Project source: Oral longitudinal project Oral horizontal project ☑ Spontaneous research

Safety and tolerability of concurrent CDK4/6 inhibitors with radiotherapy after surgery for HR+/HER2- high-risk breast cancer

Study Project Title: Safety and Tolerability Study of Concurrent CDK4/6 Inhibitors with Postoperative Radiotherapy for HR+/HER2- High-risk Breast Cancer

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1. Research background

According to data released by the World Health Organization (WHO) International Agency for Research on Cancer, the number of new breast cancer cases worldwide reached about 2.3 million in 2022, ranking first among female cancer incidences. In recent years, the incidence of breast cancer in our country has increased year by year, with 416,000 new cases of breast cancer and 117,000 deaths in our country in 2020 [2]. The current treatment methods of breast cancer are mainly closely related to the molecular typing of breast cancer. The concept of molecular typing of breast cancer was first proposed in 2000 by Professors Perou and Sorlie of Stanford University in the United States [3], and has been widely used in clinical practice. There are currently four main molecular types of breast cancer, namely: Luminal A, Luminal B, HER2 overexpression, and basal cell-like/triple negative. Among them, Luminal Type A mainly refers to high expression of ER (estrogen receptor) and PR (progesterone receptor), negative HER2 (human epidermal growth factor receptor 2), and low expression of Ki67. This type of breast cancer is sensitive to endocrine therapy and has the best prognosis, while HR-positive/HER2-negative breast cancer is also the most common subtype of breast cancer, accounting for 65%-75% of all breast cancers [4]. The main treatments for this subtype are surgery, endocrine therapy (ETs), targeted therapy, chemotherapy, antibody-drug conjugates (ADCs), and immunotherapy. Although HR+/HER2- early-stage breast cancer patients generally have a good prognosis after standard endocrine therapy, 30% of high-risk patients still have recurrence and metastasis within 5 years after standard treatment [5], and the risk of recurrence peaks within 2-3 years after surgery. Therefore,

endocrine intensive therapy for high-risk patients is currently a hot topic of clinical attention. The current evaluation criteria for high-risk patients after breast cancer surgery in our country are: 1. When the number of lymph nodes is positive 1~3, ER/PR is positive and HER2 is negative, any of the following conditions can be judged as high-risk: grade III. Tumor size (pT) greater than 5cm; Polygenic testing is at high risk. 2) If the number of lymph nodes is positive 1~3, ER is negative and PR is negative; or HER2 positive. 2. The number of positive lymph nodes is greater than or equal to 4. With the advancement of science and technology, the continuous development of targeted drugs has led to the birth of targeted drugs that can accurately act on the inside of cancer cells. The mechanism by which CDK4/6 inhibitors work is mainly due to cyclin-dependent kinase (CDK)4/6, a key regulator of the cell cycle, which can trigger the cell cycle from pre-DNA synthesis (G1 phase) to DNA replication (S1) by forming a complex with cyclin D, phosphorylating Rb, and releasing E2F [6]. In HR+ breast cancer, the CDK4/6-cyclinD-Rb pathway is very important and is a key downstream target for HR signaling. Therefore, it blocks the activity of CDK4/6 kinase, restores cell cycle control, blocks tumor cell proliferation, and inhibits the growth of breast cancer cells. Johnston et al. [7] published in The Lancet is an open-label, randomized phase III trial that included patients with early-stage HR+/HER2- breast cancer at high risk of recurrence. Early findings from this trial confirm that endocrine therapy in combination with CDK4/6 inhibitors can be used as intensive therapy for patients with early-stage HR+/HER2- breast cancer. The updated results of the study further confirmed that CDK4/6 inhibitors + endocrine adjuvant therapy can bring significant iDFS benefit (2 years: 92.7% vs 89.9% (2.8% benefit);

