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Implications of Aromatase Inhibitor Therapy in Postmenopausal Breast Cancer

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ABSTRACT

Aromatase Inhibitor(AI) therapy is a crucial treatment for regulating estrogen production that combats breast cancer in postmenopausal patients. Clinical trials have emphasized its importance, as it has surpassed its prior efficacy through each succeeding generation of AI therapy and surpassed other treatment options like estrogen modulators(Tamoxifen) and Progestin therapy (Megace/Megestrol Acetate). There is a big difference between AI therapy and other therapies, though they all ultimately attempt to stop the proliferation of cancerous cells. AI therapy has been shown to be effective; however, some side effects of its use have been challenging its place in recent studies. Many physicians have noticed and questioned its use, and future research addressing these concerns needs to be executed in order to enhance the quality of life for our breast cancer patients. In this paper, an overview of the current status of breast cancer, the details of breast cancer and its development, the different types of breast cancer, the workings of AI therapy, clinical trials of Aromatase Inhibitor therapy, a comparison of different therapies, Physician input, and future implications of its effectiveness will be discussed in detail.

Introduction

Cancer is one of the most pervasive medicinal challenges, stretching from the first discovered case in 1500 BCE Egypt to the now highly globalized society. Cancer, simply put, is uncontrollable cell growth, where abnormal cells multiply without regulation or checkpoints. Cancer is a genetic disease that develops in three main ways: mutations during cell division, damage to DNA through external substances(ex/tobacco smoke), or inheritance from one's parents. Cancer works by affecting three major genes- proto-oncogenes, tumor suppressor genes, and DNA repair genes. Compromising the ability of these genes allows certain cells to bypass developmental inspection, replicate damaged cells and cause a buildup of probable malignant tissue, and develop mutations in other genes including but not limited to the deletion or duplication of chromosomes in a cell. Cancer can spread to multiple areas of the body as well; this is called metastatic cancer and is usually attributed to stage IV cancer. Metastatic cancer can be detected under a microscope since the metastatic cancerous cells have characteristics more similar to primary cancer than the cells that grow in that area. Unfortunately, due to our bodies constantly experiencing cell division to grow and renew themselves, the risk of getting cancer is very high, especially because cancer can develop practically anywhere, leading to excessive growth of cells like lymphocytes, plasma cells, and epithelial cells, and leading to cancers of the bone and soft tissue, blood, and major organs.

Of all the different types of cancer, the most prevalent is Breast Cancer-with 290,560 new cases expected in the United States in 2022 and a mortality rate of roughly 15%. An estimated 43,250 women will die from breast cancer in 2022- making it the second leading cause of cancer death in women. Even with the advanced technology possessed today, there is no definitive cure for Breast Cancer, though there are effective treatment options that can lower the risk of fatality.

One of the prevailing regimens for treating Breast Cancer is Aromatase Inhibitor Therapy. This procedure was first observed to execute ideal outcomes in clinical trials in 1982 by British pharmacologist Angela

Brodie at the University of Maryland School of Medicine. There are various types of Aromatase Inhibitors, including Letrozole, Anastrozole, Vorozole, Exemestane, and Testolactone, though only Letrozole, Anastrozole, and Exemestane are FDA-approved. Upon their approval, however, discussion on the long-term effects of the drugs prevail to this day, including discussion on their side effects and adherence. Although aromatase Inhibitor therapy is a well-known treatment option in combating Postmenopausal Breast Cancer, further research must be done to solidify its effectiveness.

What is Breast Cancer?

The hormone process begins when gonads and adrenal glands release steroid hormones. Once synthesized, a reaction including numerous enzymes to specialize each hormone to its target tissue occurs. This reaction is well-regulated to insert steroidal hormones into the systemic circulation. Once reaching their target area/organs, these hormones simply cross the plasma membranes of certain receptors, steroid hormone receptors, and carry out their specialized activity. In the case of estrogen, estradiol is carried from the ovaries to target cells in the blood, attaching to sex-hormone binding globulin(SHBG), which transports the estradiol to the target area. Estradiol then simply diffuses across the plasma membrane of those target cells, breast cells in this case, and binds to their cytosolic estrogen receptor. Estrogen can then carry out its activity, developing the menstrual cycle, female characteristics, and reproductive system.

