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BREAST CANCER AS A MULTIFACETED DISEASE. LITERATURE REVIEW

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Abstract

Breast cancer has been the leading cause of morbidity among women for many years. In 2020, it accounted for nearly 24% of all registered cancers in the female Polish population. Key risk factors for breast cancer include female gender, age, genetic factors, and factors related to the levels of sex hormones. However, there is a need for more precise research taking into account the impact of certain chemical substances, especially medications. A primary symptom of breast cancer is a lump in the breast; therefore, self-examination and preventive screenings such as mammography and breast ultrasound are crucial. Breast cancer cells exhibit distinctive molecular markers on their surface, resulting in the categorization of the disease into biological subtypes, which continue to evolve with advancing knowledge. In the realm of surgical treatment, efforts persist to limit axillary lymph node dissection (ALND) and prevent the occurrence and treatment of lymphedema. In the field of surgical treatment, there is still a pursuit to limit the performance of axillary lymph node dissection (ALND) and prevent the occurrence of lymphedema, which could be treated by utilizing microsurgical procedures e.g. lymphovenous anastomosis (LVA). Treatment for breast cancer includes, in addition to standard chemotherapy and hormone therapy, the use of immunotherapy. The latest drugs are immunconjugates, which are a combination of a monoclonal antibody with a cytostatic agent. Promising outcomes are linked to treatments focused on identified genetic mutations in cancer cells. Ongoing studies contribute to the discovery of drug targets, enabling the introduction of novel molecularly targeted therapies. These approaches facilitate achieving longer disease stabilization even in patients with metastases. Radiation therapy remains a crucial method for treating breast cancer. Due to precise planning, based on increasingly advanced imaging methods and the application of deep inspiration breath-hold (DIBH) techniques, adverse effects of radiation are limited.

Key words: breast cancer, metastatic breast cancer, risk factors, digital mammography, lymphovenous anastomosis, molecular targeted therapy, immunoconjugates, deep inspiration breath-hold

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Introduction and objective

Among women of all age groups, breast cancer stands out as the most commonly diagnosed malignancy [1]. In the past, breast cancer was considered as one disease entity, characterized by a tumour located in the breast gland. The development of molecular research methods has proven that breast cancer is a highly diverse group of tumours, significantly influencing the prognosis and course of treatment. Therapeutic decisions are made based on numerous factors, including tumour size, stage of cancer, type and grade of histopathological malignancy, presence of immunohistochemical markers (ER, PR, HER2), proliferation marker (Ki-67), and the presence of genetic mutations and immunological markers (TILS, PD-L1) [3,4]. The increased availability of diagnostic examinations, diverse treatment methods, and the systematic introduction of targeted therapies have led to a significant upward trend in the 5-year survival rates for breast cancer among women and men from 2000 to 2019 [6,7].

This article will discuss the current state of knowledge, along with an overview of selected clinical issues, regarding the frequency of this disease, risk factors, symptoms of breast cancer, methods of diagnosis, clinicohistopathological classification, as well as treatment methods.

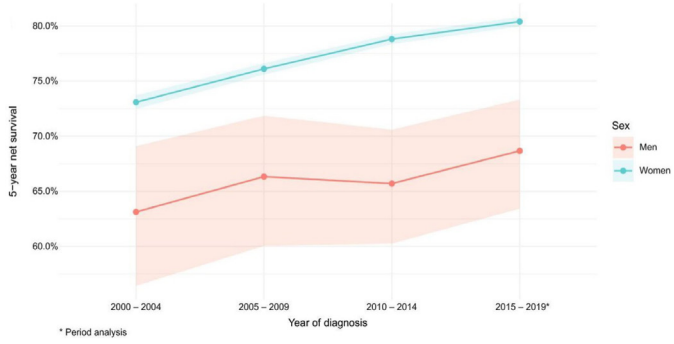

Fig. 1. 5-year net survival [7].

Epidemiology

In 2020, 17,511 women in Poland were diagnosed with breast cancer. Despite the fact that the incidence of this cancer increases with age, a significant percentage of cases are also observed among young women aged 20 to 44. Breast cancer constituted 29% of all diagnosed malignancies in this age group. Men can also be affected by breast cancer, although such cases are rare. In 2020, Poland recorded 113 cases of male breast gland cancer. Since 2007, breast cancer has not been the leading cause of cancer-related deaths among women in Poland. It is the second most common cause of death for women with cancer, following lung cancer. The mortality rate for women due to lung cancer in 2020 was 17.6%, while for breast cancer, it was 15.3% [1,2].

