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REVIEW ON BREAST CANCER TREATMENT

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ABSTRACT: Breast cancer is the most prevalent cancer among women worldwide. However, increased survival is due to the dramatic advances in the screening methods, early diagnosis, and breakthroughs in treatments. Over the course of the last decade, many acquisitions have taken place in this critical field of research in the pharmaceutical industry. Advances in molecular biology and pharmacology aided in better understanding of breast cancer, enabling the design of smarter therapeutics able to target cancer and respond to its microenvironment efficiently. Patents and research papers investigating diagnosis and treatment strategies for breast cancer using novel technologies have been surveyed for the past 15 years. Various Nano carriers have been introduced to improve the therapeutic efficacy of anticancer drugs, including liposomes, polymeric micelles, quantum dots, nanoparticles, and dendrimers. This review provides an overview of breast cancer, conventional therapy, novel technologies in the management of breast cancer, and rational approaches for targeting breast cancer.

KEYWORDS: Breast Cancer, Chemotherapy, Diagnosis, Tumor, Treatment.

INTRODUCTION

Worldwide, breast cancer is the most common cancer in women, other than no melanoma skin cancer. More than 250 000 new cases of breast cancer were diagnosed in the United States in 2017, and breast cancer will be diagnosed in 12% of all women in the United States over their lifetimes. This review summarizes evidence-based approaches to the systemic and local treatment of the three major breast cancer sub al trials or meta-analyses and guidelines of major professional societies [1]. The indices of majormedicaland oncology journals were comprehensively reviewed for articles published from January 1, 2013, to November 11, 2018, on the topic of breast cancer treatment. Articles agreed on by both authors to define modern practice were included, with priority given to prospective randomized trials and large meta-analyses that represent the first and/or the most important evidence establishing current standard of care in breast cancer.

Breast cancer is the most common cause of cancer in women and the second most common cause of cancer death in women in the U.S. Breast cancer refers to cancers originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk [2]. Worldwide, breast cancer comprises 10.4% of all cancer incidences among women, making it the second most common type of non-skin cancer (after lung cancer) and

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the fifth most common cause of cancer death. In 2004, breast cancer caused 519,000 deaths worldwide (7% of cancer deaths; almost 1% of all deaths). Breast cancer is about 100 times more common in women than in men, although males tend to have poorer outcomes due to delays in diagnosis [3]. Cancer cells are very similar to cells of the organism from which they originated and have similar (but not identical) DNA and RNA. This is the reason why they are not very often detected by the immune system, in particular, if it is weakened. Cancer cells are formed from normal cells due to a modification / mutation of DNA and / or RNA [4]. These modifications / mutations can occur spontaneously ill Law of Thermodynamics - increase of entropy) or they may be induced by other factors such as; nuclear radiation, electromagnetic radiation (microwaves, X-rays, Gamma-rays, Ultraviolet-rays etc.), viruses, bacteria and fungi, parasites (due to tissue inflammation / irritation, heat, chemicals in the air, water and food, mechanical cell-level injury, free radicals, evolution and ageing of DNA and RNA, etc.

All these can produce mutations that may start cancer. Cancer can be called therefore "Entropic Disease" since it is associated with the increase of entropy of the organism to the point where the organism cannot correct this itself External intervention is required to allow the organism to return to a stable entropic state. Cancer develops if the immune system is not working properly and / or the amount of cells produced is too great for the immune system to eliminate. The rate of DNA and RNA mutations can be too high under some conditions such as; unhealthy environment (due to radiation, chemicals, etc., poor diet (unhealthy cell environment), people with genetic predispositions to mutations and people of advanced age (above 80).

DISCUSSION

Diagnosis and Pathophysiology:

Breast cancer is a histologic diagnosis made according to standardized pathologic criteria. The most common breast cancer histology is invasive ductal carcinoma (50%-75% of patients), followed by invasive lobular carcinoma (5%-15% of patients), with mixed ductal/lobular carcinomas and other rarer histologist making up the remainder of patients. Two Main Molecular targets in breast cancer pathogenesis have been identified. One is estrogen receptor alpha (ERα), which is expressed in approximately 70% of invasive breast cancers. ERα is a steroid hormone receptor and a transcription factor that, when activated by estrogen, activates oncogenic growth pathways in breast cancer cells. Expression of the closely related steroid hormone progesterone receptor (PR) is also a marker of ERα signaling. Tumors with expression of either estrogen receptor (ER) or PR in at least 1% of tumor cells are categorized as HR+.

