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Abstract

Triple-Negative Breast Cancer (TNBC) is a highly invasive, under-researched subtype of Breast Cancer. Patients lack receptors for the protein Human Epidermal Growth Factor, and both estrogen and progesterone. This negatively impacts treatment by making all hormone-sensitive treatments unavailable to TNBC patients. Since the effectiveness of various options has remained understudied, the prognosis remains poor. This paper attempts to analyze and compare the effectiveness of various treatment options. Because TNBC is very aggressive, the standard approach is to jump in with harsh surgical procedures, including mastectomies and lumpectomies. This analysis finds that more aggressive treatment may not be necessary to treat all TNBC patients. The addition of immuno and platinum therapies to traditional chemotherapy appears to increase survival to the same extent as that of mastectomies and lumpectomies. It also appears that radiation therapy greatly enhances treatment and may be an option to avoid a full radical mastectomy as the survival rates proved to be higher in patients with radiation therapy in conjunction with lumpectomies. More research is needed; however, aggressive therapies do not need to be the first choice as the other options appear to provide just as high, if not higher survival rates.

Introduction

Breast cancer is the second leading cause of cancer deaths and the most common cancer among women. There are an estimated 281,000 cases of breast cancer amongst women in 2021. In their lifetime, 1/8 (13%) women will develop breast cancer, with an estimated 43,000 expected deaths per year. In contrast, only 1/833 males will develop it over their lifetime (BreastCancer.org, 2021B, Siegal et al., 2021).

Breast cancer has several different classifications with regard to the various receptors present on the cells for hormones that promote their growth, e.g., estrogen and progesterone.

In healthy breast tissue, these hormones bind to their receptors and in turn activate and contribute towards breast tissue formation and growth. In hormone-sensitive breast cancer patients, activation of those receptors initiates and contributes towards the cancer's growth. Treatment options in these patients generally block those receptors to slow and/or stop the tumor's growth (National Cancer Institute, 2021).

Triple-Negative Breast Cancer (TNBC) is a Breast Cancer subtype in which the patient lacks estrogen, progesterone, and Human Epidermal Growth Factor 2 receptors. This causes treatment options for TNBC patients to be more limited because hormone therapy generally targets and blocks those receptors to inhibit cancer growth. Treatment options are generally narrowed down to surgery, radiation therapy, and chemotherapy. (Center for Disease Control and Prevention, 2021) This paper will analyze various available treatments for TNBC and seek to explore the most effective options.

Methods

This comprehensive review of treatment options for TNBC was conducted based on the critical analysis of data collected from PubMed and other databases accessed through Touro College and University System's library including ProQuest and EBSCO. Among the keywords and phrases used to retrieve data included "TNBC treatment options," "TNBC meta-analysis," and "TNBC survival rates."

Genetic Component of TNBC

It has been established that the prognosis of TNBC is unfavorable due to the lack of treatment options and low survival rates. A study was aimed to identify the key genes that could be recognized as biomarkers for TNBC. Perhaps these biomarkers could promote early identification and potential treatment options for TNBC. The study identified 194 genes that were actively transcribed in TNBC patients and repressed in non-TNBC genes/patients. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway were both used to discover the biological functions of these genes. The clinical significance of the genes was then examined using the Kaplan-Meier and Receiver operating characteristic analysis. The top 20 upregulated and downregulated genes were found to be expressed consistently in all TNBC vs non-TNBC patients. Of the identified genes associated with TNBC, they were all found to be involved in negative regulation of apoptotic processes, response to drugs, and estradiol. Randomized gene samples were collected from the cell lines and revealed that the genes ART3, FABP7, and HORMAD1 were all upregulated in TNBC compared to non-TNBC tissue. In contrast, TFF1, AGR2, and FOXA1 were downregulated. These genes may serve as key biomarkers and regulators of TNBC (Zhong et al., 2020).

Correlation between TNBC and age:

Studies have found that TNBC is more prevalent amongst younger patients. In one of them it was found that of 216 Breast Cancer patients, 52% were ≤ 35, and of those 19% had TNBC, which consisted of the highest proportion of the group. Because young women diagnosed with Breast Cancer have a higher correlation to TNBC, they have a poorer prognosis. Expression of Ki-67, a protein associated with cell proliferation was also found

to be higher in the TNBC age ≤ 35 group (Ozisik et al., 2021). This may help understand why young breast cancer patients have significantly lower survival rates. One issue with this study, however, was that there was no statistical significance found between molecular breast cancer subtypes. This may either be due to their small sample size or could indicate that age is an independent prognostic factor in TNBC diagnosis and treatment.