Risk Factors

Based on numerous studies, it has been possible to identify factors that increase the risk of breast cancer. Considering the potential for preventive actions based on known risk factors, they are divided into modifiable and non-modifiable.

Among the modifiable factors are gender, age, family history, presence of genetic mutations, factors related to oestrogen metabolism and glandular tissue status, Epstein-Barr virus infection, and a history of radiotherapy [8,9]. Female gender is the primary risk factor. Physiologically elevated levels of free sex hormones and characteristic fluctuations in their levels are associated with a higher risk of breast cancer in women [11]. This cancer is rare in men, constituting 0.64% of diagnosed cases of breast cancer in Poland [1]. Another non-modifiable risk factor is age. The frequency of breast cancer increases with age, reaching its peak in the 65-69 age group. However, it is worth noting that isolated cases of this cancer can occur in very young women, even as early as 20 years of age [1,8]. Genetic predispositions also play a role in the etiology of breast gland cancer. Family occurrence of breast cancer and the presence of mutations in suppressor genes BRCA1, BRCA2 are well-known risk factors not only for breast cancer but also for other cancers, including ovarian cancer. In recent years, due to advances in clinical genetics and analytical methods, several mutations increasing the risk of breast cancer have been identified, including mutations in the genes ATM, CHEK2, PALB2, BARD1, RAD51C, RAD51D, and TP53 [12]. Risk factors related to hormonal regulation that increase the risk of breast cancer include: early age at first menstruation, first childbirth at a late age, a smaller number of childbirths, lack or short duration of breastfeeding, and late menopause. Benign proliferative changes in the breasts are common in women. Some of them can also increase the risk of breast cancer. These include atypical proliferations and pre-invasive cancers [8]. The Epstein-Barr virus is a known oncogenic virus that promotes the development of lymphatic system tumours and some epithelial cancers, including breast cancer. The first infection with the Epstein-Barr virus often occurs without symptoms. After that, the virus persists in a latent form in lymphocytes. The most well-known symptomatic infection with the Epstein-Barr virus is infectious mononucleosis. In the pathogenesis of breast cancer, with favourable additional factors, the virus participates in epigenetic processes, which can result in uncontrolled cell divisions and metastasis to other parts of the body [9]. The genetic material of the virus has also been more frequently detected in women with more aggressive biological subtypes of breast cancer [10].Another non-modifiable risk factor is exposure to ionizing radiation, especially undergoing radiotherapy to the chest in youth[8].

Among the most important modifiable factors, lifestyle-related factors and exposure to certain chemicals and drugs are considered. Proven risk factors for breast cancer include: low physical activity, obesity, alcohol consumption, smoking, insufficient vitamin D3 intake, consumption of processed food, and high intake of saturated fats [8]. Efforts are being made to study the impact of certain drugs on the risk of breast cancer. So far, it has been proven that long-term use of hormonal replacement therapy based on both, oestrogens alone and oestrogen-progestin combination preparations, increases the risk of incidence [11]. Other drugs and chemical substances which potentially increase the risk of breast cancer include diethylstilbestrol, tricyclic antidepressants, and selective serotonin reuptake inhibitors, chronically used tetracyclines and macrolides, as well as dichlorodiphenyltrichloroethane and polychlorinated biphenyls, but they require confirmation in further scientific research [8].

Symptoms

The three most common symptoms reported by women with breast cancer are a lump in the breast, enlargement of lymph nodes, and nipple discharge [14]. Breast cancer most frequently occurs in the upper-outer quadrant of the gland [14,15]. The lump may cause asymmetry and enlargement of the affected breast, leading to discomfort and a sensation of tightness as it grows. The skin over the breast affected by cancer may thicken, resembling an orange peel. In more advanced stage ulceration and the appearance of satellite nodules may occur. Occasionally, in about 1-5% of cases, rapidly increasing swelling and redness of the skin are observed, indicative of inflammatory breast cancer (IBC). Enlarged lymph nodes indicate involvement of the lymphatic system and may be the sole symptom of concealed cancer in cases where no palpable tumour is detected in clinical examination or imaging studies of the breast gland. If the lymphatic vessels are affected, discomfort and limited arm movement at the shoulder joint may occur. Breast cancer can also present as nipple discharge or retraction [16,17]. In the advanced stage, metastases of breast cancer result in symptoms associated with the growth and loss of function in the affected tissue. They are most commonly found in bones but can also occur in solid organs, lungs, skin, or the central nervous system [18,19,20].

