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Review

Preparing for the Era of Precision Medicine to Improve Individualized Outcomes in Women with Breast Cancer

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Abstract

Breast cancer (BC) is the most common cancer type among women worldwide. Patients with BC and survivors of BC often experience a plethora of undesirable, anticancer therapy-related symptoms, which deteriorate their quality of life (QoL). For this reason, the development of treatment strategies BC, which are effective, safe, and tolerable is certainly needed. Personalized medicine offers therapeutic options that are tailored to the individual needs of each patient. In addition to the development of modern target therapies, there is an important need to combat some common adverse effects of standard therapies for BC.

This article presents some recent research findings that identify selected genetic changes, which are associated with the occurrence and severity of adverse effects of the BC therapies. It focuses on typical side effects of current anticancer treatments, which reduce the QoL of BC patients and survivors. In particular, it addresses pain [including chemotherapy (CHT)-induced peripheral neuropathy (CIPN) and lymphedema], depression, cognitive dysfunction, premature menopause, and CHT-induced menopause.

It introduces some potential interventions [e.g., using nicotinamide riboside (NR) and melatonin], targeted for women with BC, who suffer from CIPN, as well as nutritional/exercise programs for necessary lifestyle modifications to reduce obesity and the risk of BC recurrence among BC survivors. As a consequence, the described approaches may be helpful in planning personalized treatment, facilitate the patient's tolerability of many currently available anticancer therapies, optimize the medication selection or dosage, and improve the patients QoL.

Keywords: Breast cancer (BC), chemotherapy-induced peripheral neuropathy (CIPN), depression, pain, personalized medicine, quality of life (QoL)

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Over the last decade, breast cancer (BC) has been the most common type of malignancy in women worldwide.[1] According to the presence of certain BC-associated biomarkers [e.g., estrogen receptor (ER), progesterone receptor (PR), and human epidermal receptor 2 (HER2)] detected in the breast tumors, BC can be classified into different sub-types.[2] Due to the growing prevalence of BC, the development of safe and effective therapeutic strategies for BC is of utmost importance. In addition to well-established treatment options [e.g., surgery, chemotherapy (CHT), radiation therapy (RT), and endocrine therapy (ET)], modern strategies, which influence the pathways of tumor signaling (e.g., targeted agents, and immunotherapy) have been applied, contributing to the improved outcomes and longer survival rates of many patients with BC.[3] However, many challenges still remain with regard to the targeted therapies. In addition to the development of resistance to treatment, leading to patient relapses, the occurrence and

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severity of adverse effects of the standard and emerging BC therapies often represent barrieres to their application.[4] Risks for developing long-term adverse effects post BC treatment are multifactorial, including the woman's age at the time of diagnosis, comorbidities, and type, dose, and duration of the antineoplastic treatment.[4] In contrast to the "one size fits all" approach to patients with BC, the individualized approaches should play the main role. Consequently, precision medicine represents a strategy for treatment and prevention of the diseases that includes the patient's genetics, cancer biological features, tumor microenvironment, patient's comorbidities, lifestyle, and QoL.[5] In precision oncology, the aim is to individualize each patient's management (according to a detailed assessment of the risk of progression or recurrence of that patient's malignancy), during every step of diagnostic work-up, treatment process, and survivorship journey.[5]

This article presents some recent research data (e.g., in the area of genetics and metabolism), associated with the adverse effects of the BC therapies. This overview briefly addresses common undesirable symptoms, related to the currently used anticancer treatments, such as pain [e.g., due to lymphedema and CHT-induced peripheral neuropathy (CIPN)], depression, cognitive dysfunction, premature menopause, and CHT-induced menopause, highlighting the patient's point of view. It also introduces obesity as an additional target for personalized interventions (such as lifestyle modification, via nutritional and exercise programs) to reduce the risk of BC recurrence among BC survivors. Moreover, it touches on the recent advances in precision medicine (e.g., genome medicine) and provides some future directions to personalized therapies, aimed at fulfilling unmet needs of patients with BC and BC survivors.

