

Targeted Therapies for Breast Cancer

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Treatment of breast cancer like most other cancers has undergone phenomenal changes in the last decade. Although traditional chemotherapy along with surgery and radiotherapy remains the backbone of treatment of breast cancer, we now have many non chemotherapeutic options especially for metastatic or stage 4 breast cancer.

Targeted therapies are drugs that block the growth and spread of cancer by interfering with specific molecules (molecular targets) that are involved in the growth, progression and spread of cancer. These therapies are currently the focus of much anticancer drug development and are a cornerstone of precision medicine, a form of medicine that uses information about a person's genes and proteins to prevent, diagnose and treat disease.

Targeted therapies differ from chemotherapy in several ways. They act on specific molecular targets associated with cancer and therefore tend to be cytostatic (block tumor cell proliferation), whereas chemotherapy acts on all rapidly dividing cells, cancerous and normal cells, cytotoxic. Although they are generally considered to be less toxic than traditional chemotherapy drugs, they do have significant side effects. Most common adverse effects with targeted therapies are diarrhea, liver problems, skin rashes, delayed wound healing, blood clotting problems and high blood pressure to name a few. Several targeted therapies are available as pills unlike chemotherapy which is usually given intravenously. Most of these drugs are available for late stage cancers, but several are used for early stage and there are many clinical trials underway, exploring these medications in early stages of cancer treatment.

Not all patients with breast cancer would be eligible for targeted therapies. In order to be treated with such therapy, patients will first have to be tested to determine whether or not an appropriate target is present. This is

sometimes referred to as cancer phenotype or in some cases whether an actionable mutation is present or not.

One of the oldest form of targeted therapy is inhibition of estrogen signaling pathway in women with estrogen receptor positive breast cancer.

Tamoxifen, a selective estrogen receptor modulator (SERM) was the first drug approved for estrogen receptor positive breast cancer. Aromatase inhibitors are another kind of targeted therapy that acts by blocking biosynthesis of estrogens and thereby blocking tumor growth of estrogen positive breast cancers.

Other forms of targeted therapies for breast cancer that are not dependent on hormone manipulation are HER-2 targeted therapies. Herceptin or trastuzumab is the first recombinant monoclonal antibody that acts by binding to HER2 receptor tyrosine kinase resulting in inhibition of downstream signaling and cytotoxicity. Other agents used for HER-2 positive breast cancers are pertuzumab, ado-trastuzumab emtansine, lapatinib and most recently approved neratinib.

Other forms of targeted therapies for breast cancer involve drugs that block mTOR pathway. Everolimus is the approved drug in this class and is used in postmenopausal women with advanced breast cancer in combination with aromatase inhibitor (hormonal) therapy.

Most recent targeted therapy in breast cancer are CDK 4/6 inhibitors that block proteins in the cell called cyclin dependent kinases. Blocking these proteins in hormone receptor positive breast cancer cells helps stop the cells from dividing. Examples of this class of medications are palbociclib, ribociclib and abemaciclib.

PARP (poly ADP ribose polymerases) inhibitors are effective in BRCA1 and BRCA2 related tumors. They act by preventing DNA damage repair and other cellular processes thereby inducing cell death or apoptosis. Patients that have triple negative breast cancer (ER, PR and HER-2 negative) have

elevated levels of PARP enzymes and are most likely to benefit from this treatment.

Immunotherapies, now approved for several different cancers, are still being studied in clinical trials for breast cancer. There are ongoing clinical trials involving checkpoint inhibitors such as pembrolizumab (PD 1 antibody) and anti CTLA antibodies such as ipilimumab. The aim of immunotherapy is activating the human immune response to recognize tumors as foreign entity and eventually kill the tumor cells.

In conclusion, this is a brief summary of some of the established targeted therapies, there are many more agents with different molecular targets being explored in clinical trials. This is very exciting and wonderful news for our patients and as a medical oncologist, I am eternally grateful to my patients and our scientists and researchers for all their dedication and hard work.

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