REVIEW ARTICLE

The New Anti-Estrogens with Anti-Cancer Properties for Breast Cancer

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Received: 01 November 2022 / Accepted: 30 January 2023

Abstract

Purpose: Considering the high prevalence of breast cancer and the radiation sensitivity of breast tissue, it is necessary to optimize the treatment process of this tumor, especially when using radiation therapy methods.

The present study was conducted to investigate the effect and complications of new anti-estrogens on the effectiveness of breast cancer treatment.

Materials and Methods: Articles were searched in PubMed, Science direct, Embassy, Cochran, and Scopus databases using the keywords Cancer AND Anti-estrogen, Breast Cancer AND anti-estrogen AND mice, Breast cancer And anti-estrogen AND rat. The authors reviewed the abstract and full text of the articles and the relevant studies were selected for systematic review.

Results: The anti-estrogens used in the reviewed studies included TAM, RAL, SS1020, SS1010, GW5638, OSP, 4-OHTAM, and TOR. Anti-estrogen-related side effects included liver and uterine complications, especially in the case of using TAM anti-estrogen (54%). Moreover, uterine hypertrophy was observed using GW5638, RAL, and SS1010 anti-estrogens; while it happened with a lower percentage than TAM, 16%, 14%, and 13%, respectively. Side effects were significantly reduced by reducing the prescribed dose. So that this reduction for TAM is from 54% to 33%. In relation to the effect of antiestrogens on tumor treatment, the most effective and least complications were related to the antiestrogen "SS1020".

Conclusion: Based on the results of reviewed studies, SS1020, which has no estrogenic and genotoxic activity, was safe and the most effective anti-estrogen against breast cancer in animals and also in humans.

Keywords: Breast Neoplasm; Anti-Estrogen; Rat; Mice.

DOI: https://doi.org/10.18502/fbt.v10i4.13731

1. Introduction

Breast cancer, which is the foremost common cancer known, is the most common cause of death in the world [1, 2]. More than 70% of patients with breast cancer are affected by the Estrogen receptor positive (ER+) type of this disease [2]. Breast tissue is very important in terms of exposure to radiation due to its high sensitivity. Therefore, it is vital to limit the radiation in radiotherapy [3] in terms of quantity and energy to keep the breast healthy [4]. Obesity threatens postmenopausal women with breast cancer because it causes complications such as increasing the amount of insulin in the blood circulation, somatomedin, estrogen, and inflammatory cytokines [5, 6]. Fortunately, there are no restrictions on breast cancer treatment methods which are divided according to the type of cancer, in particular surgery, radiotherapy, and endocrine therapy is used for ER+ patients. The other groups of treatments that are called target therapy, namely monoclonal antibody trastuzumab, aimed at HER-2 and also chemotherapy which is a proficient way to cure end-stage cancer [7-9].

For the entire life of the woman, Tamoxifen (TAM) is the first step to medicate and even forbid breast cancer. This anti-estrogen emulates an important role in diminishing the annual death rate by 31% and cancer repetition by 50% [2]. Tamoxifen (TAM) which is the first formation of Theriphenylethylene (TPE) SERMs is used as a conventional endocrine [10]. It is used to treat ER+ and women who are at risk of disease progression [11]. In addition, it is functional for metastatic cancer. Some types of metastases are dependent on hormones, which mostly occur in postmenopausal women. The estrogen receptor positive (ER+) subtype of breast cancer affects more than 70% of patients. Because of its consequences, including elevated levels of insulin, somatomedin, estrogen, and inflammatory cytokines in the blood, obesity puts postmenopausal women at risk for breast cancer. Methods such as radiology, CT scan, and MRI are used to detect masses in the breast tissue, which help us in diagnosing this disease. Fortunately, there are no limitations on the types of breast cancer that can be treated, and patients with ER+ status typically get endocrine therapy, radiation, and surgery [12]. In addition to chemotherapy, the other class of treatment known as target therapy includes the monoclonal antibody trastuzumab, which targets the HER-2 gene.

Tamoxifen (TAM) is the initial step in treating and even forbidding breast cancer for the duration of the woman's life. This anti-estrogen has a significant part in lowering the annual death rate by 31% and the recurrence of cancer by 50%. As a traditional endocrine, tamoxifen (TAM), the first of theriphenylethylene (TPE) SERMs, is used to treat ER+ and women who are at risk of the disease progressing. It also works for cancer that has spread metastatically. Some metastases, which usually affect postmenopausal women, are hormone-dependent.

