Combined use of apatinib mesylate and vinorelbine versus single use of vinorelbine in recurrent or metastatic triple-negative breast cancer: study protocol for a randomized controlled clinical trial

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Keywords: triple-negative breast cancer; apatinib; vinorelbine; advanced breast cancer; metastatic

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Abstract

Background: The emergence of new molecular targeted drugs provides new prospects for the treatment of advanced breast cancer; the future therapeutic trend includes chemotherapy combined with molecular targeted therapy. Apatinib mesylate, a novel small anti-angiogenic agent, highly selectively inhibits the activity of vascular endothelial growth factor receptor-2 tyrosine kinase. Apatinib mesylate also blocks the signaling of vascular endothelial growth factor binding to its receptor, thereby, strongly inhibiting tumor angiogenesis and exerting an anti-tumor effect. However, a randomized controlled clinical trial of apatinib combined with vinorelbine for triple-negative breast cancer (TNBC) has not been reported. We attempted to compare the therapeutic effect of vinorelbine alone or in combination with apatinib mesylate for patients with recurrent or metastatic TNBC who have received at least two drug treatments with anthracyclines and taxanes. Methods/analysis: This study is a triple-blind, randomized, placebo-controlled, parallel-group clinical trial. We plan to include 184 female patients with locally recurrent or metastatic TNBC admitted at the Liaoning Cancer Hospital & Institute, in Northeast China. All enrolled patients will be randomized to orally take vinorelbine alone (40 mg orally, thrice a week (Mondays, Wednesdays, and Fridays) in each 3-week cycle) or combined with apatinib mesylate (500 mg orally, once daily of each 3-week cycle). Radiographic assessment will be performed every 6 weeks for 36 weeks, and every 9 weeks thereafter. The primary outcome is measurement of progression-free survival and secondary outcomes include overall survival, disease control rate, objective response rate, and incidence of adverse events at grades 3 and 4 as defined by the National Cancer Institute Common Toxicity Criteria [NCI-CTC] Version 4.0. Outcome measures will be evaluated at baseline (< 2 weeks before starting treatment), every 6 weeks during treatment, and at 4 weeks and every 3 months after treatment discontinuation. Discussion: Based on the data from this trial, we hope to identify a treatment plan that is suitable for female TNBC patients in Northeast China who have been treated with anthracyclines and taxanes. Trial registration: ClinicalTrials.gov (identifier: NCT03932526). Registered on April 30, 2019.

Background

The International Agency for Research on Cancer predicts that the number of cancers in the future will increase at an annual rate of 3-5%. It is estimated that there will be 20 million new cases worldwide until 2020, and the number of deaths will reach 12 million. The incidence of cancer in low- and middle-income countries is extremely higher than that in developed countries [1]. Breast cancer is one of the malignant tumors with high prevalence in women and a common cause of death. Annually 13 million people are newly diagnosed with breast cancer, and about 400,000 people die of breast cancer with a mortality of 20-30%. In developing countries, breast cancer has become the leading cause of death in women [2].

Triple-negative breast cancer (TNBC) is a subtype of breast cancer with the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER-2), which accounts for 10-17% of all breast cancers [3]. TNBC is characterized by high heterogeneity, high invasiveness, low survival rate, early recurrence and metastasis, lack of effective treatment, and poor prognosis [4,5].

Despite significant advances in breast cancer treatment, approximately 15% of breast cancer patients are diagnosed at an advanced stage. According to staging, grading, and choice of treatment, 20-80% of all invasive breast cancer patients will eventually relapse and require a subsequent treatment [6]. Chemotherapy is the main treatment for early and advanced breast cancer, and the most effective drugs include anthracyclines and taxanes [7]. However, the increasing use of anthracyclines and taxanes in the early stage of the disease makes the choice of a second-line therapy difficult, and drug resistance often limits the choice of treatment regimens [8]. Endocrine therapy, anti-HER-2 targeted therapy and chemotherapy cannot achieve satisfactory outcomes in TNBC, as there is no corresponding hormone receptor or HER-2 expression.

The emergence of new molecular targeted therapeutics provides new prospects for the treatment of advanced breast cancer. Chemotherapy combined with molecular targeted therapy is the trend for future treatment of advanced breast cancer. Combination chemotherapy with vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) target inhibitors is one of the most promising regimens for advanced breast cancer [9]. Apatinib mesylate (Aitan) is a novel small anti-angiogenic agent that highly selectively inhibits the activity of VEGFR-2 tyrosine kinase and blocks the signaling of VEGF binding to its receptor. Thus, it strongly inhibits tumor angiogenesis and exerts anti-tumor effects. The clinical use of apatinib in breast cancer has also been reported, but the relevant research focuses on its safety and efficacy in breast cancer patients with different hormone receptor expressions [9,10]. As reported, apatinib at an initial dose of 750 mg/day or 500 mg/day was used in TNBC patients. The mean progression-free survival (mPFS) and mean overall survival (mOS) were 4.6 and 8.3 months for the former dose, and 3.3 and 10.6 months for the latter dose, respectively.[10] In advanced breast cancer, oral treatment with apatinib was used after first-line or second-line treatment failure. The objective response rate (ORR) was 40.0%, the disease control rate (DCR) was 75.0%, and the median time to progression (mTTP) was 12 months [9].

