HUMAN BIOLOGY
2024, VOL. 94, ISSUE 6
ORIGINAL ARTICLE

OPEN ACCESS

Whether AI+CDK4/6i+HP is Suitable Treatment for Three Positive Metastatic Breast Cancer Patient with Renal Insufficiency Caused by Type 2 Diabetes

Li Gang[1], Li Hanjie[1], Ge Peng[1], Yu Jiao[2*]*

ABSTRACT

Background: Hormone-receptor positive (HR+) , ERBB2 gene mutation (HER2+) breast cancer is a very common type of breast cancer, but it is relatively rare for metastatic breast cancer (MBC) who are newly treated and have renal insufficiency. In previous studies, no long-term survival reports have been found for such patients. In order to clarify the above issues, we have innovatively developed a plan that focuses on molecular targeted therapy and endocrine therapy. We reported the results of a breast cancer patient with HR+ and HER2+concurrent renal insufficiency. Although the patient did not have the opportunity to receive surgical treatment and chemotherapy, the results showed that the aromatase inhibitors (AI)+Cyclin D-cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) +trastuzumab & pertuzumab (HP) treatment was also an effective and feasible approach.

Methods: The patient with HR+ HER2-positive MBC with activating HER2 mutation(s) received AI+CDK4/6i+HP (oral letrozole 2.5 mg/day, oral abemaciclib 150mg twice/day with mandatory loperamide prophylaxis for the first 2 cycles and as needed thereafter, and intravenous trastuzumab 8mg/kg initially then 6 mg/kg every 3 weeks plus pertuzumab 840mg initially then 420mg every 3 weeks) therapy. Efficacy endpoints included progression-free survival (PFS) (RECIST v1.1). Secondary endpoints are treatment time, exploratory targets are tumor markers, and safety targets are changes of renal function. Plasma was collected during and at end of treatment. Extracted DNA was analyzed by next-generation sequencing.

Results: The duration of response time lasted for approximately 60 weeks. The treatment time was 81weeks.The PFS was 17.6 months. Responses were observed in patient within 6 weeks. Longitudinal ctDNA sequencing revealed acquisition of additional HER2 alterations, and mutations in genes including PIK3CA.Throughout the entire treatment cycle, the patient's renal function remained stable, with no significant fluctuations in creatinine, creatinine clearance rate, serum urea, and serum potassium.

Conclusion: AI+CDK4/6i+HP is a safe and effective treatment for patients with three positive metastatic breast cancer patients with renal insufficiency caused by type 2 diabetes. Throughout the entire treatment process, the patient's renal function remains stable. Further investigation is needed.

INTRODUCTION

Renal insufficiency is common in cancer patients, and the risk of renal insufficiency increases with age and the occurrence of comorbidities such as diabetes. Breast cancer is the most common cancer among women Siegel et al. (2022). The coexistence of these three situations is relatively rare in clinical practice. Numerous studies have confirmed that patients with chronic renal failure (CRF) have a higher incidence and mortality rate of malignant tumors Lowrance et al. (2014), Malyszko et al. (2020). In adults, when the creatinine clearance rate （Ccr） decreases to 20-10ml per minute, it indicates early renal dysfunction and poor prognosis for patients with chronic nephritis; Decreasing to 10-5ml per minute indicates advanced renal insufficiency; Less than 5ml per minute indicates end-stage renal insufficiency. When the estimated Ccr decreases to 10mL/min, the mortality rate of cancer patients increases by 22% Armstrong et al. (2014), Magee et al. (2014).

[1]Department of Thoracic Surgery, The Second Affiliated Hospital of Xi'an Medical University, Xi'an 710049, China.
[2]Department of Radiation Oncology, Shaanxi Provincial People's Hospital, Xi'an 710068, China.

Corresponding to: Dr. Yu Jiao, Department of Radiation Oncology, Shaanxi Provincial People's Hospital.
Dr. Ge Peng, Department of Thoracic Surgery, The Second Affiliated Hospital of Xi'an Medical University 167 Fang Dong Road, Xi'an 710038, China. E-mail: dooopenit@163.com.

Keywords: Three positive breast cancer ; Renal insufficiency ; Type 2 diabetes ; Targeted therapy ; Endocrine

Therefore, patients with renal insufficiency not only lead to various serious kidney related complications, but also limit the application of various chemical toxic drugs for cancer patients, which greatly limits the treatment of these tumor patients.

