Book Chapter

Breast Cancer Treatment in the Modern Era: A Focus on Drug Combinations

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Abstract

Breast cancer, a complex oncological challenge, requires a nuanced treatment approach. Despite effective treatments, drug-resistant tumors contribute to the majority of mortalities. The focus has shifted to combining drugs, such as chemotherapy, immunotherapy, and gene therapy, to enhance efficacy and reduce toxicities. This chapter offers a detailed exploration of the present landscape of breast cancer therapeutics, emphasizing the shift from traditional single-drug treatments to more sophisticated combination strategies. It delves into the realm of combination therapies, where diverse treatment methods such as chemotherapy, immunotherapy, Hormone therapy, and gene therapy are strategically blended to address the intricate nature of breast cancer biology. The goal is to achieve a balanced approach, maximizing effectiveness while minimizing toxicity. Ongoing research aims to diversify treatment options, envisioning a future with more personalized and comprehensive care for breast cancer patients.

Keywords

Breast Cancer; Drug-Resistant Tumors; Combination Therapies; Chemotherapy; Immunotherapy; Hormone Therapy; Gene Therapy

Introduction

Breast cancer treatments include surgery, radiation, neoadjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, and endocrine or hormone therapy. Maximum therapeutic efficacy combined with a minimum of side effects is necessary for breast cancer treatment to maintain patients' lives [1].

Because the majority of anticancer drugs do not distinguish well between cancerous and normal cells, systemic toxicity and undesirable effects of chemotherapeutics significantly reduce treatment efficacy. Additionally, acquired drug resistance may further reduce chemotherapy and other adjuvant medicines' ability to treat cancer. Although patients receiving high doses of chemotherapy may be able to overcome drug resistance, the overall survival rate did not improve due to increased treatment toxicity. In addition, the effectiveness of cancer treatment is also limited by the heterogeneity of breast cancer [2].

Furthermore, cancer patients may experience unfavorable side effects from monotherapies, which do not usually work well for them, especially in the case of metastatic cancers [3]. It has been noted that the tumor contains a variety of cell types, from them the breast cancer stem cells (BCSCs) that contribute to the aggressiveness of metastatic lesions [4]. When a tumor has been successfully treated, some cells are left behind and contribute to the tumor's recurrence. These characteristics make treating cancer patients only with monotherapy challenging [5].

Towards Combinatorial Therapies

A new and promising approach is combining cancer therapies to see whether they can complement one another in a way that lessens side effects and gets beyond the resistance of tumor cells. This has built up an efficient way to handle some of these problems by specifically targeting cancer-inducing or cell-sustaining pathways Combinatorial therapy may involve combining two distinct modalities, such as radio-immunotherapy and radio-chemotherapy, or it may involve combining two or

more therapeutic agents, such as chemotherapy medicines or other types of therapies [6,7].

Combination chemotherapy provides benefits such as improved efficacy, decreased toxicity, and a slowed or delayed formation of drug resistance since it necessitates a lower therapeutic dosage of each medicine alone. Because of these advantages, combined chemotherapy is now the most widely used technique in clinical practice [8].

Drug combinations are typically based on the following general principles: (a) without overlapping toxicities so that each drug can be administered at the appropriate dose (b) with different therapeutic mechanisms and minimal cross-resistance to suppress broad-spectrum drug resistance (c) with optimized dose ratios for synergistic or additive therapeutic effects (d) with similar solubility and permeation to ensure adequate delivery and high intracellular levels [8].

Chemotherapeutic Drugs Combination

Combination chemotherapy (or polychemotherapy) has traditionally been used to treat breast cancer to lower the risk of recurrence and improve overall response. A common regimen for breast cancer is combining an alkylating agent like cyclophosphamide with antimetabolites such as methotrexate and 5-FU. Other combinations between chemotherapies were assessed in clinical trials for breast cancer treatment and some of these combinations are approved by the Food and Drug Administration (FDA) [9].

Numerous combination therapies, including those based on paclitaxel (PTX), methotrexate (MTX), and anthracycline, have been developed throughout the years to treat various cancers. Liposomes, polymers, dendrimers, hybrid nanoparticles, inorganic nanoframes, and nanogels are just a few of the diverse nanocarriers that have been used to carry different drugs together for combination chemotherapy [10].

Currently, administering a physical mixture of two or more anticancer drugs is the only option for combination regimens for metastatic breast cancer that are available in clinics. Clinically employed combination regimens can be broadly categorized based on their mechanisms of action, including (a) nonspecific small molecule chemotherapeutic agents that can be given singly or in combination; (b) combinations of target-specific biologic agents and small molecule chemotherapeutic agents; and (c) combinations of target-specific biologic agents [11] (Table 1).