However, radiotherapy and drugs that we will talk about further are used to treat this disease.

Acting as a cell type-specific anti-estrogen this agent has been the presiding endocrine therapy for this disease with consistent effectiveness for more than 400 years [13].

This drug is used to refine the existence of ER+ cases. Tamoxifen (TAM) is a non-steroidal anti-estrogen with partial agonist activity that is widely utilized in the cure of ER+ cases. The retaliation to TAM is often time allotment consequently to the maturing of refusal [14]. Since 1973 TAM has been regarded as an additional remedy for early-stage estrogen receptor ER+ breast cancer [15]. Nevertheless, using TAM for a long period of time can make some side effects, such as uterine cancer in women. The carcinogenic properties may be caused via the imitation and/or promotion of TAM-induced. DNA is damaged along with the carcinogenic properties of the drug [15, 16]. DNA degradation products have been observed in the uterus of women and the liver of rodents because they are not easily and quickly repaired [17, 18]. In addition to this, its long-term use causes the recurrence of disease and death. This drug is futile in treating ER-receptor of cancer [19]. Tamoxifen has played a huge role in the treatment of breast cancer, but its disadvantages like uterine cancer outweigh its advantages [10]. IARC has listed TAM as a human carcinogen [18]. To reduce such side effects, tamoxifen alternatives with less carcinogenic and more therapeutic effects were produced [9]. Drug combination is one of the methods that have been investigated in many articles [11]. This drug has been listed as a human carcinogen by the International Agency for Research on Cancer [20]. To reduce these side effects, tamoxifen alternatives with less carcinogenic and more therapeutic effects were produced [11]. Drug combination is one of the methods that have been investigated in many studies [7, 20-23]

to increase the therapeutic sensitivity of tamoxifen in ER+ and ER- [24, 25].

2. Materials and Methods

This systematic review was performed to evaluate the Anti-Estrogens with anti-cancer properties for breast cancer. We searched in databases containing PubMed, Web of science, Google scholar, and science direct with different combinations of "cancer" AND "Antiestrogen" AND "mice", "cancer" AND "Antiestrogen" AND "mouse", "cancer" AND "Antiestrogen" AND "rat", "cancer" AND "Antiestrogen" AND "rabbit", "breast cancer" AND "Antiestrogen" AND "mice", "breast cancer" AND "Antiestrogen" AND "Rat". Irrelevant Articles on Laboratory Animals and breast cancer were removed. The abstracts were evaluated to check the correlation with the clinical results of the methods. Finally, 6 related articles were included in the study (Figure 1).

2.1. Criteria for Inclusion and Exclusion of Articles in the Study

The review and selection of articles and determining whether or not to include articles in the study were done by the two authors independently (ZF &FS). Dissentions were eliminated by discussion. Only original papers were selected., provided that: Antistrogensin different cancer treatments and (b) studies were excluded if: (a) abstract only, (b) review or meta-analysis, (c) non-relevant to breast cancer, (d) not relevant to Antistrogens and breast cancer treatment, (e) editorial, and (f) guideline (Figure 1).

3. Results

A few drugs are in all stages of treatment or a part of it, for example, TOR was justified by FDA in 2007 for the postmenopausal dangerous cases. The therapeutic effect of TOR is similar to tamoxifen and it has the