Vinorelbine is a semi-synthetic vinblastine alkaloid antineoplastic drug, mainly used for the treatment of non-small cell lung cancer and metastatic breast cancer. A previous multi-center clinical trial [11] used vinorelbine combined with cisplatin, capecitabine, or tegafur for the treatment of recurrent and metastatic breast cancer that occurred after treatment with anthracyclines and taxanes. The effective rate was 61.0%, with a complete response (CR) of 4.9%. This combination therapy was highly effective for multiple and single metastatic lesions, and moreover, the therapeutic efficacy was better in multiple metastatic lesions. The short-term effect was fair, with tolerance to toxicity and good safety. Studies have reported the use of vinorelbine combined with 5-fluorouracil for the treatment of advanced metastatic breast cancer, which anthracycline/taxane fails to treat, and the effective rate is 17.4-46% [12-14]. In patients with metastatic TNBC, vinorelbine or gemcitabine combined with cisplatin is preferred after failure in the treatment with anthracycline/taxane. The existing results have shown that the objective and effective rates of the experimental group and the control group were 45.45% and 46.15%, respectively, and the DCRs in the two groups were 77.27% and 80.77%, respectively. In the experimental group, the time to progression (TTP) was 2.0-18.0 months, with the mTTP of 5.0 months (95% confidence interval [CI]: 3.28-

6.72). In the control group, the TTP was 1.8-18.5 months, with the mTTP of 5.2 months (95% CI: 3.33-7.07) [15].

Study features and objectives

Currently, there are cohort studies [16-18], retrospective observations [19-22] and case reports [23,24] addressing the clinical treatment of TNBC with apatinib or vinorelbine (Table 1). However, a randomized controlled clinical trial of apatinib combined with vinorelbine for TNBC has not been reported. Female patients with TNBC in North China who have previously received anthracyclines and taxanes for the adjuvant treatment of metastatic disease will be taken as target population in this trial. We attempted to compare the therapeutic effect of vinorelbine used alone or combined with apatinib mesylate for recurrent or metastatic TNBC patients who have at least received one chemotherapy regimen, including anthracyclines and taxanes, providing clinical evidence for multi-line treatment options for advanced TNBC.

Methods And Analysis

Study design

This study is a triple-blind, randomized, placebo-controlled, parallel-group clinical trial.

A population of 184 female patients with recurrent or metastatic TNBC who have been pretreated with at least one chemotherapy regimen, including anthracyclines and taxanes, will be recruited. According to the Consolidated Standards of Reporting Trials (CONSORT) [25], the baseline, therapeutic schedules, and outcomes of enrolled breast cancer patients will be recorded, and patients' data in each center will be collected by electronic data capture system (EDC).

All enrolled patients will be randomly assigned to receive either oral apatinib mesylate in combination with vinorelbine or oral vinorelbine plus placebo until disease progression or other criteria for administration termination. A schedule of enrollment, interventions, and assessments is shown in **Figure 1** and a trial flowchart is shown in **Figure 2**. The study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance for protocol reporting (**Additional file 1**) [26].

Subjects

Female patients with breast cancer required for the trial will be recruited from Liaoning Cancer Hospital & Institute in Northeast China.

Inclusion criteria

- Female patients with recurrent or metastatic TNBC, as confirmed by histological or cytological examination

- Age 18-70 years old

- According to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [27], there is at least one measurable lesion. For non-lymph nodes, at least one lesion has a longest diameter > 1.0 cm, or for lymph nodes, at least one lesion has a minor axis diameter > 1.5 cm.

- The Eastern Cooperative Oncology Group (ECOG) scores 0-2

- Expected survival ≥ 12 weeks

- Negative for ER/PR: defined as; ER < 1% indicates positive, PR < 1% indicates positive. Negative for HER-2 refers to: IHC1+ indicates HER-2 negative, IHC2+ indicates a HER-2 uncertain case, according to specific diagnostic criteria (the Breast Cancer HER-2 Detection Guide, 2014 Edition) [28]. Further, the in-situ hybridization (ISH) method will be used to detect the HER-2 gene amplification for further diagnosis.

- All patients will be tested for bone marrow capacity, liver and renal functions within 7 days prior to enrollment and will meet the following aspects:

  1. Blood routine: absolute neutrophil (ANC) count ≥ 1.5×10^9/L; hemoglobin ≥ 9.0 g/dL; platelet count ≥ 80×10^9/L;
  2. Liver function: total bilirubin ≤ 1.5 times the upper limit of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN (patients with liver metastasis ≤ 5 × ULN); alkaline phosphatase ≤ 4 × ULN;
  3. Renal function: serum creatinine ≤ 1.5 × ULN.

- Previous use of anthracyclines and/or taxanes

- The medication history of vinorelbine meets one of the following conditions:

  1. Never or irregular use of vinorelbine (the standard use of vinorelbine is defined as the medication is given according to the instructions for at least two cycles);
  2. Advanced breast cancer patients, who undergo the standardized medication of vinorelbine for 6 months, have no progression, and vinorelbine is not used within 6 months prior to the first administration.

- Female patients of childbearing age must take adequate contraception; otherwise they must be proven to be infertile, that is:

1. Patients over the age of 50 are confirmed to have menstruation-deficient menopause for at least 12 months after stopping all exogenous hormone treatments;
2. Under the age of 50, on this basis, it is also necessary to prove that the levels of progesterone and follicle stimulating hormone are in the postmenopausal range of the research institution;
3. Female patients undergoing irreversible sterilization operations (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, etc.) are negative for pregnancy and are not lactating before administration.

- No history of serious heart, lung, liver, and kidney diseases

- Provision of written informed consent

Exclusion criteria

- Patients who receive chemotherapy, radiation therapy, targeted drugs, or hormone therapy within 3 weeks of administration

- Patients using corticosteroids for untreated brain or subdural metastatic lesions, need to have stopped it, at least for 4 weeks or until there are no signs of brain metastasis (e.g., confirmed by radiological imaging) and/or symptoms must have stabilized for at least 4 weeks, if local treatment has been completed. Enhanced computed tomography (CT) or magnetic resonance imaging (MRI) images during screening are compared with those performed at least 4 weeks earlier to determine radiological stability.