Breast cancer is when DNA mutations and damage to certain genes that regulate the process above like the P53, BRCA1, and BRCA2, cause faulty cells to multiply. These faults further lead to increased sensitivity to tumor progression. The significance of these genes is elucidated in a study on 'super p53' mice that were able to better respond to DNA damage and protect themselves from cancer compared to normal mice that didn't carry the gene(1) In another sense they can allow abnormal cell growth due to the absence of modulation, causing them to limitlessly multiply and encourage masses of tissue, tumors, to form in the breast and neighboring areas.

Types of Breast Cancer

There are different types of breast cancer that depend on the site and degree of spread. They are categorized as Non-invasive and Invasive Breast Cancers. Breast Cancer is also categorized by molecular subtype.

Non-Invasive Breast Cancer

Cancer that has not spread from the lobules or ducts where it was initially situated is described as Non-Invasive. An example is ductal/lobular carcinoma in situ. Even though the malignant cells have not extended to tissues outside the lobules, they can progress and grow into more invasive breast cancer, though they are understood just as a risky sign for the growth of invasive breast cancer. Clinical studies have been established to best treat non-invasive cancer, taking into account the pitfalls from other statistics.

Invasive Breast Cancer

In Invasive Breast Cancer, cancer cells pass through the breast to different parts of the body, either through the immune system or systemic circulation through the blood. The most common areas of spread include the brain, bones, lungs, and liver. Lifestyle plays a big role in the development of Invasive Breast Cancer. For example, in a study using Cox proportional hazards regression models, the association of a healthy lifestyle with the

possibility of attaining invasive breast cancer among 146,326 women from the UK biobank was analyzed. Results yielded that " among premenopausal and postmenopausal women, a favorable lifestyle was associated with 22% and 31% reductions in invasive cancer risk respectively" (Arthur et al. 2020). Some of the different types include Infiltrating Ductal/Lobular Carcinoma, Medullary Carcinoma, Mucinous Carcinoma, Tubular Carcinoma, Inflammatory Breast Cancer, Paget's Disease of the breast(associated), Triple-Negative Breast Cancer.

Infiltrating Ductal Carcinoma and Lobular Carcinoma(IDC and ILC)

IDC originates in the milk ducts of the breast and extends to the duct wall. In the process, it infiltrates the fatty tissue and other parts of the area. It is the most common invasive breast cancer subtype; 8 in 10 invasive breast cancer diagnoses are IDC. In fact, they account for 80% of all breast cancer diagnoses. ILC originates in the milk glands and accounts for roughly 15% of all breast cancer cases. They lack the E-Cadherin function which regulates gene activity and cell maturation, explaining their erratic growth pattern. Cells in ILC are depicted to be arranged in a single file, dispersed throughout the stroma

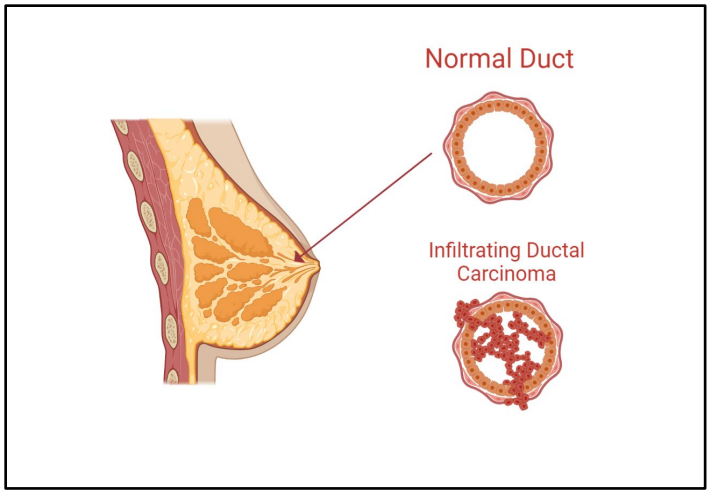

Figure 1. Normal Milk Duct vs. Infiltrating Ductal Carcinoma Milk Duct. Created and Copyrighted by Anvitha Makkena Created with BioRender.com

Aromatase Inhibitors: How They Work

Aromatase is a cytochrome P-450 enzyme that is a major cause of the conversion of androgens into estrogens in postmenopausal women. The aromatase gene promoter is sensitive to increases in inflammatory cytokines, which increase with proliferative breast cancer (Fabian 2007). Therefore, the progression of breast cancer and other breast diseases results in an increase in aromatase activity, creating lots of excess estrogens. Aromatase provides this estrogen to estrogen-sensitive tissues like the breast and uterus through autocrine processes.