Common Anticancer Therapy-Related Adverse Effects Reducing the Quality of Life in Patients with Breast Cancer

At present, commonly used anticancer therapies (e.g., CHT) cause various, undesirable symptoms, which negatively influence the QoL of BC patients and survivors (Fig. 1).[4, 6] The most commonly experienced, disturbing symptoms were classified into psychological and endocrine categories.[6] In fact, the impact of CHT on the QoL, among BC survivors, was explored using the QoL evaluation (both physical and psychological parameters) at different time points (e.g., before CHT, after the 3-rd cycle of CHT, within two–three weeks of completing adjuvant CHT, and at least 8 years after CHT). According to this study results, depressive symptoms, pain and fatigue were aggravated among the participating pre-and peri-menopausal women with BC at all stages of their therapeutic process.[7] Moreover, several clusters of undesirable symptoms, as well as their negative influence on the functional status, corresponding with BC outcomes, were noted in such patients.[8] On the other hand, however, it should be highlighted that the patients with BC, who have been diagnosed with different malignancy stages, display various

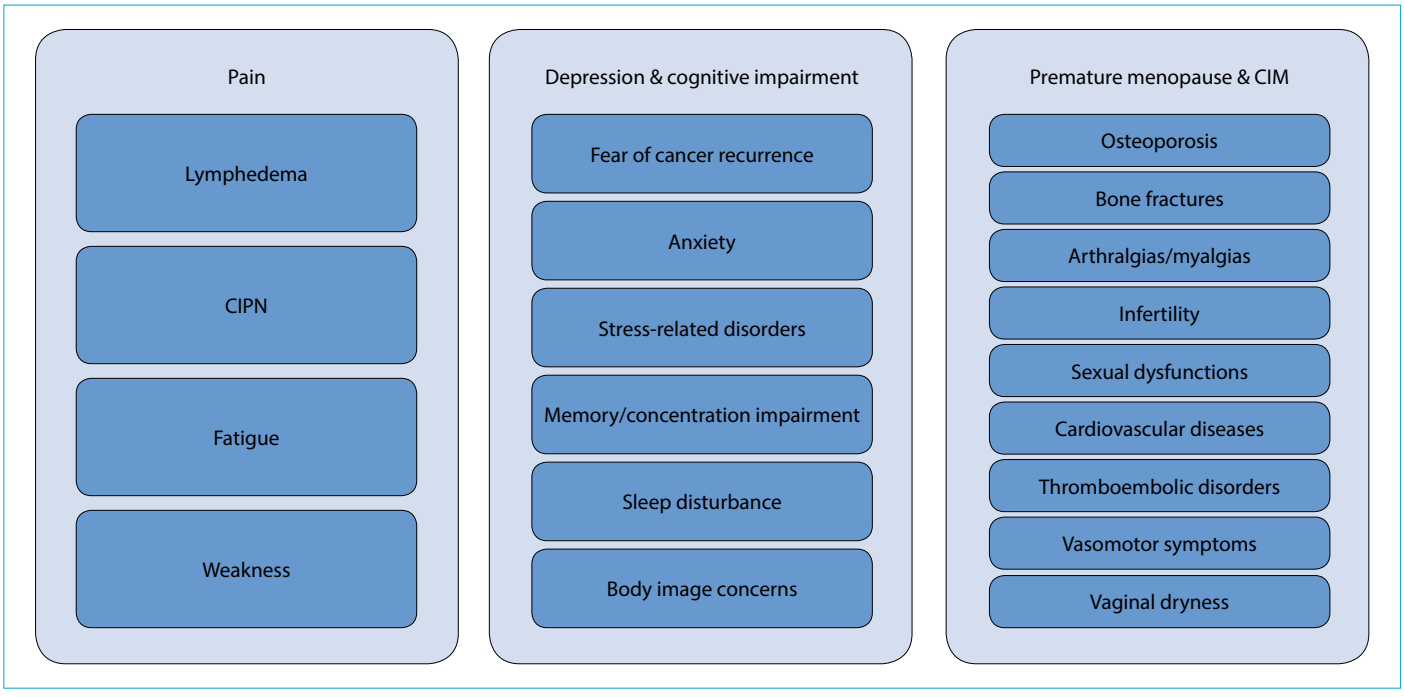

Figure 1. Common adverse effects of breast cancer treatments that decrease the patients QoL. (CIPN, chemotherapy-induced peripheral neuropathy; CIM, chemotherapy-induced menopause; QoL, quality of life).[4, 6]

perceptions of the treatment-associated adverse effects. For instance, certain negative effects may seem more acceptable to patients at the early-stage of BC, mostly because of the anticipated positive treatment results and hope of curing the BC. Conversely, the similar adverse effects, in patients with metastatic stage of BC, need to be promptly addressed and effectively managed. Since metastatic BC has usually poor outcome, focusing on satisfactory QoL is one of the main priorities for these patients. At this point, a detailed understanding of the treatment-related adverse effects is crucial to deliver the therapies characterized by a minimal toxicity.