- Patients with severe vascular diseases, including unstable angina, myocardial infarction, or severe arrhythmia in the past 6 months

- History of HIV infection or active chronic hepatitis B or C

- Patients with other serious infectious diseases

- Patients positive for ER/PR/HER-2 positive

- Patients with allogeneic organ transplants requiring immunosuppressive therapy

- History of other malignant tumors within 5 years, except for cured cervical carcinoma in situ or basal cell carcinoma of the skin

- Other destabilizing factors (such as drug abuse and medical, psychological or social conditions) that may interfere with patients or have an impact on the trial results

- Allergy to target drugs or allergy to related drugs applied in the trial

- Pregnant or lactating women

Withdrawal criteria

- Patients who have poor compliance that cannot complete medication as prescribed

- Patients who receive other anti-cancer treatments during the trial

- Patients who develop intolerable toxic/side effect will be withdrawn from the trial with the approval of the primary investigator.

- Pregnancy

- Patients that were wrongly allocated or those who receive wrong treatment

- Lost to follow-up (those that cannot be reached by the investigators)

Recruitment

Patients will be recruited from the Department of Breast Medicine, Liaoning Provincial Cancer Hospital in China, which is a center with sufficient source of advanced breast cancer patients. Liaoning Breast Cancer Treatment Center was established, to recruit patients in Liaoning Province. These ensure adequate number of patients for the trial.

The recruitment conditions for the trial will be publicized at the outpatient and inpatient departments. Patients interested in the trial can contact the project leader by telephone, email or WeChat through their attending doctor.

Recruitment conditions will be publicized at a strategic location or on a bulletin board. Patients interested in the trial can contact the project leader using the advertised contact details.

Patients who agree to participate in the trial will be asked to sign informed consent form prior to enrollment in the trial.

Randomization

Randomization will be performed by a professional, independent statistician who will not be involved in the recruitment process of the study. The statistician will use the Statistical Analysis System (SAS 9.1) software to generate a randomization sequence list, and assign each patient a serial number to complete the randomization. Sequence numbers will be sealed in opaque envelopes prepared by research

assistants who will not be involved in the recruitment process. These envelopes will be saved in a double-locked cabinet by another investigator who will not be involved in the trial.

Blinding

At the beginning of the study, nurses who will not participate in the trial will randomly dispense drugs to eligible patients based on their allocation sequence. All patients, investigators, and data analysts will be unaware of the grouping information until the end of the trial. A bleeding test [29] will be performed to ensure that each patient is blind to the grouping information. In case of emergency, the investigators can urgently determine the medication of the patients to ensure that the patients will receive timely and correct medical treatment.

Drug administration

Vinorelbine plus apatinib group: Combined administration of vinorelbine and apatinib. vinorelbine tartrate soft capsule (brand name Navelbine, registration No. H20140657; Pierre Fabre Medicament, Boulogne, France) 40 mg once orally, taken in the morning (at least 1 hour before or at least 1 hour after meals), three times a week (Mondays, Wednesdays, and Fridays), for a continuous 21-day cycle. Apatinib mesylate tablets (brand name Aitan; State Medical Permission No. H20140103), 500 mg orally, taken once a day for a continuous 21-day cycle.

Vinorelbine plus placebo group: Based on oral administration of vinorelbine, the patients will be given oral placebo (starch as an ingredient). The placebo appearance, including shape, size, color and weight, taste, labeling and packing are the same with those of apatinib mesylate tablets.

The placebo and apatinib will be manufactured by Jiangsu Hengrui Pharmaceutical Co., Ltd., China in accordance with the guidelines of Good Manufacturing Practice (Chinese Edition). The manufacturer will have no direct involvement in the study, apart from the drug manufacturing and delivery to the clinical trial centers.

An assessment will be conducted every two cycles of the above administration protocol for chemotherapy until unacceptable toxicity, disease progression, or investigator decision.

Dose adjustment

Apatinib

Principle for dose adjustment: In the case of adverse reactions associated with apatinib, the dose of apatinib will be first adjusted (**Table 2**). There are two dose levels of apatinib: 1) initial dose: 500 mg, once daily; 2) secondary dose: 250 mg, once daily. Medication will be paused if the patients cannot recover from drug toxicity. The time for each pause and the cumulative time of overall pauses per cycle are restrained not to exceed 1 week. There is a maximum of two pauses per cycle, to ensure the medication intensity in each patient (such patient who cannot meet the above criteria or a delay of the next cycle of treatment for over 2 weeks will be required to terminate the trial).

The medical dose will be adjusted at any time during each dosing cycle. Once the dose is reduced, it is not allowed to be increased to the previous level. No more than one dose adjustment is allowed for each subject. After the dose is down-regulated to 250 mg, no further dose adjustments are allowed, including up- or down-regulation for any reason. However, pause of administration is still permitted.

Vinorelbine

Drug withdrawal and re-administration: When any conditions in compliance with the criteria for drug withdrawal occur, administration of vinorelbine will be discontinued. If the patient meets the criteria of drug re-administration in all of the following cycles, the administration of vinorelbine will be resumed, but the doses that are not taken during the withdrawal period should not be replenished (**Table 3**).

Concomitant medications

Other anti-tumor drugs not approved by this protocol should be discontinued during the administration of drugs in this trial.

Conventional medications can be given symptomatically, including prophylactic antiemetics and treatment with granulocyte colony-stimulating factor for the reduction in the patient's hemogram. Hematopoietic growth factor support is permitted to avoid treatment interruption or delay. All symptomatic medications should be documented and detailed on a case report form.

Alcoholic drinks should be avoided during treatment.

