THE MANAGEMENT OF METASTATIC TRIPLE-NEGATIVE BREAST CANCER:

AN INTEGRATED AND EXPEDITIONARY APPROACH

Only those who will risk going too far
can possibly find out how far one can go.
T.S. Eliot

Katarzyna Rygiel

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The Management of Metastatic Triple-Negative Breast Cancer: An Integrated and Expeditionary Approach

Authored by

Katarzyna Rygiel
Department of Family Practice
Medical University of Silesia (SUM)
3 Maja St., 41-800, Zabrze
Poland

The Management of Metastatic Triple-Negative Breast Cancer: An Integrated and Expeditionary Approach

Author: Katarzyna Rygiel

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CONTENTS

FOREWORD

Nowadays, several women with breast cancer (BC) experience positive therapeutic effects and longer survival. However, certain BC subtypes, like triple-negative breast cancer (TNBC) (in the advanced or metastatic stages) remain the major challenge, because of their aggressive behavior, heterogeneity, high recurrence rates, and resistance to traditional therapies. One important reason why TNBC is so difficult to treat is the lack of targetable receptors (such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER 2)) on the malignant cell's surface. This feature, together with a propensity for visceral metastases, presents an unmet medical need.

Although the latest research advances in the BC area have resulted in some innovative therapeutic strategies, many of these novel agents have certain toxic effects, and therefore, careful patient selection, monitoring, and prompt treatment of side effects are required. To yield the benefits of new targeted therapies and to counteract their possible toxicities, both sides that are involved in TNBC care, the healthcare professionals and the patients must be well-prepared for long-term cooperation. Such collaborative efforts demand clinician's updated knowledge about novel therapeutic strategies and clinical trials in the TNBC area. Also, building professional relationships and communication networks with the patients and their caregivers is very important.

At the same time, the patients themselves need to be adequately informed about some basic principles of TNBC, and they should be personally engaged in the therapeutic course of their disease. For instance, the patients need to learn some skills, such as self-observation and self-care, as well as precise communication with the treatment team members. It appears that pharmaceutical care would be a perfect avenue to accomplish the objectives of safe and effective BC care. However, in the reality of typical, busy oncology centers, these necessities are often difficult to fulfill, due to various reasons (*e.g.*, lack of time, incentives, and organizational support). In the face of these demands, the book titled: "**The Management of Metastatic Triple-Negative Breast Cancer: An Integrated and Expeditionary Approach**" offers a possible solution.

One of the remarkable features of this book is a reader-friendly presentation of topics in form of the well-structured graphs and tables, which contain helpful, multidisciplinary information. A brought thematic spectrum of this book, contained in separate chapters (organized in the form of two, conveniently overlapping parts), provides a clear, comprehensive, and updated knowledge base for medical care teams in Breast Care Units and other oncology settings. It should be noted that this is another book of this author, in which she responds to the challenge of combining the efforts of members of medical care teams, with various areas of expertise (*e.g.*, physicians, pharmacists, diagnosticians, physical therapists, psychologists, and nurses) to work together, to achieve improvement in health condition and the quality of life of the patients with TNBC, and other subtypes of BC.

The author very insightfully analyses many therapeutic aspects of BC and emphasizes the crucial role of education and overcoming barriers of fear or uncertainty. Moreover, she highlights the necessity of embarking on a difficult path that leads to accomplishing beneficial effects (not only in terms of clinical parameters but also in the psychological domains of a patient's life). This is particularly important since in patients with TNBC, receiving multiple medications is often related to an adverse phenomenon of polypharmacy, often observed in multi-morbidity, associated with poly-therapy. Therefore, limiting the adverse effects of recommended therapies to a necessary minimum would be extremely beneficial (*e.g.*, with

regard to many new targeted therapies). This demanding task is primarily addressed to both physicians and pharmacists, who should create two integrated "pillars" of patient management. In addition, this book promotes the concept of patient-centered, personalized care. It encourages clinicians to be open-minded, adequately trained, and ready to constantly exchange their expertise to serve the afflicted patients with BC to improve their outcomes.