Pain is one of the most typical symptoms experienced by BC patients, who receive CHT, often because of the chemotherapy-induced peripheral neuropathy (CIPN). It has been reported that in CIPN, the changes in neurotransmission and pro-inflammatory actions of cytokines represent the main derangements within peripheral nerves, which negatively affect motor and sensory functions of the extremities.[9] Moreover, based on a recent meta-analysis, it has been shown that some additional risk factors (e.g., obesity, lower level of education, lymphedema, axillary lymph node dissection, and receiving CHT, RT, or ET) can also contribute to a greater degree of suffering from pain, among BC patients and survivors.[10] In particular, CIPN can occur in women with BC during or after completion of such treatment.[11] For instance, six years after using CHT, almost one half of BC survivors had reported numbness in the distal parts of their extremities.[11-31] Furthermore, patients with CIPN are more prone to falls and bone fractures.[12]

Depression has frequently been noted in women with BC, who received CHT. For instance, mild to moderate levels of depression were reported in approximately 50% of BC survivors, often in combination with some degree of cognitive dysfunction.[7, 13] In addition, depression, anxiety, and impairment of the QoL were noted in women with BC, both during and after finishing the anticancer therapy.[14] Similarly, according to an observational study, 22% of BC survivors displayed moderately severe to severe levels of depression. Moreover, the depressive symptoms were related to a lower QoL in these patients.[15] Cognitive impairment is one of the anticancer treatment-related symptoms, where elderly patients with BC are usually most vulnerable.[16] It is conceivable that oxidative stress and neuroinflammatory processes are involved in the mechanisms of CHT-induced cognitive deterioration.[17]

In addition, studies have revealed that many younger women with BC, who underwent CHT, have a higher risk of developing premature menopause and chemotherapy-induced menopause (CIM), which cause various gynecologic symptoms that often decrease their QoL.[18, 19] In addition, premature menopause predisposes women to increased risk of osteoporosis, bone fractures, and cardiovascular diseases (CVD).[20, 21]

Selected Personalized Medicine Strategies Focused on the Relief of Pain Induced by Anticancer Therapies in Patients with Breast Cancer

Since pain (e.g., often induced by the anticancer therapies) is one of the most prevalent symptoms in patients with BC, the detection of novel biomarkers, which are associated with pain (caused by the BC treatment) will be helpful for a design of innovative personalized strategies of the pain management among such patients. For instance, some possible avenues for alleviation of pain caused by lymphedema and chemotherapy-induced peripheral neuropathy (CIPN) have recently been considered.

Lymphedema (a painful swelling of the extremities, caused by BC treatment) represents a very common problem among BC patients and survivors.[22] According to a recent study, the BC survivors with lymphedema are characterized by certain biochemical parameters (e.g., an increased level of total polyunsaturated fatty acids (PUFA), elevated activity of fatty acid desaturase, and a higher ratio between arachidonic acid and eicosapentaenoic acid).[23] These results may indicate a possible association between the risk of lymphedema and patterns of fatty acid metabolism. Moreover, it is conceivable that the PUFA status of women with BC may play the role of biomarker for targeting pain suffered by such BC patients. That, in turn may indicate a potential modification of PUFA nutritional intake, which may be helpful in decreasing lymphedema-associated pain in women with BC. However, further large-scale studies in different ethnic populations of patients with BC are necessary to confirm these results.

For many years, it has been considered that antioxidants would reduce the effectiveness of CHT and RT (which rely on the cytotoxic actions of free radicals on neoplastic tumors, in order to exert their therapeutic effects), and thus, the main concern was that the antioxidants (which decrease the levels of free radicals) could negatively influence the patient outcomes.[24] These controversies are still a subject of intense debate.[25] A possible explanation is related to the cyto-protective actions of antioxidants and the cytotoxic effects of anticancer therapies. Hopefully, further large-scale clinical trials should explore the effects of the differences in dosage, duration, and route of administration of antioxidants, on the clinical outcomes, in patients with BC, receiving anticancer therapies.

