therapy, and patients often die because they have no drugs to treat. There are many reasons that can lead to drug resistance, such as ESR1 mutation, cytochrome P450 mutation, etc [16,17].

To reduce the drug resistance in HR+ breast cancer, adding CDK4/6 inhibitors in endocrine therapy is recommend and have been made with some success [18]. CDK4/6 inhibitor with an aromatase inhibitor nearly doubles progression-free survival (PFS). Letrozole in combination with palbociclib is a treatment option in a clinical trial. The median PFS significantly improved in the palbociclib group, better than control group with placebo added to Letrozole (24.8 months vs.14.5 months [19]. However, what cannot be avoided is the side effects in the process of clinical use, mainly neutropenia [NCT02630693]. Also, some articles indicate that endocrine therapy combined with CDK4/6 inhibitors does not fully address the issue of drug resistance [20]. Because the reason for resistance to fulvestrant combined with cdk inhibitors may be the overactive Cyclin E-CDK2 axis [21].

Resistance of mutant cancer cells to HER2+ inhibitors (e.g., tucatinib) caused by NFI deletion in HER2+ can be reduced by adding cdk inhibitors [22]. Cyclin D1-CDK4 pathway can target drug-resistant tumor cells through CDK4/6 inhibitors make them resensitive to HER2 therapy, and mediate
the resistance to HER2 targeted therapy [23–25]. Mismatch repair is a biological DNA repair mechanism, and defects in DNA mismatch repair have been linked to a wide range of disorders. Mismatch repair is a biological DNA repair mechanism, and errors in it have been linked to a number of disorders. Microsatellite instability is caused by mutations in MutL proteins, which can lead to cancer [26]. MutL deletion makes around 15% of ER+/HER2- individuals insensitive to endocrine therapies. After treatment with endocrine medications (fulvestrant), cell membrane HER2 levels increased in ER+/HER2- MutL-deficient tumors [4], suggesting that adjuvant endocrine therapy with HER2 inhibitors could improve monotherapy resistance.

A trial used a combination of three targeted drugs with different mechanisms: tucatinib, paboxinib, and fulvestrant. The investigators generated tucatinib-resistant (TR) and paboxinib-resistant (PR) subclones of BT474 and MDA-MB-361. The aim was to study cross-resistance and to explore whether triple therapy could rescue resistance. In the TR cell line with MDA-MB-361, diphtherapy (pt) did not inhibit as well as paboxinib alone. In the MDA-MB-361 PR cell line, neither monotherapy nor diphtherapy reduced the survival of cancer cells to less than 50%. When a third agent, fulvestrant, was added, the survival rate of MDA-MB-361 PR cells was reduced to about 10% [27].

2.3. Combination of Ado-Trastuzumab Emtansine (which can be named T-DM1) with tucatinib

The treatment offers a dual inhibition of ERBB2/HER2, using an alternative mechanism of receptor inhibition, in order to suppress the HER2 which expressed in one type of BC [28]. Some studies aimed to figure out how much the maximum dosage is for tucatinib, the tolerability and safety of tucatinib, the toxicity, side effect, and the efficacy of the combination treatment through several different clinical trials and experiments. According to the analysis of a clinical trial result, the maximum tolerated dosage of tucatinib is 300mg twice a day (600mg in total); other dosages of tucatinib such as 200mg and 150mg are also available and effective. The dosage of tucatinib is selective depending on the patient's current health status as well as the response to the drug in the order of the severity [29].

A database analysis collected from a clinical trial, those patients who accepted the treatment of the tucatinib and T-DM1 combination, accompanying the maximum dosage that can be tolerated, shows the number of 8.2 months (95% CI, 4.8–10.3 months) for their median progression-free survival time. Of all these patients, for those patients who had already accepted the treatment of both trastuzumab and pertuzumab, the length of median progression-free survival time for them was 6.5 months (95% CI, 4.1–9.2 months) [30].

In another clinical trial, 50 in the Study group of tucatinib and Ado-Trastuzumab Emtansine combination (tucatinib + T-DM1), the number of 8.2 months for the median PFS of the group (tucatinib + T-DM1). Of all these patients, approximately 20% of them accepts the treatment of tucatinib and T-DM1. For late-stage MBC shows prolonged PFS that was defined as > 16 months, which on behalf of a significant subgroup-patients in controlling the progress of the disease [31].

At the moment, due to the lack of clinical trials and relevant database for the tucatinib&T-DM1 combination, there are not enough database support and demonstrate its efficacy. Also, the combination has not been approved by FDA nor any other administration around the world so far. For these reasons, more researches and clinical trials need to be done for a better understanding of the safety, availability, side effect, and efficacy, which could demonstrate the effectiveness and the efficacy. Finally, it will become another available option for patients in the future.

As a result of the lacking of clinical trial databases, the rest of the research demonstrated in this article about the T-DM1&tucatinib is mainly focused on the efficacy, effectiveness, and the mechanism of the T-DM1&tucatinib combination or each of them separately.

Another experiment which evaluating the variations in the level of HER2 protein upon treatment with tucatinib. In order to figure out whether the therapy of tucatinib will augment the overall level of HER2 of the cell membrane-localized. HER2 bound to trastuzumab and then was internalized and directed towards lysosomes. As the T-DM1 was administered in combination with the tucatinib, this
phenomenon showed an increasing concentration of the adduct. This phenomenon shows the preliminary safety and efficacy of the T-DM1 and tucatinib combination [32].

In another research, that valuating the potency of tucatinib. As for the combination, a panel of BC cell lines was used for the expression of various levels of HER2. As a result, a potent anti-tumor activity was shown by the tucatinib in HER2 overexpressing cell lines. An additive or synergistic effect was produced by the combination of tucatinib&T-DM1. Apart from that, a demonstration of a subset of cell lines of reducing sensitivity to either T-DM1 was produced as the tucatinib suppresses it. This research shows that the tucatinib results in selective and potent anti-tumor activity in HER2+ tumor-derived cell lines, including cell lines that show T-DM1 or T-Ex sensitivity reduction [33].

There are still some disadvantages with the treatment. According to the database collected from the previous clinical trial, patients in the treatment showed adverse reactions during the treatment. Among them, the syndromes are nausea, diarrhea, fatigue, epistaxis, headache, constipation, thrombocytopenia, and vomiting (decrease in frequency). Besides that, among those patients who accepted the maximum tolerated dosage, over 70% of them had an increase in the transaminase levels (mostly grade 1), which demonstrates there is certain hepatotoxicity of the tucatinib [30].

3. Conclusions

BC is difficult to obtain a relatively considerable survival rate and cure rate under conventional treatment. Targeted therapy is now the focus of BC. Understanding the full effectiveness of targeted cancer therapy depends on finding the best combination therapy. One therapy alone may not meet a patient's clinical needs. Gradually, there was a double therapy, a triple therapy. In general, the three treatment drugs are Tucatinib, Capecitabine, and Trastuzumab. Different combination therapies have different effects. Each has certain side effects while alleviating disease progression, has its advantages and disadvantages. It may cause gastrointestinal injury, adverse liver reaction, cause microsatellite instability, and can lead to a variety of cancers. Finally, people should choose a more suitable drug according to the patient's illness and the patient's condition.

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