Finally, this book provides many useful, easily accessible tools to attain these goals. It would be very important for medical and pharmacy students or residents to be introduced to these integrative concepts of care from the early stages of their professional education. As an academic teacher with many years of experience, I would definitely recommend this book as a practical reference in many educational environments, for teaching multidisciplinary teams of medical professionals and students, as well as patient advocates, caregivers, and women suffering from BC.

Lucyna Bułaś
Department of Pharmaceutical Technology
Faculty of Pharmaceutical Sciences in Sosnowiec
Kasztanowa 3, 41-200 Sosnowiec
Poland

PREFACE

Despite recent therapeutic advances in **metastatic triple-negative breast cancer (TNBC),** it still remains an incurable disease. The latest progress in the TNBC research has resulted in some **innovative therapeutic options**, such as **immunotherapy, antibody-drug conjugates (ADC),** and **inhibitors of poly (ADP-ribose) polymerase (PARP)**, which can be applied in combination (or in sequence) with standard chemotherapy (CHT) regimens. Such **targeted therapies** bring some hope with regard to the prognosis for many women suffering from metastatic TNBC. However many of these novel agents have some serious **adverse effects**, and thus, the right patient selection, careful monitoring, and rapid delivery of medical therapies to relieve side effects are imperative.

To address these issues, a book titled**: "The Management of Metastatic Triple-Negative Breast Cancer: An Integrated and Expeditionary Approach"** integrates multidisciplinary knowledge and experience from the perspective of medical professionals and researchers in the TNBC area, and combines it with the patient's point of view. This book is composed of two parts.

PART 1

An Overview of the Ethnic Disparities and Current or Emerging Targeted Therapies for Patients with Advanced or Metastatic Triple-Negative Breast Cancer (TNBC).

PART 2

The Role of Patient Education, Empowerment, and Communication with Medical Teams, and Psychological or Supportive Approaches in Advanced or Metastatic Breast Cancer (BC).

The first chapter of Part 1 introduces some important aspects of ethnicity, obesity associated with metabolic syndrome and chronic inflammation, as well as reproductive, social, and environmental factors, which can greatly influence TNBC outcomes. This is critically important for an understanding of the risk, development, and progression of TNBC in various ethnic groups, such as African American (AA) and European American (EA) women. Moreover, considerations of predisposing and aggravating environmental, socioeconomic, and behavioral factors, which may have a major impact on BC prevention, course, and survival are briefly presented.

Consecutive chapters of **Part 1** discuss current and emerging targeted therapies for patients with advanced or metastatic TNBC, based on recent, major clinical trial results. Recommendations for clinicians and patients are briefly summarized at the end of each chapter. The last chapter of Part 1 describes a noninvasive "tool" of Precision Medicine that may be considered for the individualized treatment of women with BC. This tool attempts to link the main clinical objectives with the personal goals of the patients suffering from advanced or metastatic TNBC or other difficult-to-treat BC subtypes.

The initial chapters of **Part 2** provide focused psychoeducational information for patients with advanced or metastatic stages of BC (*e.g*., TNBC subtype). This information is designed to facilitate clear communication between the patients and the treatment team members. Subsequent chapters of Part 2 contain different cognitive and behavioral concepts and examples of the relevant therapeutic strategies. They include easily available techniques for coping with stress, which accompanies women with BC, during multiple diagnostic and therapeutic stages, and often aggravates their health conditions.

Traditionally, in the majority of publications concerning BC, the medical and psychological topics are usually presented as two separate groups of problems, while in reality, such a division is rather artificial, since these issues are always interrelated. To properly address this need, the book highlights an **integrative approach** to these deeply interconnected areas. Also, the added value of this book consists of **blending the latest evidence from research trials in the TNBC area with clinical practice and feasible psycho-educational approaches**, which can be suitable **for individual patients and their caregivers**. Combining targeted treatments for TNBC with effective coping with distress (commonly associated with uncertain or poor prognosis and overwhelming adverse effects of different targeted therapies) as well as simple lifestyle modifications represent the key elements, that can substantially ameliorate outcomes, even in the most vulnerable patients with metastatic TNBC.