Diagnostic

To enhance the sensitivity of breast cancer detection diagnostic methods are being systematically improved. A fundamental element of secondary prevention should be breast self-examination. Unfortunately, this examination has limitations associated with the difficulty of proper execution and a lack of regularity.

In a large group of women undergoing screening mammography, only 14% of patients regularly performed breast self-examination. Younger women and those with higher education were more likely to perform self-examinations [21,22]. X-ray mammography (MG) remains the basic screening method for breast cancer. To enhance the quality and potential for digital image processing, digital mammography is being increasingly implemented. In accordance with the goals of the National Oncology Strategy for the years 2020-2030, it is expected to become a mandatory diagnostic test [23,24]. By the decision of the Minister of Health in 2023, the age range of women covered by preventive examination was expanded from 50-69 years to 45-74 years. The examination can still be performed every two years [25]. Improvements are also being introduced in digital mammography to more effectively diagnose patients with denser breast tissue, typical for younger patients. Such examinations include Digital Breast Tomosynthesis (DBT) and Contrast Enhanced Spectral Mammography (CESM). They allow for complementary diagnostics after screening. DBT is a digital mammography examination in which the X-ray lamp moves, changing the angle of radiation emission, resulting in a reduction of image overlap. As a consequence, it significantly enhances the visualization of lesions without calcifications in dense glandular breast tissue. The disadvantages of this method include increased patient exposure to ionizing radiation and reduced potential for detecting microcalcifications compared to classical mammography. CESM is also a digital mammography examination, but during the procedure, a contrast agent is intravenously administered to the patient. It utilizes the phenomenon of tumour neoangiogenesis, which is visualized as contrast enhancement. In comparison to breast magnetic resonance imaging (MRI), CESM is more accessible, cost-effective, and has a shorter examination duration. However, the advantage of MRI lies in its ability to assess the contrast kinetics, allowing differentiation between benign and malignant changes [5,23].

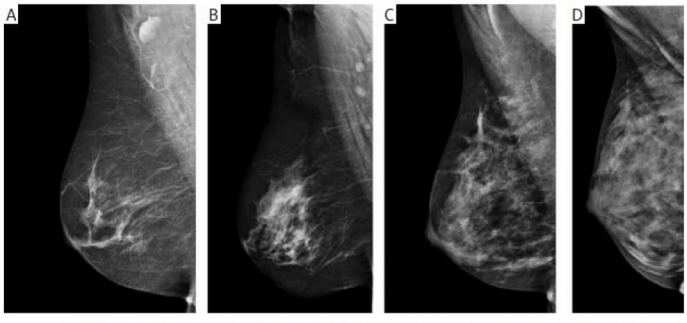

Fig. 2. Breast density categories in mammography: A) category 1 – entirely fatty breast tissue, B) category 2 - scattered fibroglandular breast tissue, C) category 3 - heterogeneously dense breast tissue:, D) category 4 - extremely dense breast tissue [25].

Due to the higher density of glandular tissue in younger women, as well as during pregnancy or breastfeeding, the primary method for assessing the breast gland in these women is ultrasound examination (USG) with an evaluation of the surrounding lymph nodes. Material sampling during biopsy is also most often done under ultrasound guidance. However, changes visible only in MRI should be marked or biopsied during this examination [5]. It is recommended to perform breast ultrasound in the first or second trimester of pregnancy in patients over 35 years old, and considering the examination based on genetic burdens and family history in pregnant women below 35 [26]. Breast MRI examination is reserved for screening individuals at high risk of breast cancer, assessing tumours before surgery, monitoring response to neoadjuvant chemotherapy, diagnosing after reconstructive procedures, investigating suspected inflammatory breast cancer, and in cases where primary examinations yield ambiguous results [5]. Diagnostic imaging for suspected metastatic breast cancer (MBC) involves chest and abdominal computed tomography (CT) as well as bone scintigraphy. These tests may also be substituted with positron emission tomography (PET). Brain MRI is the preferred examination for patients with aggressive biological subtypes of MBC who do not report symptoms, as well as for all patients with MBC who present symptoms [28].The foundation for diagnosing breast cancer lies in the histopathological examination of collected material. It is recommended to perform core needle biopsy (CNB) or vacuum-assisted core biopsy (VACB), also known as mammotome biopsy, under the guidance of ultrasound or MRI [5]. Researchers are increasingly interested in the potential benefits of conducting liquid biopsy (LS). Several studies are underway to evaluate circulating tumour cells, circulating free nucleic acids, and extracellular vesicles as potential molecules enabling swift diagnosis and monitoring of breast cancer progression in the future [29]. In the diagnosis of lymph node metastases, USG of the axillary region, fine-needle biopsy, and preoperative lymphoscintigraphy with subsequent sentinel lymph node biopsy (SLNB) are employed, based on which further diagnostic and therapeutic decisions are made. The aim of conducting this procedure is to select patients who do not require axillary lymph node dissection (ALND). All women diagnosed with breast cancer and patients at high and very high risk are recommended to receive care from a clinical geneticist and undergo genetic diagnostics, particularly focusing on the genes BRCA1, BRCA2, PALB2, and CHEK2 [5,12].