Aromatase inhibitors work by interfering with the body's ability to produce estrogen. However, they only induce a significant response in postmenopausal women. This is because compensatory physiological responses induce estrogen production in premenopausal scenarios. In premenopausal women, the gonadotropin-

releasing hormone(GnRH) stimulates the pituitary gland to produce Follicle stimulating hormone(FSH), a hormone that initiates the egg development process. This causes estrogen levels to rise in premenopausal women, whereas increased activity levels of aromatase cause estrogen levels to rise in postmenopausal women. Therefore, AIs can only effectively treat breast cancer after menopause.

Clinical Tests

The clinical parameters of three aromatase inhibitors, Anastrozole, Letrozole, and Vorozole, will be detailed and compared. For context, AC/HC stands for aminoglutethimide/Hydrocortisone, which are alternatives to endocrine therapy. Megestrol Acetate(MA) or Megace is a progestin medicine used to treat breast cancer and can be used in birth control.

Anastrozole

Anastrozole is a benzotriazole derivative, potent enough to hinder activity by 50% (Santen et al.). Approval for managing advanced breast carcinoma was based on results from two important trials that compiled 764 patients who randomly received either anastrozole medication or MA. The patients who were administered these two medications had metastatic disease and were following tamoxifen therapy given in an adjuvant setting or as first-line therapy. Results depicted similar overall response rates to both anastrozole and MA.

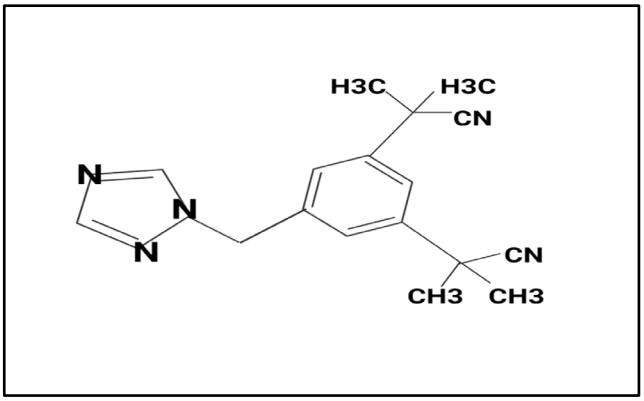

Figure 2. Structure of Anastrozole created and copyrighted by Anvitha Makkena Created with BioRender.com

Initial reports on the other hand show that anastrozole is superior to MA because it is better tolerated. For one, anastrozole was associated with less unwanted weight gain, a common symptom of MA, fewer thromboembolic events, and less dyspnea. This study conducted doses of 1mg of Anastrozole daily. Further development of this trial depicts Anastrozole to be superior to Megace in both Objective Response Rates, which accounts for both partial response(PR) and complete response(CR), and Clinical benefits. 2-year survival as well was “56.1% for the group receiving Anastrozole compared with 46.3% for the group receiving the progestin”(Santen et al.). This elucidates the superior efficacy of Anastrozole in its survival rate and reduced side effects.