Assessment

Baseline evaluations (conducted within 2 weeks of the start of protocol therapy)

- Sign an informed consent
- Demographic data

- American Joint Committee on Cancer (AJCC) tumor diagnosis and staging
- Relevant clinical disease history (diagnosis and treatment)
- Concomitant medication
- Physical examination
- Vital signs
- Eastern Cooperative Oncology Group performance status (ECOG-PS) score
- Imaging test (CT or MRI)
- Electrocardiogram
- Laboratory tests: blood routine, liver and kidney functional electrolytes (including K+, Na+, CL-, Ca^{2+}, Mg^{2+})
- Tumor markers: CA153, carcinoembryonic antigen (CEA)
- Pregnancy test (if necessary)
- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30, version 3)

During treatment (conducted every 6 weeks (two cycles))

- Physical examination
- vital signs
- ECOG-PS score
- Imaging test (CT or MRI)
- Laboratory tests: blood routine, liver and kidney functional electrolytes (including K^+, Na+, CL^-, Ca^{2+}, Mg^{2+})
- Tumor markers: CA153, CEA
- EORTC-QLQ-C30 version 3 score
- Record of adverse reactions, concomitant medications

Follow-up

4 weeks after treatment discontinuation:

- Physical examination
- Vital signs
- ECOG-PS score

- Laboratory tests: blood routine, liver and kidney functional electrolytes (including K+, Na+, CL-, Ca2+, Mg2+)
- Tumor markers: CA153, CEA
- EORTC-QLQ-C30 version 3 score
- Adverse reaction evaluation
- Concomitant medications (opioid analgesic consumption and new anticancer treatment)

Every 3 months after treatment discontinuation until a patient dies or the study closes:

During the follow-up period, ECOG-PS score, the start of new anticancer treatment(s), subsequent disease progression, and survival status will be assessed.

Outcomes

Primary outcome

PFS refers to the length of time from random enrollment to any recorded tumor progression or death from any cause. Based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, tumor conditions during the treatment and follow-up periods will be evaluated. If the patient has several indicators that can be judged as progression of disease, the PFS analysis will be performed based on the indicators that first emerged. Recurrence, presence of new lesions, or death is considered as having reached the end of the study. The use of other systemic or targeted anti-tumor therapy will also be considered as tumor progression. Tumor treatment is also considered to be tumor progression. For patients who have not progressed or died of disease at the end of the study, the time for no disease progression collected at the last follow-up is used as censored data.

Secondary outcomes

- Overall survival (OS) indicates the length of time from enrollment to death from any cause. When no information on death is collected in the clinical database, the last date when the patient is still known to have survived is used as the cut-off point.

- Disease control rate (DCR) indicates the percentage of patients with CR, partial remission, and disease stabilization; and maintenance over 4 weeks, accounts for all the subjects with evaluable efficacy.

- Overall remission rate (ORR) is the proportion of patients who achieve a complete or partial response ((CR+PR)/total number of cases x 100%), as assessed by the RECIST v1.1 [27].

- Adverse events at levels 3 and 4: Patients with adverse events at levels 3 and 4 will be assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 4.0 [30].

Other measures

- Quality of life will be assessed using the EORTC QLQ-C30 version 3.0 [31]. The scores have to be averaged and transformed linearly to obtain a range of scores, from 0 to 100, with higher scores meaning a great response level.

- General health status is assessed using the ECOG-PS scale [32]. The scale divides the patient's activity status into 0-5 levels. A higher level indicates a worse physical status.

- Laboratory examination: (1) Hematology: hemoglobin, white blood cell count, neutrophil count, and platelet count; (2) blood biochemical tests: total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum creatinine, total protein, sodium ion, potassium ion, blood magnesium, chloride, blood calcium, blood urea; and pregnancy test (if applicable); (3) tumor marker detection: CA153 and CEA.

Adverse events

Definition of adverse events

- Adverse events: An adverse event refers to any adverse medical event that occurs after a patient or clinical study subject takes a drug. This event does not necessarily have a causal relationship with the treatment. Therefore, the adverse event can be any bad or unintentional signs, including abnormalities in laboratory findings, symptoms, or transient drug-related diseases, which should be considered whether it is related to medication. Adverse events that occur before and after treatment will all be included. A safety monitoring to report adverse events or serious adverse events (SAEs) should be ensured from the enrollment of subjects to the end of the study. Therefore, adverse events that occur during the signing of informed consent and the initiation of study treatment will also be included.

- Adverse drug reactions: Any toxic and unintended reaction to a drug associated with any dose should be considered an adverse drug reaction. The response to the drug means that there is at least a reasonable possibility of causality between the drug and the adverse event, which means that this relationship cannot be excluded.

- SAEs or serious adverse reactions (SARs): An SAE or an SAR indicates any adverse medical event that occurs to any drug dose. When an SAE occurs, the subject is at risk of death rather than assuming a more serious event resulting in death; if the SAEs occur, the subject needs to be hospitalized or the length of

existing hospitalization should be extended; or any adverse event resulting in sustained or significant loss of ability/disability.

- Important medical events: A medical and scientific accreditation is required to determine the appropriateness of a prompt medical report in the case of an important medical event. These important medical events may not immediately threaten life or result in death or hospitalization, but they may harm the subject, or an intervention may be required to prevent the occurrence of the aforementioned results. Usually the following events should also be considered serious, such as some adverse events in the emergency department requiring critical care and treatments, or allergic bronchial asthma at home; dyscrasia or convulsions that do not require hospitalization; drug dependence and abuse, or malignant tumors histologically different from primary tumors.

- Other events that should be treated as SAEs: Drug exposure during pregnancy/lactation. In principle, pregnancy and lactation are included in the exclusion criteria. If a pregnancy occurs during the study period, the patient should immediately withdraw from the study and should immediately inform the investigators. The investigators should follow up the patient throughout pregnancy and postpartum. Even if the mother and child are completely normal without any adverse events, the consequences should be recorded. Even if the pregnancy does not fit into an SAE, it should be reported in the SAE report form.

- Events that should not be treated as SAEs: Disease progression does not fit into an SAE.

Recording and evaluation of adverse events

All adverse events should be recorded appropriately in a case report form. In addition, an SAE report form (including initial or follow-up reports) should also be completed.