Since the neuropathic pain caused by CHT, such as chemotherapy-induced peripheral neuropathy (CIPN), still represents unmet need among women with BC, some thera-

pies using antioxidants have been considered as potential strategies to target this refractory neuropathy. Also, an oxidative-stress-associated mitochondrial dysfunction has been revealed to be an important mechanism contributing to the appearance of neuropathic pain, invoked by CHT.[26] As a consequence, the mitochondrial dysfunction may serve as a biomarker, which could be targeted to invent some novel strategies to alleviate pain. For instance, it has been shown that melatonin, a hormone from the pineal gland and a powerful antioxidant, is able to reduce mitochondrial damage and alleviate neuropathic pain in animals treated with CHT (e.g., paclitaxel).[26] This study brings some hope for the possible future personalized management of patients with CIPN (if human studies will confirm the safety and effectiveness of this approach).[26]

In search of personalized approaches for CIPN, the role of nicotinamide adenine dinucleotide (NAD) (a coenzyme, which protects against neuronal degeneration that can be caused by neurotoxicity) and nicotinamide riboside (NR) (a precursor for the generation of NAD) have been explored.[27] It has been revealed that in animal models, treatment with NR improved the degree of tactile hypersensitivity, after delivery of paclitaxel.[28] Based on the above findings, a potential role of NR, as the future personalized treatment for CIPN among patients with BC has been suggested. Also, a recent pre-clinical study has shown that the elevation of NAD levels (an effect that is identical to the treatment with NR) by anthocyanins would lead to the reduction of pro-inflammatory gene expression (e.g., via ablation of the nuclear translocation of nuclear factor-κB (NF-κB)).[29] In general, it appears that the potential effects of NR treatment on pain reduction could be achieved via the decrease of inflammation. However, further studies in this area are mandatory to confirm this.

In addition, many genetic biomarkers, which are related to CIPN, have been detected, providing helpful directions as to how neurotoxicity induced by CHT may be decreased and managed in patients with BC (scheduled to receive CHT). For instance, it has been determined that the 3435 TT genotype of ABCB1 (a gene coding for a protein from the ATP binding cassette subfamily) can contribute to an increase in the neurotoxicity risk, in women with BC, receiving CHT with paclitaxel and docetaxel.[30] Similarly, the gene coding for a Charcot-Marie-Tooth protein, NDRG1, has been indicated to be a possible genetic biomarker for CIPN (because of the negative association between the severity of CIPN and the expression level of this gene).[31] For instance, low levels of NDRG1 in nerve tissue can predict the severe paclitaxel-induced neuropathy.[31] Furthermore, it has been revealed that the carriers of the CYP2C8 and FGD4 polymorphisms can have a higher risk of CIPN that may necessitate an early paclitaxel dose reduction in such BC patients.[32] Overall, it seems that these genes may represent innovative gene targets, related to the CHT-induced neurotoxicity. In result, such targets can be useful for the development of practical interventions to alleviate the CIPN.

Targeting Depressive, Cognitive and Menopausal Symptoms in Women Undergoing Therapies for Breast Cancer

Depression represents an important psychological problem, which often forms constellations of symptoms, including pain, fatigue, cognitive deterioration, and sleep disorders, in patients with BC undergoing anticancer therapy.[33] Compared to the general population of women, BC survivors have a 60% augmented risk of developing depression, anxiety and stress-related disorders within 10 years after BC diagnosis.[34] Moreover, depression has been related with decreased physical, mental, emotional, and social well-being among patients with BC receiving anticancer therapy, and its symptomatology vary between patients.[14, 34] In this light, personalized approaches focused on the depression should offer useful strategies for improving the QoL of women with BC. For instance, according to a recent study, the gene coding for brain-derived neurotrophic factor (BDNF) was suggested to be a gene biomarker for depression.[35] In particular, it has been detected that a genetic polymorphism in the BDNF gene (that results in a substitution of Val66 with a methionine), is related with the blood level of C-reactive protein (CRP), allowing to predict the severity level of depression.[35] Overall, these results suggest that the Val66Met polymorphism in the BDNF gene can be applied as an early indicator for the use of anti-depressive treatments (e.g., prior to the emergence of full-blown depressive symptoms).[35] In practical terms, the patients diagnosed with the Val66Met polymorphism of the BDNF gene should undergo screening for the depression, and then, treatment strategies should be tailored to the needs of individual patients.[35]