Targeted therapies have shown promising results in multiple tumor species especially for breast cancer, but patients with renal insufficiency or renal failure are often excluded from clinical trials. In clinical diagnosis and treatment, many tumor patients are accompanied by kidney function damage, cytotoxic chemotherapy drugs are usually metabolized by the liver and excreted by the kidney, so the treatment options for these patients are very limited. At present, apart from the case report by Modi, there are few studies on the treatment of breast cancer in patients with end-stage renal disease, and these patients rarely successfully complete a series of standard protocols for new adjuvant treatment and surgery Modi et al. (2018). There is a special type of breast cancer that is characterized by estrogen receptor positive (ER+), progesterone receptor positive (PR+), and ERBB2 gene mutation (HER2+), we called it three positive breast cancer（TPBC）. It accounts for 5%~10% of all breast cancer Zhao et al. (2019), Johnston et al. (2021), Dieci et al. (2020). It is known that the axis of cyclin D-cyclin-dependent kinase 4/6(CDK4/6) plays a crucial role in the cell cycle, and their dysregulation is a central mechanism in cancer biology Spring et al. (2020). CDK4/6 inhibitors (CDK4/6i) have been shown to block the cell cycle/cyclin complex by inhibiting the kinase activity of CDK, and have been shown to be effective in both hormone receptor (HR) positive BC George et al. (2021). It is well known that CDK4/6i and anti HER2 drugs have synergistic effects on hormone receptor positive HER2 positive breast cancer Yan et al. (2023). In addition, in the HER2 mutant cancer model, the inhibitory effect of naratinib trastuzumab on tumor growth and HER2 signaling is greater than that of any single drug Ivanova et al. (2020). Moreover, it has been found that HER2 positivity could induce significantly higher levels of CDK4/6 activity, suggesting that HER2-positive BC may respond to CDK4/6 inhibitors Sinclair et al. (2022). So, we hypothesize that the early treatment with three groups of drugs, namely aromatase inhibitors (AI), CDK4/6i, and trastuzumab & pertuzumab (HP), will prolong the clinical benefits of HR+HER2 mutated MBC patients. Our research focuses on a patient with three positive(ER+, PR+, HER2+) advanced breast cancer and renal insufficiency caused by type2 diabetes. Based on the existing clinical evidence-based medical evidence, we developed the treatment method of AI+CDK4/6i+HP, and further studied the efficacy and safety of this treatment method in TPBC patients with renal

METHODS

Study design and treatment

The patient initially discovered a hypoechoic mass in the left breast 4 years ago, but due to the impact of the COVID-19 pandemic, no formal treatment was given. After 1 year, the left breast mass significantly increased to 10cm, and there was local skin rupture and bleeding. After arriving at our hospital, the patient received breast ultrasound, breast MRI, chest & abdominal CT, PET-CT, tumor markers and other examinations, followed by needle biopsy of breast lesions and axillary enlarged lymph nodes. The pathological results showed that the left breast was non-specific invasive breast cancer, axillary lymph node metastatic cancer, and immunohistochemistry （IHC） showed three positive (ER+, PR+, HER2+). Chest & abdominal CT and PET-CT revealed bilateral lung metastasis, liver metastasis, and bone metastasis. The functions of the heart, liver, and lungs are normal. Unfortunately, since the patient had type 2 diabetes for ten years and the blood sugar was not controlled well, the renal function was found to be insufficiency, and the risk of chemotherapy was high and the patient refused chemotherapy. After multidisciplinary discussions, it was decided to give endocrine therapy and targeted therapy.

The patient received AI+CDK4/6i+HP (oral letrozole 2.5 mg/day, oral abemaciclib 150mg twice/day with mandatory loperamide prophylaxis for the first 2 cycles and as needed thereafter, and intravenous trastuzumab 8mg/kg initially then 6 mg/kg every 3 weeks plus pertuzumab 840mg initially then 420mg every 3 weeks) therapy. The patient also received treatment with denosumab (120mg subcutaneous injection every 4 weeks). Patient were treated until disease progression, unacceptable toxicity, or withdrawal of consent. The protocol was approved by institutional review boards at all participating institutions; written informed consent was obtained for the patient and her husband before performing study-related procedures.

Tumor assessment

According to Response Evaluation Criteria in Solid Tumours （RECIST， version 1.1), local evaluation of tumor response is performed every 3 weeks using computed tomography or magnetic resonance imaging et al. (2020). Adverse events (AEs) were classified according to Common Terminology Criteria for AEs (version 5.0) from consent until day 28 after discontinuation of study treatment. Safety was assessed with laboratory assessments included serum creatinine (SCr), creatinine clearance rate(Ccr), serum urea, and serum potassium(K+), 12-lead electrocardiograms, echocardiograms, physical

Furthermore, glycated hemoglobin (HbA1c) is used to evaluate changes in blood sugar levels in patients.

Biomarker analysis

Tumor markers including carcinoembryonic antigen (CEA) and serum cancer antigens (CA153, CA199, and CA125) were determined by chemiluminescent immunoassay every 3 weeks Zhou et al. (2006).

HER2, ER, and PR IHC and HER2 FISH scores were determined according to manufacturer specifications (HercepTest™ and IQFISH pharmDx [Agilent Dako, Santa Clara, CA]). HER2 IHC was further evaluated for H-score from original IHC images (Discovery Life Sciences GmbH, Kassel, Germany).

Furthermore, we tested the BRAC1/2, PIK3CA, AKT and mTOR gene mutation of this patient through next-generation sequencing (NGS).

Endpoints and statistical considerations

According to RECSIT 1.1, the primary endpoint is PFS, secondary endpoints are treatment time, exploratory targets are tumor markers, and safety targets are changes of renal function.