The following aspects of each event will be documented in the case report form: the adverse event will be described in medical terms, not as subjects, including date of occurrence (initial date), time of occurrence (start time), date of recovery (end date), recovery time (end time). The evaluation will be performed by the investigators according to the NCI-CTC version 4.0 [30]: level 1 = mild; level 2 = moderate; level 3 = severe; level 4 = life threatening or disabling; and level 5 = death.

If the level of alanine aminotransferase or aspartate aminotransferase is $\geq$ 3 x ULN or total bilirubin $\geq$ 2 x ULN, an SAE report may be necessary. The investigators must promptly determine whether the patient meets the Hy's Law (drug-induced liver injury [DILI]), without delay. Diagnosis and treatment of DILI cases should be described. Such SAEs that occur up to 30 days after the last dose will be recorded.

The investigators should assess the causal relationship between adverse event and target drugs. The decisive factor in the assessment is the temporal correlation between the adverse event and target drug. The causal relationship between the adverse event and target drug (or study protocol) is judged as follows: irrelevant = there is no temporal relationship between the adverse even and target drug (drug

medication is too early, too late, or not), or a reasonable causal relationship between the adverse event and another drug, concomitant disease or environment; impossible = there is a temporal relationship between the adverse event and target drug, but no reasonable causal relationship between the adverse event and the target drug; possible = there is a reasonable causal relationship between the adverse event and target drug, but with no or uncertain drug withdrawal (discontinuance) information; no doubt = there is a reasonable causal relationship between the adverse event and the target drug, with drug discontinuation or withdrawal having an effect on the adverse reaction, and no need to be proved by re-administration; definite/determined = there is a reasonable causal relationship between the adverse event and the target drug, with drug discontinuation having an effect on the adverse reaction and the adverse event occurring again after re-administration if clinically acceptable.

Consequences are defined as follows: (1) recovery with sequelae; recovery without sequelae; no recovery, but no need of treatment; no recovery, and treatment required; and death. (2) Whether the toxicity grade/severity has changed. If the same adverse event appears several times in the patient, it must be recorded and reassessed every time.

Treatments of dead cases

All deaths occurring during the study period or during the last follow-up period (30 days after the last dose) or until the disease progression (whichever occurs later) must be reported as follows:

- Deaths definitely resulting from disease progression must be reported to the research representative and must be recorded in the case report form but should not be reported as SAEs occurring during the study.

- If a death is not clearly attributed to the disease progression, the primary cause of death and the event most likely to result in death must be reported to the sponsor as an SAE within 24 hours. The report must contain comments on whether or not the disease is progressing at the same time and must identify a major cause of death and all contributory factors.

- If the cause of death is unknown, it must be reported as an SAE, but the cause of death still needs to be identified. An autopsy may be helpful in assessing the cause of death, and the autopsy results should be urgently reported to the sponsor within the specified time.

Reporting procedure for SAEs

The investigator is obliged to immediately call or fax or email information (on any serious or medically significant clinical adverse events or laboratory abnormalities during the study period, regardless of treatments received by the subject), to the Adverse Drug Reaction Monitoring Center, the sponsor, and the Ethics Committee within 24 hours.

After oral report via telephone, the written source needs to be faxed. The report should provide information on the rapporteur and receiver, including name, address, telephone, and fax numbers; and indicate that it is a "preliminary" report or a "follow-up" report. If necessary, the relevant case report form should be accompanied. The investigator should ensure that the public ethics committee or the competent authority is provided with information on any additional requirements for the death of the subject.

Monitoring of adverse events in subjects

Any adverse events that occur during the study will be monitored and followed up until the end of the study. In addition, SAEs must be reported through the SAE form.

Treatments of adverse reactions

Any dose change should be documented for a clear cause. The most adequate supportive therapy will be given for all toxicities. If the symptoms are relieved immediately after the supportive treatment, it is medically acceptable to continue with the appropriate treatment. If the investigator believes that the treatment is beneficial to the patient, the same dose of the drug plus corresponding supportive treatment will be continued. A medical reduction will be allowed as required. The study will be terminated if the medication, due to an adverse event, is delayed for more than 21 days.

- Hematological toxicity

The current cycle dose will be adjusted based on the lowest blood cell count after the last dose (**Table 4**):

If level 4 or 3 neutropenia with febrile neutropenia (> 38.5°C) or above level 3 thrombocytopenia occurs after two reductions, there is no longer a third reduction, and the investigator will determine whether the trial should be continued or not in accordance with specific conditions.

- Non-hemotoxic diarrhea including diarrhea with mucositis

The investigator will determine a reduction if non-hematologic toxicity (except vomiting and hair loss) such as diarrhea with mucositis of above level 3 appears.

- Liver toxicity

- Bilirubin: If bilirubin ≥ 1.5 times the ULN, the next cycle should be delayed. If the total bilirubin has not recovered to the ≤ 1.5 times the upper limit of normal for ≥ 3 weeks, the trial will be discontinued.

- Transaminases: Liver protection treatments will be taken if alanine aminotransferase and/or aspartate aminotransferase and/or alkaline phosphatase are at abnormal levels in the absence of the disease progression within 1 week. But if the abnormal level(s) still does not return to normal, the drug dose will be adjusted according to **Table 5**. In the next cycle, the dose should be increased to the initial level if the patient's liver function recovers.

- Peripheral neurotoxicity

When level III-IV peripheral neurotoxicity occurs and the patient's life is seriously affected (the initial dose cannot be tolerated), the investigator will decide whether to reduce the dose by 20% or discontinue the drug.

