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Emerging Treatments for Metastatic Breast Cancer

Author: Kathryn Hobbs
Major: Biochemistry & Molecular Biology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

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An estimated that 1 in 8 women will be diagnosed with breast cancer in their lifetime and 1 in 3 of those women will develop metastatic breast cancer. While many cases of breast cancer can be diagnosed in early stages through breast cancer screening, some cases that are diagnosed late or progress into metastatic breast cancer can be fatal. Several recent studies explore treatments that target metastatic breast cancer and aim to have a higher success rate than previous treatment options. One study developed nanoparticles with a formulation that was tolerated better and had higher plasma and tumor AUCs compared to the maximum dose of a commonly used chemotherapy medication. Another study aimed to identify abnormalities in patient genomes to provide individualized targeted therapy. A third treatment is a combination treatment using antiangiogenesis and immune activation to treat metastatic breast cancer. Currently researchers in this field are exploring opportunities to increase the success rates of treatment for metastatic breast cancer, by developing new chemotherapies, nanoparticles, and targeted therapies.

Introduction

Metastatic breast cancer, or stage IV breast cancer, is a stage in which the breast cancer has spread to another part of the body. Breast cancer metastasis occurs commonly within the bones, lungs, brain, or liver. Metastatic breast cancer is extremely difficult to treat as in many cases it can resurface in other areas of the body years after the initial diagnosis and treatment.

Historically the death rates of metastatic breast cancer have been large, but with advanced developments in screening, treatments, and management the rates have significantly dropped in the last 30 years.

Recent Progress

The first treatment study discusses the modification of one of the most popular chemotherapeutic drugs, Paclitaxel. Paclitaxel is commonly used to treat lung, ovarian, and breast cancers, but due to a low solubility in water it is formulated in a mixture of 50:50 polyoxyethylated castor oil (Cremophor EL) and dehydrated ethanol. Polyoxyethylated castor oil is known to cause serious side effects due to its relative toxicity. Additionally, Paclitaxel is known to be an active substrate of P-glycoprotein, which pumps PX out of cells and resists the drug.

In this study Ma. P. et al. have formulated a PX derivative, the C22-PX conjugate. It is composed of a novel fatty acid-PX derivative of 2'-behenoyl to the C-2' hydroxyl position of Paclitaxel. The conjugate converts to active PX when metabolized in the body and is more soluble than the traditional Paclitaxel, even with the absence of Cremophor EL and ethanol. The C22-PX conjugate was also shown to be less

toxic, had a longer half-life, and had a higher maximum tolerated dose than Paclitaxel[2].

In the second study Andre F. et al. recruited patients with metastatic breast cancer to perform biopsies. These samples were used in comparative genomic hybridization array and sanger sequencing from which they assessed therapeutic targets based on identified genomic alterations. They hypothesized that screening for targetable genomic abnormalities could help identify specific oncogenic events to be blocked by targeted therapy, each alteration can be targeted by a specific drug.

They first determined that genetic alterations are only targetable if the genetic changed interrupt protein functions, pathways, or both; in which they can specifically be targeted by drugs or therapies. Gene gains and losses were also defined as targetable if the comparative genomic hybridization assay peak indicated alterations. Of the 423 patients 46% had at least one targetable alteration, of which 55% had multiple targetable alterations[1].

In the final study by Zhou, P. et al. discusses the crucial role that copper plays in breast cancer progression. Copper is required for tumor cell secretion of several angiogenic factors, which promote tumor blood vessel growth. The previous method of targeting copper was highly effective yet had unavoidable side effects due to targeting copper throughout the body. In this study they developed a pH-sensitive polymeric copper chelator that possesses the ability to directly target the tumor instead of the whole body.

This chelator is used to prepare nanoparticles for targeted delivery to the tumor and for a controlled release of a toll-like receptor that has anti-tumor effects through activating dendritic cells. By combining copper chelation and immune activation they hope to treat metastatic breast cancer more effectively[3].

Discussion

The first treatment presents a very promising option for chemotherapeutic drugs, by developing a derivative of an already popular drug, improvement of treatment is likely. The increased maximum tolerated dose using C22-PX nanoparticles allows for more C22-PX to circulate for the bloodstream, increasing the spread throughout the body. This, coupled with a longer half-life could mean that the C-22 PX nanoparticles are significantly more potent and effective in treating metastatic breast cancer.

The second treatment provides a possible benefit to individualized treatment for patients to assess their treatment options and select the best possible course. New strategies for those who experience consistent and resistant metastatic breast cancer are very desirable, as it has a significant death rate and is currently not a curable disease. It also proposes a screening method that could change how metastatic breast cancer is diagnosed. With new comprehensive methods that cover the root of genetic alterations, treatments can be specifically prescribed to meet the individual's needs and increase success.

The third treatment provides a new dual action approach to treating metastatic breast cancer by utilizing both copper chelation and immune activation at the site of the tumor. They found that the developed nanoparticles could successfully target cancerous cells due to their need for a considerably higher concentration for copper, which is not found in healthy cells. The nanoparticles also significantly impaired the angiogenic activity of the cancerous cells. Their results also showed high rates of dendritic activation at the site of the tumor.

All three treatment types show very promising treatments for metastatic breast cancer. They all aim to reduce the death rate and control the progression, each with significant results.

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