

Specified Treatments for Common Breast Cancer Cases Containing a p53 Mutation Review

By Aspen Lee

Author Bio

Aspen Lee is a freshmen student attending Santa Fe Christian School in San Diego, California. She hopes to pursue her dream of becoming a neurosurgeon or oncologist. As an avid enthusiast of mathematics, she aspires to major in Applied Mathematics or Neuroscience along with continuing such research and intern opportunities throughout high school.

Abstract

With breast cancer being one of the most common causes of death, many researchers have looked into mutations that commonly appear and how they could affect the treatment a patient decides to receive. Mutations in gene TP53 are present in over one third of breast cancer cases, so it is a frequent mutation that is carefully researched and examined. This study aims to review how a mutation in p53 gene in breast cancer patients can influence the form of treatment. Elimination and reviewing of open-source papers, resulted in constant keywords added to the search for specified treatments in modern-day medical technology that have been used or will be in the future. COTI-2 and APR-246 are the compounds that at the time this research was most recently completed, in 2023, have been undergoing clinical trial to be used on patients showing this mutation. Although there have been published papers on this mutation for decades, there is yet to be enough research completed to know whether or not these compounds will positively or negatively impact the process of p53 mutation present treatment plans.

Keywords: Cancer, p53, Mutation, Breast+cancer, COTI-2, APR-246, Treatment, TP53, Female

Introduction

In the United States, breast cancer is the second leading cause of cancer death (Breast Cancer Statistics, 2022). Per every 100,000 women, about 380 are diagnosed with breast cancer and 125 pass away from the disease based on data gathered from 2016-2020 (USCS Data Visualizations, 2023). Triple-Negative Breast Cancers (TNBC) are around 10-15% of all breast cancer cases (American Cancer Society, 2023b); this subtype appears when a patient does not express the three hormone receptors: not containing estrogen or progesterone receptors and make minimal or an over exceeding amount of the HER2 protein, or the human epidermal growth factor receptor 2 (American Cancer Society, 2023a). Tending to spread and grow faster, this breast cancer has been found to have a mutation in gene TP53 in 80% of all cases, even though p53 is only mutated in 30-35% of total breast cancer cases (Duffy et al., 2018). Gene TP53 encodes for protein p53, and its role in the human body is to suppress and stop tumor growth or formation when the cell undergoes cell division (Information (US), 1998).

As a vital protein to prevent cancer formation, it is referenced to as the Guardian of the Genome (Lane, 1992), and it protects the integrity of DNA in the cell (Borrero & El-Deiry, 2021). The activated tumor suppressor protein promotes cell cycle arrest when damage in the DNA is prevalent and induces apoptosis or DNA repair (Ozaki & Nakagawara, 2011). Due to the importance of TP53's function, when mutated, the altered DNA goes undetected, and all genes that are initiated by p53 result in malfunction: DNA damage repair pathways, apoptosis regulation, and cell cycle arrest (Kaur et al., 2018). The multiple treatments for breast cancer, including p53 mutated cases, consist of chemotherapy, radiation, surgery, targeted drug therapy, among others (American Cancer Society, 2023a), but for mutations in p53, specific target drug compounds are constantly undergoing clinical trials to be used in the medical fields for mostly TNBC cases (Duffy et al., 2017). Reactivation of gene TP53 is a commonly targeted gene when treating breast cancer, for when p53 is not functioning properly, the damaged cell will continuously divide amidst going undetected by tumor suppressors (Synnott et al., 2018). The objective of this literature review is to review studies done on whether a mutation in female breast cancer patients in p53 can help determine which type of treatment to use.