Criteria for re-administration/cycle delay

Patients who meet all of the following criteria can receive the planned treatment:

- Absolute neutrophil count > 1500/mm^3
- Platelets > 100,000/mm^3
- Treatment-related non-hematologic toxicity has been eliminated at baseline or ≤ level 1 (except for level 2 alopecia or level 2 fatigue).
- If the patient cannot meet the criteria, the planned treatment should be delayed.
- Re-evaluate the patient's conditions at least once a week.
- The medication on the 8th day of each cycle cannot be delayed for over 1 week, otherwise, the medication will be cancelled. The medication time of the next cycle will not change.
- If there is failure of recovery from treatment-related toxicity to baseline or level 1 (except level 2 and level 2 fatigue) within 3 weeks as scheduled (i.e., the start of each new cycle is delayed for over 21 days as compared with the scheduled time), the patient will withdraw from the trial.
- For patients who are effective in the treatment, they can continue to use the drug with the consent of the sponsor.

Monitoring

Progression of the trial, adverse events, and data quality will be monitored by an Independent Data (and safety) Monitoring Board (IDMB) independent of the trial sponsor. The IDMB will be responsible for reporting the security data in the trial to the primary investigator. The primary investigator will submit a list of all suspected SAEs to the Independent Ethics Committee (IEC), as well as a summary of all reported SAEs every 6 months.

Audits

An inspector will review the incoming data monthly and generate a data query if necessary. The inspector will review whether each electronic case report form is completed accurately. All discrepancies in the electronic case report form will be corrected by the investigator or authorized personnel in an appropriate manner.

Data management

Data entry and management are the responsibility of an independent data administrator using the EpiData 3.1 software (The EpiData Association, Denmark, Europe). In order to ensure the accuracy of the data, the data will be input and proofread using a double-data entry strategy by two data administrators independently. The data administrators will list the questions in the case report form in the Data Request Queue (DRQ); and the investigator will respond and return as soon as possible. The data administrators will then modify, confirm, and enter the data according to the investigator's responses. Another DRQ can be submitted if necessary. All original files will be kept in accordance with the deadlines set by the Good Clinical Practice of China, and clinical data will be kept by the investigators for 5 years, starting from the end of the clinical trial. All the clinical data of this trial will be the property of the sponsor, and the investigators will have no right to disclose these data to a third party without written approval by the sponsor.

Sample size

Based on previous experience [33] and pilot study results, the mPFS was estimated to be 4.4 months in the vinorelbine monotherapy group and 6.7 months in the vinorelbine + apatinib group. The recruitment time is expected to be 26 months and the follow-up time is planned for 15 months. Taking α = 0.05 (two sides), β = 0.25, the required sample size of 168 was calculated if the subjects in the two groups are enrolled basically at a ratio of 1:1, using PASS 11 (NCSS Statistical Software, Kaysville, Utah, USA). Assuming a loss rate of 10%, the lost-to-follow-up cases, the final sample size of 184 will be required.

Statistical analysis

All validity indicators (PFS, OS, DCR, ORR) will be analyzed based on the full analysis set and the per-protocol set. According to the principle of intention-to-treat analysis, the full analysis set (the main analysis set for determining the efficacy of this trial) will include data of all subjects who will at least take the target drugs once. Per-protocol set will be the data of all cases who meet the criteria of the trial

protocol, have good compliance, take at least one cycle of target drugs, do not take any banned drugs during the trial period, and have the complete lists to be filled out in the case report form. No imputation will be made for missing data. A safety analysis (incidence of adverse events) will be conducted on a safety analysis set, which will be the dataset of all enrolled patients who will at least take target drugs once, and have post-medication safety records. No interim analysis will be performed.

Statistical analyses will be performed by a statistician using SPSS 22.0 software (IBM, Armonk, NY, USA). Continuous variables will be statistically expressed as the mean, standard deviation, median, minimum, and maximum, while categorical variables will be expressed as numbers and percentages.

Descriptive statistics will be performed on feature data at baseline. For categorical variables, DCR, ORR, and the incidence of adverse events will be compared between groups using the Spearman's chi-square test or Fisher's exact test. For continuous variables, PFS, OS, EORTC QLQ-C30 score, ECOG PS score, and laboratory indicators will be compared between groups using an independent sample t-test or Mann-Whitney U test. All statistical analyses will be performed based on a two-sided test. A P value of ≤ 0.05 will be considered statistically significant and the 95% CI will be calculated.

Survival data (PFS and OS) will be estimated using the Kaplan-Meier method. Differences between grouped survival profiles will be assessed with the Log-rank test. Cox proportional hazard model will be used to assess the effects of variables on patients' survival. Hazard ratios and the 95% CI will be recorded for each factor on the basis of intergroup differences (that is, age, TNM staging, tumor differentiation status, lymph node metastasis, chemotherapy cycles), which can identify the influence of competing risk factors for the outcome event. All reported P-values will be based on two-sided tests, and the CI will assume a significance of 0.05.

Quality control

The clinical research unit must provide a clinical research base for drugs research with clinical research conditions as determined by the National Medical Products Administration of China. Investigators must be clinically trained physicians who work under the direction of a senior professional. Pre-test clinical wards must meet the requirements of standardization to ensure that rescue equipment is fully functional. Each subject will be given medications by professional caregivers in order to learn more about the medications taken, ensuring the subject's compliance. The study protocol must be strictly executed in the research center, and the case observation form should be filled out truthfully. The standard operating rules of clinical trials should be followed and implemented in the research center. All the clinical procedures will be supervised, all data record will be con confirmed that they have been reported correctly and completely; and all case report forms are correctly filled out and consistent with the original data. In the event that an SAE occurs in the research center, it will be promptly reported to each research unit and, if necessary, the trial will be temporarily discontinued.

Ethics and dissemination

Ethics and informed consent

- The trial will be performed in accordance with the following conditions: 1) the study protocol, written informed consent, data to assist in the participation and compensation measures for the subject will be fully approved by the IEC; 2) the sponsor will receive a copy of the IEC approval document. A supplement scheme that increases the risk to the subjects and corresponding modified informed consent will be timeously submitted to the IEC for review, and this scheme will be implemented after approval by the IEC.