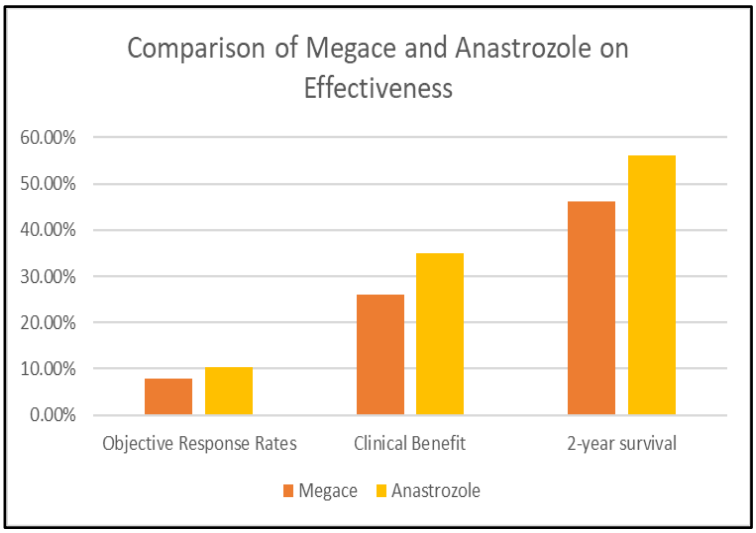

Figure 3. Graph of the Objective Response Rates, calculated by (PR+CR), Clinical Benefit, and 2-Year survival for both Megestrol Acetate and Anastrozole, which shows that Anastrozole has higher efficacy in all categories, suggesting the use of Anastrozole over Megace for second-line therapy as of today. Created by Anvitha Makkena

Letrozole

Letrozole is also a potent non-steroidal competitive inhibitor and possesses considerable selectivity for aromatase. Prior trials established letrozole's selectivity, from not showing any signs of change in levels of gonadotropins, ACTH, cortisol, aldosterone, or TSH. Other clinical studies have established letrozole's capabilities in inhibiting aromatase, noting how just 0.25 mg daily caused maximal suppression of plasma and urinary estrogens. In this study, a highly sensitive DNA-based estradiol bioassay was used to evaluate estradiol levels. Estradiol levels were decreased by 95% to levels of 0.05-0.07pmol/L(Santen et al.). Not to mention other studies have already shown the efficacy and lack of toxicity from early trials of letrozole(Iveson et al. 1993).

Approval of Letrozole was based on two randomized trials similar to the design of the anastrozole studies (Dombernowsky et al., Mouridsen et al. 2003). In the first, 551 patients with metastatic breast cancer were assigned to receive 2.5 mg of letrozole(n=174), 0.5 mg(n=188), or Megestrol Acetate(MA), 160 mg (n=189) once daily in a double-blind setting. The data were analyzed for tumor progression and other safety variables following 33 months and survival up to 45 months. Results concluded that Letrozole had a more significant impact, producing a significantly higher overall response rate(24%) in comparison to MA(16%, P=0.04) and 0.05mg of letrozole(13%, P=0.004) Duration of the objective response as well was much longer for letrozole compared to MA (Cox Regression, P=0.02). Letrozole, 2.5 mg, is also superior in time to treatment failure (P=0.04 for MA and 0.002 for letrozole 0.5mg). For time to progression, Letrozole 2.5 mg was superior to Letrozole 0.5 mg (P=0.02). This data shows Letrozole was better tolerated than MA, relating back to adverse effects mentioned earlier about weight loss and dyspnea, and that the dose had a noteworthy effect on survival in favor of letrozole 2.5(Figure 6).

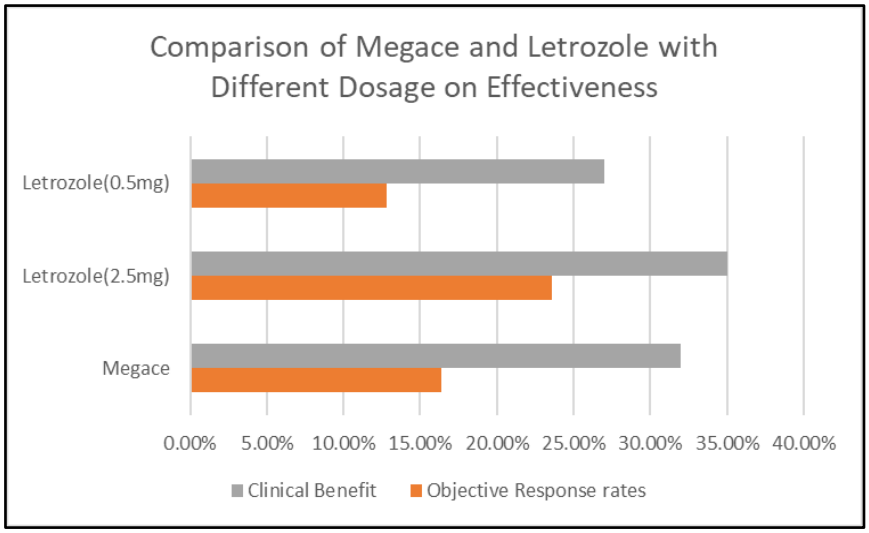

Figure 4. Graph of Clinical Benefit and Objective Response Rates for Letrozole(0.5mg), Letrozole(2.5mg), and Megace, exhibiting the efficacy of Letrozole over MA and the importance of dosage. Created by Anvitha Makkena

