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Precision Pharmacotherapy for Breast Cancer: Application and Prospect from Molecular Subtyping to Targeted Therapy

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Abstract. Breast cancer is the most common cancer in women worldwide, with over one million new cases globally each year, which poses a severe threat to women's health. It has many different types; at the same time, traditional chemotherapy does not work well and causes obvious side effects. Precision treatment, which focuses on specific parts of cancer cells by identifying unique molecular markers of cancer cells, accurately blocking their growth signals or disrupting DNA repair pathways, and minimizing damage to normal cells, has become a key way to help patients get better. This study organized how breast cancer is classified (using ER, PR, HER2, and Ki-67) and analyzed how key targets and their drugs work. It used existing research and clinical data, covering international clinical trial results from the past decade and data from authoritative databases such as PubMed; summarized effects and common side effects of these drugs and ways to deal with them; and looked at new steps in the future. Results show precision treatment works better—for example, it raises the 5-year survival rate by 20%-30% for HER2-positive patients and has fewer side effects. This study gives useful help for doctors' work and research on breast cancer precision treatment.

Keywords: Breast Cancer, Molecular Subtyping, Precision Pharmacotherapy, Targeted Therapy, Biomarkers (ER, PR, HER2, BRCA)

1. Introduction

Due to the different situation of each patient and the multiple causes of breast cancer, the pharmacotherapy is of diversity. Though traditional chemotherapy can work somehow, it does not recognize the difference between the normal cell and the cancer cell, which will kill both kinds of cells at the same time. Not only does it cause the hard side effects, but it also makes life discounted for patients.

However, with the development of molecular biology, especially the progress in gene detection and protein analysis technologies, doctors will divide breast cancer into various types according to biomarkers (ER, PR, HER2) in different cancer cells, which has become the standard operation now. In this way, it could directly guide precise targeted therapy, like focusing therapy on HER2, endocrine therapy that regulates hormones in the body, and so on, and totally change the therapy methods for breast cancer.

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In this research, the final purpose is to talk all-round about this classification of cancer, how to help professors and clinical doctors to choose the targeted drugs accurately, how the main targeted drugs work, the actual therapeutic effect, analyze their side effects and provide corresponding measures, and finally discuss the possible future development directions in this field, such as novel biomarker discovery and combination therapy optimization.

2. Subtypes of breast cancer molecular: the foundation of precision therapy

2.1. The clinical value of core biomarkers

Systematically analyze the detection standards and significance of ER, PR, HER2 and Ki-67--including their indicative role in tumor biological behaviors (e.g., activity, invasiveness) and specific value as core bases for treatment decisions.

2.2. Classification and characteristics of major molecular subtypes

Based on the expression status of the mentioned biomarkers, define Luminal A, Luminal B, HER2-overexpressing, and triple-negative breast cancer subtypes, and explain the epidemiological characteristics, pathological morphological features, and clinical prognostic differences of each subtype.

2.3. Sorting of subtype-guided treatment strategies

Clarify the preferred treatment pathways for each molecular subtype (e.g., endocrine therapy as the mainstay for Luminal A, combination of anti-HER2 targeted therapy for the HER2-overexpressing subtype) according to clinical guidance and evidence-based medical evidence [1], and intuitively present the relations between subtype definition, core characteristics and preferred treatment strategy through Table 1, the match between each molecular subtype and its treatment plan fits well with the biological traits of the subtype.

Table 1. Definitions, characteristics and preferred treatment strategies of major molecular subtypes of breast cancer (example framework)

Molecular Subtype	Definition (Biomarker Expression)	Core Characteristics	Preferred Treatment Strategy
Luminal A	ER+/PR+, HER2-, low Ki-67	Slow proliferation, good prognosis	Endocrine therapy
Luminal B	ER+/PR±, HER2±, high Ki-67	Rapid proliferation, moderate prognosis	Endocrine therapy ± targeted therapy ± chemotherapy
HER2-overexpressing	ER-, PR-, HER2+	High invasiveness	Anti-HER2 targeted therapy ± chemotherapy
Triple-negative	ER-, PR-, HER2-	Rapid proliferation, poor prognosis	Chemotherapy as mainstay, immunotherapy for select cases [2]