3 years: 89.2% vs 84.4% (gain 4.8%); 4 years: 85.8% vs 79.4% (benefit 6.4%)) and a 33.6% reduction in the risk of invasive disease or death (HR: 0.664, P<0.001). The DRFS-free survival rate of distant recurrence (DRFS) in the intention-to-treat (ITT) population increased with the extension of follow-up, and the DRFS rate of CDK4/6 inhibitor + endocrine adjuvant therapy increased by 5.9% (88.4% vs. 82.5%) at 4 years. A randomized, open-label, global multicenter phase III clinical trial initiated by Slamon et al. [8, 9] included a total of 5101 patients with stage II-III. early-stage HR+/HER2- breast cancer at risk of recurrence from 20 countries, randomly divided into two groups in a 1:1 ratio, respectively receiving CDK4/6 inhibitors (400 mg/day, 3 weeks of administration + 1 week of discontinuation for 3 years) + endocrine therapy (AI for ≥ 5 years, men and premenopausal women receiving OFS treatment at the same time) or endocrine therapy alone. The results of the trial, presented at the 2023 ASCO Congress, showed that patients treated with CDK4/6 inhibitors + endocrine therapy (AI+OFS) had longer iDFS than ET alone (90.4% vs 87.1%), with an absolute difference of 3.3%. The recurrence wind direction was reduced by 25.2% (HR: 0.748; 95% CI: 0.618-0.906; P=0.0014), and the safety was good. The recent SABCS congress presented the final iDFS data for the study with a median follow-up of 33.3 months [10]. At a median follow-up of 33.3 months, the 3-year iDFS rates in the CDK4/6 inhibitor + NSAI group and the NSAI group were 90.7% (95%CI: 89.3%-91.8%) and 87.6% (95%CI: 86.1%-88.9%), respectively. Compared with NSAI alone, the CDK4/6 inhibitor + NSAI group showed a significant benefit in 3-year iDFS (HR: 0.749; 95% CI: 0.628-0.892; P=0.0006), and the safety was consistent with the results of previous studies. These studies suggest that CDK4/6i combined with endocrine therapy has good safety

and efficacy.

At the same time, radiotherapy is not only an important means of comprehensive treatment of breast cancer, which can reduce the recurrence rate and prolong survival of patients after breast-conserving surgery and high-risk mastectomy surgery. Adjuvant radiotherapy is mainly aimed at killing potential residual tumor cells in the ipsilateral breast after breast cancer surgery, chest wall after mastectomy, and regional lymph nodes, thereby reducing the risk of recurrence, prolonging patient survival, and improving the cure rate. Preclinical studies [11] have shown potential synergistic effects of radiotherapy combined with CDK4/6 inhibitors. Some preclinical studies [12-15] have also shown that CDK4/6 inhibitors can sensitize radiotherapy by anti-angiogenesis, inhibition of DNA damage repair, and inhibition of mammalian rapamycin target protein signaling, which provides a theoretical basis for radiotherapy combined with CDK4/6 inhibitors for the treatment of ER+Her2- metastatic breast cancer. Guerini et al. [16] reported 18 cases of metastatic breast cancer treated with CDK4/6 inhibitors combined with radiotherapy, with pain control in all patients within 3 months after the end of radiotherapy, with a median follow-up time of 13.7 months (range 2~29 months), and by the end of follow-up, a total of 6 patients had tumor recurrence (including 3 deaths), and another 12 patients had no tumor progression and were still receiving CDK4/6 inhibitor therapy. Compared with historical data, radiotherapy combined with CDK4/6 inhibitors controlled distant metastases of breast cancer similar to radiotherapy alone, but overall survival was prolonged and there was no increase in adverse effects. A study published by Beddok et al. [17] in 2020 evaluated the safety and efficacy of radiotherapy

(local breast and lymph node irradiation) in combination with piperciclib in nine patients with de novo metastatic breast cancer. Two patients discontinued pipercilib during radiotherapy due to grade 2 radiation dermatitis, pain, and grade 2 radiation esophagitis. Because of the lack of studies on radiotherapy in combination with CDK4/6 inhibitors, most radiation oncologists preferred to suspend CDK4/6 inhibitors during radiotherapy because the safety of this combination was still unclear at the time. In a study by Meattini et al. [18], 5 patients who received palliative radiotherapy combined with rebocillin and letrozole for metastatic breast cancer had 2 grade III.~IV. adverse reactions, including 1 case of neutropenia and 1 case of gastrointestinal adverse reactions. In the preclinical trial of 5 patients with metastatic breast cancer who received palliative radiotherapy combined with pipesciclib and fulvestrant reported by Hans et al. [19], all patients had good local tumor control and pain relief, and the adverse reactions of this treatment regimen were mainly reflected in the blood system, with a total of 2 cases of grade III. neutropenia, 2 cases of grade III. thrombocytopenia, and 1 case of grade III. anemia, as well as 2 cases of grade I.~II. gastrointestinal adverse reactions, and no skin adverse reactions were observed. Among the 18 patients treated with radiotherapy combined with CDK4/6 inhibitors, 11 patients developed grade III.~IV. neutropenia within 3 months after radiotherapy, and 4 patients who had been treated with CDK4/6 inhibitors for more than 3 months before the start of radiotherapy had previously experienced grade III.~IV. hematologic adverse reactions, and 1 case had grade III. gastrointestinal adverse reactions. Although the incidence of hematologic adverse reactions was high in the above clinical trials, the addition of radiotherapy did not