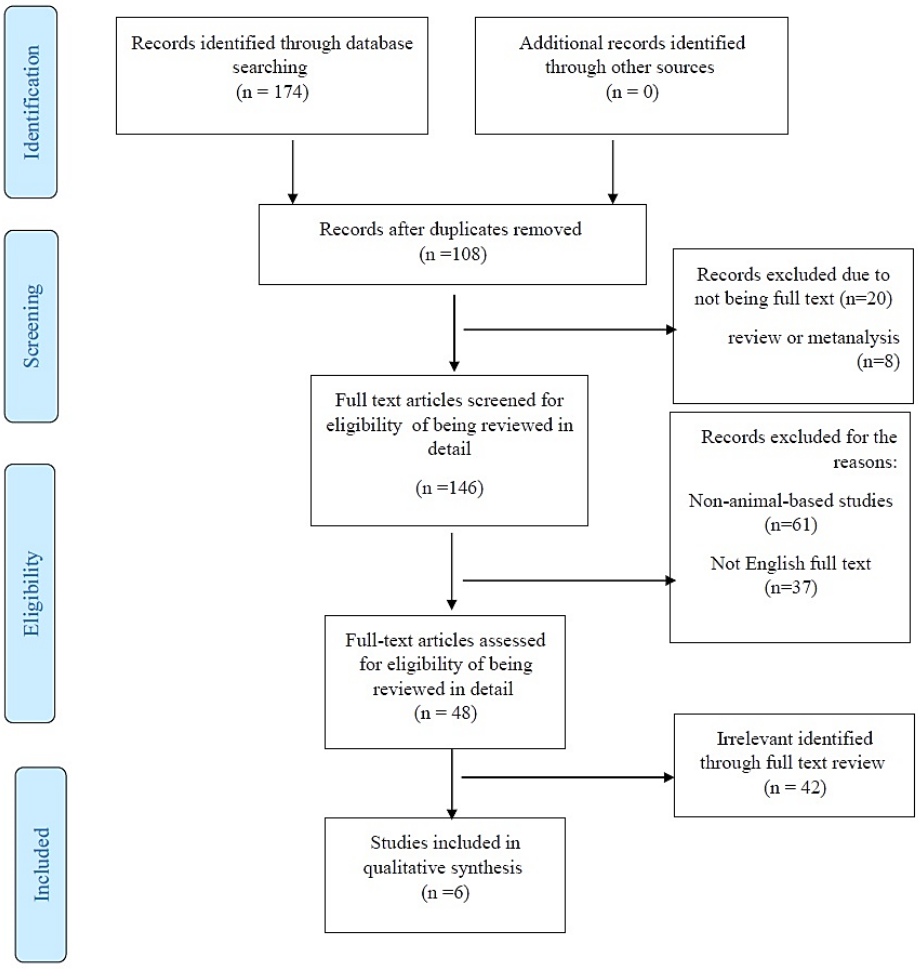

Figure 1. Article Selection Process

same effect as tamoxifen on cancer growth. People with breast cancer are also similar; therefore, this drug is not often used. Raloxifene has been used to treat osteoporosis since 1998 and was approved via FDA in 2007 for postmenopausal women with high a probability of conflict [15]. RAL does not cause conflict for the uterus and does not cause the side effects that Tamoxifen has on the uterus. Unlike tamoxifen, TOR does not cause liver cancer. Although the function of the drug is similar to tamoxifen, no DNA degradation products were observed in the liver in rodents [26]. Despite all this, there is a need to find better alternatives [11, 15]. The article aims to collate newly developed drugs, evaluate the treatment rat for one type of breast cancer as well as checking their side effects, and finally choosing one of the drugs with the best therapeutic effects and the least risk for patients. Therefore, a total of 174 records were obtained, and based on the explanations given in Figure 1, 6 studies were selected. Among these 6 reviewed papers, 6 articles (100%) reported the clinical use of TAM for breast cancer treatment. In addition, each of the articles used different and unique medicines in addition to Tamoxifen, which respectively includes Compound (11, 12, 16, 17, 19, 28), E2, (SSD1010, SSD1020, GW5638, and RAL), SK, SS5020, and SIM. A summary of the results and the used drugs of previous related studies are presented in Table 1.

3.1. Drug Types and Related Results

Evidence supports the role of 17&-estradiol (E2) in carcinogenesis and the large majority of breast

Table 1. Summary results of reviewed related papers

Author	Cancer type	Animal type	Used medicine	effect
Elnakib *et al.* (2021)[10]	Breast cancer	Rat	TAM Compound 11 Compound 12 Compound 16 Compound 17 Compound 19 Compound 28	Compound 12 prevents the activity of MCF-7 and has no side effects of uterine cancer
Rondón-Lagos *et al.* (2016)[14]	Breast cancer	Rat	TAM E2	The combination of these two substances in a low dose not only does not cure, but also causes chromosomal abnormalities.
Santosh laxmi *et al.* (2010)[11]	Breast cancer	Rat Nude mice	TAM SS1010 SS1020 GW5638 RAL	SS1020 has been shown to have estrogenic and genotoxic effects relative to other antiestrogens without causing liver problems.
Lin *et al.* (2020)[1]	Breast cancer	Mice	TAM SK	The combination of these two drugs has a strong effect In improving the condition of areas including breast cancer, especially type -Er cancer
Suzuki *et al.* (2011)[15]	Breast cancer	Rat	TAM SS5020	SS5020 which does not have uterotrophic activity, unlike TAM does not have a destructive effect on DNA.
Ibrahim *et al.* (2019)[2]	Breast cancer	Mice	TAM SIM	The combination of these two not only has anti-carcinogenic properties, but also has anti-angiogenic, anti-metastasic, and anti-inflammatory in MCF-7 breast cancer.