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3. Key targets and their drug mechanisms

3.1. HER2 target

Human Epidermal Growth Factor Receptor 2 (HER2) is a member of the EGFR (Epidermal Growth Factor Receptor) protein family, and it plays a key role in regulating cell growth and division. In about 15%-20% of breast cancer cases, HER2 is overexpressed or the gene is multiplied in cancer cells. This abnormal activation turns on downstream signaling pathways (such as the PI3K-AKT and MAPK pathways) to speed up tumor growth and spread. For this reason, HER2 has become the core target for treating HER2-positive breast cancer, a subtype that was once associated with poor expected outcome before targeted drugs appeared.

There are two main categories of HER2-targeted drugs, each with distinct working ways. The first category is monoclonal antibodies, which act by binding to the HER2 protein on cancer cell surfaces. The most widely used one is trastuzumab, it attaches to the domain that is outside the cell of HER2, directly preventing HER2 from combining with other EGFR-family receptors (a process called "dimerization"), and dimerization is essential for HER2 to send growth signals into cells. Clinical data from large trials like HERA proved that adding trastuzumab to chemotherapy increased overall survival rates from 75% to 84% in early HER2-positive breast cancer patients. At the same time, trastuzumab triggers a process known as antibody-dependent cellular cytotoxicity (ADCC), which acts as a marker to attract immune cells like natural killer cells. These immune cells recognize the trastuzumab-bound cancer cells and release cytotoxic substances to kill the abnormal cells. Another monoclonal antibody, pertuzumab, binds to a different part of HER2 than trastuzumab (domain II of HER2 instead of domain IV). This unique binding site lets it block a broader range of dimerization (including HER2-HER3 pairs, which are common in tumor growth) and enhances trastuzumab's effect. Clinically, the combination of trastuzumab and pertuzumab is often used as first-line therapy for advanced HER2-positive breast cancer.

The second category is antibody-drug conjugates (ADCs), which combine the targeting ability of monoclonal antibodies with the cell-killing power of chemotherapy drugs. T-DM1 is a typical example: it links trastuzumab to DM1, a type of microtubule inhibitor. In the ELIMIA trial, T-DM1 showed significant advantages over lapatinib plus capecitabine, with median progression-free survival (PFS) of 9.6 months versus 6.4 months and overall survival (OS) extended by 4 months (29.9 vs 25.9 months). trastuzumab acts as a guide to deliver DM1 directly to HER2-positive cancer cells—this targeted delivery reduces damage to normal cells. Once inside the cancer cell, the conjugate breaks down, releasing DM1. DM1 then attaches to microtubules (structures that help cells divide), stopping cell division and eventually causing cancer cell death. DS-8201 is a newer ADC that also uses Trastuzumab as the targeting part, but it is linked to a different chemotherapy drug (DXd). What makes DS8201 stand out is its "surrounding effect" and superior efficacy. In the DESTINY-Breast03 trial, DS-8201 reduced the risk of disease progression or death by 72% compared to T-DM1, with a 1-year PFS rate of 75.8% versus 34.1% and an objective response rate (ORR) of 79.7%, including 16.1% complete responses [3]. This effect allows DS-8201 to work for more cases, including patients who stopped responding to Trastuzumab or T-DM1 [4].

3.2. ER/PR targets (hormone therapy)

Estrogen Receptor (ER) and Progesterone Receptor (PR) are proteins on the surface (or inside) of some breast cancer cells. When hormones like estrogen bind to ER/PR, the receptors become activated and move into the cell nucleus, where they attach to specific genes and promote cancer cell

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growth. This subtype—HR-positive (hormone receptor-positive) breast cancer—accounts for 70%-80% of all breast cancer cases, making ER/PR the most common targets in breast cancer treatment. Hormone therapy works by blocking hormone-receptor interactions or reducing hormone levels in the body, and it includes three main types of drugs.