Time Correlation

One study followed TNBC patients over 10 years, and interestingly enough found that risk and recurrence rates were not the same throughout the study. In the first five years following diagnosis, the patients had much higher death rates, 70% during that time frame. Additionally, the first five years showed a greater likelihood of recurrence, whereas those rates were significantly lower in the second five years. No recurrence was found after 8 years. These results suggest that TNBC patients who survive longer may have lower risks of death as they age (Dent et al., 2007). Additionally, these results show us the ambiguity of TNBC. Much research on illness impact, treatment, and survival is needed to further broaden the approach towards TNBC.

What is Fueling TNBC Growth

If progesterone, estrogen, and the protein HER-2 are not fueling TNBC growth, what is? One study found that phosphatase PTP4A3 was required for TNBC growth in vitro and in vivo, indicating its role in TNBC development (Hollander et al., 2016). It has also been found that the transcription factor c-Myc drives glucose metabolism in TNBC cells, involving the repression of thioredoxin interacting protein (TXNIP). This protein is a negative regulator of glucose uptake and aerobic glycolysis; so, its repression provides cells methods by which to metabolically fuel themselves and bypass apoptosis. The Mychigh/TXNIPlow ratio gene signature is correlated with overall decreased survival and metastatic-free survival in TNBC patients (Shen et al., 2015).

Treatment Options:
Hormone Receptor-Positive Breast Cancer

Traditional hormone therapy, which is not available for TNBC patients, works via several methods in which the interactions between hormone and receptor are blocked. These include blocking the production of hormones and blocking hormonal action on tumor cells. Tamoxifen therapy is one such example that acts as an estrogen antagonist in estrogen receptor-positive breast cancer cells. One study revealed that Tamoxifen treatment for 5 years decreased recurrence and death by 41% and 34%, respectively (Drãgãnescu and Carmocan, 2017). Another traditional method in treating hormone receptor-positive breast cancer patients is the use of aromatase inhibitors. This class of medication blocks the production of the enzyme aromatase, which turns androgenic hormones into estrogen. This treatment option is used in postmenopausal women because estrogen is primarily inhibited from being formed from the adrenal glands and other organs in the body. A study evaluating the impacts of aromatase inhibitor treatment found that median free survival was 23.8 months for these patients (Tripathy et al., 2018, Khanna, 2020).

Treatment options for hormone receptor-positive breast cancer have shown meaningful results. Significant amounts of patients showed a decreased recurrence, death, and progression-free survival. In contrast, one study that followed 1600 patients over a span of 10 years found that patients with TNBC were more likely to have died (42 vs 28%) compared to those with other cancers. Additionally, all deaths of TNBC patients were within 10 years of diagnosis whereas with other cancers patients lived up to 18 years post-diagnosis. (Dent et al., 2007). It is apparent that TNBC patients are at a disadvantage concerning survival rate and prognosis.

Triple-Negative Breast Cancer
Radiation Therapy Combinations

Whole breast radiotherapy and breast-conserving surgery have reduced recurrence rates from 10 to 2%. Postoperative radiation therapy has been shown to drastically minimize recurrence. A study found that patients who are treated with a radical mastectomy without radiation therapy had a significant risk of recurrence compared to those who received the mastectomy followed by adjuvant radiation therapy. The study followed 768 patients for over 7.2 years. They were split into 3 groups: Patients receiving Breast-Conserving therapy (lumpectomy and radiation therapy), Modified radical Mastectomy, and Modified mastectomy with radiation therapy. These groups had five-year recurrence-free survival of 94%, 85%, and 87% ($P < 0.001$). Five-year overall survival was also measured and was found to be 87%, 82%, and 68% ($P = 0.002$). The higher percentage of overall survival in the Breast-conserving therapy group and modified radical mastectomy + Radiation therapy group show promising treatment methods for TNBC patients. Various factors also impact survival, this includes tumor grade, size, and status (Abdulkarim et al., 2011).

Discussions regarding radiation treatment post radical mastectomy have been controversial. However, several

studies have found that postoperative radiation therapy following a radical mastectomy, in comparison to patients only receiving mastectomies, was significantly more efficient with lower recurrence and higher survival rates. One study found that the recurrence rate for patients treated with radiation after their mastectomy vs no post-operative radiation was 11.7% and 25.4%, respectively. The use of radiation therapy significantly lowers recurrence (Abdulkarim et al., 2011). Another study aimed to compare the effects of both chemotherapy in conjunction with radiation therapy vs chemotherapy alone. The study involved 681 TNBC patients all of whom received a mastectomy. The five-year recurrence-free survival rates were found to be 13.7% higher in the group treated with both treatments (88.3% vs 74.6%). Additionally, five-year overall survival was also higher in the group treated with both (90.4% as opposed to 78.7%) (Wang et al., 2011). It appears that there is increased improvement in patients receiving radiation therapy after mastectomy and even more so with chemotherapy.