Note: TAM: Tamoxifen, E2: [17β-estradiol, SS1010:2E-3-{4-[(Z)-4- chloro-1,2-diphenylbut-1-enyl]phenyl}acrylic acid,SS1020:2E-3-{4-[(E)-4-chloro-1-(4-hydroxyphenyl)-2-phenylbut-1-enyl]-phenyl} acrylic acid, RAL: compounds 4-hydroxytamoxifen, toremifene, ospemifene, raloxifene,Sk: Shikonin,SS5020: benzopyran antiestrogen, 2E-3-{4-[(7-hydroxy-2-oxo-3-phenyl-2H-chromen-4-yl)-methyl]-phenyl}-acrylic acid. SIM: Simvastatin.

carcinomas are dependent on estrogen. In the study for the determination of the effects of low doses of E2 and TAM (10&8) mol L(&1) and 10(10&6) mol L(&1), respectively, on karyotypes of MCF7, T47D, BT474, and SKBR3 breast cancer cells by comparing the results of conventional karyotyping and multi-FISH painting with cell proliferation.

Karyotypes of both ER+ and ER& breast cancer cells increased in complexity after treatments with E2 and TAM leading to specific chromosomal abnormalities, some of which were consistent throughout the treatment duration. This genotoxic effect was higher in HER2+ cells. These in vitro results provide insights into the potential role of low doses of E2 and TAM in inducing chromosomal rearrangements in breast cancer cells [14]. At the human equivalent doses of TAM, SS1020 had antitumor potential much higher than that of TAM, RAL, and GW5638 against 7, 12-dimethylbenz(a)anthracene-induced mammary carcinoma in rats. The growth of human MCF-7 breast cancer xenograft implanted into athymic nude mice was also effectively suppressed by SS1020.

SS1020, lacking estrogenic and genotoxic actions and having strong antitumor potency superior to that of TAM and RAL, could be a safer alternative for breast cancer therapy and prevention [11]. Results of the assessment of the combination effects of SK and 4-OHT on human breast cancer cells, MCF-7 (ER +) and MDA-MB-435S (ER -), in vitro and in vivo and to investigate the underlying mechanisms indicated that SK and 4-OHT synergistically inhibited MCF-7 and MDA-MB-435S cell proliferation and promoted apoptosis by reducing mitochondrial membrane potential and increasing the intracellular ROS level. The combination of SK and 4-OHT activated the mitochondrial-dependent apoptosis and the death receptor pathways, significantly regulating the PI3K/AKT/Caspase 9 signaling pathway. Compared with SK and 4-OHT alone, the combination of SK and 4-OHT could better inhibit tumor growth in mice [1].

Unlike TAM, SS5020 exhibits no genotoxic activity to damage DNA. Furthermore, SS5020 does not present significant uterotrophic potential in rats. At the human equivalent molar dose of TAM (0.33 or 1.0 mg/kg), SS5020 had much stronger antitumor potential than those same antiestrogens against 7,12-dimethylbenz(a)anthracene-induced mammary carcinoma in rats. The growth of human MCF-7 breast cancer xenograft implanted into athymic nude mice was also effectively suppressed by SS5020. SS5020, lacking genotoxic and estrogenic actions, could be a safer and stronger antiestrogen alternative to TAM and RAL for breast cancer therapy and prevention [15].

Tamoxifen (TAM) is a nonsteroidal antiestrogen drug, used in the prevention and treatment of all stages of hormone-responsive breast cancer. Simvastatin (SIM), a lipid-lowering agent, has been shown to inhibit cancer cell growth.

Results showed that the combination treatment decreased the oxidative stress markers, glucose uptake, VEGF, and MMP 2 &9 in the cell line compared to TAM-treated cells. Drug interaction of TAM and SIM was synergistic in T47D by increasing the apoptotic makers Bax/BCL-2 ratio and caspase 3 activity. Moreover, the combined treatment decreased the protein expression of TNF-α, NF-kB compared to the control. SIM may serve as a promising treatment with TAM for improving the efficacy against estrogen receptor-positive (ER+) breast cancer [2].

Compound 12 (E/Z-1-(2-{4-[1-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-propenyl]-phenoxy}-ethyl)-piperidine) showed an appreciable relative ERα agonistic activity in a yeast estrogen screen (YES) assay. It successfully inhibited the growth of the MCF-7 cell line with GI50 = 0.6 µM, and it was approximately three times more potent than TAM.