In a second study, the overall survival(OS) and efficacy data for letrozole and tamoxifen, a different treatment for breast carcinoma, were analyzed. This phase III trial contained 916 patients who were treated with 2.5 mg of letrozoles (n=458) or 20 mg of tamoxifen(n=458).Updates on efficacy were reported at 32 months. Once again, letrozole was superior in time to progress(9.4 v 6 months respectively, P<0.0001), time to treatment failure(9 v 5.7 months respectively, P<.0001), overall response rate(32%v 21% respectively, P=0.0002), and overall clinical benefit. OS was also longer for letrozole than tamoxifen(34 v 30 months respectively). The difference in OS isn't statistically significant, however, survival improved in the letrozole category over the first 2 years of the study(16 v 9 months respectively, P-Value=0.0005) (Table 1).

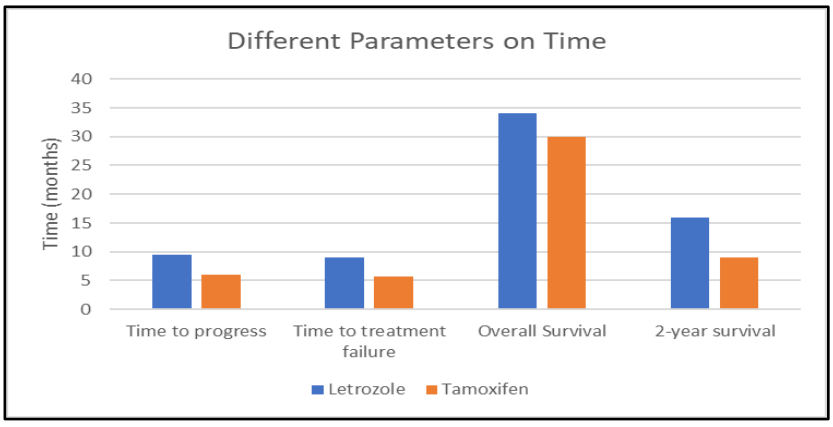

Figure 5. Letrozole and Tamoxifen were compared based on Time to Progress, Time to Treatment Failure, Overall Survival, and 2-year Survival. Created by Anvitha Makkena

Vorozole

Like Letrozole and Anastrozole, Vorozole is another potent aromatase inhibitor and has similar clinical success to both. Vorozole is superior to aminoglutethimide in clinical benefit (47% v 37%, respectively, P=0.017). Its effectiveness compared to megestrol acetate was roughly the same, though vorozole had fewer side effects. Further clinical development of vorozole, due to the acceptance of letrozole and anastrozole, has been neglected.

Comparison of AIs

The potency of different AIs is compared using the isotopic kinetic technique(Grodin et al. Jones et al.1992). Using this, Anastrozole inhibits aromatase by 93%; letrozole by 99%; vorozole by 98% (Figure 8)(Santen et al. 1999). AIs have improved their ability to inhibit aromatase by every succeeding generation. Aminoglutethimide, for example, is a first-generation AI with an inhibition percentage of 91%. Vorozole, a second-generation AI, has an inhibition percentage of 93%. Letrozole, a third-generation AI, has an inhibition percentage of 99%.

