Current and Prospective Treatments for Triple Negative Breast Cancer

Sofia Green

Abstract

Triple negative breast cancer (TNBC) is a highly heterogeneous and aggressive subtype of breast cancer characterized by a lack of expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). TNBC accounts for 15-20% of all breast cancers and has the poorest prognosis of all breast cancer subtypes. TNBC is especially challenging to treat because of a lack of well-defined molecular targets, and current treatments for TNBC, especially chemotherapy, often result in resistance, recurrence, and off-target toxicity. A promising solution for these challenges is precision medicine, a therapeutic approach that involves tailoring treatment to the individual patient by identifying the specific mutations driving their disease. This review will explore the current treatment options for TNBC, specifically chemotherapy and immunotherapy, emphasizing the limitations of these common modalities of treatment. Using precision medicine approaches, it may be possible to tailor currently available treatments to individual patients to improve outcomes and lessen side effects. This paper will also address the phenomenon of cancer resistance, one of the key challenges in treating TNBC, and highlight how precision medicine can address this issue.

Introduction

Triple negative breast cancer (TNBC) is a subset of breast cancer lacking overexpression of the breast cancer-associated markers estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) (Derakhshan and Reis-Filho). TNBC accounts for approximately 15%–20% of all breast cancers and is considered the most heterogeneous and aggressive subtype of breast cancer (Masci et al.). Additionally, approximately 19% of TNBCs have a mutation in the BReast CAncer gene (*BRCA*) (Derakhshan and Reis-Filho). TNBC tumors are considered highly aggressive due to their rapid proliferation and high likelihood of local and distant recurrence. TNBC therefore has the poorest prognosis of the breast cancer subtypes (Clusan et al., Zagami and Carey).

ER and PR are types of hormone receptors expressed by the luminal cells lining the inner space of mammary ducts. ER and PR both regulate cellular functions that can promote the development of breast cancers, namely ER positive and PR positive subtypes (Derakhshan and Reis-Filho). HER2 is a membrane-associated cell signaling receptor that is overexpressed in about 20% of BCs. When activated, HER2 sends potent proliferative and anti-apoptotic signals to the cell (Gutierrez and Schiff). Breast cancer subtypes that are positive for these receptors, as well as those overexpressing HER2, can be treated with targeted therapeutics. Targeted therapies can specifically inhibit proteins that are frequently mutated or altered in cancer to selectively target cancer cells. Many drugs have been approved to specifically target these mutated pathways, allowing for selective treatment of cancers (Zagami and Carey). Due to the absence of well-defined molecular targets such as ER and PR receptors in TNBC, finding

effective treatment for TNBC has proven more difficult. Additionally, TNBC rapidly develops resistance to many treatments through multiple mechanisms, providing another challenge in treating TNBC (Li et al.).

A promising option for the treatment of TNBC is precision medicine (PM). Precision medicine methods are based on the selection of suitable biomarkers to determine the optimal targeted therapy for a specific subset of patients. TNBC is associated with high interpatient heterogeneity. Precision medicine is tailored to the individual patient's disease, genetic background, environment, and lifestyle. Thus, adopting effective, personalized therapies for patients with TNBC may help to improve treatment outcomes and reduce recurrence (Subhan et al.). In this paper, I will discuss how precision medicine can be applied to TNBC, and its potential benefits for TNBC treatment.

Precision Medicine

PM describes an approach to cancer treatment that accounts for the heterogeneity between patients. These heterogeneities can arise from the genes, environment, and lifestyle of each patient. The precision medicine approach is based on the identification of biomarkers that may predict the efficacy of targeted treatment in a specific subset of patients (Subhan et al.). Through knowledge of the breast cancer subtypes and whole genome sequencing of individual patients, patients can be split into subgroups based on their targetable mutations. This ensures that they only receive treatment that will be effective against their specific mutation. This is known as patient stratification (Weng et al.).