Collect data using an electronic data collection system. Perform efficacy analysis after at least one efficacy evaluation and safety analysis after at least one dose of study treatment. All statistical analyses were performed using SAS (version 9.2).

RESULTS

Patient characteristics

The patient was a 66-years old woman. The weight was 55 kilograms and the height was 165cm.The Karnofsky(KPS) score was 80 points. The maximum diameter of breast tumors is 10 centimeters, and treated with denosumab due to bone metastasis. The overall treatment time for the patient was 81 weeks, and the patient withdrew from this study due to disease progression.

Efficacy

After 6 weeks of treatment with the given regimen, the patient began to show effectiveness, and it was observed that both the primary and metastatic lesions of the tumor had reduced to a certain extent. The duration of response time lasted for approximately 60 weeks. The PFS was 17.6 months. Please refer to Figure 1-3 for details.

Figure 1: shows the changes in the surface of the left breast tumor. A: At 3 weeks, it can be seen that the tumor invades the skin, leading to skin ulceration and bleeding, with a range of approximately 5cmX5cm; B: At 18 weeks, surface ulceration area of the tumor was significantly reduced, with a size of approximately 2cmX3cm; C: At 36 weeks, the ulceration of the tumor basically disappeared and began to show signs of regression; D: At 63 weeks, the tumor significantly subsided and the ulcerated surface showed a scabbing state; E: At 72 weeks, the area of tumor invasion of the skin increased to a certain extent, but the surface scabs still existed without ulceration; F: At 81 weeks, two new satellite metastases appeared around the tumor as indicated by the arrow.

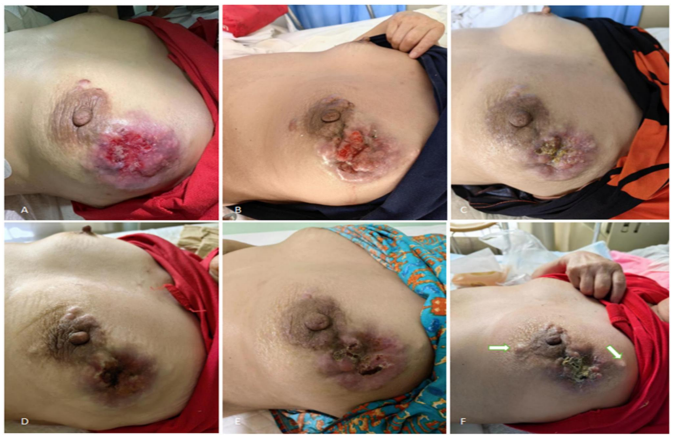
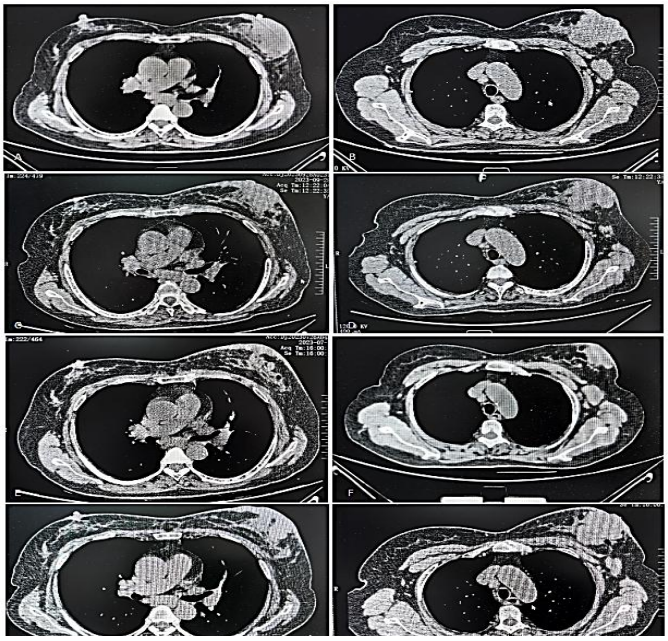
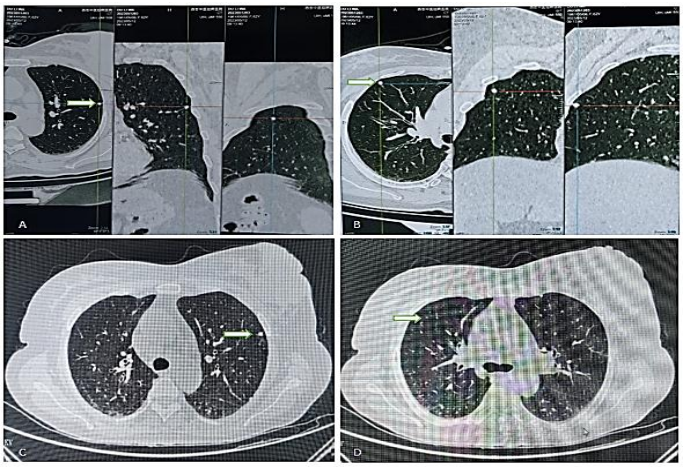