Importantly, this book **bridges the gap between the strictly clinical or research-related aspects of BC management and the personal needs and expectations of patients with BC**. It also invites medical professionals who are physicians, psychologists, pharmacists, and researchers in the field of BC to conduct open **dialogues with patients, aimed at their practical education and support**. It also includes helpful **resources for the support of both the patients and their medical caregivers**, as "partners" and "co-passengers" of their joint "expedition" to conquer BC and reclaim the necessary balance or comfort in life.

In addition, this book presents a **novel concept of a challenging journey for patients with TNBC** (or other aggressive subtypes of BC, especially in advanced or metastatic stages), which can be perceived or interpreted as a series of stimulating "adventures" and meaningful educational events. This, in turn, can shed some bright light on a serious, chronic disease, like BC, and its interconnected risk factors. Such an approach may **positively influence the attitude of many women suffering from BC**. Hopefully, instead of approaching a diagnosis and therapy of TN BC as a terrifying "war", composed of devastating "battles", the patients may **change their perspective on this life-threatening disease**, and view it as a real **opportunity to use the modern armamentarium of current pharmacologic therapies and noninvasive, cost-effective, feasible psychological, and supportive modalities to improve their outcomes.**

Finally, the **purposely changed narration**, used in many chapters, is **intended to re-direct many suboptimal cognitive and emotional stereotypes**, which are often perpetuated by numerous patients with BC. To accomplish these long-term goals, it is necessary **to teach the medical team members to positively "re-orient" women with BC,** so that they can stay **motivated, and engaged in active participation in their oncology care**. It requires a lot of time, effort, initiative, expertise, and cooperation within multidisciplinary teams of medical providers. However, in the long run, this may **beneficially transform the approach to BC, its management, and prevention**. Simultaneously, well-educated and empowe- red patients may be able to communicate and integrate their efforts with the professional actions of the medical teams, in charge of their care.

Katarzyna Rygiel
Department of Family Practice
Medical University of Silesia (SUM)
3 Maja St., 41-800, Zabrze
Poland

Part 1

An Overview of the Ethnic Disparities and Current or Emerging Targeted Therapies for Patients with Advanced or Metastatic Triple-Negative Breast Cancer (TNBC).

“What lies behind us and what lies before us are tiny matters compared to what lies within us.”

Oliver Wendell Holmes

CHAPTER 1

Unraveling Ethnic Disparities in Triple-Negative Breast Cancer (TNBC): Exploring The Impact of Metabolic, Reproductive, Environmental, and Social Factors on the Disease Course in African-American (AA) Women Population

Abstract: Triple-negative breast cancer (TNBC) is a particularly **aggressive subtype** of **breast cancer (BC)** in which the expression of the **estrogen receptor (ER), progesterone receptor (PR)** and **human epidermal growth factor receptor (HER2)** is absent or very low. TNBC consists of approximately 15-30% of the invasive BC cases in the United States (US) Women with TNBC represent a heterogeneous population with regard to their ethnicity and biology including the genetic make-up metabolic or hormonal profile as well as the socioeconomic status (SES) cultural behavioral educational levels. Notably **African-American (AA)** women usually have a **higher prevalence of TNBC and a worse prognosis** compared to **European-American (EA)** or Non-Hispanic White (NHW) women. The goal of this chapter is to elucidate the possible interplay of inherited and acquired, often lifestyle-related risk factors which can stimulate the initiation and development of the most aggressive subtypes of TNBC in AA women compared to their EA (or NHW) counterparts. In particular this chapter explores some ethnic disparities in TNBC mainly in the example of the US where such disparities have been studied in clinical research. This chapter also focuses on differences in TNBC risk factors healthcare patterns clinical outcomes between AA and EA (or NHW) women. It briefly discusses the multi-factorial etiology of these disparities *e.g* genetic, hormonal, metabolic, behavioral, cultural, socio-economical and environmental. Presented short analysis of a dynamic blend of inherited and acquired variables also provides some directions for the reduction of these disparities, to improve TNBC outcomes, among women from ethnic groups, such as AA.

Keywords: Acquired, Ethnic groups, Healthcare disparities, Inherited, Risk factors, Triple-negative breast cancer (TNBC).