Methodology

To write this literature review, it was selected only from recent open source papers published in the last 10 years (2013-2023). The search was carried out using the PubMed database (pubmed.gov) and consisted of the key words "breast+cancer treatments mutations". Thousands of papers came up on the research that was later refined with additional new key words "p53 therapy female". The papers found were narrowed down to around 100 papers. All of them were read, analyzed and separated into papers that were inside the scope of the research or not. There were limited papers regarding p53 mutations in breast cancer and their relation to treatments for female patients, but molecules APR-246 and COTI-2 consistently appeared in many papers. To follow up on those new keywords, papers about the two molecules when appearing in breast cancer led to a total of 25 open source papers published in the past ten years (2013-2023) to be selected. After the selection, the final number of papers used for the results of this review was 14 published papers.

Results

3.1 Mutant p53 as a Therapeutic Target in Breast Cancer Treatment and Therapy

According to Silwal-Pandit et al. (2017) in their study of a cohort of 1420 TP53 mutation samples as a prognostic or predictive tool in breast cancer treatment, the results showed that it is subtype-specific for that mutation to be prognostic. At the time the study was completed, they concluded that the predictive value of the mutation was still debated. They showed through the research that the TP53 mutations in breast cancer can result in a LOF (loss-of-function), GOF (gain-of-function), or LOH (loss-of heterozygosity) (Silwal-Pandit et al., 2017).

According to Duffy et al. (2017), their first study to see if p53 mutations in breast and ovarian cancer cases could be a target for new treatments showed that the methylated form of PRIMA-1 (APR-246) and COTI-2 are just some of the compounds that can reactivate a mutated p53 by converting it to have wild-type properties. In the existing preclinical models, it was proven that they demonstrate anticancer

activity in p53. As of 2017, the two compounds undergoing clinical trials were the APR-246 and COTI-2 compounds as mentioned above. When this study was completed, only APR-246 was used on patients during the trial with advanced serous ovarian cancer, and COTI-2 was in a phase behind in the clinical trial, used on patients with advanced gynecological cancer. Neither have been officially proved to be a useful treatment to human cancer in general (Duffy et al., 2017).

3.2 Mutations in p53 and Their Responses to Different Therapies

In Shahbandi et al. (2020), and their review of studies with different concluding results regarding p53 mutations in breast cancer and its responses to treatments, the review shows how each patient used in the studies had a specific form of treatment that had a more negative or positive effect on the results. From their prior knowledge knowing that each patient has a treatment regimen according to their physician, the studies are all a combined representation of the data, when in truth it is shown to not depict each subtype. There were also many cases where certain patients would receive a treatment others didn't, which resulted in an inaccurate study completed as there is no constant for everyone with different mutations of p53 (Shahbandi et al., 2020).

According to Bertheau et al. (2013), their study of p53 in breast cancer subtypes' responses to chemotherapy showed that their new insights into p53 would relate only to that specific type of chemotherapy. In their study, they took many different TP53 tumors and measured their responses to the different chemotherapies, many not showing a complete response at all. Using the information that mutations in p53 occur in 30% of breast cancer cases, with a high 80% in triple-negative breast cancer cases as well, they worked to see if it would make p53 a helpful biomarker for breast cancer management, in particular chemotherapy treatment plans. Their study showed that wild-type TP53 is found to be often resistant to chemotherapy (minimal/lack of response) while TP53 mutated non-inflammatory locally advanced breast cancers had over 50% of complete response. In the end of their study, they concluded that it would be necessary to continue more research to show from findings if TP53 would be a beneficial

biomarker (Bertheau et al., 2013).

3.3 Possible Treatments for Mutations in p53

According to Zatloukalova et al. (2018), the study done on all the researchers knew on PRIMA-1 and COTI-2, importantly shows how COTI-2 is still undergoing clinical trials to be used on breast cancer patients. PRIMA-1's methylated form is APR-246 and is known to be able to reactivate p53 when mutated. Not much was discovered regarding PRIMA-1 and COTI-2, but COTI-2 was found to be capable of inducing apoptosis in the cell (Zatloukalová et al., 2018).