Figure 2: Changes in the size of the left breast tumor with reduced pulmonary artery and aortic arch planes on chest CT. A: At 3 weeks, the pulmonary artery plane showed a left breast tumor size of 6cmX5cm, which invaded the skin but did not invade the pectoralis major muscle; B: At 3 weeks, the aortic arch plane showed a left breast tumor with a size of 4cmX6cm, which invaded the skin but did not invade the pectoralis major muscle; C: At 18 weeks, the pulmonary artery plane showed a left breast tumor size of 5cmX3cm; D: At 18 weeks, the aortic arch plane showed a left breast tumor size of 4cm by 4cm; E: At 63 weeks, the



pulmonary artery plane showed a left breast tumor size of 4cmX2cm; F: At 63 weeks, the aortic arch plane showed a left breast tumor size of 3cmX2cm; G: At 81 weeks, the pulmonary artery plane showed a left breast tumor size of 5cmX4cm; H: At 81 weeks, the aortic arch plane showed a left breast tumor size of 3cmX5cm, which was close to the pectoralis major fascia.

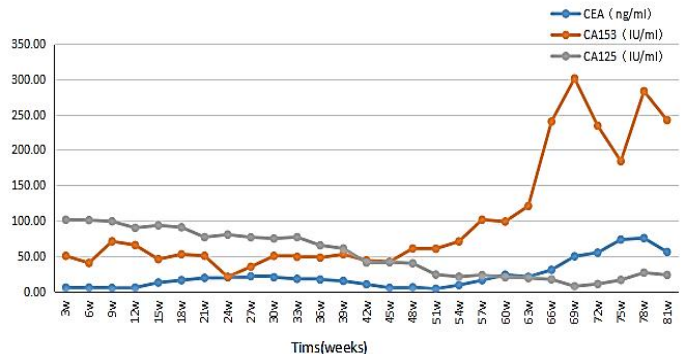
Figure 3: Changes in lung metastasis lesions (arrow). A: At 3 weeks, a 5mm x 5mm metastasis lesion can be seen in the upper lobe of the left lung; B: At 3 weeks, a metastatic lesion with a size of 5mm by 5mm can be seen in the upper lobe of the right lung; C: At 63 weeks, there was no significant change in the metastatic lesion in the upper lobe of the left lung; D: At 63 weeks, the metastatic lesion in the upper lobe of the right lung disappeared.



Biomarkers

Longitudinal ctDNA sequencing revealed acquisition of additional HER2 alterations. The NGS results of this patient indicate no PIK3CA mutation. The BRAC1/2, AKT, and mTOR genes also showed no mutations. After the start of treatment, the three serum tumor markers related to breast cancer showed a significant downward trend, but with the continuation of treatment, the three tumor markers increased again from 66 weeks (Supplementary Figure 4).

Figure 4: Changes in the levels of three tumor markers during the treatment cycle.



Safety

The most common treatment-emergent AEs are summarized. Diarrhea of grade 2 occurred after the start of treatment and was transient (approximately duration 7 days). After treatment with loperamide, diarrhea symptoms were significantly relieved. Throughout the entire treatment cycle, the patient's renal function remained stable, with no significant fluctuations in creatinine, creatinine clearance rate, serum urea, and serum potassium, as shown in Figure 5-8. The median value of SCr was 200μmol/L. The median value of Ccr is 20ml/min. The median value of serum urea was 15mmol/L. The median value of K+ was 4mmol/L. The patient's blood sugar control was good, with a median HbA1c was 6% (Supplementary Figure 9).

Figure 5: Changes in creatinine levels during the treatment cycle.

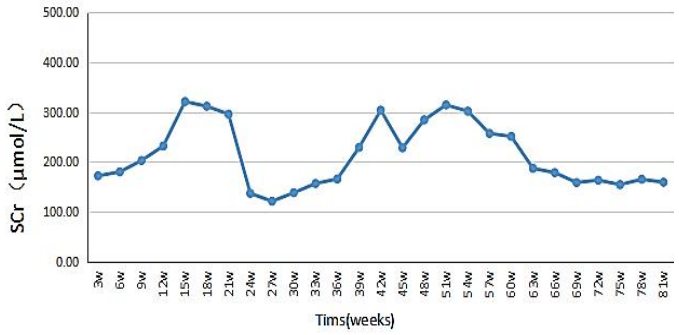


Figure 6: Changes in creatinine clearance rate of patient during the treatment cycle.

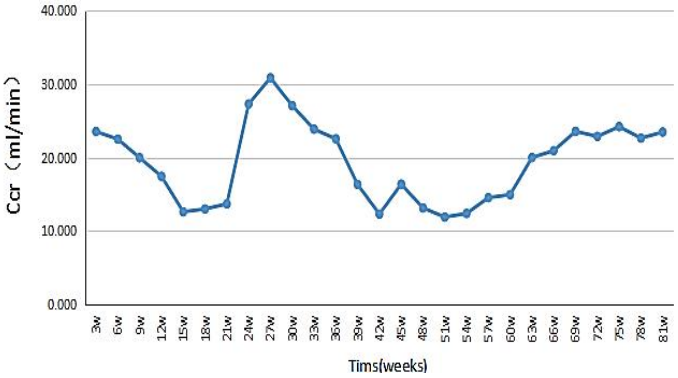


Figure 7: Changes in urea levels during the treatment cycle.

