Research Project Design Document

Project Name: A Prospective Study of Memantine Hydrochloride for the Treatment of Prostate Cancer Patients

Department: Department of Urology

Institution Address/Postal Code: 87 Dingjiaqiao, Gulou District, Nanjing, Jiangsu Province, 210009

Principal Investigator: Bin Xu

Telephone/Email: +86 18012949196

Supervising Department: Zhongda Hospital, Southeast University

Version:02
Version Date: July 22, 2025

1. Rationale

Prostate cancer (PCa) has become a major threat to the health of the male urogenital system. According to the global cancer statistics report from the WHO's International Agency for Research on Cancer, there were 1,414,259 new cases of prostate cancer worldwide in 2020, accounting for 7.3% of all malignant tumors and ranking third in incidence after breast and lung cancer. The incidence of prostate cancer exhibits significant geographical and ethnic disparities. Historically, data has shown a lower incidence in Asia compared to regions like Europe, America, Australia, and New Zealand. However, with an aging population, changes in lifestyle, and the popularization of screening methods such as prostate-specific antigen (PSA) testing, the incidence of prostate cancer in our country is also on a year-over-year rise.

Prostate cancer is often staged according to disease progression, with classifications such as metastatic hormone-sensitive prostate cancer (mHSPC), non-metastatic castration-resistant prostate cancer (nmCRPC), and metastatic castration-resistant prostate cancer (mCRPC). Androgen deprivation therapy (ADT) is a cornerstone in the treatment of prostate cancer, and many patients who experience recurrence after local therapy or develop distant metastases are sensitive to ADT. Nevertheless, a significant number of patients experience disease progression despite ADT, with some developing castration-resistant prostate cancer (CRPC), which eventually evolves into mCRPC. Therefore, there is an urgent need to develop novel and effective therapeutic strategies to manage disease progression.

The tumor microenvironment (TME), comprising immune cells, the extracellular matrix, and non-malignant cells within the tumor region, plays a crucial role in tumor initiation and development and is a key focus for scientific research. The relationship between the immune system and tumors is currently a major research focus in the field of oncology. The TME plays a critical role in modulating the immune response in cancer patients. Tumor cells and their microenvironment typically produce a large number of immunoregulatory molecules that can have a negative (inhibitory) or positive (stimulatory) impact on the function of immune cells. This has been confirmed in prostate, breast, pancreatic, and gastric cancers.

It is now known that neuroendocrine differentiation (NED) and neuroendocrine prostate cancer (NEPC) are significant contributors to castration resistance in prostate cancer, often occurring after long-term castration therapy in CRPC patients. This is characteristically marked by decreased expression of prostate-specific markers like the androgen receptor (AR) and prostate-specific antigen (PSA), alongside increased expression of neuro-associated markers such as chromogranin A, synaptophysin, and neuron-specific enolase. Patients with prostate cancer featuring neuroendocrine (NE) characteristics respond poorly to chemotherapy, have a poor prognosis, and most have a survival period of less than one year. Given the significant role of neuroendocrine differentiation in the progression of prostate cancer, our team aims to investigate the

long-term concurrent use of memantine hydrochloride in some prostate cancer patients. The goal is to reduce neuroendocrine differentiation in prostate cancer, thereby overcoming castration resistance and drug resistance in advanced stages. NMDA receptor antagonists, such as the representative drug memantine, are used to treat Alzheimer's disease by regulating glutamate activity, primarily in moderate to severe cases. Memantine has minimal side effects when administered at low doses over the long term, making it an excellent candidate for combination therapy. Therefore, exploring the use of memantine hydrochloride in prostate cancer patients to reduce neuroendocrine differentiation and overcome castration resistance and drug resistance in advanced disease holds significant guiding value for the clinical treatment of neuroendocrine CRPC.

1.1Research Status

Tumors are one of the greatest threats to human health today. Based on whether a tangible mass can be detected through imaging, tumors can be broadly classified into two types: solid tumors and non-solid tumors. Among these, solid tumors such as lung, liver, pancreatic, gastric, and colorectal cancer are the more common type. Traditional treatment methods for solid tumors, whether surgical resection, radiotherapy, or chemotherapy, have focused solely on the tumor itself, lacking intervention in the tumor microenvironment. Recent research indicates that the development and progression of solid tumors are not only influenced by the accumulation of genetic mutations within tumor cells; the tumor microenvironment also plays a crucial role in the progression of solid tumors.