Biological subtypes of breast cancer

The material collected during diagnostics is assessed based on histopathological criteria. Through molecular studies of gene expression in breast cancer, we can distinguish five biological subtypes of this tumour. These are specifically the subtypes: luminal A, luminal B, with overexpression of HER2 protein, basal, and "normal breast type" [3]. Consensus in pathomorphological diagnostics and clinical practice led to the creation of a breast cancer classification based on the recommendations of the experts at the St. Gallen Conference in 2015. Based on histological type, steroid receptor status, HER2 gene expression, and proliferation index, specialists classified breast cancer into surrogates: luminal A, luminal B HER2-negative, luminal HER2- positive, non-luminal HER2-positive, triple-negative breast cancer (TNBC), and special types of breast cancer.

Biological Subtype of Invasive Breast Cancer		Oestrogen Receptor (ER)	Progesterone Receptor (PgR)	HER2 expression	proliferation marker (Ki-67)
Non-Specific Type (NST) Breast Cancer and Lobular Carcinoma	luminal A	+	+	-	< the median for the centre
	luminal B HER2-negative	+	every	-	≥ the median for the centre
		+	< 20%	-	Every
	luminal HER2-positive	+	every	+	Every
	non-luminal HER2-positive	-	-	+	Every
	triple-negative breast cancer (TNBC)	-	-	-	Every
Special Types of Cancer	Hormone-dependent (tubular, lobular, and mucinous)	+	+	typically negative	
	Hormone-independent (apocrine, medullary, glandular-cystic, metaplastic, secretory, lipid-rich cell carcinoma, and salivary gland-type carcinomas)	-	-	typically negative	

Table 1 [4,5].

This classification was influenced by systemic treatment methods [30,31,32]. Biological subtypes also differ in prognosis and the effectiveness of specific treatment methods. The most common subtype is luminal breast cancer, accounting for approximately 70% of all subtypes. HER2-positive and TNBC cancers, each account for approximately 15%, occurring more frequently in younger patients and being linked to a more aggressive course [3,33]. This classification may soon undergo modifications due to further developments in molecular research. There are initial reports about distinguishing a subtype of breast cancer with low HER2 protein expression (HER2-low). Previously, such results in immunohistochemical testing, did not suggest the use of anti-HER2 treatment. However, ongoing research could lead to revisions in these recommendations, potentially enhancing the effectiveness of breast cancer treatment [34]. There is also an increasing number of studies on the presence of the androgen receptor (AR) in patients with TNBC. Its presence is associated with better prognosis but a less favourable response to cytostatic drugs. The presence of AR could provide grounds for identifying another group of patients where personalized treatment with antiandrogen drugs would be justified. These drugs are already used in oncology for the treatment of prostate cancer in men [35].

Treatment

While devising a treatment plan for breast cancer, a combination of various therapeutic methods is applied sequentially or simultaneously, depending on the biological subtype, the stage of tumour advancement determined in the TNM classification, histopathological malignancy, a taking into account the presence of genetic mutations and specific immunologic markers. Breast cancer treatment methods include surgery, systemic treatment in the form of hormone therapy, chemotherapy, and molecularly targeted drugs, as well as radiotherapy. The introduction of targeted therapies in breast cancer treatment has allowed for better control of this tumour, even in patients at the advanced stage IV.