INTRODUCTION

Triple-negative breast cancer (TNBC) is a particularly aggressive subtype of breast cancer (BC), in which the expression of the **estrogen receptor (ER),**

Katarzyna Rygiel

progesterone receptor (PR), and **human epidermal growth factor receptor (HER2**) is absent or very low [1]. TNBC consists of approximately 15-30% of the invasive BC cases in the United States (US) [1]. In general, **African-American (AA) women** have a **higher incidence of TNBC, worse outcomes**, and higher mortality rates compared to European-American (EA) (or non-Hispanic White (NHW)) women [2]. In addition, TNBC is more prevalent in western sub-Saharan African patients compared to their EA (or NHW) counterparts [2]. TNBC risk factors and possible causes can be divided into inherited (or biologic) and acquired (or non-biologic) categories [3]. An inherited or genetically determined ancestry and acquired or socio-environmental factors can considerably influence the outcomes of patients with TNBC [3]. This is a complicated network that is very difficult to untangle and classify into separate domains. However, there are some distinctive patterns that can be recognized. For instance, the genes that women inherit, affect the way how they metabolize certain medications, what adverse effects they may experience from specific pharmaceutic agents, and what kind of therapies could be the most suitable or contraindicated for them.

A recent study has indicated certain similarities in TNBC, especially with regard to genetics, tumor biology, and environmental risk factors, which were noted in African and AA patients with BC [4]. Also, various observations suggest that the West African origin of women afflicted with BC could have been related to their inherited susceptibility to TNBC [5, 6]. Moreover, some changes in the expression of many genes, connected with the cell's growth, differentiation, invasion, and metastasis, have been revealed in BC tumors of AA females, to a higher degree than in the EA (or NHW) women [7]. In addition to genetic or molecular differences, an advanced BC presentation at diagnosis, and a higher burden of metabolic comorbidities, certain unequal socioeconomic standards (*e.g.*, residential, occupational, or educational) can contribute to poor survival rates, especially among AA women [8]. Similarly, various socio-environmental determinants widely influence how the surrounding world interacts with women with BC, from different ethnic populations [9]. In this dynamic exchange process, both conscious and unconscious biases may, to some degree, have an important impact on shaping bilateral relationships between women with BC (or at high risk for BC) and the medical systems or local community services, where they live, work or go to school.

The aim of this chapter is to elucidate the potential interplay of biological and non-biological risk factors, which can stimulate the initiation and development of the most aggressive subtypes of TNBC. In particular, this chapter explores ethnic disparities in TNBC between AA women and their EA counterparts (mainly in the example of the US, where such disparities have been studied in clinical research). It focuses on some differences in TNBC risk factors, healthcare patterns, and

clinical outcomes, between AA and EA (or NHW) women. It briefly discusses the multi-factorial etiology of these disparities (*e.g.*, genetic, hormonal, reproductive, metabolic, behavioral, cultural, socioeconomic, and environmental). This chapter also indicates some clear directions, on how to reduce the above-mentioned disparities, in order to improve TNBC outcomes, especially among AA women.

HOW CAN WE APPROACH ETHNIC DISPARITIES IN TNBC SURVIVAL? – A ROADMAP OF POSSIBLE UNDERLYING BIOLOGIC AND NON-BIOLOGIC RISK FACTORS OR CAUSES OF TNBC IN AA *VS.* EA (OR NHW) WOMEN

It should be highlighted that certain differences in the genetic makeup and the tumor biology of BC exist between AA women and their EA (or NHW) counterparts.

Although it has been reported that BC incidence rates are similar for AA and EA (or NHW) women, the TNBC incidence rates in the younger group (*e.g.*, before 45 years of age) are higher among AA, compared to EA (or NHW) females [9]. In contrast, in the older group (*e.g.*, between 60 and 84 years of age), the BC incidence rates are higher in EA (or NHW) women than in their AA counterparts. Nevertheless, AA women have a higher probability of dying from BC at any age [9, 10]. In light of such ethnic disparities in BC survival, some specific BC risk factors and possible causes have been proposed (*e.g.*, relevant to the hormonal, metabolic, and reproductive processes) [11].