Small-molecule chemotherapeutic agents can appear in many active combination chemotherapy regimens in metastatic breast cancer. Anthracycline-based regimens, often known as anthracycline antibiotics, are a class of widely used and researched medications used in cancer chemotherapy [12]. They are derived from the Streptomyces bacteria. Anthracyclines work by three different mechanisms: (1) intercalating between base pairs of the DNA/RNA strand to inhibit DNA and RNA synthesis, which stops the replication of quickly proliferating cancer cells; (2) inhibiting topoisomerase II to prevent the relaxing of supercoiled DNA, which stops DNA transcription and replication; and (3) producing iron-mediated free oxygen radicals to harm DNA and cell membranes [12,13].

To improve the anti-cancer activity, anthracycline combinations were made, such as doxorubicin or epirubicin with cyclophosphamide; doxorubicin, cyclophosphamide, and fluorouracil; and epirubicin with cyclophosphamide and fluorouracil. In comparison to single-agent regimens or combinations not based on anthracyclines, these regimens are both more active and toxic [9].

In addition, taxane-based regimens, which include paclitaxel (Taxol) and docetaxel (Taxotere), disrupt the microtubules' functions which are essential for cell division, so they are known as mitotic inhibitors. As compared to anthracyclines, taxanes have reduced bioavailability [14].

Taxanes and anthracyclines typically do not produce overlapping toxicities with existing therapies. An anthracycline/taxane

combination's overall increased toxicity may be compensated by its significantly higher therapeutic benefits [15].

Additionally, in multidrug-resistant (MDR) tumors, some multidrug regimens without anthracyclines or taxanes show high response rates. For instance, combining the nontaxane Ixabepilone with capecitabine leads to a longer progression-free survival than capecitabine by itself. For the treatment of metastatic breast cancer, another combination regimen is cyclophosphamide, methotrexate, and fluorouracil [16-18].

Table 1: Mixtures of non-specific small molecule drugs used in chemotherapy. OS stands for overall survival, PFS is an acronym for progression-free survival, RFS represents replace-free survival, RR is short for response rate, and TTP denotes time to progression [11].

Classes	Combination	Advantages	Disadvantages
Anthracycline-based	Doxorubicin or epirubicin + Cyclophosphamide Doxorubicin or epirubicin + Fluorouracil	Improved RR	No significant difference in time to progression or survival
Taxane-based	Doxorubicin or Gemcitabin + Paclitaxel Doxorubicin or Capecitabin + Docetaxel	Improved RR, PFS, TTP, and OS	More hematologic and non-hematologic toxicity, cardiotoxicity
Other combinations	Ixabepilone + Capecitabine Cyclophosphamide + Methotrexate + Fluorouracil	Improved RR and TTP in heavily pretreated patients Improved RR, RFS, and OS	Peripheral neuropathy Rapid bone loss

Immunotherapy Combinations

Another effective therapy for cancer treatment is immunotherapy. Although immunotherapy has been used to treat a variety of tumors such as multiple myeloma, pancreatic, ovarian, and skin cancer, it is less frequently utilized than

standard therapies and surgery. Though immunotherapy is sometimes effective, not all patients benefit from it [19].

Recently, the combined drug therapy (CDT) strategy has been widely used for immunotherapy checkpoint inhibitors to effectively target triple-negative breast cancer (TNBC) [19]. According to a study, the combination of the doxorubicin-loaded cyclic octapeptide liposomes and the mTOR inhibitor rapamycin prevented the production of hypoxia-inducible factor-1 alpha (HIF-1α) in TNBC cells [20]. The progression-free survival (PFS) of TNBC patients significantly improved when chemotherapy and phosphoinositide 3-kinase (PI3K)/AKT/mTOR inhibition were combined [21]. Another study revealed that TNBC cells' ability to activate tumor-infiltrating T lymphocytes was significantly boosted by the combination of suppression of cyclin-dependent kinase 4/6 (CDK4/6) and PI3Kα [22] (Figure 1).

Figure 1: The figure illustrates the various phases of the cancer immunity cycle, our body's innate defense mechanism against cancer. The cycle initiates

with the release of tumor antigens from cancer cells. Dendritic cells capture these antigens and journey to the lymph nodes to present them to T cells. Upon antigen presentation, T cells activate and return to the tumor to eliminate cancer cells. The figure also highlights potential disruptions to the cancer immunity cycle, such as loss of tumor antigens, diminished MHC presentation, an immunosuppressive tumor microenvironment (TME), and immune cell dysfunction. Furthermore, the diagram outlines potential therapeutic strategies to enhance the immune response against cancer. These include cancer vaccines, anti-PD1/PD-L1 therapy, and adoptive cell transfer [23].