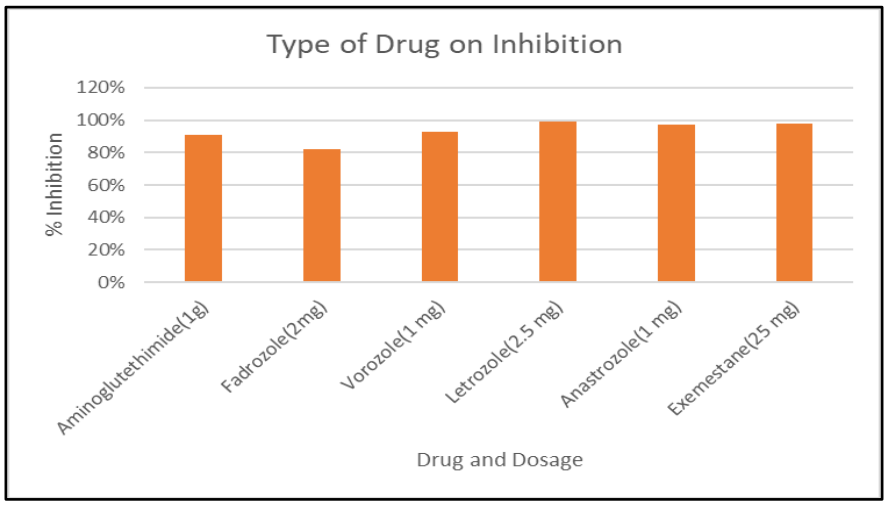

Figure 6. Graph of AIs from different generations, including their dosage level, and their percent of inhibition of Aromatase. Created by Anvitha Makkena

Difference Between AI Therapy and Other Therapy

It is important to remember that in cancerous situations, estrogen promotes the growth of malignant epithelial cells by binding and activating the Estrogen Receptor(ER), which then binds to genes responsible for cell division and hindrance cell death. There are ways to prevent the progression of this malignant process that progresses breast cancer; in fact, there are 3. The first way is to prevent estrogen from binding to ER. Tamoxifen and Raloxifene, selective ER modulators, do just that. Another way is by reducing or removing the expression of ER. An example of this is fulvestrant, which lowers the number of ERs available to bind to estrogen. The last way is AIs. Earlier, Aromatase Inhibitors were discussed in detail, mentioning their ability to lower estrogen levels in postmenopausal women specifically by blocking aromatase's activity, directly interrupting estrogen's

main source of production. This ultimately prevents estrogen from binding to ERs, stopping the pathway that encourages cell division and the development of breast cancer.

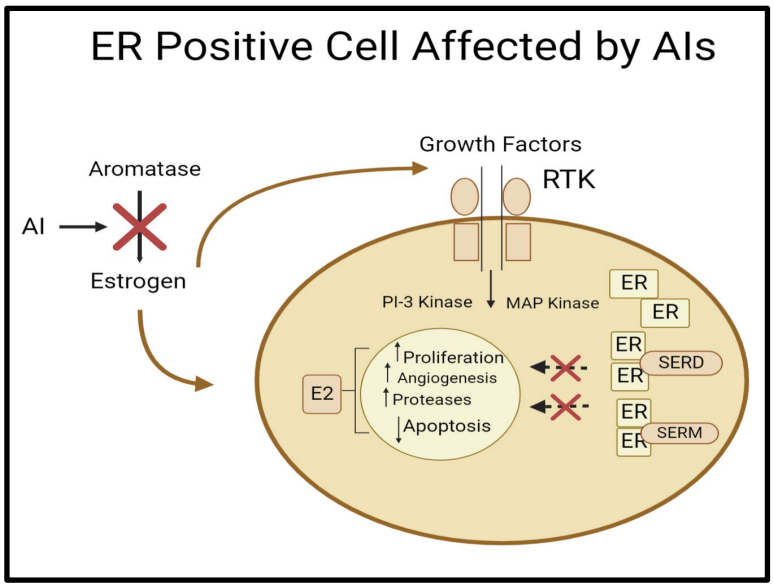

Figure 7. Metabolic pathway of an ER Positive Cell affected by AIs. The image portrays the blockage of cellular responses as a result of the usage of AI. RTK stands for a Receptor tyrosine kinase, which controls biological functions like cell growth when activated; ER stands for Estrogen Receptor; SERD stands for selective estrogen receptor down-regulator, which binds to ERs and induces proteasomal degradation and ultimately inhibits the ER signaling pathway; SERM stands for Selective Estrogen Receptor Modulator, which blocks estrogen receptors; E2 stands for estradiol. Created and Copyrighted by Anvitha Makkena Created with BioRender.com

What Do Physicians Think?