The use of endocrine agents to downregulate ER signaling is the primary systemic therapy for ER-positive or PR-positive breast cancers. The second main molecular target is epidermal growth factor (ERBB2, formerly HER2 or HER2/neu), a transmembrane receptor tyrosine kinase in the epidermal growth factor receptor family that is amplified or overexpressed in approximately 20% of breast cancers, and is associated with poor prognosis in the absence of systemic therapy. Tumors with amplification or overexpression of the gene ERBB2 are

ERBB2+. Patients with ERBB2-amplified or -overexpressing breast cancer benefit from ERBB2-targeted therapy, including anti-ERBB2 antibodies (such as trastuzumab and pertuzumab) and small-molecule tyrosine kinase inhibitors (such as lapatinib and neratinib). Triple-negative breast cancer, which makes up approximately 15% of all breast tumors, is characterized by the lack of expression of molecular targets ER, PR, or ERBB2. Triple-negative tumors have a high risk of distant relapse in the first 3 to 5 years following diagnosis The specific molecular pathophysiology of triple negative breast cancer remains poorly understood. Distinct prevalences, prognoses, and systemic therapy options characterize the three breast cancer subtypes: HR+, ERBB2+, or triple-negative. Triple-negative breast tumors are more likely to occur in women who are younger, black, or Hispanic, whereas HR+ tumors are more likely in older women.

Systemic Therapy for No Metastatic Breast Cancer:

Endocrine therapy, which counteracts estrogen-promoted tumor growth, is the primary systemic therapy for HR+/ERBB2− breast cancer. Standard endocrine therapy consists of oral antiestrogen medication taken daily for 5 years, and options differ according to menopausal status. Tamoxifen is a selective estrogen receptor modulator that competitively inhibits estrogen's binding to ER and is effective in both pre- and postmenopausal women. Aromatase inhibitors (anastrozole, exemestane, and letrozole) decrease circulating estrogen levels by inhibiting conversion of androgens to estrogen6 and are effective only in postmenopausal women (including those who are postmenopausal because of medical ovarian suppression or oophorectomy). Typical adverse effects of endocrine therapy are listed [5]. Five years of tamoxifen for patients with HR+ breast cancer reduces the breast cancer recurrence rate by approximately 50% in the first 5 years after diagnosis compared with no endocrine therapy. The absolute benefit of tamoxifen is proportional to the risk associated with a given tumor. For example, a woman with an anatomic stage III HR+ breast cancer may have a 50% 5-year risk of recurrence without systemic therapy reduced to 25% with a 5-year course of tamoxifen. A woman with anatomic stage I HR+ breast cancer and a 10% 5-year risk of recurrence without systemic therapy has her recurrence risk reduced to 5% with a 5-year course of tamoxifen. Compared with 5 years of tamoxifen, 5 years of aromatase inhibitor in a postmenopausal woman is somewhat more effective. In a meta-analysis of 31 920 women, tamoxifen was associated with a 10-year breast cancer recurrence risk of 22.7% vs 19.1% for aromatase inhibitors [6].

A "switch" strategy (initial 2-3 years of tamoxifen, followed by aromatase inhibitor for completion of a 5-year course of endocrine therapy) is equivalent to 5 years of aromatase inhibitor use for breast cancer mortality, and is a viable strategy for women who wish to mitigate toxicities from both classes of endocrine therapy. Because absolute benefit is related to risk, in low risk patients, the added benefit of aromatase inhibitors over tamoxifen is small, and treatment decisions should be guided by adverse effects. Even in higher-risk women, intolerance of an aromatase inhibitor should lead to substitution of tamoxifen. When treating a premenopausal woman with endocrine therapy, the first decision is whether to treat with

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ovarian suppression using gonadotropin-releasing hormone agonists, such as leuprolide acetate and goserelin, or oophorectomy to induce menopause; the second decision, if inducing menopause, is whether to treat with tamoxifen or aromatase inhibitor. These approaches have been compared in two large clinical trials (combined N = 5738). A small but significant improvement in 8-year overall survival was observed with ovarian suppression plus tamoxifen compared with tamoxifen alone (93.3% vs 91.5%, respectively; P = 0.01). Ovarian suppression plus aromatase inhibitor is not associated with better survival compared with ovarian suppression plus tamoxifen; however, the former combination shows a modest improvement in 8-year freedom from distant recurrence compared with ovarian suppression plus tamoxifen (91.8% vs 89.7%, respectively; P = 0.02). Overall, adding ovarian suppression to either tamoxifen or aromatase inhibitor is indicated in premenopausal women with higher-risk disease, with aromatase inhibitors favored for those at the highest risk. Patients with HR+ breast cancer are at risk of recurrent disease even multiple decades after primary diagnosis. Therefore, studies have evaluated extending both tamoxifen and aromatase inhibitors beyond the typical 5-year duration [7]. Two randomized trials compared 5 vs 10 years of tamoxifen, and showed a small but significant improvement (2.8% absolute improvement) in breast cancer mortality with a 10-year course of therapy. As expected, higher rates of endometrial cancer and thromboembolic disease were observed with longer therapy (Table 2). Separate trial evaluated 5 vs 10 years of aromatase inhibitor use, and found a small reduction in distant recurrences with longer therapy. There was no significant improvement in overall survival with extended-duration aromatase inhibitor therapy, whereas new-onset osteoporosis and fracture (known adverse effects of aromatase inhibitors) were both significantly more common. Therefore, extending endocrine therapy provides small benefits but adds toxicity and thus warrants consideration in high-risk patients. Clinicians must decide when to add chemotherapy to endocrine therapy for patients with HR+/ERBB2− breast cancer. Clinic pathologic features, such as anatomic stage and tumor grade, are important but imperfect components of risk and chemo sensitivity assessment. Multiple RNA-based genomic risk scores have been developed to estimate prognosis and predict chemotherapy benefit [8].

