Unlocking the Potential of Targeted Cancer Therapy for Precision Medicine

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This article will cover how newer personalized oncology medications are being developed, mostly discussing their use in breast cancer. Two novel targeted therapy drugs that have shown significant promise in treating certain types of metastatic cancers will also be discussed. It is important for clinicians to have awareness of these therapies as more cancer patients gain access to them.

Targeted Cancer Therapy

In the ever-evolving landscape of medical advancements, targeted therapy drugs have emerged as transformative agents in the fight against various cancers. Unlike traditional chemotherapy which kills rapidly dividing cells,

targeted therapies specifically go after cancer cell vulnerabilities and spare more healthy cells.

Personalized cancer therapy is a treatment strategy that tailors interventions to individual patients based on the unique characteristics of the tumor. It involves the use of genetic, immunological, and further “downstream” proteomic profiling (The proteome is the entire set of proteins that can be expressed by a genome, cell, tissue, or organism) to provide therapeutic alternatives and prognostic information about cancer.[1] This approach can help identify potential therapy options for patients with known specific genomic alterations.[2] Personalized therapy can be targeted to inhibit the oncogenic drivers of a tumor. It is additionally used for immunotherapies that harness the antitumor potential of a patient's immune cells.[3] The goal is to match the right drug to the right patient, taking into account factors such as prognosis, genetic characteristics of the cancer, response to past treatment, and monitoring of therapy.

Predicting Response to Treatment

Treatment response to different targeted breast cancer therapies (as well as other cancers), can now be predicted using clinical data and machine learning algorithms. These approaches utilize multiple measurements, such as histopathology, imaging results, and molecular profiling, to create personalized multiscale models of breast cancer treatment regimens and responses.[4,5] Next-generation sequencing (NGS) is a new technology for DNA and RNA sequencing that can sequence large amounts of genes rapidly. Recent studies have shown NGS of circulating tumor DNA (ctDNA) may reveal potential genomic alterations in breast cancers, allowing for more precise individual treatments.[6]

Artificial intelligence Can Predict Response to Therapy

Artificial intelligence (AI) models have been developed to predict the response to breast cancer targeted therapy. These models utilize various data sources such as imaging data, molecular data, and demographic data in an attempt to accurately predict the outcome of therapy prior to treatment.[7] AI-based pipelines* have been used to extract histopathologic features from whole slide images and develop machine learning models to predict neoadjuvant

chemotherapy (NAC)** response in human epidermal growth factor receptor 2 (HER2)-positive breast cancers.***[8] Another AI-based approach, called the CDK4/6i Response Model (CRM), combines genomic data and signaling pathway activity profiles to evaluate a breast cancer patient's sensitivity to CDK4/6 inhibitor-based therapies.****[9] Additionally, AI has been used to predict the effect of preoperative chemotherapy from histopathologic images, achieving high accuracy in predicting the response to neoadjuvant chemotherapy in triple-negative breast cancer (TNBC).*****[10,11] These AI models and pipelines have the potential to guide personalized medicine and improve therapeutic decision-making in breast cancer treatment.

* AI-based pipelines are an interconnected series of operations that control how data moves through artificial intelligence.

**Neoadjuvant chemotherapy (NAC) is treatment given as a first step to shrink a tumor before surgery.

***A cancer that tests positive for HER2, a protein which promotes the growth of cancer cells.

****Cyclin-dependent kinase 4 (CDK4) and CDK6 may become overactive and lead to increased growth of some cancers

*****Triple-negative breast cancer (TNBC) does not have estrogen, progesterone or HER2 receptors on the cancer cells.

By incorporating drug pharmacokinetics and pharmacodynamics, these models can simulate the effects of different therapy regimens on tumor growth and response.[12] Predictive biomarkers, identified through genomic, proteomic, and machine learning approaches are essential tools for selecting the most effective treatment for individual patients.[13]

The use of personalized classifiers on subsets of patients with similar characteristics, has shown improved prediction accuracy for breast cancer metastasis.[14] Early molecular profiling and the identification of treatment targets plays a crucial role in personalized treatment, particularly for aggressive subtypes such as TNBC. Bayesian optimization (a method used to

help evaluate and improve machine learning) and likelihood-free inference methods help probability models in estimating the likelihood that therapeutic parameters will function as intended. This can help evaluate individualized parameters and assist in making reliable predictions for the outcome of personalized therapy.