The first type is Tamoxifen, a member of the Selective Estrogen Receptor Modulator (SERM) class. It works by competing with estrogen to bind to ER/PR in breast tissue. Once bound, it stops the receptors from activating growth genes, thus slowing tumor growth. Unlike pure anti-estrogens, tamoxifen has weak estrogen-like effects in other parts of the body. For example, it can help maintain bone density, reducing the risk of osteoporosis, and lower cholesterol levels, which is beneficial for premenopausal patients. Clinically, tamoxifen is the first-choice drug for premenopausal HR-positive breast cancer patients, and it is usually taken orally for 5-10 years to reduce comeback risk.

The second type is aromatase inhibitors (AIs), which are mainly used for postmenopausal HR-positive patients. After menopause, women no longer produce estrogen in the ovaries, but small amounts of estrogen are still made by converting male hormones (androgens) into estrogen—this process is carried out by an enzyme called aromatase. AIs block aromatase activity, drastically reducing estrogen levels in the body. There are two subclasses of AIs: non-steroidal AIs (such as letrozole and anastrozole) and steroidal AIs. Both types work similarly, but steroidal AIs may have a slightly different side effect profile. Compared to tamoxifen, AIs lower estrogen levels more effectively and reduce recurrence risk by an additional 10%-15% in postmenopausal patients, so they are often used as first-line therapy for this group [5].

The third type is Fulvestrant, a Selective Estrogen Receptor Degrader (SERD). Unlike tamoxifen or AIs, fulvestrant binds to ER and causes the receptor to break down inside the cell, and this completely removes the "growth switch" for cancer cells. The phase III FALCON trial demonstrated that fulvestrant at about 500 mg provided a 2.8-month longer median PFS (16.6 vs 13.8 months) compared to anastrozole in first-line treatment of postmenopausal women with advanced HR-positive breast cancer, reducing the risk of progression by 20%. Fulvestrant is given by injection once a month and is mainly used for advanced HR-positive breast cancer patients who have stopped responding to tamoxifen or AIs. It is especially effective for patients with ER-positive, HER2-negative advanced breast cancer, as it avoids the drug resistance that can develop with long-term Tamoxifen use [6].

3.3. PARP target

PARP (Poly ADP-Ribose Polymerase) is an enzyme found in almost all cells, and its main job is to repair small DNA damages. For normal cells, this repair function is essential for maintaining DNA stability, but for cancer cells with specific genetic changes (like BRCA1 or BRCA2 mutations), PARP becomes a "lifeline", and this is where PARP inhibitors work, based on the principle of "synthetic lethality."

"Synthetic lethality" means that two single-gene problems are harmless on their own, but together they kill the cell. Normal cells have two main DNA repair pathways: one dependent on BRCA1/2 for repairing large double-strand breaks and one dependent on PARP (for small single-strand breaks). That is how it applies to PARP targeting. If a cell has a BRCA1/2 mutation, as seen in 10%-20% of triple-negative breast cancer cases, it loses the BRCA-dependent repair pathway, but it can still use PARP to fix small damages. However, if a PARP inhibitors blocks PARP-dependent DNA repair. For BRCA-mutated cancer cells (losing BRCA repair), this double repair loss causes fatal DNA damage, while normal cells (intact BRCA) stay unharmed. Olaparib (oral, for BRCA-

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mutated TNBC) showed in the OlympiAD trial that PFS rose from 4.2 to 7 months, cutting progression risk by 42%. It's the first approved PARP inhibitor for breast cancer, with more long-term data [7]. Trials (e.g., MEDIOLA) test its combo with immunotherapies, which fills TNBC treatment gaps, aiding hard-to-treat cases [8].

4. Common side effects and management strategies of targeted drugs

Although targeted drugs work by acting precisely on tumor targets, they may still cause side effects due to small amounts of target expression in normal tissues or off-target effects (Table 2). In clinical practice, we need to balance efficacy and safety through standard monitoring and personalized intervention [9].