In general, BC subtypes include the ER-positive and HER2-positive, the ER-positive and HER2-negative, and the basal-like (BL) BC, which is considered to be synonymous with the triple-negative (TNBC) (characterized by an absent or very low expression of the ER, PR, and HER2). In fact, TNBC usually represents the most aggressive BC subtype [1, 9, 11]. Notably, the incidence of TNBC in AA, predominantly in younger females, is two times higher than the one in EA (or NHW) women [9, 10]. Also, it has been noted that pregnancy and multi-parity augment the risk of TNBC (while these reproductive factors decrease the risk of HR-positive BC) [12]. Since AA usually have more children at a younger age, and they engage in short breastfeeding periods, their risk of TNBC increases, compared to EA (or NHW) women [12]. Moreover, according to a recent study, it has been shown that TNBC in women of African ancestry was characterized by a more common loss of androgen receptor (AR) expression, and worse overall survival (OS) compared to those of European ancestry [13]. Notably, AA women with an AR-negative TNBC have expressed a specific molecular signature, and predominance of BL1, BL2, and immunomodulatory (IM) subtypes of TNBC (Fig. **1**) [13].

CHAPTER 2

A Closer Look at the Androgen Receptor (AR)-positive and AR-negative Metastatic Triple-Negative Breast Cancer: Can We Apply Novel Targeted Therapeutics?

Abstract: Based on the **androgen receptor (AR)** expression, **triple-negative breast cancer (TNBC)** (that is estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) negative), can further be divided into **AR-negative TNBC** (also known as **quadruple-negative breast cancer (QNBC)**, a more frequent TNBC subtype) and AR-positive TNBC.

The paucity of treatment targets makes QNBC very difficult to manage. Moreover, in the absence of AR expression, many breast cancers (BCs) often display aggressive behavior, leading to negative outcomes in afflicted women. At present, some novel therapeutic targets have emerged, and hopefully, the relevant targeted strategies will improve the survival of patients with QNBC.

This chapter briefly outlines the main TNBC subtypes and focuses on the AR expression (its presence *vs.* absence), and potential treatment approaches, including **AR antagonists (ARA**). In addition, this chapter overviews certain molecular characteristics of TNBC and presents recently approved targeted therapies.

Keywords: Androgen receptor (AR), AR antagonists (ARA), Antibody drug conjugate (ADC), Immune checkpoint inhibitors (ICI), Poly ADP-ribose polymerase (PARP) inhibitors, Quadruple-negative breast cancer (QNBC), Triple-negative breast cancer (TNBC).

INTRODUCTION

Triple-negative breast cancer (TNBC), characterized by the negative **estrogen receptor (ER), progesterone receptor (PR**), and **human epidermal growth factor receptor 2 (HER2)** expression, usually demonstrates higher rates of relapse, greater metastatic potential, and shorter overall survival (OS), compared to other **breast cancer (BC**) subtypes [1]. It has been suggested that TNBC could be sub-divided into a more prevalent, **androgen receptor (AR)-negative subtype**, also known as **quadruple-negative breast cancer (QNBC)** subtype,

Katarzyna Rygiel

and a **"classical", AR-positive TNBC subtype** (Fig. **1**) [1]. It appears that multiple, interrelated genetic and environmental factors can influence the incidence, course, and prognosis of this devastating malignancy, across different ethnic and socioeconomic populations of women [2]. In comparison to other BC subtypes, TNBC and QNBC are characterized by a more invasive tumor behavior (*e.g.*, frequent local recurrences and distant metastases) and resistance to treatment, leading to negative outcomes [3]. Also, these aggressive BC subtypes have been more prevalent among women of African origin, and in the pre-menopausal group (*e.g.*, below 50 years of age) [2]. In addition, some major factors related to the augmented risk of TNBC and QNBC involve metabolic disorders (*e.g.*, obesity, metabolic syndrome (MS), pre-diabetes, and type 2 diabetes mellitus (T2DM), reproductive factors (*e.g.*, short breastfeeding period, high parity, oral contraceptive usage for over one year, and gestational diabetes), inappropriate nutrition (*e.g.*, the predominance of highly caloric and processed food, rich in saturated fats, trans-fats, and refined carbohydrates), physical inactivity, and low socioeconomic status or educational level. In particular, **obesity, accompanied by metabolic dysfunctions and pro-inflammatory conditions, a sedentary lifestyle, and a brief lactation** period has been associated with **abnormal secretion of androgens** [4]. The heterogeneous nature of TNBC and QNBC, as well as the diversity of the afflicted patient populations, require individualized and comprehensive management strategies. Recently, some innovative therapeutic targets have emerged, which could possibly improve the survival of many women suffering from this malignancy [5].