Breast Conservation Options

Due to the high-risk, aggressive features of TNBC, concerns regarding surgical approaches to treatment have been raised. Harsher procedures such as mastectomies may appear to be a more effective treatment option; however, several studies analyzed this approach in comparison to those receiving other, less-aggressive operations, such as lumpectomies, which are done to conserve breast tissue.

One study analyzed TNBC patients who received a lumpectomy that was followed by reemission, and they found that of 46 of those patients, 51% subsequentially had residual invasive disease (Sioshansi et al., 2012). These rates show that following lumpectomy, TNBC patients have an elevated risk of residual invasiveness compared to those with other breast cancer subtypes. The study suggested that this may be due to the increased tumor burden associated with TNBC. Lumpectomies alone therefore do not appear to be as effective.

Researchers have investigated whether a lumpectomy is as effective as mastectomy in TNBC patients. In another study of 288 TNBC patients, 111 TNBC patients received lumpectomy to reserve breast tissue while the rest had a total mastectomy. The patients in the lumpectomy group were found to have increased overall survival, (85% vs 81%) after a 102-month follow-up (P=0.56). These patients also had an increased rate of disease-free survival at 10 years (P=0.42) (De-la-Cruz-Ku et al., 2020). These results indicate that lumpectomy may be more effective in the treatment of early-stage TNBC; however, more research is needed due to the lack of statistical significance in these results.

A meta-analysis of twenty-two studies further followed whether breast conservation therapy is as effective as a total mastectomy for treating TNBC patients. This study found that the TNBC patients who received breast-conserving therapy had lower recurrence and metastasis rates, as well as a more favorable prognosis (Wang et al., 2013).

Another study compared survival rates of TNBC patients in 2 groups: Lumpectomy patients with radiation therapy, and mastectomy patients without radiation therapy. The study intended to see if radiation therapy following a lumpectomy could have comparable results to the mastectomy group. Results were analyzed by comparing the amount of stromal tumor-infiltrating lymphocytes (TILs) post-treatment. Higher TILs correspond to greater amounts of helper and cytotoxic T cells that are present to fight and destroy tumor cells. In this study of hormone receptor-positive and negative patients, 46% had TNBC. In the group with high TILs, the patients who received lumpectomy followed by radiation therapy had an overall 5-year survival of 100% in comparison to 86% in the mastectomy group (P = 0.028). This indicates that radiation therapy in conjunction with a lumpectomy may be a good treatment option for some patients. The groups with lower TILs however did not have statistically significant survival differences, with survival at 5 years being 86% in the mastectomy and 81% in the lumpectomy with radiation therapy group (P= 0.241). Although these results show promising options for patients, they cannot be generalized to all TNBC patients because the study population had a mixture of various breast cancer subtypes (Mouabbi et al., 2021).

Androgen Receptor Inhibition

A subtype of TNBC has been found and classified to express an androgen receptor. Patients in this group were found to develop androgen receptor tumors that contribute to their illness. This serves as an additional option for treatment- including blocking and inactivating the receptors to reduce cancer growth. In a study aimed to test the use of androgen receptor antagonists/inhibitors, patients were treated with enzalutamide. The results found that progression-free and overall survivals were 2.9 and 12.7 months respectively (Traina et al., 2018). The treatment was tolerated, and this suggests that it may be useful in patients with this TNBC subtype. It was also found that patients in this subtype express high levels of PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase), catalytic alpha mutations and the use of PI3K inhibitors may enhance treatment and survival; however, more research is needed to explore this potential option (Lehmann et al., 2014).

Immunotherapy Option

Immunotherapies with various synthetic treatments aim to enhance the immune system's ability to fight the disease. The use of immunotherapy for TNBC has been largely analyzed. Tecentriq is one immunotherapeutic that acts as an "immune checkpoint inhibitor." Immune checkpoints serve as regulatory mechanisms in the immune system to prevent immune responses from being too strong and inadvertently destroying healthy tissue. Cancer cells often utilize immune checkpoints to their advantage by shielding them and overcoming identification and destruction by the immune system. This treatment method utilizes inhibitors that serve to target the checkpoint proteins, enhance the immune systems' ability to kill cancer cells, and prevent the metastasis of the cancer cells (BreastCancer.org, 2021A). A study analyzed the impacts of Tecentriq along with another traditional chemotherapy, Abraxane, which is often administered to impede the cancer cells' ability to grow and divide. (BreastCancer.org, 2020). This study split the patients into 2 groups; 50% were treated with Abraxane and Tecentriq whereas the other 50% were administered Abraxane and a placebo. The patients were followed up for 12.9 months, and it was found that progression-free survival was greater for patients treated with the combination (7.2 vs. 5.5 months). Overall survival was also improved in these patients (21.3 vs 17.6 months) (DePolo, J., 2018). This suggests that treatment and survival may be enhanced with the use of immunotherapy in addition to standard chemotherapy drugs.