Organoid Cells

Breast cancer organoids (miniaturized in vitro organ models developed from a patient's tumor cells), are valuable tools for studying breast cancer.[15–18] Organoids mimic the characteristics of the original tissue, and retain expression patterns, mutations, and responses to treatments, making them suitable for preclinical drug testing, guiding personalized therapy decisions and disease modeling. Advances in organoid technology have led to the development of living biobanks, allowing for the cryopreservation of organoids to test treatment options and provide personalized medicine platforms.

Additionally, the development of micro-organospheres (MOS), which are much smaller than typical organoids, allows drug sensitivity and dosing studies for a patient's specific cancer type with much faster turnaround times. Studies have shown that MOS can be generated from patient biopsies within 10-14 days.[19,20]

New Targeted Therapies for Breast Cancer

Recently discovered targeted therapies, including differentiated targeted and immunotherapies, for breast cancer have shown promise in improving patient outcomes.[21] Studies have identified potential therapeutic targets such as histamine receptors , transforming growth factors, cyclin-dependent kinases, and poly (ADP-ribose) polymerase. Additionally, the activation of endoplasmic reticulum stress(ERS)* and its downstream signaling pathways have been implicated in breast cancer progression, making them potential targets for therapy. Other potential targets and inhibitors for the treatment of breast cancer include PI3K (phosphoinositide 3-kinases) inhibitors, AKT (serine/threonine kinase) inhibitors, m-TOR (mammalian target of rapamycin) inhibitors, tyrosine kinase inhibitors, CDK inhibitors, DDR (DNA damage

response), angiogenesis, the cell cycle, HDAC (histone deacetylases) inhibitors, and drugs targeting breast cancer stem cells, monoclonal antibodies and PARP (poly (ADP-ribose) polymerase) inhibitors.[22–26]

*Endoplasmic reticulum stress (ERS) occurs when the endoplasmic reticulum starts misfolding proteins which can lead to cell death.

Additionally, targeting breast cancer stem cells (BCSC) using nanoparticle-based systems appears to be a promising strategy to deliver anti-BCSC medications to targeted locations thus overcoming biodistribution obstacles.[27]

Antibody-drug Conjugates

Antibody-drug conjugates (ADCs) have shown promise in breast cancer therapy, as well as other types of cancer. They consist of a monoclonal antibody combined with a chemotherapy drug. The monoclonal antibody attaches to a specific receptor on the cancer cell's surface and then enters the cell where the chemotherapy drug is released. This allows directed therapy against the cancer with less destruction of normal cells. There has been some research with innovative non-internalizing ADCs, where the monoclonal antibody does not enter the cell, which may decrease drug resistance and enhance effectiveness.[28]

Two novel ADC targeted therapy drugs have shown significant promise in treating certain types of metastatic cancers are sacituzumab govitecan-hziy (brand name Trodelvy) and fam-trastuzumab deruxtecan-nxki (brand name Enhertu). It is important for primary care physicians and clinicians to be aware of these therapies to allow more cancer patients to gain access to them.

Sacituzumab govitecan (Trop-2-directed antibody-drug conjugate)

Sacituzumab govitecan is FDA approved for the treatment of adult patients with unresectable locally advanced and metastatic cancer for both TNBC and hormone receptor-positive, HER2-negative breast cancer who have received two or more prior therapies.[29] It is also approved for bladder cancer and

cancers of the urinary tract that have spread or cannot be removed by surgery, and who have received a platinum-containing chemotherapy medicine and also received an immunotherapy medicine. It is an antibody-drug conjugate (ADC), which permits specific targeting of cancer cells while limiting the exposure of healthy cells.