Triple-Negative Subtype:

Given the relatively unfavorable prognosis, chemotherapy is generally administered to all patients with triple negative breast tumors larger than 5 mm, even with negative axillary nodes. Chemotherapeutic agents are the only agents approved by the Food and Drug Administration (FDA) for treating non metastatic triple-negative disease. Because deficient DNA damage repair is a biological hallmark of some triple-negative tumors, investigations of the DNA-crosslinking platinum chemotherapies have been of interest in triple-negative disease. Two trials have randomized patients with triple-negative breast cancer to receive neoadjuvant chemotherapy with or without carboplatin, and both demonstrated a significant improvement in pathologic complete response (pCR) at surgery with the addition of carboplatin (from 41% to 54% in one trial and from 37% to 53% in the other).

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However, only one of the trials demonstrated a significant improvement in disease-free survival in the carboplatin-containing group, and in this case, the other components of the chemotherapy regimen were not consistent with standard therapy and did not include an alkylating agent. Therefore, the role of platinum salts in the treatment of patients with stage I-III triple-negative breast cancer remains uncertain. For triple-negative tumors treated with neoadjuvant chemotherapy, pCR (all tumors gone from the breast and lymph nodes) at surgery is a highly favorable prognostic biomarker. In a met analysis of patients treated with neoadjuvant chemotherapy, prognosis was improved in patients with triple-negative breast cancer (N = 1157) who achieved pCR compared with those who did not (hazard ratio, 0.24 for event-free survival with pCR). New treatment approaches for patients with triple-negative disease who do not achieve pCR are needed, and platinum chemotherapy is one strategy being evaluated in several clinical trials. To date, the only evidence-based adjuvant escalation strategy available in this setting is single-agent capecitabine, as discussed here.

ERBB2+ Subtype:

The development of ERBB2-targeted therapy has been one of the greatest advances in breast cancer treatment. Trastuzumab, a monoclonal antibody targeting the extracellular domain of ERBB2, first entered clinical trials in the 1990s. Four randomized adjuvant trials demonstrated that the addition of 1 year of trastuzumab to standard adjuvant chemotherapy markedly improved disease-free survival and overall survival for patients withERBB2+ breast cancer, with disease free survival hazard ratios of 0.48 to 0.75 favoring trastuzumab containing regimens. While several different chemotherapy regimens combined with trastuzumab were studied across these trials, the two guideline-preferred neoadjuvant/adjuvant accompanying chemotherapy regimens in stages II and III ERBB2+ breast cancer in the United States are Adriamycin/cyclophosphamide paclitaxel and docetaxel/carboplatin (see notable toxicities in Table 2).50The 1-year duration of neoadjuvant/adjuvant trastuzumab comes from prospective comparisons showing 2 years is no better than 1,whereas therapy for less than 1 year is inferior to 1 year inmost, but not all, studies. Even 9 weeks of adjuvant trastuzumab is superior to none for patients with ERBB2+ breast cancer.54 Following the significant effectiveness of trastuzumab for preventing recurrences and death from ERBB2+ breast cancer, subsequent investigations have focused on (1) decreasing the number of accompanying chemotherapy agents in lower-risk patients and (2) adding novel agents in higher-risk patients. In a single-group trial, 406 patients with tumors that were mostly less than 2 cm and node negative were treated with adjuvant paclitaxel for 12 weeks and the standard 1 year of adjuvant trastuzumab. The 7-year recurrence free interval was 97.5%, with 5 local-regional recurrences and 4 distant recurrences at 7-year follow-up. Given the excellent long term outcomes and reduced toxicity of single-agent accompanying chemotherapy, paclitaxel/trastuzumab is now the standard of care for patients with small, node-negative ERBB2+ tumors.