Cognitive impairment is a multifactorial phenomenon associated with CHT, ET, and anesthesia during surgery, in which the patient's age, comorbid conditions, and genetic factors are strongly related to risk for cognitive decline in patients with BC.[36] Deterioration of cognition, including difficulties with memory, concentration, and executive functions, has been reported in approximately one third of BC survivors (e.g., after CHT completion).[36] In accordance with this, a recent study has revealed that a polymorphism in the IL1R1 gene (IL1R1 gene product participates in promoting inflammation) is related with a higher level of cognitive functions in BC survivors.[37] This finding has suggested a possible biomarker to detect patients receiving CHT, who may have a low risk of cognitive dysfunction, and do not require intervention for this reason.

Premature menopause is caused by the decline of ovarian functions (a deficiency in estrogen production) in women below 40 years of age, and particularly young patients with BC, treated with CHT, can suffer from ovarian failure, causing chemotherapy-induced menopause (CIM), which negatively influence their QoL.[38] Identification of genetic polymorphisms that are related to production and metabolism of estrogen may provide genetic biomarkers, which can be targeted to address symptoms of premature menopause or CIM, among women with BC. For instance, a recent study has shown that single nucleotide polymorphisms (SNPs) in the genes coding for estrogen receptors (ESR1 and ESR2) were related with premature ovarian failure (which is a component of premature menopause).[39] This report may indicate some innovative biomarkers, which can be targeted for the treatment of BC patients, who suffer from premature menopause. In addition, it provides a direction for further research, relevant to the mechanisms, by which SNPs can contribute to premature menopause and CIM. This approach may bring helpful information to the development of personalized therapies that may improve the management of menopausal symptoms among such patients.[39]

CHT, RT, and certain targeted BC treatments are related with increased risk of developing cardiotoxicity.[40] In particular, cardiovascular (CV) complications, such as arterial hypertension, cardiac arrhythmias, coronary heart disease (CHD), heart failure (HF), valvular diseases, peripheral vascular disease (PVD), stroke, pulmonary hypertension, and pericardial diseases are the most prevalent.[40] For instance, anthracycline-induced dose-dependent cardiotoxicity has been reported, especially during the first year after CHT completion.[41] It should be highlighted that elderly age is an important risk factor for doxorubicin-induced cardiotoxicity.[41] In addition, cisplatin can also augment the risk of CV events, even several years after the treatment termination.[41] Moreover, it has been revealed that cardiotoxic adverse effects were present in approximately one third of BC survivors, who were treated with trastuzumab for HER2-positive BC.[42] RT is also related with a different CV complications, including the pericardial, myocardial, valvular diseases, CHD, and arrhythmias.[43] Also, BC survivors are at higher risk for thromboembolic disorders, due to increased platelet adherence and thrombus formation in arteries post RT.[43] Furthermore, adjuvant ET (e.g., tamoxifen) can augment the risk of venous thromboembolism.[44]

Obesity as an Additional Target for Personalized Strategies in Breast Cancer Survivors

Obesity has not been considered as a "direct" adverse effect of CHT for treatment of BC. However, an elevation of the body mass after BC diagnosis is related with increased risk of malignant recurrence.[45] This finding indicates that introducing the interventions focused on prevention obesity, in women with BC and BC survivors is of utmost importance. In accordance to that, a recent study has found the association between SNPs of some genes and changes in body mass index (BMI), in BC survivors. These genes are coding for proteins, which are involved in adipose tissue metabolism (e.g., ADIPOR1, coding for adiponectin receptor 1, participating in signaling pathways regulating oxidation of fatty acids; FTO, coding for fat mass and obesity-associated protein, and FNDC5, coding for a hormone for white fat conversion to brown fat).[46] The detection of these SNPs, which are related with weight gain in BC survivors has shown innovative biomarkers that may identify individual BC patients or survivors, who would require certain interventions to prevent them from weight gain. Adding such interventions (e.g., lifestyle modifications to reduce obesity risk in personalized cancer treatment for BC survivors) should decrease their risk of BC recurrence. These interventions (e.g., nutritional and exercise programs) appear acceptable to patients with BC undergoing anticancer treatments as well as to BC survivors.[47]