This chapter briefly outlines the main TNBC and QNBC subtypes and describes the current and future research directions in this area. It focuses on the AR expression (its presence *vs.* absence), and potential treatment approaches, including **AR antagonists (ARA**) and some recently approved molecular targeted therapies.

Various Molecular Subtypes of TNBC

TNBC has been divided into the following molecular subtypes: **basal-like subtypes (BL1** and **BL2), mesenchymal (M**), **mesenchymal stem-like (MSL), immunomodulatory (IM), a**nd **luminal androgen receptor (LAR)** (Fig. **2**) [3, 5, 6]. According to a similar categorization, the BL1 and BL2 can also be presented as **basal-like immunosuppressed (BLIS**), and **basal-like immune activated (BLIA)** subtypes [7]. It has been reported that different TNBC subtypes revealed significant variability in response to neoadjuvant or adjuvant **chemotherapy (CHT)**. It should be underscored that **BL1** has shown a more beneficial response to CHT than the LAR subtype [8]. Conversely, TNBC presents a greater sensitivity to CHT than the non-TNBC subtypes. On the other

hand, however, several women with advanced or metastatic TNBC have been resistant to standard CHT regimens (*e.g.*, anthracycline and taxanes) [3, 4]. This unmet need is one of the driving forces behind searching for innovative treatment targets and compatible diagnostic tests or biomarkers [3, 9].

THE UNDETERMINED PROGNOSTIC VALUE OF ANDROGEN RECEPTOR (AR) IN WOMEN WITH TNBC

Androgen receptor (AR) may serve as the prognostic biomarker in BC [10]. Based on a recent multi-institutional study, it has been shown that AR-positive status was consistent with a more favorable prognosis among groups of women from the US and Nigeria [10]. In contrast, a worse prognosis was reported among their counterparts from Ireland, Norway, and India [10]. In addition, no prognostic value was noted in the group of women from the UK [10]. Interestingly, it has been reported that the ER status affects the prognostic value of AR. For instance, the AR expression suggests a good prognosis in the ER-positive BC, but the significance of AR expression in the ER-negative BC is still unclear [11].

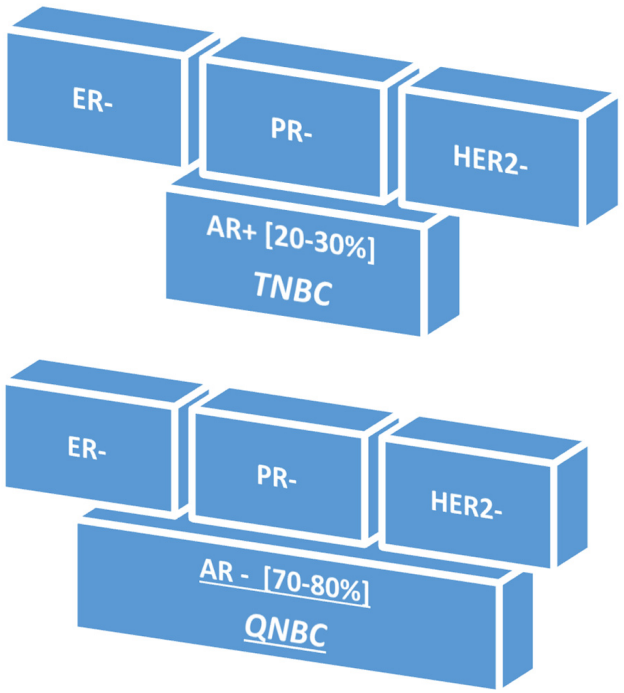

Fig. (1). A receptor profile of the Triple-negative breast cancer (TNBCs) and Quadruple-negative breast cancer (QNBC) [1, 5]. Abbreviations: AR, Androgen receptor; ER, Estrogen receptor; HER2, Human epidermal growth factor receptor 2; PR; Progesterone receptor.