Katherine Clifton, a physician at Siteman Cancer Center at Washington University of St.Louis, states that "aromatase inhibitors are incredibly important and are the mainstay of treatment for patients with early-stage breast cancer who are postmenopausal to help prevent recurrence. They do have side effects, most often joint pain and decreased bone density. Patients take them daily for 5-10 years and we see them every 6 months to 1 year while they are on treatment to make sure they are tolerating treatment." This input accurately reflects the data compiled from clinical tests and even represents the current state of AI usage in today's medical settings. By mentioning recurrence, Clinton has brought up the increased use of AI in adjuvant therapy. Her input aligns with studies that have revealed just that, some going as far as stating that "AI has largely replaced tamoxifen for preferred treatment"(Fabian 2007), which in turn emphasizes the inclination toward AI therapy.

What Future Research Needs to Be Done?

There are lots of benefits of AI, however, some additional research must be done in order to solidify its utilization, especially honing in on its side effects. As Clinton mentioned earlier, joint pain and decreased bone density are common reactions to AI usage. In a recent study, AI and its association with Musculoskeletal Syndrome

were illuminated, taking on the name of Aromatase Inhibitor-Associated Musculoskeletal Syndrome(AIMSS). This syndrome restricts the toleration of AI usage and results in bone loss and arthralgias. With postmenopausal women already harboring an increased susceptibility to osteoporosis, which is bone loss due to estrogen depletion, AI should be re-evaluated as a treatment option upon the discovery of AIMSS. AIMSS affects up to half of the women on AI therapy and is very detrimental to adherence to treatment. A meta-analysis of 21 studies amassing 13,177 patients reported a prevalence of arthralgia in women on AI therapy ranging from 20-74%, with a collective estimate to be around 46%.(Beckwee et al. 2017). Another study estimated an even higher percentage of AIMSS prevalence. In this trial, 56 consecutive patients on AI therapy were analyzed and interviewed based on their state of arthralgia from therapy. 61% reported having bone pain/arthralgia, with 30% having severe cases,41% having continuous pain, 50% having central pain, and 79% having peripheral pain(Presant et al. 2007).This flips the perspective on AI therapy and suggests further research on other therapy in combination, like exercise therapy, be coupled with it to increase tolerance. It also suggests that further research on the management of accompanied pain with AI therapy be embraced to improve the quality of life.

Another issue that needs to be researched is resistance to AI. Many forms of resistance have been identified, emphasizing the complexity of the ER signaling pathway and its role in the recurrence of breast cancer. Recent studies have addressed this resistance and have suggested the usage of therapeutic intervention with PI3K/AKT/mTOR cell signaling and cyclinD1/cyclin-dependent kinase 4/6 cell cycle pathways along with combination strategies to target cell cycle pathways(Mills et al. 2018). Intervention with P13K/AKT/mTOR cell signaling has shown some merit in preclinical studies and works by inhibiting a subclass unit of PI3K, which inhibits the signals that initiate cell-cycle proliferation and cell survival(Figure 10)(Xu et al.2020).

