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Establishment and Real-World Application of an Adverse Reaction Monitoring System for Targeted Therapy of Antitumor Drugs

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Abstract: This multicenter prospective observational study aims to construct an adverse reaction monitoring system for molecular targeted antitumor drugs and explore its real-world application. By recruiting patients receiving molecular targeted therapy from outpatient, inpatient, and pharmacy settings, we collected comprehensive data including patient demographics, disease information, treatment regimens, and adverse reactions. The adverse reactions were graded according to CTCAE v5.0. With a planned enrollment of at least 100,000 patients over five years, this study will conduct descriptive analysis and build prediction models for adverse reactions. The results will contribute to establishing a national monitoring network and database, updating clinical guidelines, and enhancing the safety of molecular targeted therapy.

Keywords: Adverse reaction monitoring; Molecular targeted antitumor drugs; Real-world study

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1. Introduction

Molecular targeted therapy refers to therapeutic drugs designing for a protein molecule, nucleotide fragment, or gene product in tumor cells that causes tumorigenesis and progression. It is mainly divided into two categories: monoclonal antibodies and small molecule compounds. The advent of molecular targeted therapy has revolutionized cancer treatment. Since the approval of rituximab for CD20-positive non-Hodgkin's lymphoma in 1997 by the US FDA, a plethora of targeted drugs have emerged, such as EGFR inhibitors (e.g., erlotinib, gefitinib), ALK/ROS1 inhibitors (e.g., crizotinib, entrectinib), and HER2 inhibitors (e.g., trastuzumab, pertuzumab), significantly improving patient prognosis across various malignancies including lung cancer, breast cancer, colorectal cancer, leukemia,

lymphoma, melanoma, kidney cancer, gastric cancer, gastrointestinal stromal tumors, liver cancer [1, 2].

Although molecular targeted drugs act on specific targets in tumor cells and have fewer and milder adverse reactions than traditional cytotoxic drugs, since the targets of molecular targeted drugs are also expressed in normal tissues, they can also produce adverse reactions, including systemic, gastrointestinal, skin, liver, kidney, heart, and coagulation adverse reactions. Systemic adverse effects may manifest as fatigue, fever, and joint pain. Gastrointestinal disturbances like diarrhea, vomiting, and liver toxicity (e.g., elevated ALT, AST, and ALP) are common, often attributed to cytochrome-mediated liver metabolism [3]. Skin toxicities, including rash and itching, can impact patients' quality of life [4]. Hematological and cardiac toxicities, such as neutropenia and QT interval prolongation, also pose significant clinical concerns [5–13].

Notably, real-world patients often differ from those in clinical trials, with more complex comorbidities and prior treatment histories, yet existing research, primarily from phase II~III trials and small-sample hospital-based studies, fails to adequately capture this diversity [14–17]. Therefore, a large-scale real-world study is imperative to comprehensively assess adverse reactions and optimize drug safety management.

2. Materials and methods

2.1. Study design

This is a multicenter, prospective, observational study with no intervention in clinical diagnosis or treatment. It adheres to ethical principles, ensuring patient consent and privacy protection. The duration of the study is 5 years. No randomized or protocol-driven treatment will be administered or provided to subjects during the study. Treatment decisions, if clinically appropriate, will be made at the discretion of the physician.

Patients receiving targeted therapy from outpatient and inpatient wards in the study center voluntarily join the study, sign the informed consent form. Physicians collect baseline characteristics and monitor patients in the hospital to determine whether adverse reactions occur. If adverse reactions occur, record the type, severity of adverse reactions, intervention, and discharge. Outside the hospital, the hospital system follows up regularly, and patients fill out follow-up information, including medication compliance, possible adverse reactions, and researchers follow up accordingly. In the non-study centers, Patients receiving targeted therapy from inpatient and outpatient clinics learn about the project through their doctors or the project's official website, and voluntarily join the project by signing the informed consent form and uploading a baseline character. The regional research team monitors adverse reactions of the patients. Patients complete monthly questionnaires on medication compliance, diet, exercise, disease progression, and any adverse reactions through the patient portal, which are automatically entered into the follow-up database. After patients submit possible adverse reaction information, it will be automatically forwarded to the researchers associated with the patient. The investigator records, grade the AR, and follow up using the intelligent assistance management system. When patients revisit the same center, treatment plans, and examination are automatically collected through the outpatient hospital information system.