PM is already being utilized in breast cancer using drugs that target the ER, PR, and HER2 receptors and has had a positive impact on patient outcomes. However, because TNBC lacks these clear targets, it is challenging for doctors and scientists to use precision medicine in TNBC treatment (Subhan et al.). Precision medicine is not yet used broadly due to a lack of data and high costs, but scientists are actively working to overcome these hurdles (Prosperi et al.).

PM treatments may help solve many of the common challenges in TNBC treatment. Firstly, by targeting specific mutations or pathways, precision medicine may reduce the off-target toxicity often present with chemotherapy regimens (Subhan et al.). Secondly, TNBC has a high rate of resistance and recurrence when treated with general chemotherapy and other standard treatments (Nedeljković and Damjanović). Precision medicine may help to reduce the rates of resistance and recurrence by targeting cells that express the specific mutations facilitating disease progression (Subhan et al.).

Resistance

Resistance is one of the major challenges in cancer treatment tha precision medicine may help address. Especially in metastatic cancers, chemotherapy resistance accounts for 90% of therapeutic failures (Nedeljković and Damjanović). Resistance may be partly attributed to the heterogeneity of the tumor microenvironment . The tumor microenvironment includes tumor cells, cancer-associated fibroblasts, immune cells, natural killer cells, tumor-associated macrophages, vasculature, and extracellular components such as the extracellular matrix, cytokines, chemokines, metabolites, and exosomes. Many of the components of the tumor microenvironment can interact with each other, thus altering the external environment of the tumor and ultimately leading to drug resistance (Liu et al.).

Hypoxia

Hypoxia is a main mechanism by which resistance can develop in TNBC. Hypoxia occurs when tissues have insufficient oxygen supply. Angiogenesis, the formation of new blood vessels, is one of the hallmarks of cancer. As tumors grow, they create new blood vessels to transport blood to regions of the tumor that are too far away from the existing vessels. The blood vessels formed during tumor angiogenesis are often disorganized or leaky, and as a result, the ability of the vessels to transport oxygen is impaired (Ferrari et al.). This means that certain parts of the tumor that are reliant on these disorganized blood vessels do not receive sufficient oxygen. Hypoxia is an important factor in the TME and is associated with aggressiveness, invasiveness, and resistance to therapy (Nedeljković and Damjanović). Hypoxia contributes to chemoresistance in multiple ways. Firstly, insufficient vasculature hinders drug penetration into the tumor. Second, the acidic TME that results from hypoxia reduces the uptake of anti-cancer drugs. Further, the cytotoxic components of many drugs are oxygen-dependent (Ferrari et al.) .Additionally, hypoxia activates immunosuppressive pathways and acts as a barrier to immune effector cells (Nedeljković and Damjanović). Finally, hypoxia leads to cellular adaptations that hinder successful treatment, including increased expression of ABC transporters, decreased proliferation, modulation of cell senescence and apoptosis, induction of autophagy that aids in tumor survival, genetic instability and subsequent selection of aggressive phenotypes, upregulation of proangiogenic factors, and repression of E-cadherins that promotes metastatic spread (Nedeljković and Damjanović, Ferrari et al.).

The mutations that drive ABC transporter and hypoxia related resistance provide targets for PM. For example, identifying which patients overexpress the ABCC1 protein can help stratify patients for treatment that targets the production of that protein, thus decreasing the likelihood of ABC transporter-driven resistance (Ferrari et al.).

Current Treatments

Due to the lack of clear molecular targets for TNBC drugs, the standard of care for non-surgical TNBC remains conventional chemotherapy (Li et al.). However, most of these treatments are associated with numerous negative side effects and lack the desired specificity to effectively treat the cancer and prevent recurrence (Medina et al.). Many different types of chemotherapy are currently approved for TNBC treatment, and choosing what kind to use is dependent on the characteristics of the TNBC in the individual. The current major modalities of treatment are chemotherapy, immunotherapy, radiation, and surgery. Precision medicine can aid in deciding which modality of treatment to use depending on tumor location, presence of mutations, and expression of antigens.