Chemo-Immunotherapy Combinations

The combination of chemotherapy and immunotherapy (chemo-immunotherapy) explores the hypothesis that combination therapy may act synergistically against different cancers. Immunotherapy's ability to elicit particular immune responses has a significant prognostic and predictive impact on cancer patients receiving chemotherapy in these combination systems. While this is happening, chemotherapy can improve immunotherapy by increasing tumor cells' susceptibility to the cytotoxic effects of T-lymphocytes (CTLs) and decreasing immunosuppression by removing regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [24].

According to a number of results from clinical trials, atezolizumab (programmed cell death-ligand 1 (PD-L1) antibody) and pembrolizumab (PD-1 antibody) are both promising immunotherapies when used in conjunction with chemotherapy as a treatment for metastatic and advanced TNBC [25-30].

Immunotherapy-Hormone Therapy Combinations

Also, according to a few studies, the combination of immunotherapy with endocrine or hormone therapy appears promising. In a recent trial, two patients with metastatic HR-positive breast cancer benefited from the combination of antiestrogen medications (letrozole or tamoxifen) plus immunotherapy (pembrolizumab) [31]. The patients displayed greater T-cell receptor diversity following treatment, which is

reportedly associated with a better prognosis after immunotherapy. Although the study was modest and the research is still in its early phases, larger sample sizes are needed to corroborate these findings [31].

In patients with estrogen receptor (ER)-positive metastatic breast cancer, first-line salvage hormone treatment (HT) is combined with recombinant interferon-beta/interleukin-2 as immunotherapy. Multiple types of solid and hematological cancers have been treated with recombinant interleukin-2 (IL-2), which can boost lymphocytes (mainly natural killer cells) and lymphokine-activated killer (LAK) cells [32-34].

Moreover, previous studies in which aromatase inhibitors (Letrozole or Anastrozole) or Fulvestrant were used as endocrine therapy combined with CDK 4/6 inhibitors (such as Palbociclib or Abemaciclib) were proven to increase endocrine sensitivity in patients with HR+, HER2-advanced, or metastatic breast cancer. This combination is more effective than endocrine therapy alone; however, not all are successful [35].

Gene Therapy-Chemotherapy Combinations

Gene therapy, which involves delivering functional DNA or RNA to suppress undesirable gene expression or downregulate disordered genes, has recently been used to supplement chemotherapy in the treatment of cancer. Due to their dissimilar physicochemical characteristics, co-administration of a medication and gene is extremely difficult. Plasmid DNA (pDNA), small interfering RNA (siRNA), and microRNA (miRNA) have been added to these combinational systems to mix with chemotherapy medicines [10].

Chemotherapy combined with siRNA-based gene therapy has the potential to significantly improve cancer treatment over chemotherapy alone. The effect of siRNA in sequence-specific gene silencing has a synergetic apoptotic effect with chemotherapy. For example, using cationic micelles, co-delivery of SN-38 and human vascular endothelial growth factor (VEGF)-targeted siRNA (siVEGF) was accomplished [36]. Before

complexing with a drug-loaded micelle, the siVEGF was attached to a Polyethylene Glycol (PEG) chain to produce siRNA-PEG to increase the stability and lengthen the retention duration of siRNA in the blood circulation. The SN-38-loaded siRNA-PEG micelleplex provided synergistic therapeutic effects by passively targeting the tumor while simultaneously facilitating VEGF silencing and chemotherapy [36].

Due to the increased therapeutic results, miRNA-based gene therapy combined with chemotherapy is currently the subject of extensive research. Apoptosis induction, blocking of autophagy, reversal of the epithelial-to-mesenchymal transition (EMT), inhibition of tumor angiogenesis, and downregulation of ATP-binding cassette (ABC) transporters are all benefits of this therapy [10]. One method of miRNA-based cancer therapy involves using miRNA mimics to directly upregulate tumor-suppressive miRNAs, which have the potential to reprogram cancer cells by building RNA-induced silencing complexes.

Conclusion

In conclusion, the multifaceted landscape of breast cancer treatment demands innovative approaches to optimize therapeutic outcomes while minimizing toxicity and recurrence. The exploration of drug combinations, spanning traditional chemotherapy, immunotherapy, and gene therapy, unveils a promising horizon for tailored interventions. Combinatorial strategies, such as anthracycline and taxane regimens, showcase enhanced efficacy, while immunotherapy combinations and chemo-immunotherapy unveil novel synergies against metastatic breast cancer. Furthermore, the integration of gene therapy, employing siRNA and miRNA, underscores the potential for sequence-specific gene silencing and apoptosis induction. This comprehensive overview underscores the evolving paradigm in breast cancer treatment, emphasizing the pivotal role of combination therapies in shaping more effective, individualized, and less toxic interventions for diverse stages and subtypes of the disease. As challenges persist, continuous refinement of drug utilization and administration remains paramount for advancing the field and realizing the potential of personalized treatments in the future.

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