The study will rely on modern information technology to establish a nationwide molecular targeted anti-tumor drug adverse reaction monitoring network and long-term monitoring database to provide data support for the subsequent update of the guideline and consensus. At the same time, by collecting patients' disease information, explore the establishment of adverse reaction prediction models for targeted drugs with different mechanisms, and provide reference tools for safe use of drug. During the research process, ethical standards will be strictly obeyed to ensure that the rights of the subjects are fully protected. Subjects will be recruited through the project's official website, and the patient's personal information will be strictly confidential. The research data will be managed

using an electronic medical record system to ensure that the data collection is accurate, complete, and timely.

2.2. Subjects

Patients receiving molecular targeted therapy from outpatient, inpatient, and pharmacy settings voluntarily join the study, sign informed consent, accept follow-up, and report adverse reactions. For patients who experience adverse reactions, researchers follow up on the adverse reaction intervention and outcomes, regularly summarize and analyze the data, and report the occurrence of adverse reactions of different molecular targeted drugs in real world.

2.2.1. Inclusion criteria

(1) Both male and female patients aged 18 years or older
(2) Clinically and pathologically diagnosed with malignant tumors (solid and/or hematological).
(3) Prescribed molecular targeted drugs by clinicians and having received at least one dose.
(4) Willing and able to undergo long-term follow-up and provide consent.

2.2.2. Exclusion criteria

(1) Mental disorders or language impairments precluding examination or follow-up.
(2) Pregnant or lactating women.
(3) Severe comorbidities with a life expectancy of less than 1 month.
(4) Other conditions deemed inappropriate by investigators.

2.3. Recruitment

For the study centers, all patients who meet the inclusion and exclusion criteria are monitored for adverse reactions, which include both in-hospital and out-of-hospital monitoring. During in-hospital molecular targeted drug treatment, adverse reactions are promptly reported by clinical physicians, clinical pharmacists, or nursing staff, and relevant information is filled out. After discharge, patients receive regular follow-ups through their mobile devices and self-report any adverse reactions. The pharmacists at the study centers follow up on the adverse reactions reported by patients and fill in the relevant information.

For the non-study centers, Patients who are undergoing molecular targeted drug treatment and are willing to be monitored for adverse reactions can learn about the project from their physicians or the project's official website and voluntarily join the trial. The process is the same as the out-of-hospital monitoring process for patients at study centers.

2.4. Endpoints and definitions

The primary outcome was the spectrum and severity of adverse reactions per SOC and CTCAE v5.0 after molecular targeted drug treatment. Adverse reactions were defined as: not detected before treatment; or stopped before treatment started and reappeared during treatment; or persisted and worsened in severity during treatment compared with the situation before treatment. The spectrum and severity of adverse reactions were summarized according to SOC and CTCAE classifications. The adverse reactions were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0, which is developed by the National Cancer Institute (NCI) of the United States (CTCAE v5.0 is the latest version and was released in November 2017). The preferred terms of the system organ class (SOC) were used to describe adverse events. Secondary outcome was DCR, such as progressive disease (PD), stable disease (SD), complete response (CR), partial response (PR), and death, intervention and outcomes, correlation with molecular targeted drugs, direct or indirect medical costs after AE occurs.

Demographic Information (Age, Gender), Disease (diagnosis, pathological diagnosis, stage, course, comorbidities or complications), Treatment (monotherapy or combination, drugs for related comorbidities), laboratory tests including complete blood count, liver function, renal function, tumor biomarkers, coagulation, imaging examinations including CT/MRI/Ultrasonography/PET-CT, physical examination (blood pressure, heart rate, height, weight), quality of life assessment including SDS/SAS, daily steps, ECOG, medication (DOR and DOT) will also be collected.

2.5. Data management

Researchers input patient baseline information through the EDC platform and collect various data monthly via the patient mobile terminal and other terminals. The adverse reactions were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The preferred terms of the system organ class (SOC) were used to describe adverse events. Data is collected through multiple means with minimum manual entry. Logic verification and other functions are added to enhance data quality control, and different data permissions are assigned to researchers. For data preservation, all data is entered into the electronic platform and stored in the cloud, regularly backed up by the main study center and will be preserved for 10 years after the study's end. Patient privacy will be encrypted.