additionally increase the incidence and severity of adverse reactions compared with CDK4/6 inhibitors combined with endocrine therapy for metastatic breast cancer [20-23], and hematologic adverse reactions were easily controlled and did not lead to permanent discontinuation of CDK4/6 inhibitors. A meta-analysis [24] evaluated the safety and feasibility of CDK4/6i in combination with radiotherapy, and the results showed that the addition of radiotherapy to CDK4/6i in patients with HR+/HER2- advanced breast cancer is safe and well-tolerated as a viable treatment option, and its overall incidence of adverse reactions is comparable to that of CDK4/6i alone. From the above studies, it can be seen that the addition of RT on the basis of CDK4/6 inhibitors has a synergistic effect, but may this combination increase the risk of adverse reactions, and how much does the adverse risk increase? The conclusion is still uncertain. There is currently a lack of prospective data evaluating the safety of CDK4/6 inhibitors in combination with RT.

Therefore, based on the above studies, we propose the following design: to explore the tolerability and safety of postoperative radiotherapy combined with CDK4/6 inhibitors and endocrine adjuvant therapy in patients with high-risk breast cancer after HR+/HER2- surgery. At the same time, because breast cancer has gradually become a chronic disease, it affects the patient's life for a long time. Patient-reported outcome [25], or patient-reported outcome, is a report that directly reflects the patient's assessment of their own health status. It emphasizes the outcome of the assessment of one's own illness and corresponding treatment feelings that are directly reported by the patient and are not modified or interpreted by others. While conducting research, we will also use PRO scales (FACT-B, FACT-ES, FACT-F) to evaluate

patients' multi-dimensional feelings such as physical function, emotional state, and treatment-related symptoms during treatment, so as to obtain more realistic and reliable data on the patient's symptom assessment and gain.

2. Research purpose

1. Primary objective: This study aims to observe the tolerability and safety of postoperative adjuvant radiotherapy combined with CDK4/6 inhibitors in patients with hormone receptor-positive, HER2-negative high-risk breast cancer.

2. Secondary Objectives:

（1） To explore the combined gain of radiotherapy combined with CDK4/6i in 1+1>2 clinical practice.

（2） To evaluate the progression-free survival (PFS) and overall survival (OS) of patients receiving this combination therapy regimen

3. Study design type, principles and study steps

1. Study design

This study is a prospective, exploratory, observational, single-center study.

2. Sample size and grouping method

Sample content estimate: Thirty patients with HR+/HER2- high-risk early breast cancer will be collected. As TITE-CRM trial designs typically include 24 to 36 participants (Daniel Normolle JCO 2006). And the simulation study showed that 30 patients had good operability in the correct selection of MTD. Therefore, 30 patients will receive this combination regimen.

Group method: There was no control group in this study.

3. Research period

May 2025 to May 2026

4. Subject selection

Selection Criteria:

1. Age 18-60 years old, gender is female

2. Postoperative pathological examination confirmed the diagnosis of HR+, HER2- invasive breast cancer:

1) ER positive and/or PR positive is defined as: all tumor cells stained positively

The proportion of tumor cells ⩾ 10%;

2) HER2 negativity is defined as: standard immunohistochemistry (IHC) test is 0/1+;

ISH test is negative.

3. Radical surgery or breast-conserving surgery to randomization no more than 6 months;

4. Radical surgery Postoperative pathological examination showed the presence of lymph nodes in the ipsilateral axilla of the breast lesion

Metastasis (Lymph node micrometastasis, ipsilateral internal mammary lymph nodes, and supraclavicular lymph nodes are allowed.)

but the number of metastases in ipsilateral medial mammary lymph nodes and supraclavicular lymph nodes is not included in the positive one

calculation of sexual lymph nodes), the specific requirements are as follows:

1) Number of lymph node metastases⩾ 4;

2) When the number of lymph node metastases is 1 to 3, at least one of the following high-risk factors must be met:

i. Postoperative pathological detection of primary tumor diameter ≥5cm;

ii. Primary lesion histology grade III (excluding grade II-III);

iii. Invasive cancer residue in breast lesions after neoadjuvant therapy;

iv. Ki-67≥30%。

6. Eastern Cooperative Oncology Group (ECOG) physical status score of 0-2 points.

7. Willing and able to comply with the planned visits with the consent of the person and signed the informed consent form

visual examination, study treatment plan, laboratory tests, and other research procedures.