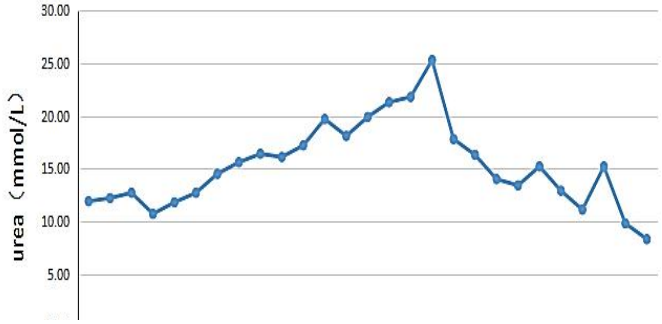


Figure 8: Changes in serum potassium levels of patient during the treatment cycle.

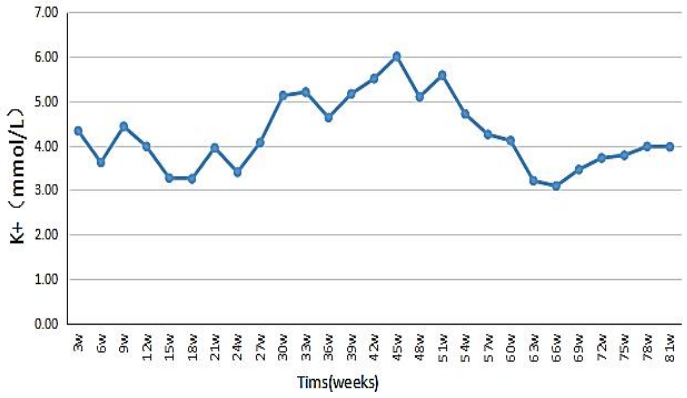
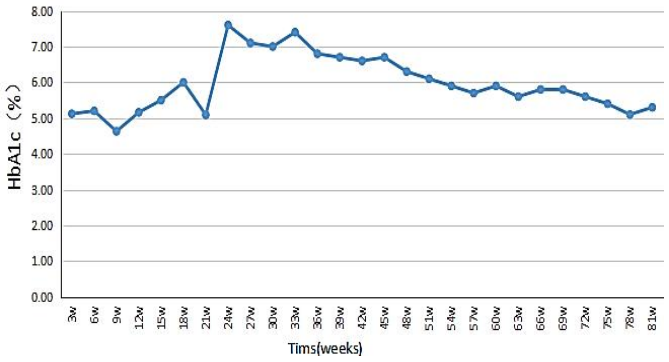


Figure 9: Changes in glycated hemoglobin levels in patient during the treatment cycle.



DISCUSSION

The guidelines of the National Cancer Comprehensive Network(NCCN), the European Society of Medical Oncology(ESMO), and the Chinese Society of Clinical Oncology(CSCO) all indicate that anthracycline drugs+cyclophosphamide→paclitaxel+trastuzumab(AC →TH) can be used as adjuvant chemotherapy for breast cancer and positive lymph nodes in patients with ER+/PR+/HER2+; After chemotherapy, patients with ER+ or PR+ should receive adjuvant endocrine therapy Gradishar et al. (2018). At present, domestic and international guidelines recommend that the preferred treatment for TPBC is chemotherapy combined with targeted therapy, but patients with ER expression greater than 30% benefit less from the combination of anti HER2 targeted therapy and chemotherapy Montemurro et al. (2012).

Doctors and pharmacists must simultaneously consider the benefits of cancer treatment and the impact of anti-tumor drugs on residual kidney function in patients, and choose appropriate methods to balance the efficacy and safety of drugs. In response to the relatively low response rate of TPBC receiving anti HER2 targeted therapy combined with chemotherapy, it is urgent to explore new methods and optimize treatment strategies. The combination of endocrine therapy and targeted therapy with dual pathway blockade can better control the growth of TPBC tumors, especially for patients who are unable to tolerate chemotherapy and need to maintain treatment stability due to the combination of chemotherapy and targeted therapy. At present, various anti-HER2 targeted drugs are constantly emerging, as well as the clinical application of cyclin dependent kinase 4/6 (CDK4/6) inhibitors. The clinical application of different anti-HER2 targeted drugs combined with CDK4/6 inhibitors in TPBC is constantly being explored and studied. With the clinical application of pertuzumab, dual target combination chemotherapy has effectively improved the survival rate of patients.