Advances in Molecular Targeted Therapies for Breast Cancer–Focus on the Pi3k-Akt-Mtor Axis

At present, a remarkable progress in molecular science has provided more effective, safe, and acceptable to patients precision medicine solutions. For instance, actionable gene changes ("druggable" mutations) that can influence treatment selection have been found across various malignancies, including BC.[48] In fact, deregulation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway has been considered to play a crucial role in the development and progression of BC tumors.

Various PI3K inhibitors are still undergoing exploration.[48] For instance, buparlisib is in a phase 3 study (BELLE-2) that compares buparlisib with placebo in combination with fulvestrant, among postmenopausal HR-positive and HER2-negative BC, who progressed on or after aromatase inhibitor.[49] The benefit of buparlisib was larger in case of PI3K pathway-activated patients.[49] Similarly, in phase 3 study (BELLE-3), buparlisib was compared with placebo in combination with fulvestrant, among postmenopausal HR-positive and HER2-negative BC patients, who had relapsed on or after ET and mTOR inhibitors (Table 1).[50]

The mTOR inhibitor everolimus has been approved and applied in combination with aromatase inhibitor exemestane.[51] A phase 3 study (BOLERO-2) has evaluated the efficacy of everolimus in combination with exemestane among patients with HR-positive advanced BC (after a therapy

with nonsteroidal aromatase inhibitor) and has revealed that progression-free survival (PFS) was significantly longer with everolimus.[51] Furthermore, an analysis of genetic alterations in cancer-related genes (from tumor samples from the BOLERO-2 study) has confirmed the benefit of PFS with everolimus (that was consistent across gene changes in FGFR1, CCND1, and PIK3CA) (Table 1).[52]

Many AKT inhibitors have been explored among women with BC. In a phase 2 trial (LOTUS), ipatasertib was assessed in combination with paclitaxel.[53] In this study, among women with metastatic triple-negative breast cancer (TNBC), the median PFS was longer with ipatasertib, compared to placebo.[53] In addition, in the patients with PTEN-low tumors, the benefit of ipatasertib appeared to be even better (median PFS was almost two times longer) (Table 1).[53] Also, according to the first-in-human (phase 1) study, ralimetinib (a selective oral p38 MAPK inhibitor), seems to have a good safety profile, among patients with advanced cancer.[54]

Epigenetics relates to changes in gene expression, which are not accompanied by alterations in the corresponding DNA sequence.[55] Epigenetics may offer some innovative options to BC prevention and to overcoming the resistance to ET in patients with BC.[55] Histone deacetylase (HDAC) controls the level of acetylation of histones and has influence on gene expression. Different HDAC inhibitors have been explored, including entinostat (an oral isoform-se-

Table 1. Selected targeted therapies for patients with breast cancer based on recent clinical studies