Platinum-Based Chemotherapy

Platinum-based chemotherapy is a form of treatment that utilizes the metallic properties of platinum to destroy rapidly multiplying cells, including cancer cells. These drugs work by attaching to the DNA of cancer cells. The cell then works to remove the drug from the DNA; however, the cell is unable to do so which causes cell death and prevents the cancer's growth (University of Nottingham, 2020). Platinum-based treatments appear to be controversial due to their high toxicity rates; however, some studies have analyzed the implications of platinum-based chemotherapy in the treatment of TNBC patients. One study compared and analyzed the impacts of platinum vs non-platinum-based chemotherapy in TNBC patients. 70% of 495 patients received platinum-based chemotherapy, and of that group, 71% received it as their initial treatment. The overall survival was 19.2 vs 16.8 months for platinum vs. non-platinum-based treatment ($P = 0.439$). These results show that platinum-based chemotherapy may be impactful in treating TNBC patients; however, the small sample size and lack of statistical significance suggest a need for further research.

A meta-analysis (with 2946 patients) of 11 studies sought to discover platinum implications of patients with different stages of TNBC. Three of the studies utilized a platinum drug in combination with the Taxane regimen. It was found that the patients receiving both platinum chemotherapy and Taxane responded better compared to those only receiving Taxane (45 vs 38%, $P < 1x10\text{-}4$). Another 2 subgroups were compared, with and without the addition of platinum chemotherapy to the anthracycline regimen, a chemotherapy regimen that includes usage of compounds that aid in damaging cancer cells' DNA and preventing their reproduction (BreastCancer.org, 2012). Here, platinum chemotherapy did not show any additional benefits in addition to the anthracyclines. Finally, another 3 studies from the meta-analysis evaluated how platinum chemotherapy impacts the progression-free survival of metastatic TNBC patients. The different rates between the addition of platinum chemotherapy to the non-platinum were not statistically significant ($P = 0.24$), suggesting that platinum drugs may not impact survival upon metastasis (Pandy et al., 2019). Overall, it can be concluded that platinum drugs in addition to standard chemotherapy are not one-size-fits-all. Its addition to some standard chemotherapy regimens has shown to improve response and survival; however, because several studies had statistically insignificant results, more research is needed.

An additional study aimed to compare the impacts of platinum-based chemotherapy on TNBC patients that had lung metastasis. The patients in the platinum group had sufficiently longer median free survival (10 months vs 6 months), and also a higher overall survival (32 vs 22 months), with both of these tests giving statistically significant results (P for both tests < 0.05) (Hong et al., 2014). This suggests that even patients whose cancer has metastasized (due to TNBC) can benefit more from the addition of this treatment.

A major dilemma may be faced by TNBC patients and oncologists. Is it necessary to approach this disease with surgical treatments when other options such as immunotherapy and platinum-based chemotherapy appear to be effective? The answer is complex and would need to be determined on a patient-by-patient level; however, the results given above provide evidence that surgical methods in the treatment of TNBC are not necessarily more effective, and other less invasive/aggressive methods may be just as promising. The regimens appear to produce a more favorable prognosis when chemotherapy is used in conjunction with immuno- and platinum therapy as opposed to the use of chemotherapy alone.

Conclusion

Treatment options for TNBC patients are limited and require more research. Many oncologists believe that because TNBC is such an aggressive cancer, harsher treatment options are necessary to remove it, such as surgeries (eg. Mastectomies). As the first line of treatment, this may not be necessary, because other options including immuno and platinum chemotherapies are proving to be as effective. If taking the surgery route, a complete radical mastectomy is not always needed, because lumpectomies in conjunction with radiation therapy prove to have very effective outcomes. The immuno and platinum treatments with chemotherapy are also showing relatively high survival rates and are comparable to those of surgical approaches. This suggests that TNBC patients may do just as well with less aggressive treatment options; however, more research is needed to evaluate the effectiveness and efficiency of all currently available possibilities.

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