According to Kaur et al. (2018), their study of mutations in p53's role in breast cancer therapeutic strategies, they showed that TP53 is a tumor suppressor gene that has been found to be mutated in breast cancer along with other forms of cancer. Due to this mutation, it results in the malfunctioning of the DNA damage repair, apoptosis, cell-cycle arrest, and more. So researchers have been focusing on therapeutic strategies for the mutations in p53 and have used many molecules to target the treatment of TP53. Many of these molecules have not yet reached the clinical trial stage except for APR-246 and COTI-2 (Kaur et al., 2018).

According to Duffy et al. (2018), in their study of having the common mutation of p53 be a biomarker or therapeutic target for breast cancer treatment, they found that there was not enough study done to confirm if it could be identifiable as a biomarker. What they did find was that APR-246, COTI-2 and other molecules are possible treatment options for patients with that mutation from the disease. "TP53 (p53) is the most frequently mutated gene in invasive breast cancer. Although mutated in 30–35% of all cases, p53 is mutated in approximately 80% of triple-negative (TN) tumors (i.e., tumors negative for ER, PR, and HER2)" (Duffy et al., 2018).

3.4 COTI-2 as Target Treatment for p53 Mutations

According to Synnott et al. (2019), in their study to see if future researchers could use COTI-2 as a possible target treatment for mutations in p53 in breast cancer cases, went through the process of creating an MTT array of 18 breast cell lines. Through immunofluorescent staining, specific antibodies for p53 were used to determine the binding to COTI-2 in those cells to then measure the apoptosis afterwards. The results determined that triple-negative breast cancers were more responsive to the treatment and also induced apoptosis, so the researchers determined that using COTI-2 as a target treatment for p53 mutations would not only be possible but also an effective approach for treatments (Synnott et al., 2020).

According to Tang et al. (2023), in their recent study on COTI-2's ability as a reactivator drug, they took the protein from COTI-2 treated cells and through western blot analysis, they were able to look closely into the results of COTI-2. Mutations in p53 have been found from previous studies to enhance MYC stability, so a reactivation in p53 would give it wild-type functions and destabilize MYC. Through tests, they proved that statement to be true, by using p53 activator, COTI-2, and destabilization in MYC occurred in each of the five cell lines containing mutated p53 used in the research. Analysis on the data showed that the COTI-2 has no effect on MYC degradation on the wild-type p53 cell line (Tang et al., 2023).

3.5 APR-246 as Target Treatment for p53 Mutations

According to Synnott et al. (2018), in their study of using RNA-sequence analysis to follow the effects on breast cancer cell lines after APR-246 was tested on the gene expressions. Nine breast cell lines were used and each response to APR-246 in the mutated p53 cell was recorded. The APR-246 at the time of publication was at stage 2 of the clinical trial, and during this, the researchers found the newly-developed molecule binds covalently to thiol groups in the mutated p53. This allowed for APR-246 to be a target treatment, as it reactivates tumor suppressor gene p53 and induces apoptosis. Not only has this study demonstrated the accurate targeting of the

mutated protein, but also could independently mediate anti-cancer activity no matter the state of TP53's mutated status (Synnott et al., 2018).

Conclusion

Mutations in p53 are common in breast cancer female patients, and as the results show, there is yet to be a type of treatment that induces apoptosis in every case. Compounds such as APR-246 and COTI-2 are constantly being retested and are undergoing multiple clinical trials to someday be used on real patients. But all papers have concluded that there is not enough data displayed to confidently state that the on mutation in p53 will determine the treatment. There have been thousands of papers published regarding p53 mutations in breast cancer, but limited amounts on specific treatments and their relation to each mutation. In the future years, many groups of researchers are going to continue to show their results in a yearly matter for the progress on most-tested molecule compounds, APR-246 and COTI-2.