Surgical Treatment

Surgery is the fundamental method for treating breast cancer and can be employed at every stage of treatment. It can be considered at any stage of the disease, even in individual cases with patients having distant metastases, in conjunction with systemic treatment [36]. There are two main surgical procedures for breast cancer treatment. One of these procedures is mastectomy, involving the complete removal of the breast, while the other is breast-conserving surgery (BCS). The latter entails the removal of a specific quadrant of the gland containing the tumour or mass, along with a margin of healthy tissue, and marking the edges of the excised lesion. For women diagnosed with inflammatory breast cancer, mastectomy with delayed reconstruction is the primary method of treatment. For pre-invasive cancers and those in stages I and II, in the absence of contraindications, the preferred method is BCS with possible subsequent radiotherapy. In these stages, in the case of aggressive phenotypes and patients with tumours larger than 3cm, it is recommended to administer systemic treatment before the BCS.

As mentioned earlier, SLNB is a diagnostic method for detecting metastases to the axillary lymph nodes during surgery. Based on research, a standard procedure has been established depending on the clinical assessment of lymph node involvement to minimize the need for avoidable axillary lymph node dissection (ALND) [5,16,37]. The ALND procedure carries the risk of secondary lymphedema in the limb without axillary lymph nodes, significantly reducing the quality of life for patients. The incidence of this complication can be as high as 50%. The most commonly used conservative treatment includes manual lymphatic drainage and compression therapy, but the effects are often unsatisfactory. Surgical treatment options, such as liposuction, reconstruction of lymphatic vessels, autologous lymph node transplantation, and lymphovenous anastomosis (LVA), are also possible. The latter method, with the development of microsurgical techniques, is becoming increasingly promising, It has shown a 30% reduction in arm volume. Additionally, more than 4/5 of patients observed a moderate to significant improvement in functioning. Efforts are also being undertaken to carry out preventative LVA procedures after ALND, particularly in cases where lymphedema has not yet manifested [38,39].

In the face of the increasingly common use of neoadjuvant chemotherapy, clinicians face the dilemma of determining the optimal timing for performing SLNB in patients who, prior to preoperative clinical assessment, did not exhibit lymph node metastases (cN0). This issue has sparked numerous discussions, yet the findings remain inconclusive. Proponents of conducting SLNB before initiating chemotherapy argue for more effective sentinel lymph node identification and a reduced risk of overlooking metastases in the lymph nodes. However, such an approach may contribute to a higher rate of ALND. In contrast, researchers advocating for perfor-

ming SLNB after neoadjuvant treatment argue that the goal of preoperative chemotherapy is to limit the extent of surgery, including ALND. They contend that by sampling a larger number of nodes, the rate of false-negative results decreases. Additionally, it is essential to consider that preoperative chemotherapy induces changes that may disrupt lymphatic drainage.

The consensus of experts from the 2015 St. Gallen Conference recommends performing SLNB on at least three nodes in patients after neoadjuvant treatment, where clinical suspicion of lymph node metastases existed. If cancer cells are detected in at least one node, ALND should be performed [32,40,41].

Reconstructive procedures are a crucial component of comprehensive care for patients. In the context of surgical breast cancer treatment, procedures involve amputation with simultaneous or subsequent reconstruction. In the case of BCS, there is an option for symmetrisation of the second breast. Women with a confirmed genetic mutation in the BRCA1 or BRCA2 gene, a positive family history of breast cancer, and meeting other criteria have the option of undergoing prophylactic mastectomy with reconstruction [5].

Systemic Treatment

With the development of molecular research, we observe ongoing improvements in methods for systemic breast cancer treatment. Fundamental approaches to systemic treatment include hormone therapy, chemotherapy, and molecularly targeted drugs. Decisions regarding treatment are made based on tissue parameters obtained from biopsies, which are assessed in the pathological report.

Luminal cancers

For each subtype of luminal breast cancer, hormonal therapy can be applied.

The condition is having an ER status higher than 1%. The choice depends on menopausal status. In premenopausal women, tamoxifen (TAM), an antiestrogenic drug, is used. After achieving ovarian suppression, either through the use of synthetic gonadotropin-releasing hormone analogues (GnRH) or surgical removal of the ovaries, aromatase inhibitors (AI) such as letrozole and anastrozole can be initiated. The use of AI is more beneficial in younger patients, those with elevated risk factors, and in lobular carcinoma. In postmenopausal women, TAM and AI are used sequentially. As the degree of staging increases, the duration of hormonal treatment should be extended and fall within the range of 5 to 10 years [5,37,42]. In advanced and metastatic luminal cancers with HER2-negative status, besides TAM and AIs, other hormonal drugs such as fulvestrant, megestrol acetate, medroxyprogesterone acetate or oestrogens, are used in combination with CDK4/6 inhibitors or alpelisib. In luminal cancers, oestrogens, through signalling pathways, increase the expression of cyclin D and cyclin-dependent kinases 4 and 6 (CDK4/6), leading to uncontrolled cancer cell proliferation. CDK4/6 inhibitors, as modern targeted drugs, selectively inhibit cyclin-dependent kinases 4 and 6, and significantly prolong progression-free survival (PFS) when are combined with hormonal therapy [43,44,45].