2.6. Sample size and statistical analysis

This study will monitor all molecular targeted drugs. To discover possible rare adverse reactions, at least 100,000 cancer patients will be enrolled, and subgroup analysis will be performed by different mechanisms of the drugs. Statistical methods include descriptive statistics and advanced modeling techniques to analyze adverse reaction patterns and build prediction models. Statistical analysis of adverse reactions will be performed by different treatment, and stratified analysis will be performed by disease, age, gender, and previous treatment. The adverse reactions were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The preferred terms of the system organ class (SOC) were used to describe adverse events. The measurable data were described by methods including mean, standard deviation, median, quartile, maximum, minimum, and analyzed by methods such as t-test or rank sum test. The count data will be described by methods such as frequency and frequency (constituent ratio), and analyzed by methods such as chi-square test. Statistical significance is defined as $p < 0.05$. The data will be grouped by disease and stage, and modeled using methods such as generalized linear models. Independent variables were screened, the effects of each variable on adverse reactions were analyzed. Adverse reaction prediction model will be established and fitted.

2.7. List of drugs involved in the study

Table1. Table of drugs involved in the study

Name	Indications
Anlotinib Hydrochloride Capsules	Locally advanced or metastatic non-small cell lung cancer that has progressed or recurred after receiving at least two systemic chemotherapy regimens in the past
Gecacitinib Hydrochloride Tablets	Myelofibrosis (PMF), secondary myelofibrosis due to polycythemia vera (PPV-MF), and secondary myelofibrosis due to essential thrombocythemia (PET-MF)
Almonertinib Mesilate Tablets	Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and who have a positive T790M mutation
Flumatinib Mesylate Tablets	Adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic phase

Table 1 (Continued)

Name	Indications
Adebrelimab Injection	First-line treatment for extensive-stage small cell lung cancer, firstline treatment for limited-stage small cell lung cancer, and perioperative treatment for resectable non-small cell lung cancer
Adebrelimab Injection	First-line treatment for extensive-stage small cell lung cancer, firstline treatment for limited-stage small cell lung cancer, and perioperative treatment for resectable non-small cell lung cancer
Cetuximab N01 Injection	Wild-type RAS metastatic colorectal cancer
Famitinib Malate Capsules	Patients with recurrent or metastatic cervical cancer who have failed previous platinum-based chemotherapy but have not received bevacizumab treatment before
Apatinib Mesylate Tablets	Atients with advanced gastric adenocarcinoma or gastric-esophageal junction adenocarcinoma who have experienced progression or recurrence after receiving at least two systemic chemotherapy regimens in the past
Bevacizumab Injection	Metastatic colorectal cancer and advanced, metastatic or recurrent non-small cell lung cancer
Unecritinib Fumarate Capsules	Adult patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer (NSCLC)
Envonalkib Citrate Capsules	The treatment of patients with ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not received treatment with ALK inhibitors

3. Discussion

This multicenter, prospective, observational study provides a comprehensive analysis of the spectrum and severity of adverse reactions (ARs) in patients undergoing molecular targeted therapy (MTT) for malignant tumors. With a large sample size of at least 100,000 participants, our findings will offer valuable insights into the real-world management of ARs associated with MTT. The use of CTCAE v5.0 for grading ARs and SOC for describing adverse events ensures standardization and comparability with other studies in the field. The primary outcome, which focused on the spectrum and severity of ARs post-MTT, should reveal a diverse range of reactions, highlighting the heterogeneity in patient responses to these therapies.

A key strength of this study is its large-scale, multicenter design, which enhances the generalizability of our findings to diverse patient populations. The inclusion of both inpatient and outpatient settings, as well as the integration of non-study centers, further broadens the applicability of our results. However, the study is not without limitations. The observational nature of the study limits causal inferences, and the reliance on physician discretion for treatment decisions may introduce variability in patient management. Additionally, while this study aimed to recruit a large and diverse cohort, the exclusion of patients with mental disorders, language impairments, or severe comorbidities may limit the full representation of the patient population. Selection bias due to voluntary participation also warrants consideration.

4. Conclusion

In conclusion, this study will provide a robust dataset on the spectrum and severity of ARs associated with MTT, and may enhance the personalized approach to manage the adverse reactions. In the future, longer follow-up can be conducted to assess the long-term ARs and evaluate the efficacy of interventions aimed at managing these reactions.

Disclosure statement

The authors declare no conflict of interest.

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