Based on the design of the TAnDEM study Kaufman et al. (2009) and the CLEOPATRA study Baselga et al. (2012), the PERTAIN study Rimawi et al. (2018) was conducted to investigate whether first-line use of AI combined with trastuzumab and pertuzumab can improve efficacy in patients with advanced TPBC. The study demonstrated that compared to AI combined with trastuzumab, the combination of AI and dual targets can significantly prolong progression free survival(PFS) (18.89 months vs.15.80 months HR 0.65; 95% CI, 0.48-0.89; P=0.0070). It is worth noting that enrolled patients are allowed to use induction chemotherapy before endocrine therapy and targeted therapy. More than 55% of the two groups of patients first received chemotherapy combined with targeted therapy, followed by endocrine combined with targeted therapy. Therefore, PERTAIN research is not simply a combination of endocrine targeted therapy, but rather an endocrine maintenance therapy based on chemotherapy stability. Therefore, AI combined with dual target therapy can serve as a maintenance treatment method for patients with remission through chemotherapy combined with dual target therapy. In the final analysis of the CLEOPATRA study Swain et al. (2020), researchers compared long-term and non-long-term responders to dual target therapy and found that HER2 IHC 3+and PIK3CA mutations had the greatest difference between the two populations. Patients with HER2 3+and without PIK3CA mutations had a higher probability of achieving long-term remission. Our study also confirms this point. The NGS results of this patient indicate no PIK3CA mutation, and her PFS reached 18 months.

The PERNETTA study (NCT01835236) Huober et al. (2019) compared the 2-year overall survival(OS) and disease-free survival(DFS) of TPBC using dual target combination endocrine therapy with sequential endocrine therapy using dual target combination chemotherapy.

The results showed that the first-line treatment PFS of TPBC using dual target combination chemotherapy was shorter(8.3 months vs. 23.7 months), but there was no difference in the 2-year OS rate compared to the chemotherapy group(75.0% vs. 74.2%), Moreover, chemotherapy is associated with more adverse reactions, indicating that omitting the chemotherapy regimen for some patients is also an option when using first-line dual target HER2 therapy combined with endocrine therapy and second-line T-DM1 treatment.

At present, there is an endless stream of targeted drugs against HER2. It is worth exploring whether the combination therapy of targeted drugs with different mechanisms of action, such as small molecule TKI and large molecule monoclonal antibodies, can further improve the survival benefits of TPBC patients. The AlterNATIVE Phase III randomized controlled study Johnston et al. (2021) showed that dual HER2 therapy with lapatinib, trastuzumab, and AI showed better PFS efficacy benefits compared to trastuzumab and AI in TPBC patients (median PFS, 11 months vs. 5.6 months; HR 0.62; P=0.0063). This combination therapy provides an effective and safe treatment plan for such patients. The CLEOPATRA study Baselga et al. (2012) showed a PFS of 12.4 months for the dual target combination chemotherapy, while the AlterNATIVE study Johnston et al. (2021) achieved a PFS of 11 months for the dual target combination endocrine therapy, indicating that chemotherapy can be avoided for highly selective patients, and the dual target combination endocrine therapy is expected to become a recommended regimen for TPBC treatment.

Trastuzumab and pertuzumab are biological macromolecules with molecular weights between 140-150kDa, and their ability to penetrate cell membranes is poor. Usually in the human body, they are metabolized into peptides and amino acids through circulating phagocytes or their target cells, rather than through the liver and kidneys. Theoretically, baseline liver and kidney dysfunction has little effect on the clearance of trastuzumab and pertuzumab Maly et al. (2014). Although there have been reports that the use of trastuzumab can cause reversible damage to fetal renal function, there is no effect of trastuzumab on renal function in adults, and there are few reports of using targeted drugs in baseline renal failure patients Gottschalk et al. (2011).

According to FDA guidelines, if the molecular weight of a drug is less than 69kDa, experiments should be designed to evaluate the impact of renal dysfunction on drug metabolism in patients. Generally speaking, in this study, the targeted drug has a molecular weight range cannot be filtered by the glomerulus and eliminated from the body through the kidneys. However, the elimination mechanism of biological macromolecules is much more complex than non-specific and unsaturated catabolism.

With the continuous improvement of CDK4/6 inhibitor combined with endocrine therapy in the treatment of HR positive/HER2 negative breast cancer, this scheme provides a new idea for the treatment of TPBC advanced breast cancer. CDK is a protease that regulates various stages of the cell cycle, and its continuous activation can lead to tumor cell proliferation Bury et al. (2021). CDK4/6 inhibitors mainly inhibit the G1-S phase of cells, thereby inhibiting the DNA replication process and achieving anti-tumor effects Beykou et al (2022).

Several preclinical trials have shown the combination of CDK4/6 with other targeted drugs plays a favorable antitumor role in breast cancer cells. PATRICIA study Ciruelos et al. (2020) is a prospective, multicenter and open phase II clinical study, which aims to evaluate the efficacy and safety of CDK4/6 inhibitor palbociclib+trastuzumab combined or not combined with endocrine therapy in HER2 positive advanced breast cancer patients. The results show that the PFS rate for ER positive combined or not combined with letrozole for 6 months is 42.8%(12/28) and 46.4%(13/28), The results indicate that CDK4/6 inhibitors combined with targeted therapy against HER2 and endocrine therapy have a better prognosis.