In patients with hormone receptor-positive, HER2-negative breast cancer, the most common of all breast cancer subtypes, mutations in the PIK3CA gene often occur. This can lead to excessive activation of the PI3K signalling pathway, causing uncontrolled proliferation of cancer cells and the activation of the oestrogen receptor despite hormonal treatment. Understanding these mechanisms allowed the development of a targeted drug, alpelisib, an α-specific inhibitor of phosphatidylinositol 3-kinase (PI3Kα), prolonging PFS in patients with progression of advanced breast cancer [46]. Among women with locally advanced or metastatic breast cancer resistant to AI treatment, the use of combination therapy with everolimus and hormonal drugs, such as exemestane or fulvestrant, has been observed to improve PFS compared to using hormonal therapy alone. However, this serine-threonine kinase inhibitor (mTOR) is not currently covered by drug programs in Poland, and it would be justified to conduct additional comparative studies of its effectiveness, in relation to CDK4/6 inhibitors, in the future [47].

HER2-positive cancers

HER2-positive breast cancer, identified by the presence of the human epidermal growth factor receptor 2 (HER2), is associated with an aggressive course. However, due to significant advancements in targeted therapies, the prognosis has been improving. A breakthrough in the treatment of this breast cancer subtype was the approval in 1998 of the first monoclonal antibody directed against the extracellular domain of the HER2 receptor, trastuzumab (T). Currently, it is used in both, early and metastatic breast cancer, in combination with taxane chemotherapy [5]. Its effectiveness has been confirmed in clinical trials. In the HERA study, one year of trastuzumab use, increased the 10-year PFS by 6.8% and the 12-year overall survival (OS) by 6.5% for women with early breast cancer compared to the control group. Among patients with distant metastases, trastuzumab extended PFS by 2-11 months and OS by 5-8 months [48,49]. Since then, the use of immunotherapy in the treatment of this subtype has been improved. Nearly 15 years later, another monoclonal antibody targeting the HER2 receptor, pertuzumab (P), was approved for treatment. The first-line treatment for metastatic HER2-positive breast cancer is a combination of immunotherapy in the form of dual blockade (T + P) and chemotherapy (docetaxel (D) or paclitaxel (PTX)) for a period of 4-6 months. In the CLEOPATRA study, evaluating the effectiveness of pertuzumab, an extension of PFS by almost 19 months was observed, and OS was calculated at 37% over an 8-year observation period [50,51]. After the completion of chemoimmunotherapy, the dual blockade alone is administered [5]. Furthermore, the EORTC 75111-10114 study revealed a PFS extension of more than 50% with the addition of oral metronomic chemotherapy involving cyclophosphamide to immunotherapy (P+T) in patients with stage IV cancer [52]. The next lines of metastatic breast cancer treatment are also based on molecularly targeted drugs. They reach the cancer cell using anti-HER2 antibodies

and then release a substance that destroys it. These medications include trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd). They are called immunoconjugates. They are composed of trastuzumab and cytostatic drugs: microtubule inhibitor (DM1) and topoisomerase I inhibitor (DXd). These are very promising drugs used in metastatic breast cancer. T-DXd shows greater effectiveness in extending PFS then T-DM1. The median was almost 29 months for T-DXd, while for T-DM1, it was just under 7 months. Immunoconjugates also provide high efficacy in treating patients with metastases to the central nervous system (CNS) [5,53]. In the treatment of metastatic HER2--positive breast cancer, especially cases with metastases to the CNS, tyrosine kinase inhibitors of EGFR and HER2 receptors, lapatinib, neratinib, and tucatinib, could be used in combination with capecitabine or trastuzumab. The breast cancer drug program in Poland include only lapatinib [5].