Chemotherapy

Chemotherapy uses chemical compounds to kill rapidly dividing cells in the body. It is meant to target tumor cells, but often has adverse side effects, killing other rapidly dividing cells such as hair, skin, and white blood cells (Li et al.). For this reason, it is important to explore precision medicine to help doctors decide which chemotherapy to use for each patient and identify the best target for treatment.

Microtubule targeting agents.

Microtubule targeting agents (MTAs) are one class of chemotherapy that inhibits mitosis (Li et al.). These drugs are usually not prescribed alone, but rather in combination with other chemotherapy drugs or immunotherapies (Li et al.). Microtubules play a key role in many important cellular functions, such as motility, division, shape maintenance, and intracellular transport (Masci et al.). Motility and division are especially important in TNBC. Metastasis is one of the greatest challenges in the clinical treatment of cancer, and cell motility is the mechanism that allows cancer cells to migrate to other organs and tissues (Stuelten et al.). Cancer cells also undergo uncontrolled division due to deregulation in the cell cycle. MTAs work by blocking the function of cellular microtubules, thus leading to abnormal spindle fiber function and chromosome misalignment. This permanently activates the spindle assembly checkpoint and results in the arrest of the cell cycle and the induction of apoptosis. While these drugs are generally highly effective, they are not targeted drugs, and are therefore not a good fit for precision medicine. Their mechanism of action causes them to target any rapidly dividing cells, such as bone marrow cells, not only those that are cancerous (Chan et al.). This inability to distinguish between healthy cells and cancer cells accounts for many of the unfavorable side effects of chemotherapy, such as hair loss, infections, and peripheral neuropathy (Zajączkowska et al.).

Platinum

Platinum-based anticancer drugs were one of the first chemotherapies developed, and they are still in use today. Cisplatin was the first Pt-based chemotherapy approved for human patients. Cisplatin has demonstrated therapeutic effects on malignant tumors (Zhang et al.). However, cisplatin is a nonspecific chemotherapy agent that causes systemic toxicity in addition to killing cancer cells. Therefore, cisplatin has many undesirable side effects such as dose-limiting toxicity and myelosuppression (García Sar et al.). Due to this, carboplatin was designed to offer improved safety and tolerability, and lower systemic toxicity. Less toxicity is achieved because of the different inhibitory effects on nuclear DNA synthesis (Vermorken et al.). Because it has a lower toxicity, carboplatin can be used as high dose chemotherapy. However, carboplatin and other Pt-based drugs are still not targeted, and not a good fit for precision medicine (Zhang et al.).

PARP Inhibitors

Poly (ADP-ribose) polymerases (PARPs) are a class of enzymes that facilitate the transfer of ADP-ribose to target proteins. PARPs are involved in various cellular processes, such as transcription, replication, DNA repair, and apoptosis (Masci et al., Morales et al.). As previously mentioned, about 19% of TNBCs have *BRCA* gene mutations (Derakhshan and Reis-Filho). The *BRCA* genes play an important role in DNA repair via homologous recombination (HR) and are associated with a hereditary predisposition to developing female breast cancer (Masci et al.). When cancer cells are deficient in or have a mutated/ineffective *BRCA* gene, they display impaired HR and are ineffective in repairing damaged chromosomes. Thus, they are more reliant on PARP activity and sensitive to its inhibition (Morales et al.). PARP inhibitors (PARPi) have recently been closely examined as one of the most promising targeted strategies to treat TNBC as they prevent cancer cells from repairing themselves. It has been demonstrated that the use of PARPis can create synthetic lethality and increased tumor cell

death by blocking the mechanism that allows these cells to repair their DNA. Thus, PARP family proteins represent attractive targets for the treatment of TNBCs that harbor a mutant *BRCA* allele. The use of PARPis in *BRCA* mutant cancers is a clear example of PM. The stratification of patients through precision medicine will help doctors identify which patients would benefit most from PARPi treatment. Although *BRCA*-deficient tumors are more susceptible to the action of PARPis, about 40% of *BRCA* deficient TNBC patients do not respond to PARPis due to the emergence of drug resistance mechanisms in TNBC (Masci et al.).