Compound 12 is a promising candidate for further development due to its inhibition activity on MCF-7 proliferation with moderate AlkP activity and no potential uterotrophic effects [10].

4. Discussion

During the last 4 decades, several molecules have been used as antiestrogens in the compounds. Advances in the use of alternative and safer antiestrogens, which have greater clinical benefits than TAM and RAL, are essential for the debarment and treatment of breast cancer. The side effects of antiestrogens on the uterus have been the main reason for not continuing their use in clinical research [15]. A high level of recombinant DNA was detected in the liver of TAM-treated mice, a high level of recombinant DNA was detected, while no recombinant DNA was detected by TOR, SS1020, and SS1010. Accordingly, researchers prioritized safer compounds without estrogenic and genotoxic potential [26]. To

determine the estrogenic activity of SS1020 and SS1010, SS5020, E2, SK, SIM, GW5638, RAL and their combination, they used the uterotrophic method on mice and based on their results, it was proved that it is not genotoxic. GW5638 had less uterotrophic activity than TAM. However, like RAL, GW5638 had weak estrogenic potential. SS1020 had fewer effects than SS1010, but it did not have any special side effects on the uterus. Compared to other antiestrogens TAM, RAL and GW5638, SS1020 has shown higher antitumor effects.

Based on the results of animal experiments, lower uterine activity is associated with higher antitumor activity against ER-positive mammary tumors. Indeed, SS1020 exhibited potent antitumor potency against ER-positive human MCF-7 breast cancer xenografts implanted in autemic nude mice. At a dose equivalent to 10 mg/kg TAM, growth was completely suppressed; while TAM did not significantly lead to growth inhibition. Accordingly, SS1020 has been found to have no genotoxic or estrogenic activities. Furthermore, in studies conducted on DMBA-induced mammary cancer mice or euthymic nude mice with mammary cancer transplants, it has greater antitumor activities compared to TAM, RAL, and GW5638. Based on the observed results, SS1020 can be a safe alternative as an antiestrogen for the prevention and treatment of breast cancer [15].

In other studies, SS5020, as a new benzopyran antiestrogen, did not have significant estrogenic effects or additional DNA synthesis in studies involving mice. Similar to phenylethylene as a novel antiestrogen, compared to TAM, RAL, and SP500263, SS1020, SS5020, and SS1020 showed greater antitumor potency in DMBA-induced breast cancer in mice and MCF-7 human breast cancer grafts implanted in nude mice Atimi. Meanwhile, in relation to MCF-7 breast cancer xenografts, the antitumor power of SS5020 was lower compared to SS1020 [11]. In addition, SS5020 can be used more safely in the form of benzopyran for the prevention and treatment of breast cancer. So far, no specific side effects have been observed in animals treated with SS5020 and SS1020. Based on this, the long-term examination of these compounds within the pre-clinical stage and the verification of their impacts can give the possibility of clinical examinations in the future [11, 15]. SK is a common active compound derived from the root of Chinese herbal medicine that has a long history of use. This compound is known as an anti-breast cancer compound as well as other cancers. Accordingly, SK may be employed to prevent the resistance of ER+ breast cancer cells to TAM [1]. In other related studies, the investigation of another drug such as sim showed that its combination with TAM caused antagonistic drug interactions when examining MCF-7 breast cancer, but included anti-angiogenic, anti-metastatic, and anti-inflammatory properties [2].

Moreover, Compounds 12 and 19 were investigated in an ovariectomized mouse model and based on the results, they show strong anti-neoplastic activity. After treatment with E2 and TAM, by causing certain chromosomal abnormalities, the karyotype of ER+ and ER- breast cancer cells found new changes, so that some of these tumors showed increased resistance during the treatment [10]. More genotoxic effects were observed in HER2+ cells. The sensitivity of ER-/HER2+ SKBR3 cells to TAM and the aggravation of chromosomal abnormalities were proven. The results of laboratory studies have proven the high potential of low doses of E2 and TAM in causing chromosomal rearrangements in breast cancer [14].

5. Conclusion

In general, according to Table 1, the results of studies have shown that the TAM is known as the effective and basic medicine for breast cancer treatment, while it has harmful side effects such as causing uterine cancer and liver diseases. In order to improve the treatment of this disease, it is important to use other medicines or a combination of TAM that have fewer adverse effects and more therapeutic effects, and reduce the possibility of the patient's involvement with other cancers.

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