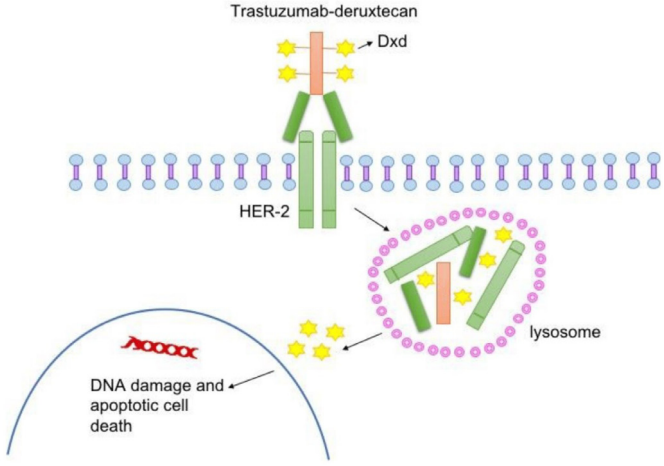

Fig. 3. Mechanism of action of T-DXd [54].

Triple-negative breast cancers (TNBCs)

Chemotherapy is the primary systemic treatment for TNBC. According to expert recommendations, anthracyclines, taxanes, and alkylating agents are used. In more advanced TNBC cases, it appears justified to incorporate an antimetabolite, a precursor to 5-fluorouracil, like capecitabine, and also platinum derivatives. In cases of ineffectiveness in prior treatment lines, eribulin, which inhibits cell division by affecting tubulin, may be considered [5,55]. Monoclonal antibodies are also being explored in TNBC treatment. Despite past beliefs, this breast cancer subtype is also immunogenic. Sacituzumab govitecan is administered in metastatic breast cancer and is available free of charge in Poland under the drug program. It is an immunoconjugate composed of a monoclonal antibody targeting the Trop-2 protein, found on up to 88% of TNBC cells, and the cytotoxic drug SN-38, an inhibitor of topoisomerase I. The use of this drug has resulted in an almost 50% extension of PFS compared to chemotherapy alone, as well as an extension of OS by about 4 months [56]. This breast cancer subtype may also exhibit increased expression of programmed death-ligand (PD-L1). Upon binding to the programmed death 1 receptor (PD-1) on the surface of T lymphocytes, this ligand inhibits the activation of the immune system, hindering the recognition and removal of cancer cells. Pembrolizumab is an example of a drug which inhibits this signalling pathway. It is a humanized monoclonal antibody that blocks PD-1. Further research is needed to determine the effectiveness of using this drug in TNBC and other cancers treatment [57,58]. For patients with germline mutations in the BRCA1 and BRCA2 genes, molecularly targeted drugs can also be applied. These include poly-(ADP-ribose) polymerase (PARP) inhibitors: talazoparib and olaparib. They exhibit high toxicity specifically targeting cells with mutations in the BRCA1 and BRCA2 genes. Talazoparib is available in the drug program in Poland for the treatment of metastatic breast cancer in both: luminal resistant to hormone therapy and TNBC [5,59].

Radiotherapy

Radiotherapy is used for both local and distant metastatic breast cancer treatment. In patients who have undergone BCS, it complements surgical treatment, reducing the risk of adverse events. Radiotherapy protocols are continually refined to minimize unwanted side effects. The technique that reduces the cardiotoxicity of radiotherapy is deep inspiration breath--hold (DIBH). This technique is conducted using a breath-monitoring device, where the accelerator operates only when the patient achieves an appropriately deep breath-hold. During inhalation, the heart moves away from the chest wall, resulting in a reduced radiation dose to the heart, left anterior descending coronary artery and lungs. Radiotherapy is also employed in the treatment of breast cancer metastases. It can be applied for radical treatment as well as palliative pain relief and prevention of fractures in bone metastases. It is also applicable in metastases to the central nervous system (CNS). For solitary lesions, stereotactic radiotherapy or surgical resection of the metastasis followed by radiotherapy is employed, but in the case of multiple metastases within the CNS, whole-brain irradiation is used. [5,60,61].

Summary

Breast cancer may seem like a single disease, but molecular studies demonstrate that various proteins are expressed on the surface of its cells, influencing different prognoses, courses, and therapeutic possibilities. A review of the literature suggests a continual increase in researchers' enthusiasm for molecularly and genetically targeted therapies, providing substantial optimism for further advancements in the treatment of this cancer and which may serve as the basis for identifying additional biological subtypes in the future.

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