Molecular target	Medication name	Clinical study phase	Study design; patient population; outcomes [reference number]
PI3K inhibitor	buparlisib	BELLE-2 phase 3	Buparlisib vs. placebo in combination with fulvestrant; postmenopausal HR-positive, HER2-negative BC patients (who progressed on or after AI); PFS was improved on buparlisib.[49]
	buparlisib	BELLE-3 phase 3	Buparlisib vs. placebo in combination with fulvestrant; postmenopausal HR-positive, HER2-negative BC patients (who relapsed on or after ET and mTOR inhibitor); PFS was improved on buparlisib.[50]
mTOR inhibitor	everolimus	BOLERO-2 phase 3	Everolimus in combination with exemestane; patients with HR-positive advanced BC (after a therapy with nonsteroidal AI); PFS was longer with everolimus.[51]
AKT inhibitor	ipatasertib	LOTUS phase 2	Ipatasertib in combination with paclitaxel; patients with metastatic TNBC; PFS was longer with ipatasertib (compared to placebo).[53]
HDAC inhibitors	entinostat	ENCORE 301 phase 2	Entinostat in combination with exemestane, compared to exemestane alone; patients with ER-positive BC; PFS was improved on entinostat.[55]
CDK4/6 inhibitors	palbociclib	PALOMA 2 phase 2	Palbociclib in combination with an AI; postmenopausal patients with HR-positive, HER2-negative, advanced or metastatic BC; PFS was improved on palbociclib (median PFS=24.8 vs 14.5 months).[56]
	ribociclib	MONALEESA 7 phase 3	Ribociclib in combination with an AI (as initial ET); peri-menopausal patients with HR-positive, HER2-negative metastatic BC; PFS was improved on ribociclib (median PFS=23.8 vs 13.0 months).[57]
	abemaciclib	MONARCH 2 phase 3	Abemaciclib in combination with fulvestrant; patients with HR-positive, HER2-negative advanced BC (who progressed on ET); PFS was improved on abemaciclib.[58]
PARP inhibitors	olaparib	OlympiAD phase 3	Efficacy and safety of olaparib compared to standard CHT (vinorelbine, eribulin, or capecitabine); patients with gBRCA mutations, HER2-negative metastatic BC (who had received no more than two lines of CHT for their metastatic BC); PFS was improved in the olaparib group.[59]
	talazoparib	EMBRACA phase 3	Efficacy and safety of talazoparib compared to standard CHT (capecitabine, eribulin, gemcitabine or vinorelbine); patients with gBRCA mutations, HER2-negative, advanced or metastatic BC; PFS and QoL were improved in the talazoparib group.[60]

AI: Aromatase inhibitor; BC: Breast cancer; PI3K: the phosphoinositide 3-kinase; mTOR: Mechanistic target of rapamycin; g: Germline; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; ER: Estrogen receptor; gBRCAm: Germline BRCA-mutation; CHT: Chemotherapy; ET: Endocrine therapy; m: Metastatic; AKT: Protein kinase B; HDAC: Histone deacetylase; CDK: Cyclin dependent kinase; PARP: Poly (ADP-ribose) polymerase; PFS: Progression-free survival, TNBC: Triple negative breast cancer; vs.: Versus.

lective HDAC inhibitor targeting resistance to ET in patients with ER-positive BC).[55] A phase 2 trial (ENCORE301) assessed entinostat in combination with exemestane (in comparison with exemestane alone), and has shown that entinostat significantly improved PFS (Table 1).[55]

The cyclin D-cyclin dependent kinase (CDK) 4/6-inhibitor of CDK4 (INK4)-retinoblastoma (Rb) pathway plays a key role in controlling cell cycle. Consequently, CDK4/6 inhibitors induce cell cycle arrest in the G1 phase (preventing the proliferation of malignant cells)[56] Recently, three CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) have been found beneficial among patients with ER-positive metastatic or relapsed BC (Table 1).[56-58]

BRCA1 and BRCA2 represent key proteins in the process of homologous recombination repair of double-strand DNA breaks. Germline BRCA mutations (gBRCA mutation) have been reported in 5–10% of BC cases.[59] In patients with gBRCA mutations, the function of BRCA can be deficient, and the homologous recombination repair of double-strand DNA breaks is impaired. In this situation, poly (ADP-ribose) polymerase (PARP) inhibitors induce synthetic lethality.[59] Olaparib, a PARP inhibitor, has been explored in a phase 3 trial (OlympiAD).[59] Olaparib (as a single agent) has been compared to standard CHT (vinorelbine, eribulin, or capecitabine) in women with a gBRCA-mutated HER2-negative metastatic BC (who had received no more than two lines of CHT for metastatic BC) and PFS was improved in the olaparib group.[59] In addition, a phase 3 trial (EMBRACA) has investigated talazoparib (a PARP inhibitor, which blocks the PARP enzyme and traps PARP on DNA strand, and thus, prevents DNA damage repair) in women with advanced BC and a gBRCA mutation.[60] Based on the EMBRACA trial findings, it has been reported that talazoparib significantly improved PFS and QoL (compared to placebo) in this patient population (Table 1).[60]

Further Directions

To accomplish the personalized medicine goals, a development of the "Knowledge Network", a precise disease classification system (e.g., based on molecular biology), is going to be created [61]. This will incorporate genomic data from several fields (e.g., DNA sequencing, molecular biotechnologies, basic and clinical research data, reports from observational studies, and patient's medical records) that are necessary to analyze relations between the various clusters of information. In this way, a more accurate classification of malignancies, such as BC, will facilitate a proper selection of possible targeted treatments (Fig. 2).[61]