While effective in treating TNBC, specifically in the neoadjuvant setting, meaning before the main treatment is given, conventional chemotherapy is not the most promising future for the treatment of TNBC. Drug resistance and recurrence continue to be a problem when treating patients, and the non-specific nature of chemotherapies causes many unwanted side effects. Precision medicine provides a more promising treatment style as it identifies strategic biomarkers to target for treatment. This provides a more selective chemotherapy regimen which would create fewer negative side effects (Medina et al.).

Immunotherapy

One example of a precision medicine treatment in current use is immunotherapy. In cancer, the immune system is often suppressed by tumor cells or the TME (Luo et al.). This suppression allows cancer cells to avoid detection by the immune system and thus avoid elimination by activated immune cells (Thomas et al.). Immunotherapy is a treatment strategy that stimulates the patient's own immune system to kill cancer cells (Liu et al.). Treatment with immune checkpoint inhibitors (ICIs) has been shown to induce a cell death response in metastatic breast cancers (Thomas et al.). Two main types of immunotherapies are ICIs and chimeric antigen receptor T (CAR-T) cell therapies (Thomas et al.; Nasiri et al.). The immunogenic landscape of some subsets of TNBC resembles that of lung cancers, which have been proven to benefit from immunotherapies, thus creating opportunities for the development of TNBC-targeting immunotherapies (Luo et al.).

Immune Checkpoint Inhibitors

Tumors adapt many mechanisms to avoid detection by the immune system, one of which is the activation of inhibitory pathways governed by immune checkpoints (Thomas et al.). An example of one such pathway is the interaction between programmed cell death protein-1 (PD-1) which is a checkpoint receptor expressed on the surface of many immune cells, and PDL-1, its receptor, usually expressed on tumor cells (Tang et al.). This pathway is the main target of many ICI drugs as it is highly expressed in TNBC. ICIs aim to target these pathways, which release the immune system from inhibition and revive the anti-tumor immune response, allowing tumor cells to be eradicated (Thomas et al.).

As previously mentioned, TNBC is a disease with high tumor heterogeneity (Masci et al.). Because of this, it has been suggested that only a subset of TNBC patients could benefit from ICI therapy. This presents a challenge in treatment, as it must be determined which patients would benefit most from ICI treatment. Thus, various parameters have been defined to help evaluate the potential efficacy of ICIs in TNBC and other breast cancers (Luo et al.). The unique nature of each patient’s TNBC provides another argument for the use of precision medicine as a more effective treatment method.

Currently, the use of ICIs in combination with chemotherapy is being investigated. Chemotherapy can potentially enhance the immune response following ICI therapy as it has been found to increase the release of tumor cell antigens, promote the activation of dendritic cells, and trigger the production of PD-L1. This combination therapy has shown promising results in metastatic, locally advanced, and early-stage TNBC (Luo et al.).

CAR-T Cell Therapies

CAR-T cells are genetically modified T lymphocytes that use the individual's immune system to recognize and target cancer cells expressing certain tumor-associated antigens and eradicate them. While CAR-T therapy has been very effective in treating hematologic neoplasms, such as B cell lymphoma, it has proven much more challenging to use as a treatment for cancers with solid tumors, such as TNBC (Nasiri et al.).

For CAR-T therapy to be effective against metastatic TNBC, an appropriate target antigen must be identified (Toulouie et al.). Because of the high heterogeneity of TNBC tumors, it can be difficult to find an appropriate target. Tumor cells may express different antigens on their surface, and some may not express antigens that have been identified for treatment at all. This causes CAR-T cells to have difficulty recognizing malignant cells, thus leading to disease escape and recurrence (Nasiri et al.). CART-T cells are customizable to a patient's specific antigens, therefore offering a huge potential for PM. Gene sequencing and the stratification of patients through precision medicine will help to identify these antigens and provide treatment that directly targets them (Subhan et al.).