In patients with higher-risk ERBB2+ breast cancer, the agent's pertuzumab and neratinib further lower the risk of recurrence below what is observed with standard trastuzumab-containing regimens. Pertuzumab is a monoclonal antibody targeting the ERBB2 dimerization

domain. In a phase 3 randomized trial of 4804 patients with stage I-III ERBB2+ breast cancer, pertuzumab led to a small but statistically significant improvement in 3-year invasive disease-free survival (94.1% with pertuzumab vs 93.2% with placebo; hazard ratio, 0.81 [95% CI, 0.66-1.00]; P = .045). In subgroup analyses, risk reduction with pertuzumab was observed in node-positive and HR− patients but was not observed in node negative and HR+ subgroups, though the trial did not have statistical power to evaluate these individual subgroups and follow-up was relatively short.56 At this time, treatment regimens incorporating pertuzumab are reasonable to use in high-risk patients defined by tumor size and nodal status, while the added toxicity and cost in lower-risk patients is difficult to justify. Neratinib is an oral small-molecule tyrosine kinase inhibitor of multiple HER family members, including ERBB2.A randomized phase 3 trial of 2840 patients compared 1 year of adjuvant daily neratinib vs placebo following completion of neoadjuvant/adjuvant chemotherapy plus trastuzumab forERBB2+ breast cancer. Invasive disease free survival at 5 years favored neratinib (90.2% with neratinib vs 87.7% with placebo; hazard ratio, 0.73 [95% CI, 0.57-0.92]; P = .008). In contrast to the pertuzumab adjuvant trial, this invasive disease-free survival advantage was observed only in the HR+ subgroup and not in HR− patients, though reasons for this are unclear. At present, there is no direct evidence to support using adjuvant neratinib in a pertuzumab-treated patient, or vice versa, as the major trials of each agent did not include use of the other. Finally, to date, neither agent has shown overall survival benefit when administered as adjuvant therapy.

CONCLUSION

Targeting cancer cells while avoiding noncancerous cells is the Holy Grail of cancer therapy. Many different systems and strategies have been designed for drug targeting to tumors over the years. Improved insights into the genetic and (patho-) physiological processes contributing to malignant transformation and tumorigenesis have resulted in the development of several novel chemotherapeutic drugs and strategies. Over the course of the last decade, many acquisitions have taken place in this critical field of research in the pharmaceutical industry. For these reasons, emerging pharmaceutical and nanotechnology companies try to increase their patent portfolio to increase their commercial value for possible buyouts by big pharmaceutical firms. Such acquisitions show the importance of this area of research and, most importantly, highlight the global need for effective and safe pharmaceutical chemotherapeutic agents that have the potential to target tumors like breast cancer with minimal toxicity and side effects. Unfortunately, these factors affected the quality and value of patents registered currently for the management of breast cancer. Most of the reviewed patents were extremely broad within their scope, unclear, and unorganized to avoid any specifications of the invention. This prevents researchers and scientists from reproducing the patents results and conclusions. This could also be attributed to the company's urge to gain maximum intellectual properties rights. Furthermore, multiple patents were found to be describing the same product exactly. Such flaws in the patents system need stricter regulations during patents filing to protect consumers as well as inventors.

REFERENCES

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[1] Association of Breast Surgery at, "Surgical guidelines for the management of breast cancer," *Eur. J. Surg. Oncol.*, 2009, doi: 10.1016/j.ejso.2009.01.008.

[2] J. Ferlay *et al.*, "Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012," *Int. J. Cancer*, 2015, doi: 10.1002/ijc.29210.

[3] M. Akram, M. Iqbal, M. Daniyal, and A. U. Khan, "Awareness and current knowledge of breast cancer," *Biological Research*. 2017, doi: 10.1186/s40659-017-0140-9.

[4] P. Eroles, A. Bosch, J. Alejandro Pérez-Fidalgo, and A. Lluch, "Molecular biology in breast cancer: Intrinsic subtypes and signaling pathways," *Cancer Treatment Reviews*. 2012, doi: 10.1016/j.ctrv.2011.11.005.

[5] M. Reich, A. Lesur, and C. Perdrizet-Chevallier, "Depression, quality of life and breast cancer: A review of the literature," *Breast Cancer Research and Treatment*. 2008, doi: 10.1007/s10549-007-9706-5.

[6] S. Macdonald, R. Oncology, and M. General, "Breast Cancer Breast Cancer," *J. R. Soc. Med.*, 2016.

[7] I. Kümler, M. K. Tuxen, and D. L. Nielsen, "A systematic review of dual targeting in HER2-positive breast cancer," *Cancer Treatment Reviews*. 2014, doi: 10.1016/j.ctrv.2013.09.002.

[8] S. Maximiano, P. Magalhães, M. P. Guerreiro, and M. Morgado, "Trastuzumab in the Treatment of Breast Cancer," *BioDrugs*. 2016, doi: 10.1007/s40259-016-0162-9.