- The trial will be conducted in accordance with the guidelines of Good Clinical Practice, the guiding principles of the Declaration of Helsinki, as well as applicable local laws and regulations. The study protocol was approved by the Ethics Committee of the Liaoning Provincial Cancer Hospital in October 17, 2018 (approval No. 20180948-2) (**Additional file 2**) and the trial has been registered at ClinicalTrials.gov (identifier: NCT03932526). This research plan refers to protocol V2.0.

- Written informed consent will be given by each subject prior to the participation in the trial. The investigators will be responsible for the complete and comprehensive introduction of the study purpose, roles of drugs used, possible side effects and risks to the subjects or their designated representatives. The subjects will be informed of their right, risks assumed and benefits. The investigator will inform the participants that participation in the study is voluntary and that they can withdraw at any time. Finally, it will be ensured that subjects understand that the investigator will maintain their records for long-term follow-up, and that their records may be viewed by relevant management officers, within the limits of relevant laws and regulations. Subject's privacy will be protected.

Dissemination

The final research results will be disseminated through publications in peer-reviewed academic journals or at international academic conferences.

Protocol amendments

All amendments to the protocol will only be signed and dated by the Department of Breast Medicine, the Liaoning Provincial Cancer Hospital, China, approved by the IEC, before release. There should be no protocol deviation during the study, but the investigator should promptly deal with it if or when it occurs. In the case report form and in the original case report, the protocol deviation and the protocol deviation table, and its reasons will be recorded. These will be saved in the research unit by the sponsor.

Principle of confidentiality

During the collection and use of patients' data, full patient confidentiality will be maintained with compliance with relevant laws and regulations that protect the subjects' privacy. The investigator will obtain the consent of each subject prior to the collection of personal data. The subject has the right to obtain his/her personal data through the investigator, and to modify the errors or incomplete data. Not all personal information will be obtained nor disclosed to unauthorized others; these will not be destroyed accidentally or illegally, neither will it be lost or altered accidentally. Throughout the study period, the sponsors with access to the subjects' personal data will keep such confidential.

Compensation

Fund for drug therapy will be provided by the pharmaceutical company manufacturing the target drugs; they have no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Each patient having provincial, municipal, remote, or new rural cooperation medical insurance will be subsidized with RMB 600 yuan after completing one chemotherapy cycle. Self-paying patients will be given the next cycle of chemotherapy free (chemotherapy drugs only) after each cycle of chemotherapy.

Compensation mechanism: The specific compensation standards and methods will be clarified before the trial, and the sponsor will provide the Clinical Trial Insurance for each subject. Treatment cost for drug-related adverse events and corresponding economic compensation will be undertaken by the sponsor.

Discussion

A traditional chemotherapy's anti-tumor effect relies on a single maximum tolerated dose. Despite its wide use, it is not convenient for those that often need frequent visits to the hospital for infusion or hospitalization. To reduce chemotherapy side effects, longer intervals are left between chemotherapy cycles. This prospective randomized controlled trial in Liaoning Province of Northeast China will be the first to analyze the efficacy of apatinib-targeted therapy combined with vinorelbine chemotherapy in treating recurrent or metastatic TNBC patients who have received at least two regimens containing anthracyclines and taxanes. There are still some limitations of the trial, as follows: The subjects are limited to the northern Chinese population; hence, there are limitations of generalizability of the results. Constraints of research time and funding result in a relatively small sample size.

Based on the data from this trial, we hope to identify a treatment plan that is suitable for female TNBC patients in Northeast China who have been treated with anthracyclines and taxanes, which is of great

clinical significance.

Trial status

The trial was registered at ClinicalTrials.gov (identifier: NCT03932526) on April 30, 2019. Patient recruitment will begin in June 2019, and end in August 2022. Analysis of primary outcome measure will be completed in December 2022. The study will end in June 2023. This research plan refers to protocol V2.0.

Abbreviations

TNBC: triple-negative breast cancer; NCI-CTC: National Cancer Institute Common Toxicity Criteria; ER: estrogen receptors; PR: progesterone receptors; HER-2: human epidermal growth factor receptor 2; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor; mPFS: mean progression-free survival; mOS: mean overall survival; ORR: objective response rate; mTTP: median time to progression; CR: complete response); TTP: time to progression; CI: confidence interval; EDC: electronic data capture system; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; ECOG: Eastern Cooperative Oncology Group; ANC: absolute neutrophil; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CT: computed tomography; MRI: magnetic resonance imaging; AJCC: American Joint Committee on Cancer; ECOG-PS: Eastern Cooperative Oncology Group performance status; CEA: carcinoembryonic antigen; EORTC QLQ-C30, version 3: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; RECIST: Response Evaluation Criteria in Solid Tumors; OS: Overall survival; DCR: Disease control rate; SAEs: serious adverse events; SARs: serious adverse reactions; DILI: drug-induced liver injury; IDMB: Independent Data Monitoring Board; IEC: Independent Ethics Committee; DRQ: Data Request Queue.

Declarations

Availability of data and materials

The results of this study will be disseminated via peer-reviewed publications and conference presentations. No data are available at the moment.

Authors' contributions

TS and SW conceived the study and participated in its design and coordination. SW drafted and wrote the manuscript. LZ and HL participated in the design of the study and performed the statistical analysis. JX and CJ participated in the study design and coordination and helped draft the manuscript. All authors read, revised and approved the final manuscript.

Ethics approval and consent to participate

The trial will be conducted in accordance with the guiding principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Liaoning Provincial Cancer Hospital (approval No. 20180948-2) in October 2018. All patients will provide written informed consent prior to the participation in the trial.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding statement

Funding for the drug therapy will be provided by the pharmaceutical company manufacturing the target drugs and the sponsor will provide the Clinical Trial Insurance for each subject. Treatment cost for drug-related adverse events and corresponding economic compensation will be undertaken by the sponsor.