The tumor microenvironment is closely related to tumor development and progression. For instance, in the context of tumor immunity, NMDA receptor antagonists promote T-cell and NK-cell-mediated anti-tumor immunity. The combination of NMDA receptor antagonists with anti-PD-1 therapy can eliminate the majority of established preclinical liver tumors. These studies highlight the significant research value and immense potential of NMDA receptor antagonists (memantine hydrochloride) for anti-tumor applications.

1.2The Rationale and Significance of This Study

In 2013, an article published in

Cell on the treatment of pancreatic neuroendocrine tumors with NMDA receptor antagonists reported that treating tumor-derived cell lines with these antagonists inhibited tumor cell proliferation and invasion. This revealed that, beyond their traditional role in neurons, NMDA receptors induce a glutamatergic signaling autocrine loop in human tumors, stimulating malignancy. In 2023, an article in

Cell Biology on the effective inhibition of tumor-associated macrophage (TAM) immune activity by NMDA receptor antagonists discovered the important role of

these antagonists in anti-tumor immunity in hepatocellular carcinoma. Our team plans to conduct a single-arm, prospective study in collaboration between Zhongda Hospital, Southeast University, and Lianyungang First People's Hospital. Information on patients receiving prostate cancer treatment will be obtained from the electronic medical record systems of both hospitals. Patients who meet the inclusion and exclusion criteria will be selected and administered memantine hydrochloride in a clinical drug trial. Through long-term follow-up, we will compare their outcomes with a historical external control group of prostate cancer patients who received traditional therapy to study the impact on patient prognosis.

2. Research Content

2.1 Research Objectives

To conduct a prospective study evaluating the effect of long-term combination therapy with memantine hydrochloride on the prognosis of patients with prostate cancer.

2.2 Research Scope

(1) Selection of Study Sites: This study will be conducted at the Department of Urology, Zhongda Hospital, Southeast University, and the Department of Urology, Lianyungang First People's Hospital.

(2) Selection of Study Subjects: Information of patients receiving treatment for prostate cancer will be retrieved from the multi-center electronic medical record systems. Patients who meet the inclusion and exclusion criteria will be screened and enrolled in this clinical trial with memantine hydrochloride.

Sample Size: It is planned to enroll a total of 15 patients from the multi-center sites who are receiving treatment for prostate cancer and will be on long-term combination therapy with memantine hydrochloride.

（3）Sample Size Calculation Method: According to previous literature, the median time from randomization to objective tumor progression or all-cause death (PFS) is approximately 6 months. Assuming the PFS for the investigational combination therapy is approximately 8 months, with a one-sided alpha of 0.05, a sample size of N=88 would be required based on a single-sample log-rank test. However, due to the small number of such patients and the difficulty in recruitment, we will first conduct an exploratory evaluation of PFS in 15 patients. If the efficacy meets expectations, the sample size will be expanded.

Table 1: Number of events and sample size given different median survival time (in months). The result for initial user input is highlighted in yellow.

Medium survival time for treatment	6.5	7	7.5	8	8.5	9	9.5	10
Number of required events	965	261	125	75	51	38	30	24
Sample size	1073	295	144	88	62	46	37	31

Study Period August 2025 - June 2028.

(4)Subject Recruitment and Allocation Method Information of patients who have undergone radical prostatectomy will be obtained from the electronic medical record systems of Zhongda Hospital and Lianyungang First People's Hospital. Patients meeting the inclusion and exclusion criteria will be selected, administered memantine hydrochloride for the clinical drug trial, and followed long-term. Their prognosis will be compared with an external historical control group of prostate cancer patients who received traditional treatment.

(5) Informed Consent of Study Subjects Informed consent will be obtained from the subjects, and they will sign an informed consent form. Subjects without a comorbidity of Alzheimer's disease will also receive and sign an informed consent form for off-label use of the drug.

(6) Evaluation Endpoints Post-operative patients will undergo regular follow-up checks of blood PSA levels and imaging studies to determine the presence of biochemical or imaging recurrence. Disease-free survival will be used as a key indicator to measure prognosis.

(7) Intervention Methods No intervention methods.

3. Research Methods

(1) Study Design

This study will adopt a single-arm, prospective research design.

(2) Inclusion and Exclusion Criteria

Inclusion criteria for subjects are as follows:

- Age ≥18 years.