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of the outside world (Dalglish, 2004). Sensory information is received by the brain stem and then passed on to the limbic system. Subsequently, limbic system structures – specifically the hypothalamus, amygdala, and hippocampus, and parts of the thalamus – produce physiological changes that are carried out by the endocrine and autonomic nervous systems (Longe, 2022). For instance, after sensing danger, the brain sends a neural signal to the pituitary gland to release the ACTH hormone, causing the adrenal glands to produce cortisol – an anxiety hormone that induces the “fight-or-flight” response – which result in physiological changes, such as increased heart rate and respiration. (Longe, 2022).

Mechanisms of the Auditory System

Sensory activity begins in the ear, which is split into three divisions: external, middle, and inner. Sound waves from the external environment vibrate the eardrums, which are connected to ear bones that carry sound waves to the cochlea in the inner ear. The cochlear hair cells then turn the mechanical sound waves into neural signals that are sent to the brain by the auditory cortex in the temporal lobes (A. Bennet & D. Bennet, 2008; Schaefer, 2017). Boso et al. (2006) suggested that the processing of musical stimuli mainly occurs in right hemispheric structures, but a later study by A. Bennet and D. Bennet (2008) revealed how the whole brain is involved in musical processing. The temporal lobe in the right hemisphere detects musical elements such as pitch, harmony, and beat, while the temporal lobe in the left hemisphere evaluates lyrics and changes in rhythm and frequency. Finally, the frontal lobe connects the auditory information with thought and interacts with the limbic system to induce emotions (A. Bennet & D. Bennet, 2008).

Physiology of Music-Evoked Emotions

Music evokes responses in limbic structures, such as the amygdala and hippocampus (Koelsch, 2010; Koelsch, 2014; Schaefer, 2017). The amygdala receives information from the central auditory systems and processes emotions in response to the sensory information. The hippocampus plays a role in forming social attachments – music acts as a social function for creating and maintaining social connections – and long-term musical emotive memory (Schaefer, 2017). Certain musical features are associated with specific

physiological responses; consonance influences the paralimbic and cortical brain areas, musical tempo is related to cardiovascular dynamics, and loudness is associated with “psychoneuroendocrinological” responses to music (Schaefer, 2017). Furthermore, musical tension constructed through structural and tonal fluctuations contributes to physiological activity. The buildup of tension is perceived as unpleasant stimuli, and the resolution of tension is affiliated with relaxation and reward, which ultimately activates brain regions associated with reward such as the amygdala, hippocampus, and other structures in the limbic system. (Koelsch, 2014).

Along with activating parts of the brain, listening to music can also affect the autonomic nervous system, as shown through changes in heart and respiration rates, temperature fluctuations, and skin responses (Habibi & Damasio, 2014). Neuroendocrine changes (hormonal changes in the brain and body) also occur in response to music due to physiological processes. For instance, cortisol is a hormone that is associated with psychological and physiological stresses, and listening to classical choral, meditative, or folk music decreases the level of cortisol (Schaefer, 2017).

Pleasant vs Unpleasant Music

When listening to music is a pleasurable experience, the listener may experience physiological changes such as increased heart rate, respiration, and decrease in temperature. Pleasant music has also been shown to activate the dopaminergic reward system and lead to an increase in endogenous dopamine release (Habibi & Damasio, 2014). Additionally, pleasant music activates brain structures, including, but not limited to, the inferior frontal gyrus, the ventral striatum, and the anterior superior insula (Boso et al., 2006). On the other hand, when the listener perceives the music as unpleasant, the human sensory system is incapable of properly discerning dissonant stimuli, causing an irritating sensation (Habibi & Damasio, 2014). Consequently, Habibi and Damasio (2014) and Koelsch et al. (2006) found that unpleasant music activates the amygdala, hippocampus, parahippocampal cortex, and the temporal poles, whereas pleasant music leads to deactivations in those structures. Certain negative induced emotions, such as fear, result in an increased heart rate. Other emotions, such as non-crying sadness, result in a decreased heart