MonarcHER study Tolaney et al. (2020) In TPBC patients with advanced breast cancer who have received at least second-line anti HER2 treatment, we evaluated the phase II clinical study of the CDK4/6 inhibitor abemaciclib+trastuzumab ±fulvestrant, compared with trastuzumab+chemotherapy. The main endpoint of the study was PFS. The group of abemaciclib+trastuzumab+fulvestrant significantly improved PFS compared with the group of trastuzumab+chemotherapy(8.32 months vs. 5.7 months, HR=0.067, P=0.051), There was no significant difference in PFS between the abemaciclib+trastuzumab group and the trastuzumab+chemotherapy group(5.65 months vs. 5.69 months, HR=0.94, P=0.77).The objective response rate(ORR) results of abemaciclib+trastuzumab+fulvestrant group were significantly higher than those of the other two groups, confirming that the three drug combination regimen can still achieve certain clinical remission in TPBC patients after treatment. Therefore, targeted combination endocrine therapy has the potential to replace traditional chemotherapy combined with anti HER2 targeted therapy in the population of TPBC advanced patients who have failed anti HER2 treatment.

Zhang et al. (2022) conducted a Phase Ib clinical study(LORDSHIPS) on the first/second line treatment of advanced TPBC patients with a combination regimen of dalpiciclib, pyrotinib, and letrozole. The study included 15 patients with advanced TPBC, with a median follow-up time of 11.4 months. In terms of efficacy, the ORR reached 66.7%, with a median PFS of 11.3 months. Among them, the ORR of the first line treatment subgroup against HER2 was 85.7%, and the median PFS had not yet been achieved; The ORR of the anti HER2 second-line treatment subgroup was 50.0%, with a median PFS of 10.9 months, indicating that this regimen may benefit more from first-line treatment. Compared with palbociclib, the combination of abemaciclib and endocrine therapy may prolong invasive disease-free survival (iDFS) in ER+/HER2- BC patients and have a good safety Harbeck et al. (2021). Moreover, abemaciclib combined with fulvestrant in treating ER+/HER2− BC patients significantly improved PFS and ORR Sledge et al. (2017). So, in this study, we chose abemaciclib as the CDK4/6i.Several clinical trials related to CDK4/6 inhibitors are underway and we expect good results.

Combining anti HER2 targeted therapy with endocrine therapy with CDK4/6 inhibitors is expected to achieve greater benefits for advanced TPBC patients. With the continuous updating of clinical research data and the continuous improvement of evidence-based medical evidence, the efficacy of rescue treatment plans for late stage TPBC patients is gradually becoming clear. The endocrine targeting combined with anti HER2 targeting treatment plan is expected to become one of the optional options for late stage TPBC patients.

From the above studies, we can conclude that endocrine therapy and targeted therapy are safe and feasible for patients with triple-positive breast cancer combined with renal insufficiency or renal failure.

However, the above conclusions have not been confirmed by large-scale prospective studies. Therefore, for tumor patients with baseline renal failure or renal insufficiency, targeted and endocrine therapy choices should consider changes in renal function, so that patients have more treatment options in balancing patient organ function and tumor treatment benefits.

DECLARATIONS

Authorship contribution statement

Li Gang: Conceptualization, Investigation, Writing–original draft. Li Hanjie: Investigation. Ge Peng: Investigation & editing. Yu Jiao: Conceptualization, Investigation, Writing–review & editing.

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.

Data availability

Data will be made available on request.

Acknowledgments

This work was supported by General Project-Social Development Field of Shaanxi Province Key Research & Development Plan (grant No. 2021SF-306) and The Second Affiliated Hospital of Xi'an Medical University Doctor 's foundation(X2Y-R9).

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, et al. 2022. Cancer statistics, 2020. CA Cancer J Clin. 72(1):7-33.

2. Lowrance WT, Ordoñez J, Udaltsova N, et al. 2014. CKD and the risk of incident cancer. J Am Soc Nephrol. 25(10):2327-34.

3. Malyszko J, Tesarova P, Capasso G, et al. 2020. The link between kidney disease and cancer: complications and treatment. Lancet. 396(10246):277-87.

4. Armstrong AE, Dargart J, Reichek J, et al. 2014. Irinotecan and temozolomide for treatment of neuroblastoma in a patient with renal failure on hemodialysis. Pediatr Blood Cancer. 61(5):949-50.

5. Magee C. 2014. Kidney disease and death from cancer. Am J Kidney Dis. 63(1):7-9.

6. Modi G, Madabhavi I, Patel A, et al. 2018. Treatment of breast cancer in a patient of Alport syndrome-induced chronic renal failure: A triumph story. J Cancer Res Ther. 14(2):462-64.

7. Zhao S, Liu XY, Jin X, et al. 2019. Molecular portraits and trastuzumab responsiveness of estrogen receptor-positive, progesterone receptor-positive, and HER2-positive breast cancer. Theranostics. 9(17):4935-45.