• Patients with mCRPC who have previously failed first- and second-line treatments. Patients with comorbid Alzheimer's disease will be prioritized for enrollment.

• Patients with complete baseline clinical data who agree to long-term follow-up.

• ECOG performance status of 0-1.

Exclusion criteria for subjects are as follows:

• Patients with metastatic prostate cancer at initial diagnosis who have not progressed to mCRPC.

• Patients currently with other primary tumors.

(3) Enrollment and Treatment Plan

Information of patients who have undergone radical prostatectomy will be obtained from the electronic medical record systems of Zhongda Hospital and Lianyungang First People's Hospital. Patients who meet the inclusion and exclusion criteria will be selected, and after signing the informed consent form, will be administered memantine hydrochloride. The baseline treatment regimen will be determined by the attending physician based on a comprehensive assessment of the patient's prior first- and second-line treatments, disease progression, and individual physical condition. This ensures that each subject can participate in this study while continuing to receive clinically recognized, effective standard-of-care treatment.
The baseline treatment will follow the principle of conventional androgen deprivation therapy (ADT) combined with a novel endocrine therapy. The specific plan is as follows:

Androgen Deprivation Therapy (ADT): All enrolled subjects will continue to receive treatment with a gonadotropin-releasing hormone (GnRH) agonist or antagonist to maintain serum testosterone at castration levels (< 50 ng/dL).
Novel Endocrine Therapy: On top of continuous ADT, the attending physician will select a novel endocrine drug that the patient has not previously used, primarily abiraterone acetate (in combination with prednisone) or enzalutamide.
The study drug,
memantine hydrochloride, will be used in combination with this baseline therapy.

The study medication regimen is as follows: For the first 3 weeks of treatment, the dose will be gradually increased by 5 mg each week to reach the maintenance dose. The dose for the first week is 5 mg once daily, 10 mg once daily for the second week, and 15 mg once daily for the third week. Starting from the fourth week, the recommended maintenance dose of 20 mg once daily will be administered. One month after starting the study drug, patients will return to our hospital for follow-up checks of blood PSA levels and imaging studies (including pelvic CT, prostate MRI,

etc.). If the patient experiences no significant drug-related discomfort and no biochemical or imaging recurrence, subsequent follow-ups will be scheduled every 3 months. The medication dosage will be adjusted by the physician based on the follow-up results.

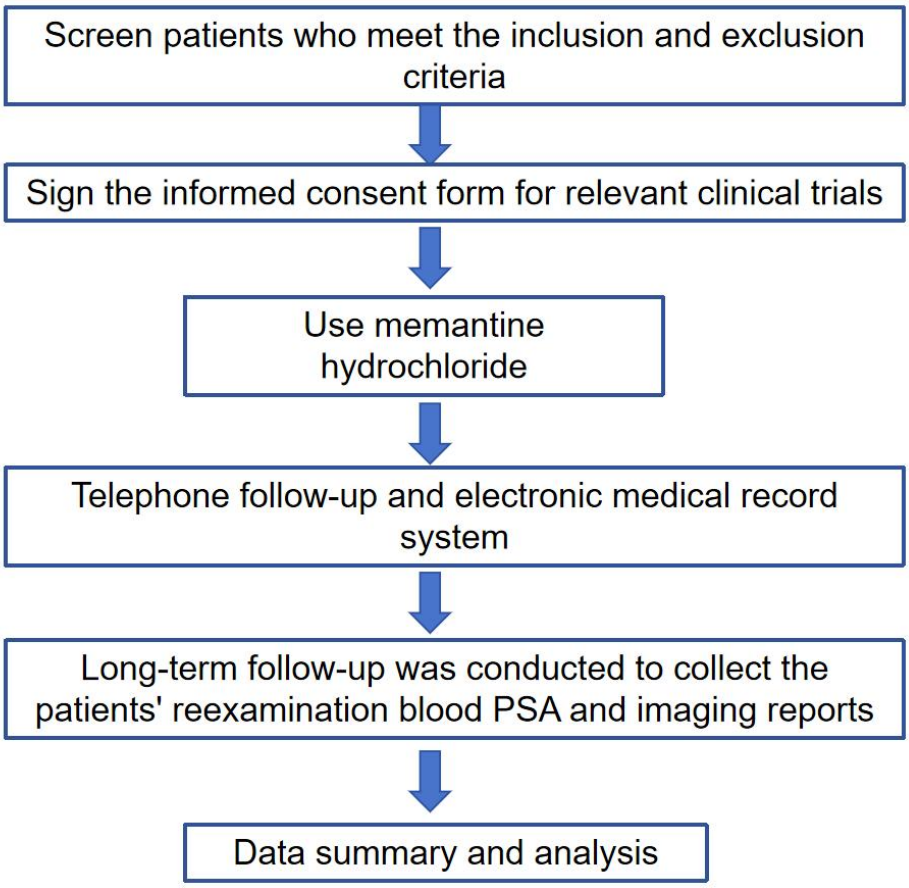
Efficacy Evaluation:

Post-operative patients will undergo regular follow-up checks of blood PSA levels and imaging studies to determine the presence of biochemical or imaging recurrence. Progression-free survival (PFS) and disease control rate (DCR) will be used as important indicators to measure short- and long-term efficacy.

(4) Statistical Analysis:

Categorical data will be described using counts and percentages. For comparisons of continuous data between groups, independent t-tests or Mann-Whitney U tests will be used; for within-group comparisons, paired t-tests or Wilcoxon signed-rank tests will be used. Categorical data will be analyzed using the χ^2 test or Fisher's exact test. All statistical tests will be two-sided, and a p-value of less than or equal to 0.05 will be considered statistically significant.

4. Technical Roadmap



5. Feasibility Analysis

(1) Theoretical Feasibility: Regarding research on NMDA receptor antagonists, an article in *Cell* on treating pancreatic neuroendocrine tumors showed that using NMDA receptor antagonists on tumor-derived cell lines inhibited tumor cell proliferation and invasion. This revealed that, in addition to their traditional role in neurons, NMDA receptors induce a glutamatergic signaling autocrine loop in human tumors that stimulates malignancy. Furthermore, an article in

Cell Biology on the effective inhibition of tumor-associated macrophage (TAM) immune activity by NMDA receptor antagonists discovered the important role of these antagonists in anti-tumor immunity in hepatocellular carcinoma.

(2) Clinical Operational Feasibility: This is a single-arm, prospective study. Information on patients receiving prostate cancer treatment will be obtained through multi-center electronic medical record systems. The drug experiment will be conducted using memantine hydrochloride, with regular follow-ups and phone calls to collect data on patient outcomes.

6. Innovation of the Project

In the tumor immunity context, memantine hydrochloride promotes T-cell and NK-cell-mediated tumor immunity; combining NMDA receptor antagonists with anti-PD-1 therapy can eliminate most established preclinical liver tumors. It has minimal side effects during long-term low-dose administration, making it an excellent choice for combination therapy. Therefore, exploring the use of memantine hydrochloride in prostate cancer patients to reduce neuroendocrine differentiation and overcome castration resistance and drug resistance in advanced stages offers significant guidance for the clinical treatment of neuroendocrine CRPC.

7. Research plan and predicted progress

Work Progress	Main Content
AUG 2025 to Dec 2027	Enroll relevant clinical research patients and conduct clinical experiments.
Jan 2028 to Jun 2028	Complete clinical data collection and analysis.

8. Expected Research Outcomes

The application of memantine hydrochloride in prostate cancer patients is expected to reduce neuroendocrine differentiation, overcome castration resistance and drug resistance in advanced prostate cancer, and demonstrate a degree of safety and efficacy in the clinical treatment of neuroendocrine CRPC.

Work Basis and Conditions

Research Experience Related to This Project: The Department of Urology at Zhongda Hospital, Southeast University has established a relatively comprehensive clinical database for malignant tumors of the urinary system. The department frequently performs radical prostatectomies and communicates well with patients regarding informed consent. Our team has completed the relevant literature search and has already constructed a knowledge framework regarding neuroendocrine differentiation in prostate cancer and memantine hydrochloride.

Budget

The main expense for this project is the cost of the study medication. According to the research plan, the 15 patients are expected to require a total of 91 boxes of memantine hydrochloride (Memantine) during the study period, with a total drug cost of 2,075 RMB. This cost will be covered by the project team.

Apart from the aforementioned drug costs, this study will not incur other additional expenses. All research data (such as blood PSA levels, imaging results) will be obtained from the patients' routine clinical follow-ups, requiring no payment for extra examinations.