Conclusion

PM may be a promising future treatment for TNBC. Precision medicine provides new, effective approaches to the leading challenges in TNBC treatment, such as resistance, recurrence, and off-target toxicity. Many predictive biomarkers already exist in breast cancer that can be targeted with precision medicine (Subhan et al.). By dedicating more work to subtyping and understanding the different kinds of mutations that lead to TNBC, doctors can better stratify patients and provide therapy targeted specifically to their mutation (Weng et al.). The development of new and improved gene sequencing technologies continues to raise hope for the success of precision medicine in breast cancer and TNBC (Subhan et al.). If applied broadly, this field of medicine will likely improve patient outcomes in TNBC and other diseases, and reduce the normal complications associated with cancer treatment.

Work Cited

Chan, K. S., et al. “Mitosis-Targeted Anti-Cancer Therapies: Where They Stand.” *Cell Death & Disease*, vol. 3, no. 10, Oct. 2012, p. e411. *PubMed Central*, https://doi.org/10.1038/cddis.2012.148.

Clusan, Léa, et al. “A Basic Review on Estrogen Receptor Signaling Pathways in Breast Cancer.” *International Journal of Molecular Sciences*, vol. 24, no. 7, Apr. 2023, p. 6834. *PubMed Central*, https://doi.org/10.3390/ijms24076834.

Derakhshan, Fatemeh, and Jorge S. Reis-Filho. “Pathogenesis of Triple-Negative Breast Cancer.” *Annual Review of Pathology*, vol. 17, Jan. 2022, pp. 181–204. *PubMed Central*, https://doi.org/10.1146/annurev-pathol-042420-093238.

Ferrari, Paola, et al. “Molecular Mechanisms, Biomarkers and Emerging Therapies for Chemotherapy Resistant TNBC.” *International Journal of Molecular Sciences*, vol. 23, no. 3, 3, Jan. 2022, p. 1665. *www.mdpi.com*, https://doi.org/10.3390/ijms23031665.

García Sar, Daniel, et al. “Reduction of Cisplatin-Induced Nephrotoxicity in Vivo by Selenomethionine: The Effect on Cisplatin-DNA Adducts.” *Chemical Research in Toxicology*, vol. 24, no. 6, June 2011, pp. 896–904. *PubMed*, https://doi.org/10.1021/tx200085n.

Gutierrez, Carolina, and Rachel Schiff. “HER 2: Biology, Detection, and Clinical Implications.” *Archives of Pathology & Laboratory Medicine*, vol. 135, no. 1, Jan. 2011, pp. 55–62. *PubMed Central*, https://doi.org/10.1043/2010-0454-RAR.1.

Li, Yun, et al. “Recent Advances in Therapeutic Strategies for Triple-Negative Breast Cancer.” *Journal of Hematology & Oncology*, vol. 15, no. 1, Aug. 2022, p. 121. *BioMed Central*, https://doi.org/10.1186/s13045-022-01341-0.

Liu, Yang, et al. “Advances in Immunotherapy for Triple-Negative Breast Cancer.” *Molecular Cancer*, vol. 22, no. 1, Sept. 2023, p. 145. *BioMed Central*, https://doi.org/10.1186/s12943-023-01850-7.

Luo, Chenyi, et al. “Progress and Prospect of Immunotherapy for Triple-Negative Breast Cancer.” *Frontiers in Oncology*, vol. 12, 2022, p. 919072. *PubMed*, https://doi.org/10.3389/fonc.2022.919072.

Masci, Domiziana, et al. “Recent Advances in Drug Discovery for Triple-Negative Breast Cancer Treatment.” *Molecules*, vol. 28, no. 22, 22, Jan. 2023, p. 7513. *www.mdpi.com*, https://doi.org/10.3390/molecules28227513.

Medina, Mauricio A., et al. “Triple-Negative Breast Cancer: A Review of Conventional and Advanced Therapeutic Strategies.” *International Journal of Environmental Research and Public Health*, vol. 17, no. 6, 6, Jan. 2020, p. 2078. *www.mdpi.com*, https://doi.org/10.3390/ijerph17062078.

Morales, Julio C., et al. “Review of Poly (ADP-Ribose) Polymerase (PARP) Mechanisms of Action and Rationale for Targeting in Cancer and Other Diseases.” *Critical Reviews in Eukaryotic Gene Expression*, vol. 24, no. 1, 2014, pp. 15–28.