Mechanism of Action

- Sacituzumab govitecan-hziy consists of a monoclonal antibody targeting human trophoblast cell-surface marker 2 (Trop-2). Trop-2 is a transmembrane protein involved in calcium signal transduction that is overexpressed in many epithelial cancers including TNBC.
- Sacituzumab govitecan-hziy also contains a chemotherapy drug, SN-38, that damages cancer cell DNA and prevents further cell division.
- First, the monoclonal antibody binds to Trop-2 proteins on cancer cells and then enters the cells.
- SN-38 is then released inside the cell to attack the cancer cell's DNA.

Approved Uses

- Metastatic TNBC after two or more prior systemic therapies
- Metastatic hormone receptor-positive, HER2-negative breast cancer after two or more prior systemic therapies
- Locally advanced or metastatic urothelial cancer (cells from the bladder, urethra or ureters) after receiving platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor (programmed cell death protein 1, programmed cell death-ligand 1)
- Still Investigational - other solid tumors expressing Trop-2

Benefits and Advantages

- Higher response rates and longer survival compared to standard chemotherapy
- More targeted, so lower rates of severe neutropenia than standard chemotherapy
- Can provide a benefit after multiple previous treatments have failed

Clinical Success and Efficacy

Recent studies have demonstrated a significant improvement in progression-free survival and overall response rates in patients receiving Sacituzumab govitecan-hziy, providing more hope for those facing advanced or metastatic breast cancer. In a phase 3 ASCENT trial Sacituzumab govitecan-hziy extended median survival to 12.1 months compared to 6.7 months on standard chemotherapy in previously treated metastatic TNBC. [30]

Side Effects to Monitor

- Low blood cell counts, nausea, fatigue, alopecia
- Monitor closely for neutropenia
- Diarrhea is common but generally manageable
- Patients who carry the gene for UGT1A1*28, can have increased risk of getting side effects, especially neutropenia (low white blood cell counts), with or without a fever, and anemia (low red blood cell counts).[31]
- Patients receive treatment until disease progression or unacceptable toxicity occurs

In summary, Sacituzumab govitecan-hziy is a newer ADC bringing targeted chemotherapy delivery to hard-to-treat metastatic breast and bladder cancers.

Fam-Trastuzumab Deruxtecan-nxki (HER2-directed antibody-drug conjugate)

Fam-trastuzumab deruxtecan-nxki is another ADC, that is FDA approved for adult patients with unresectable or metastatic HER2-positive solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. It is currently used to treat HER2-positive breast and gastric cancers.

Fam-trastuzumab deruxtecan-nxki is a targeted therapy used for HER2-positive breast cancer, a subtype that often poses significant challenges in treatment. By specifically targeting HER2 receptors, fam-trastuzumab deruxtecan-nxki aims to disrupt the signaling pathways that drive cancer growth, offering a promising avenue for patients resistant to traditional HER2-targeted therapies. Fam-trastuzumab deruxtecan-nxki is an ADC, that allows precise targeting of cancer cells and direct cytotoxicity. This approach maximizes the therapeutic impact on cancer cells while minimizing harm to surrounding healthy tissues.

Approved Uses

- HER2-positive metastatic breast cancer
- HER2-positive metastatic gastric/GE junction adenocarcinoma
- Still investigational for lung, colorectal, and other HER2-positive cancers

Benefits and Advantages

- Significantly higher response rates and survival benefit compared to lapatinib plus capecitabine (two HER-2 blockers)
- Delivers chemotherapy directly to cancer cells sparing healthy cells
- May provide benefit after previous treatments that are no longer working

Clinical Success and Efficacy

The clinical breakthroughs associated with fam-trastuzumab deruxtecan-nxki are reshaping the treatment paradigm for HER2-positive breast cancer. Studies have demonstrated favorable response rates, even in patients who have experienced disease progression on other HER2-targeted therapies.