Exclusion Criteria:

1. Diagnosis of HER2-positive breast cancer by pathological examination (HER2-positive definition: standard immunization

Histochemistry (IHC) test is 3+ or ISH test is positive).

2. Recurrent disease locally or regionally in which breast malignancy has occurred.

3. The clinical stage of the tumor is stage IV (metastatic) breast cancer.

4. Bilateral breast cancer (including contralateral carcinoma in situ).

5. History of severe lung diseases such as interstitial pneumonia.

6. Previous treatment with CDK4/6 inhibitors and other anti-tumor biologics

therapy, targeted therapy, or tumor immunotherapy.

7. Major surgical procedures, any investigational drugs, and others within 4 weeks prior to randomization

Anti-cancer therapy or use of immunomodulators (excluding surgery for

breast cancer, chemotherapy, radiotherapy and

endocrine therapy).

8. Presence of other serious physical or psychiatric illness or laboratory abnormalities that may increase participation

risks of the study, or interfering with the results of the study, and the investigator deems it unsuitable to participate in this study

Research patients.

Midway exit criteria:

1. Subjects withdraw informed consent to participate in the study and refuse further follow-up;
2. Other circumstances in which the investigator deems it necessary to withdraw from the study, such as subjects due to incarceration

the ability to express one's will freely due to prohibition or isolation, etc.;

3. Loss to follow-up;
4. Subject death;

5. Research steps and related examinations

5.1. Screening period

Screening assessment of patients was performed during the patient's pre-hospitalization, and the investigator screened pre-hospitalized patients eligible for enrollment from the electronic inpatient medical record system. Informed consent signed by the subject must be obtained prior to any study-specific procedures or assessments. The personal information, disease history, family history, marital and childbearing history, postoperative pathology and other related laboratory tests of

pre-hospitalized patients were queried and collected from the electronic inpatient medical record system, and whether the subjects were eligible for inclusion in this study were clarified.

5.2.Observation and data collection period

After the patient is enrolled, the next patient's CDK4/6i dose is determined based on the DLTs observed in all previously evaluated patients by dose allocation model (empirical logic model, obtained using the R dfcrm software package). CDK4/6i (abeciclib, oral) is 50 mg bid starting at the other dose levels: 100 mg bid, 150 mg bid. At the same time, since the routine hospitalization time of radiotherapy patients is about 36 days, the patient's vital signs, test items, adverse reactions and related treatment measures will be recorded on D10, D20, D30, and D40 respectively during the hospitalization of patients using radiotherapy combined with CDK4/6 inhibitor combination treatment regimen. If the patient's radiation therapy is delayed for any reason, the recording time should be postponed according to the actual situation. (The day before radiotherapy (T0), the 4th week during radiotherapy, (T1), after radiotherapy (T2), 1 month after radiotherapy (T3), and 3 months after radiotherapy (T4)) The patients were evaluated by FACT-B, FACT-ES, and FACIT-F scales.

5.3.Data analysis period

The tolerability and safety of the combination treatment regimen were evaluated by statistical methods, and the changes in the quality of life of the patients during the quality of life period were evaluated to form the study conclusions. Data cleaning and preprocessing, safety analysis (incidence and severity of AEs; Serious adverse events and treatment

correlation analysis), results summary and report.

4. Evaluation indicators/research endpoints

1. Observe indicators

(1) Primary endpoints: To determine the incidence of early DLTs (early adverse reactions related to radiotherapy combined with CDK4/6i), and to determine the MTD of radiotherapy combined with CDK4/6i and the tolerability and safety of the combination treatment regimen.

(2) Secondary endpoints:

• Subjects' quality of life measurement scales FACT-B, FACT-ES, FACT-F questionnaire scores;

5. Arrangement of visits and data collection during the study

This study mainly collected the patient's laboratory examinations in the electronic medical record system during hospitalization, such as blood routine, liver and kidney function, electrolytes, tumor markers, etc., as well as the adverse event record form (including occurrence time, grading, treatment and outcome).