Nasiri, Fatemeh, et al. “CAR-T Cell Therapy in Triple-Negative Breast Cancer: Hunting the Invisible Devil.” *Frontiers in Immunology*, vol. 13, Nov. 2022, p. 1018786. *PubMed Central*, https://doi.org/10.3389/fimmu.2022.1018786.

Nedeljković, Milica, and Ana Damjanović. “Mechanisms of Chemotherapy Resistance in Triple-Negative Breast Cancer—How We Can Rise to the Challenge.” *Cells*, vol. 8, no. 9, 9, Sept. 2019, p. 957. *www.mdpi.com*, https://doi.org/10.3390/cells8090957.

Prosperi, Mattia, et al. “Big Data Hurdles in Precision Medicine and Precision Public Health.”

BMC Medical Informatics and Decision Making, vol. 18, no. 1, Dec. 2018, p. 139. *Springer Link*, https://doi.org/10.1186/s12911-018-0719-2.

Stuelten, Christina H., et al. “Cell Motility in Cancer Invasion and Metastasis: Insights from Simple Model Organisms.” *Nature Reviews. Cancer*, vol. 18, no. 5, May 2018, pp. 296–312. *PubMed Central*, https://doi.org/10.1038/nrc.2018.15.

Subhan, Md Abdus, et al. “Recent Advances with Precision Medicine Treatment for Breast Cancer Including Triple-Negative Sub-Type.” *Cancers*, vol. 15, no. 8, Apr. 2023, p. 2204. *PubMed Central*, https://doi.org/10.3390/cancers15082204.

Tang, Qing, et al. “The Role of PD-1/PD-L1 and Application of Immune-Checkpoint Inhibitors in Human Cancers.” *Frontiers in Immunology*, vol. 13, 2022, p. 964442. *PubMed*, https://doi.org/10.3389/fimmu.2022.964442.

Thomas, Remy, et al. “Immune Checkpoint Inhibitors in Triple Negative Breast Cancer Treatment: Promising Future Prospects.” *Frontiers in Oncology*, vol. 10, Feb. 2021, p. 600573. *PubMed Central*, https://doi.org/10.3389/fonc.2020.600573.

Toulouie, Sara, et al. “Chimeric Antigen Receptor T-Cell Immunotherapy in Breast Cancer: Development and Challenges.” *Journal of Cancer*, vol. 12, no. 4, Jan. 2021, pp. 1212–19. *PubMed Central*, https://doi.org/10.7150/jca.54095.

Vermorken, J. B., et al. “Carboplatin versus Cisplatin.” *Annals of Oncology*, vol. 4, 1993, pp. S41–48. *DOI.org (Crossref)*, https://doi.org/10.1093/annonc/4.suppl_4.S41.

Weng, Lijuan, et al. “The Molecular Subtyping and Precision Medicine in Triple-Negative Breast Cancer---Based on Fudan TNBC Classification.” *Cancer Cell International*, vol. 24, Mar. 2024, p. 120. *PubMed Central*, https://doi.org/10.1186/s12935-024-03261-0.

Zagami, Paola, and Lisa Anne Carey. “Triple Negative Breast Cancer: Pitfalls and Progress.”

Npj Breast Cancer, vol. 8, no. 1, Aug. 2022, pp. 1–10. *www.nature.com*, https://doi.org/10.1038/s41523-022-00468-0.

Zajączkowska, Renata, et al. “Mechanisms of Chemotherapy-Induced Peripheral Neuropathy.” *International Journal of Molecular Sciences*, vol. 20, no. 6, 6, Jan. 2019, p. 1451. *www.mdpi.com*, https://doi.org/10.3390/ijms20061451.

Zhang, Chunyu, et al. “Platinum-Based Drugs for Cancer Therapy and Anti-Tumor Strategies.” *Theranostics*, vol. 12, no. 5, Feb. 2022, pp. 2115–32. *PubMed Central*, https://doi.org/10.7150/thno.69424.