4.1. HER2-targeted drugs (e.g., trastuzumab, pertuzumab)

Drugs like trastuzumab, and pertuzumab (for HER2-targeted treatment) are mostly used for HER2-positive breast cancer. Their main side effects and how to deal with them are of three kinds:

• Heart problems: This is the most worrying side effect. It may make LVEF (a heart index) drop or cause heart failure. Do a heart ultrasound/MRI before treatment, and every 3-6 months when taking the drug. If LVEF drops a lot, stop the drug for a short time and use beta-blockers or ACEI drugs.

• Infusion reactions and diarrhea: Infusion reactions usually happen when taking the first dose. Check vital signs (like temperature, and blood pressure) of patients and take preventive medicine first. For mild to moderate diarrhea, change the diet to feel better. For bad cases, use loperamide and take electrolyte supplements.

4.2. Endocrine therapy drugs (e.g., tamoxifen, Aromatase Inhibitors (AI))

Side effects are directly related to hormone regulation, requiring targeted management based on drug type: common and drug-specific side effects: Hot flashes happen often—first try things without medicine, like wearing breathable clothes, and not having caffeine. If it's bad, use venlafaxine. Drugs that are called aromatase inhibitors often cause common pain and high cholesterol, and you should check cholesterol every 6-12 months and use statins if it's too high. The drug tamoxifen may make the lining of the uterus thicker—patients need a gynecological ultrasound every year. If the lining is ≥10mm thick, they need a hysteroscopic biopsy.

4.3. PARP inhibitors (e.g., olaparib, niraparib)

Mainly used for BRCA-mutated breast cancer. Side effects mainly appear in the blood and digestive systems: (1) Blood system problems: Anemia and low platelet count are common. Remember to check the complete blood count every 2-4 weeks. In the situation of mild anemia, iron supplements are needed. In severe cases, blood transfusion or erythropoietin is required. Use pause treatment if the platelet count is too low and avoid difficult activity. (2) Nausea and tiredness: Most cases are mild to moderate. Nausea can be relieved by eating small meals often or using ondansetron. For tiredness, keep a balance between rest and activity; if it is severe, the patients need to use methylphenidate.

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Table 2. Common side effects of targeted drugs and their monitoring & management

Drug Category	Specific Drugs	Main Side Effects	Monitoring & Management
HER2-targeted drugs	Trastuzumab, pertuzumab, pyrotinib	Cardiotoxicity, infusion reactions, diarrhea	Monitor LVEF; premedicate for infusions; use loperamide for diarrhea.
Endocrine drugs	Tamoxifen, aromatase inhibitors	Hot flashes, joint pain, endometrial thickening, dyslipidemia	Non-drugs for hot flashes; monitor endometrium/lipids; use NSAIDs for joint pain.
PARP inhibitors	Olaparib, niraparib	Hematological toxicity, nausea, fatigue	Check CBC regularly; use antiemetics for nausea; balance rest/activity for fatigue.

5. Conclusion

Molecular typing is the basis for precision treatment of breast cancer. It plays a key role in clinical practice by helping doctors gain a clearer understanding of each patient's unique cancer characteristics, as it helps identify different subtypes of the disease, which is necessary to develop targeted treatment plans [10].

Drugs targeting HER2, HR and PARP have significantly improved survival outcomes for patients with the corresponding breast cancer subtypes. For instance, HER2-targeted drugs work wonders for patients with HER2-overexpressing breast cancer, while HR-targeted drugs are highly effective for those with HR-positive subtypes. These drugs work by focusing on specific parts of cancer cells, stopping tumor growth more effectively than traditional treatments. While these drugs have specific side effects, their safety is generally under control. This is made possible through effective pharmaceutical monitoring and proper management strategies. Doctors can track potential side effects and take steps to reduce their impact. In the future, breast cancer precision treatment will continue to develop. It will move towards more detailed disease subtypes, more effective combination treatment plans and ways to overcome drug resistance [11]. For example, researchers are working to split existing subtypes into smaller, more precise groups so treatments can match even tiny differences in cancer cells; they are also testing new mixes of targeted drugs to make treatment stronger, and studying how to stop cancer cells from evading drug effects. The final goal is to achieve true personalized treatment so that every patient can get the best treatment plan for themselves [12].

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