- In the DESTINY-Breast 02 trial, fam-trastuzumab deruxtecan-nxki extended progression-free survival to 17.8 months compared to 6.9 months on the treating physician's choice of other chemotherapy.[32]
- The DESTINY-Gastric 02 trial showed clinically meaningful improvement in objective response rate and overall survival compared to standard chemotherapy for gastric and gastro-esophageal junction cancers.[33]

- Trials have consistently shown significant response rates and durable remissions in patients with HER2-positive breast cancer who have either stopped responding or not responded to prior therapies.
- The drug's ability to traverse the blood-brain barrier adds an extra layer of promise for patients with brain metastases.

Side Effects to Monitor

- Low blood cell counts, nausea, fatigue, alopecia (hair loss)
- Interstitial lung disease (ILD) is rare but may increase mortality if it occurs. Monitor pulmonary function and watch for signs of ILD.
- Patients receive treatment until disease progression or unacceptable toxicity occurs.

Monitoring Treatment and Follow-Up of Both ADC Drugs

During and after treatment with Sacituzumab govitecan-hziy or fam-trastuzumab deruxtecan-nxki, clinicians should:

- Monitor blood cell counts, electrolytes, liver/kidney function
- Specifically, watch for ILD with fam-trastuzumab deruxtecan-nxki
- Watch for signs of infection
- Assess clinical response with imaging every 3 months (CT scan of the chest/abdomen/pelvis and either bone scan or PET/CT scan.)
- Provide supportive care for side effects
- Check for late effects of chemotherapy (including adverse cardiac and hematologic effects)

Primary Care Clinicians Should Consider Referring Eligible Patients Including:

- Those with metastatic triple negative breast cancer after 2 or more different courses of therapy
- Patients with metastatic hormone receptor-positive, HER2-negative breast cancer after 2 or more different courses of therapy

- Cases of urothelial cancer post-platinum chemotherapy/immunotherapy
- HER2-positive breast cancer or gastric/gastroesophageal junction adenocarcinoma progressing after other anti-HER2 options have been tried.

Indicators That Patients Could Benefit from ADC Treatment

- Disease progression despite multiple treatments
- Presence of actionable genetic markers like HER2 mutations or Trop-2 overexpression
- Patient has a strong cancer performance status and adequate organ function to tolerate intravenous therapy with the ADC medication.

FAQs

Question 1: **How are these drugs administered?**

Both fam-trastuzumab deruxtecan-nxki and sacituzumab govitecan-hziy are given as intravenous infusions, typically in outpatient infusion centers. Treatment is repeated every 1-3 weeks depending on protocol.

Question 2: **How long is treatment given?**

Patients receive treatment until disease progression or unacceptable toxicity occurs. Some people have prolonged responses measured in years.

Question 3: **What kind of testing is needed before starting treatment?**

Testing for HER2 or Trop-2 biomarkers via immunohistochemistry or by FISH (fluorescence in situ hybridization) is required to determine if the cancer will respond.

Question 4: What are costs and coverage?

These are newer therapies that can be expensive and coverage varies based on indication and insurer which needs to be confirmed.

Question 5: **What should patients expect from treatment?**

Most patients tolerate treatment relatively well and can expect stabilization or tumor reduction for a period of time before the cancer develops resistance. Quality of life is often maintained or improved.

Patient Education and Empowerment

Educating patients about the availability and efficacy of Sacituzumab govitecan-hziy and fam-trastuzumab deruxtecan-nxki is a crucial aspect of family and primary care medicine. Empowering patients with knowledge about these targeted therapies fosters informed decision-making and facilitates a collaborative approach to treatment planning.

Conclusion

Newer methodologies such as the use of AI and NGS is allowing the creation of more individualized cancer therapies.

The antibody-drug conjugates sacituzumab govitecan-hziy and fam-trastuzumab deruxtecan-nxki have transformed the treatment landscape for certain types of metastatic breast cancer, gastric cancer, and urinary tract cancers. By precisely targeting cancer cells and mostly sparing healthy cells, they offer better efficacy and tolerability than conventional chemotherapy. Primary care physicians should be aware that these targeted therapies may extend patient survival by over a year.

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