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Additional Files

Additional file 1: SPIRIT checklist.

Additional file 2: Ethics committee approval.

Tables

Due to technical limitations, tables 1 -5 are only available as a download in the supplemental files section.

Figures

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT	-t1	0	t1	t2	t3
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Demographic & Medical data	X				
Allocation		X			
INTERVENTIONS*:					
Experimental group		X			
Control group		X			
ASSESSMENTS:					
Vital sign	X		X	X	
Physical exam	X		X	X	
Concomitant medication[a]	X		X	X	
ECOG PS	X		X	X	
Laboratory examination[b]	X		X	X	
Electrocardiography	X		X	X	
Imaging examination	X		X	X	X
EORTC QLQ-C30	X			X	X
Response status			X	X	
Adverse events			X	X	
Survival status					X

Figure 1

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure. -t1: Baseline evaluations (conducted within 2 weeks of the start of protocol therapy); t0: random allocation; t1: during treatment (conducted every 6 weeks (two cycles)); t2: patients will be monitored for new or existing AEs at 4 weeks after treatment discontinuation; t3: follow-up for survival will be monitored every 3 months after treatment discontinuation until a patient dies or the study closes. * Eligible patients will be randomly

assigned to orally take vinorelbine plus placebo (control group) or combined with apatinib mesylate (experimental group). "a": Concomitant medication includes opioid analgesic consumption and new anticancer treatment. "b": Laboratory examinations include hematology (hemoglobin, white blood cell count, neutrophil count, and platelet count); blood biochemical test (total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum creatinine, total protein, sodium ion, potassium ion, blood magnesium, chloride, blood calcium, and blood urea); pregnancy test (if applicable); and tumor marker detection (breast cancer-associated antigen CA153 and carcinoembryonic antigen). ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30.
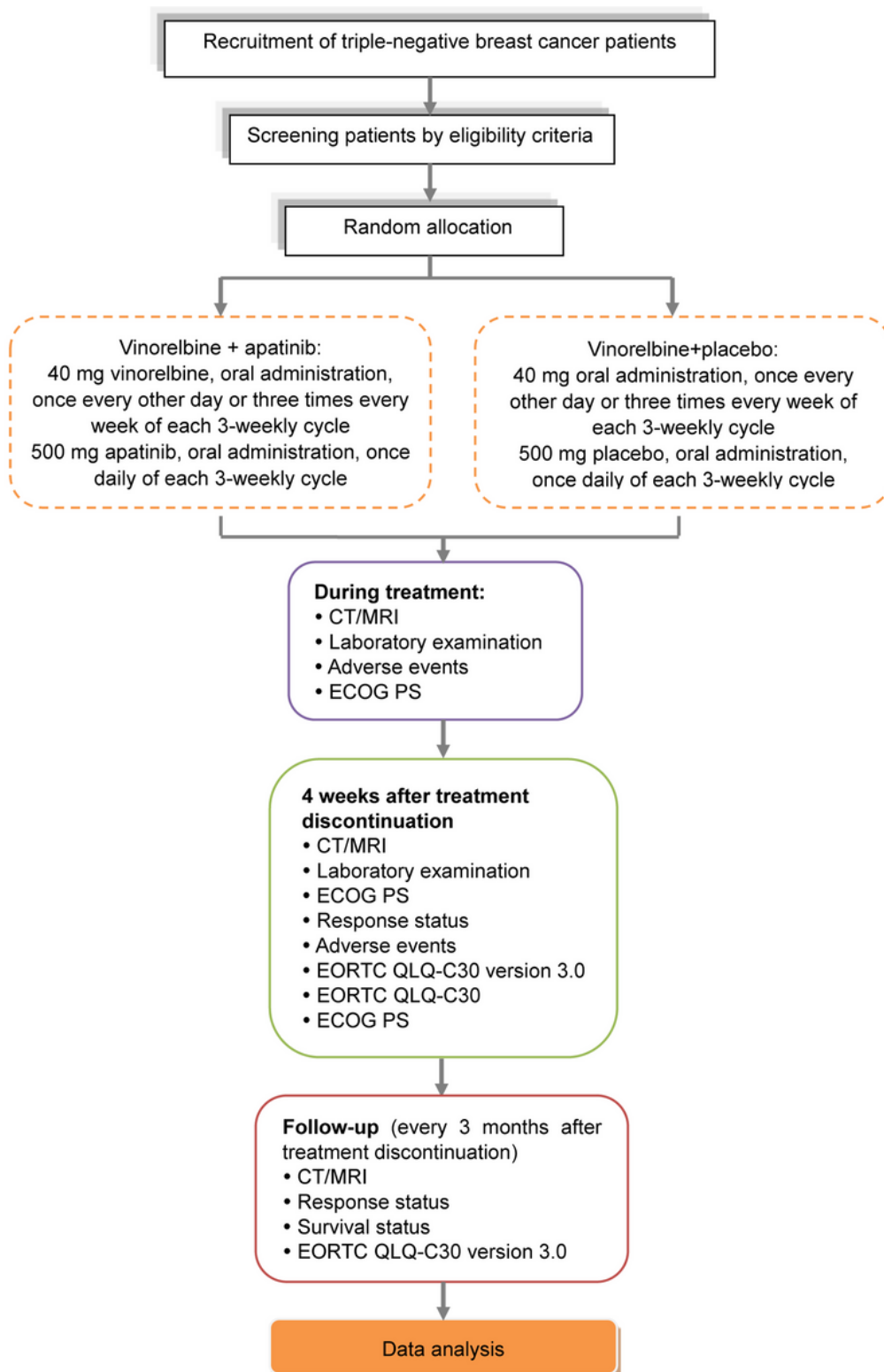
Figure 2

Schedule of enrollment, interventions and assessments. ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, version 3, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; CT, computed tomography; MRI, magnetic resonance imaging.