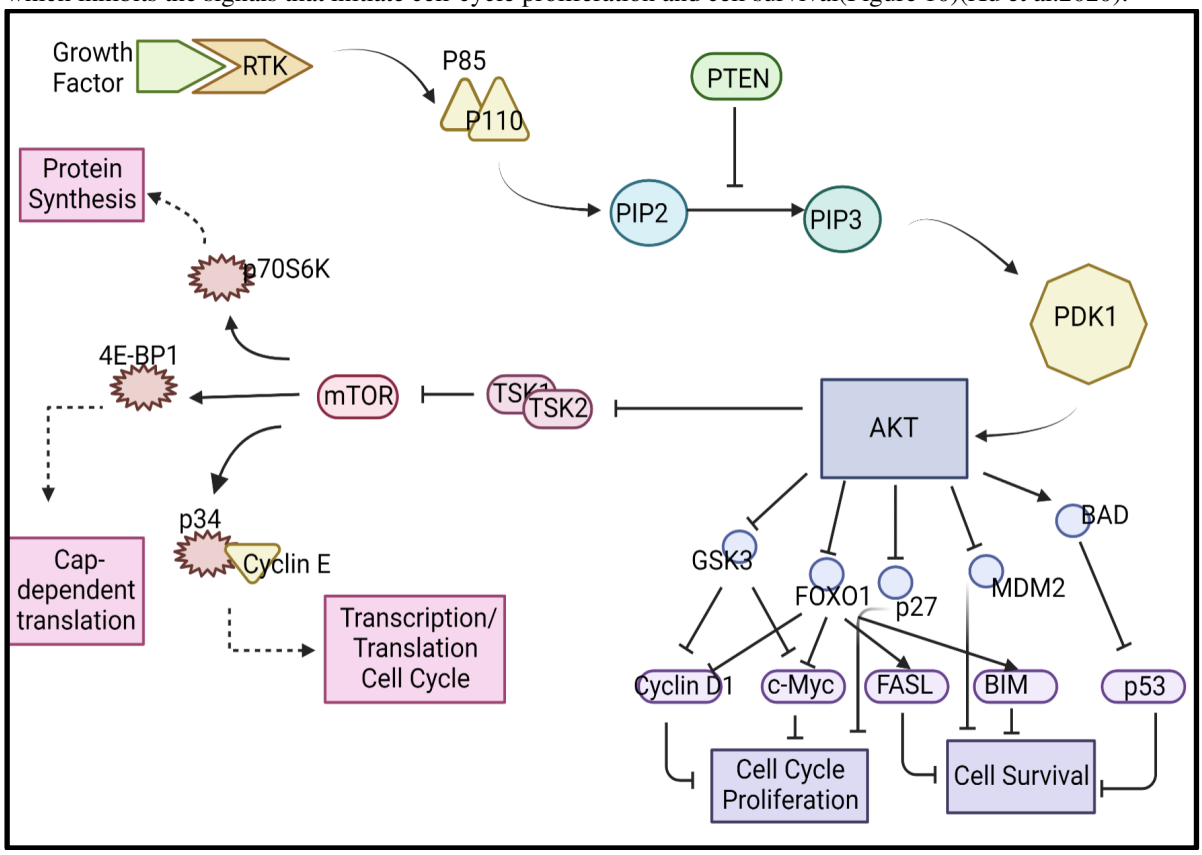

Figure 8. PI3/AKT/mTOR signal transduction pathway.

This process is vital to tumorigenesis and aids in the development of malignant tumors. It is partly responsible for regulating cell survival and migration; an example of how this pathway contributes to cell proliferation is that molecules like mTOR are activated by AKT, promoting the binding of cyclin D1 to a cyclin-

dependent kinase(CDK)(not shown) and ultimately encouraging protein synthesis along with progressing the cell cycle, hence cell proliferation. High-intensity cyclin D1 presence accelerates a cell's transition from the G1 to the S phase, ultimately accelerating cancer development, which is why the inhibition of such a pathway is a key topic of future research. RTK, once again, stands for receptor tyrosine kinase. PTEN is a tumor suppressor that works oppositely to the conversion of PIP2 to PIP3, interfering with cell proliferation. When PTEN is inhibited, AKT is activated along with the pathways. AKT is a serine/threonine protein. mTOR is also a serine/threonine protein that specifically senses nutritional signals and controls cell growth.

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Conclusion

Breast Cancer has increased in incidence over the last decade and is still the most prevalent cancer to this day. Though clinical technology has been made to counter and cure it, Breast Cancer prevails to be a leading cause of death in women. With the application of AI in clinical settings, Breast Cancer can be countered efficiently. AIs have demonstrated their abilities toward uniquely combating breast cancer, more direct and competent than other treatments including tamoxifen and Megace, as illustrated prior. Upon advancement, it has improved its capabilities of reducing estrogen production through each generation of use. From first-generation AI aminoglutethimide to third-generation Letrozole, AIs have become more recognized as a mainstay therapy, emphasized by their increase in use. Regardless of their achievements, however, frequent use can lead to side effects, including joint pain and bone density loss. This is seen as a dire issue, as postmenopausal women already face issues with osteoporosis, and the inclusion of therapy that furthers this loss is detrimental to the well-being of these patients. Not to mention, an increase in resistance to AI therapy has been observed in recent studies, and though measures to address issues of this nature have been tested in preclinical studies (ex/ inhibition of PI3K/AKT/mTOR cell signaling), they haven't been fully implemented and approved in clinical application. Thus, further research is necessary for the free utilization of Aromatase Inhibitors to treat Postmenopausal Breast Cancer.

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