1 month and 3 months after the end of the combination treatment program, the patient was followed up in the outpatient clinic due to routine clinical diagnosis and treatment, and the follow-up evaluation and PRO scale questionnaire score were performed during the outpatient review.

6. Clinical evaluation

Safety evaluation: Safety will be monitored by assessing adverse events and laboratory data, and the severity of adverse events and early and late toxicities will be graded using NCI CTC-AE version 4.03.

7. Project risk and benefit assessment

1. Risks: Patients may be at risk of privacy leakage.
2. Benefit: Patients have no direct benefit.

8. Subject protection measures

1. Participation in this study is completely voluntary, and the study subjects have the right to refuse to participate in the study, which will not affect the doctor's treatment of the study subjects. Even if the study subject agrees to participate in the study, he or she can withdraw from the study at any time during the study process, which again does not affect due rights.

2. This study is an observational study, which will not affect the effect of treatment, the risk is small, and if there are corresponding adverse reactions, our department will provide symptomatic supportive treatment for the patient to minimize the damage.

3. To protect your privacy, we will mark your personal information with a research number in a non-personally identifiable way. The results of this project study may be published in medical journals, but we will keep your research records confidential as required by law. Your personal information will be kept strictly confidential and will not be disclosed unless required by relevant laws.

9. Quality control and quality assurance of research

1. The subjects have good compliance.

2. Study participants are professionally trained.

10. Data preservation

Saved in written form in a locked file cabinet and saved in a computer in an encrypted folder.

11. Statistical processing

The results of this study were mainly statistically descriptive. The measurement data lists the mean, standard deviation, median, maximum value, and minimum value, and the numerical data and grade data list the frequency (composition ratio), rate, and trusted interval. All statistical analyses will be programmed and calculated using SAS 9.0 or above statistical analysis software. All statistical tests were two-tailed tests, and a P value of less than or equal to 0.05 would be considered statistically significant for the difference tested, with confidence intervals of 95% confidence.

1) Basic characteristics of the patient

Quantitative data such as age, height, and weight were calculated, including mean, standard deviation, median, maximum, and minimum values, and qualitative data such as gender and ECOG score were calculated for frequency and percentage.

2) Efficacy analysis

i. DLTs: Defined as any grade ≥3 adverse events (AEs) including NCI-CTCAE v.4.03 scores, which are related to CDK4/6i and/or radiation therapy;

ii. MTD: Defined as the dose closest to the probability of DLT occurrence but less than or equal to 25%.

3) Dose escalation model

CDK4/6 inhibitor dose allocation will be centrally defined by modeling the probability of DLTs based on DLTs observed in all previously evaluated patients. The dose-toxicity relationship will be empirical model. Intra-patient dose escalation is not allowed, and dose skipping during escalation is not allowed.

4) Safety analysis

The safety analysis will be based on the safety set, and the safety analysis will be limited to descriptive statistical summary, mainly including the following aspects: basic characteristics of the patient (including socio-demographic information, past medical history and previous medication history); The incidence of adverse events, the incidence of grade 3 and above adverse events, as well as their clinical characteristics, severity, time of occurrence, duration, treatment and prognosis, and the correlation between them and combination treatment regimens; Changes in vital signs, physical examination, laboratory tests before and after medication, and relationship with the trial drug when abnormal changes occur. The severity of AEs is graded according to NCI CTCAE V5.0 (grade 1 to 5). The incidence of adverse events occurring after treatment will be summarized by systemic organ classification (SOC) and preferred term (PT).

15. Ethical considerations

The study will follow the relevant regulations of the World Medical Assembly "Declaration of Helsinki" and other relevant regulations, and the clinical study will be carried out before the study begins and the study protocol is approved by the ethics committee. Before each subject is selected for this study, the investigator is responsible for fully and comprehensively introducing the purpose, procedures and possible risks of this study to the subject or his legal representative, as well as the corresponding information of alternative treatment, and signing a written informed consent form to let the subjects know that they have the right to withdraw from this study at any time, and the informed consent form is kept as a clinical study document for future reference. The personal privacy and data confidentiality of the

subjects will be protected during the research process.

16. Data confidentiality

The results of this research may be published in medical journals, but we will keep patients' information confidential as required by law, unless required by relevant laws, patients' personal information will not be disclosed. When necessary, government management departments, hospital ethics committees, and their relevant personnel may consult the patient's information in accordance with regulations.

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