8. Johnston SRD, Hegg R, Im SA, et al. 2021. Phase III, Randomized Study of Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade with Lapatinib Plus Trastuzumab in Combination with an Aromatase Inhibitor in Postmenopausal Women with HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: Updated Results of ALTERNATIVE. J Clin Oncol. 39(1):79-89.

9. Dieci MV, Guarneri V. 2020. Should triple-positive breast cancer be recognized as a distinct subtype? Expert Rev Anticancer Ther. 20(12):1011-1014.

10. Spring LM, Wander SA, Andre F, et al. 2020. Cyclin-dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: past, present, and future. Lancet. 395(10226):817-27.

11. George MA, Qureshi S, Omene C, et al. 2021. Clinical and Pharmacologic Differences of CDK4/6 Inhibitors in Breast Cancer. Front Oncol. 11:693104.

12. Yan M, Niu L, Lv H, et al. 2023. Dalpiciclib and pyrotinib in women with HER2-positive advanced breast cancer: a single-arm phase II trial. Nat Commun. 14(1):6272.

13. Ivanova E, Kuraguchi M, Xu M, et al. 2020. Use of Ex Vivo Patient-Derived Tumor Organotypic Spheroids to Identify Combination Therapies for HER2 Mutant Non-Small Cell Lung Cancer. Clin Cancer Res. 26(10):2393-03.

14. Sinclair WD, Cui X. 2022. The Effects of HER2 on CDK4/6 Activity in Breast Cancer. Clin Breast Cancer. 22(3): e278-e85.

15. Smyth LM, Piha-Paul SA, Won HH, et al. 2020. Efficacy and Determinants of Response to HER Kinase Inhibition in HER2-Mutant Metastatic Breast Cancer. Cancer Discov. 10(2):198-13.

16. Zhou L, Liu J, Luo F. 2006. Serum tumor markers for detection of hepatocellular carcinoma. World J Gastroenterol. 12(8):1175-81.

17. Gradishar WJ, Anderson BO, Balassanian R, et al. 2018. Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 16(3):310-20.

18. Montemurro F, Rossi V, Rocca MC, et al. 2012. Hormone-receptor expression and activity of trastuzumab with chemotherapy in HER2-positive advanced breast cancer patients. Cancer. 118(1):17-26.

19. Kaufman B, Mackey JR, Clemens MR, et al. 2009. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol. 27(33):5529-37.

20. Baselga J, Cortes J, Kim SB, et al. 2012. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 366(2):109-19.

21. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al. 2018. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. J Clin Oncol. 36(28):2826-35.

22. Swain SM, Miles D, Kim SB, et al. 2020. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 21(4):519-30.

23. Huober J, Ribi K, Weder P, et al. 2019. Pertuzumab (P)+trastuzumab (T) with or without chemotherapy both followed by T-DM1 in case of progression in patients with HER2-positive metastatic breast cancer (MBC) - The PERNETTA trial (SAKK 22/10), a randomized open label phase II study (SAKK, UNICANCER, BOOG). Ann Oncol.

24. Maly JJ, Macrae ER. 2014. Pertuzumab in Combination with Trastuzumab and Chemotherapy in the Treatment of HER2-Positive Metastatic Breast Cancer: Safety, Efficacy, and Progression Free Survival. Breast Cancer (Auckl). 8:81-8.

25. Gottschalk I, Berg C, Harbeck N, et al. 2011. Fetal Renal Insufficiency Following Trastuzumab Treatment for Breast Cancer in Pregnancy: Case Report und Review of the Current Literature. Breast Care (Basel). 6(6):475-78.

26. US Food and Drug Administration. 2022.

27. Bury M, Le Calvé B, Ferbeyre G, et al. 2021. New Insights into CDK Regulators: Novel Opportunities for Cancer Therapy. Trends Cell Biol. 31(5):331-44.

28. Beykou M, Arias-Garcia M, Roumeliotis TI, et al. 2022. Proteomic characterisation of triple negative breast cancer cells following CDK4/6 inhibition. Sci Data. 9(1):395.

29. Ciruelos E, Villagrasa P, Pascual T, et al. 2020. Palbociclib and Trastuzumab in HER2-Positive Advanced Breast Cancer: Results from the Phase II SOLTI-1303 PATRICIA Trial. Clin Cancer Res. 26(22):5820-29.

30. Tolaney SM, Wardley AM, Zambelli S, et al. 2020. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial. Lancet Oncol. 21(6):763-75.

31. Zhang J, Meng Y, Wang B, et al. 2022. Dalpiciclib Combined with Pyrotinib and Letrozole in Women with HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer (LORDSHIPS): A Phase Ib Study. Front Oncol. 12:775081.

32. Harbeck N, Rastogi P, Martin M, et al. 2021. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 32(12):1571-81

33. Sledge GW Jr, Toi M, Neven P, et al. 2017. MONARCH 2: Abemaciclib in Combination with Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 35(25):2875-84.