Translating the promise of precision medicine, which is aimed at providing the best available treatment for every individual patient, requires that treatment teams (e.g., physicians and researchers) will apply various resources (e.g., large sets of medical data), and connect this information with the particular patient's personalized clinical context.[61]

Furthermore, current advances in molecular targeted agents, including PI3K/mTOR inhibitors, CDK4/6 inhibitors, and PARP inhibitors, have improved the medical outcomes and QoL in many patients with BC.[62] However, the predictive factors of these therapies still need to be explored in detail. In addition, the genetic biomarkers need to be identified, in order to predict the individual risk of developing common adverse symptoms, associated with particular anticancer treatments.[62] Despite recent progress in the detection of novel biomarkers that affect the treatment efficacy and adverse symptom severity, the molecular mechanisms of how they exert their effects are still not well understood.[62] Therefore, further studies in this area are warranted to enable the development of further strategies that can optimize anticancer therapies for BC patients, not only by augmenting the treatment effectiveness, but also by improving the QoL of women with BC, undergoing the long and complicated diagnostic and therapeutic journey.

Conclusion

In the context of women with BC, precision medicine (the term that is preferable to "personalized medicine") relates to the tailoring of medical treatment to the individual characteristics of each patient (e.g., meaning the creation of therapies unique for a given patient). In addition, the precision

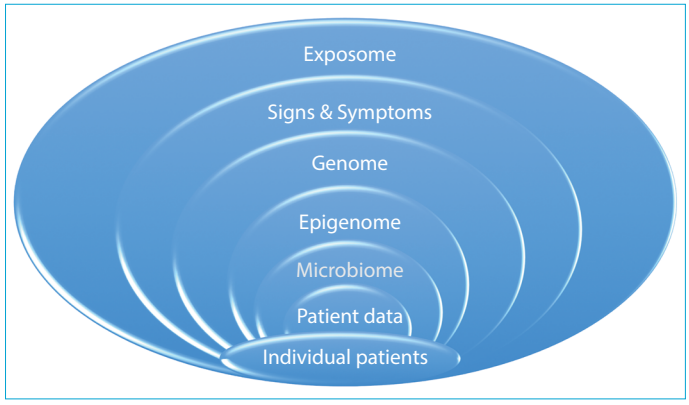

Figure 2. Individual patient-centered information to build a biomedical Knowledge Network for research and clinical medicine (Explanation of definitions: Exposome–a characterization of exogenous & endogenous exposures that have differential effects on disease predisposition at various stages during a person's lifetime; Genome-the full sequence of genetic material encoded in DNA; Epigenome-chemical compounds that modify/mark the genome; "instruct" the genome what to do, where to do it, and when to do it; various cells have different epigenetic marks; Microbiome - the collective genome of microflora).[61]

medicine classifies patients with BC into subpopulations that vary in the response to particular therapeutic agents. As a consequence, therapeutic or potentially preventive interventions are focused on the individuals, who will benefit from such approaches and also, will experience minimized side effects (that leads to improved QoL). Due to numerous adverse effects of the currently used anticancer regimens, many patients with BC suffer from different therapy-related symptoms during their treatment process. Since this situation can lead to the treatment termination, personalized therapies addressing this particular area of the individual patient's needs deserves special attention. Recently, various genomic changes (e.g., gene overexpression or SNPs), which may influence the undesirable symptoms among individual patients with BC, have been revealed. In addition, some biomarkers have been identified, which can serve as possible tools for guiding the appropriate treatment selection and reducing discomfort in many patients with BC.

In summary, the precision medicine offers individualized treatment, providing each women with BC with the accurate diagnostic work-up and targeted therapy, according to the specific cancer's genetic profile (based on a panel of gene assays and other predictive and prognostic tests). Further studies need to be conducted in several areas related to BC detection, diagnosis, treatment, and survivorship. It is expected that further research studies will combine panels of molecular assays to drive more accurate, personalized treatment choices. In addition, clinical measurements of survival and toxicity parameters should be gathered, to facilitate the further advances in precision management, for a growing population of women with BC.

Disclosures

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