CHAPTER 3

Liquid Biopsy: Insights Into Monitoring Tumor Dynamics and Response to Therapy in Patients with Breast Cancer

Abstract: The ability to identify the molecular features of metastatic breast cancer (BC) provides a unique insight into a patient's therapeutic options and the opportunity to follow the BC progress over time. A classical **tissue biopsy** remains the standard procedure to describe tumor biology and guide treatment choices.

However, a **liquid biopsy**, which can provide medical practitioners with the opportunity to **detect genomic mutations** and **monitor therapeutic effect**s, can play a prominent role in the diagnosis, therapy, and prognosis of patients with different malignancies, including metastatic BC. In fact, the liquid-biopsy-based therapeutic interventions led to the approval of **alpelisib (a PI3K inhibitor)** in patients with **hormone receptor (HR)-positive, human epidermal growth factor receptor2 (HER2)-negative,** advanced or **metastatic BC**, in whom BC had progressed on or after therapy with an **aromatase inhibitor** (**AI)**.

This chapter describes a **liquid biopsy in BC.** It explores its potential for clinical applications in early **diagnosis, monitoring treatment response, detecting minimal residual lesions, predicting risk of progression** or **recurrence,** and **estimating prognosis**. It compares a **liquid biopsy** with a **tissue biopsy**, and outlines the **benefits** and **limitations** of each of these procedures, focusing on patients with metastatic BC. Moreover, this chapter analyses the results from recent studies relevant to liquid biopsies in BC (*e.g.***, circulating tumor cells (CTCs)** and **circulating tumor DNA (ctDNA))**.

Keywords: Alpelisib (A PI3K Inhibitor), Breast cancer (BC), Circulating tumor cells (CTCs), Circulating tumor DNA (ctDNA), Liquid biopsy, Targeted therapy.

Katarzyna Rygiel

INTRODUCTION

A classical **tissue biopsy** still remains the standard procedure to assess **tumor biology** and **guide treatment choices** in patients with cancer [1]. Recently, it has been suggested that **liquid biopsy** provides some valuable **insights into malignant tumor dynamics,** and thus, it can play a **beneficial role in personalized oncology management**.

At present, many research efforts are being made to understand how to use **liquid biopsy** as a surveillance instrument for women with **breast cancer (BC**). However, a lot of work still needs to be done before applying **liquid biopsy** as a standard tool to clinical practice. According to a recent systematic review, **liquid biopsy** has been particularly useful for the early **detection of genomic mutations** and **timely monitoring of the treatment effects** [1]. Such information may be skillfully combined with the **traditional tumor tissue biopsy** to allow physicians to make the most accurate **decisions** regarding possible **targeted therapy** options, in given clinical contexts. However, the liquid biopsy has some **limitations** for its common use in clinical practice (*e.g.*, a liquid biopsy may not be sensitive enough to detect some relevant mutations), and thus, it **has not yet been incorporated into routine clinical diagnostics** for patients with malignancies [1]. Nevertheless, the liquid biopsy, as a potential **diagnostic** and **prognostic aid**, has a great chance to become a valuable tool for the management of women with metastatic **BC** [1].

In brief, a **liquid biopsy** is a process of **obtaining tumor-derived materials,** including DNA, RNA, intact tumor cells, or extracellular vesicles from body fluids such as blood, urine, saliva, stool, or cerebrospinal fluid [2]. Currently, the progress in highly sensitive assays, which can identify a very small amount of tumor-derived materials, in the body fluids, has augmented the significance of liquid biopsy as a reasonable modality that can be added to traditional tumor biopsy (*e.g.*, in women with metastatic BC) [2]. In particular, a liquid biopsy allows for the detection of **circulating tumor cells (CTCs**) and **circulating tumor DNA (ctDNA)** in the circulating blood (plasma fraction) [2]. It is a noninvasive or only mini-invasive procedure since such materials are obtained *via* a blood draw or body fluid collection. Moreover, it represents a convenient and attractive methodology, for both the patients and the medical staff [2]. Some other remarkable benefits include its ability to "decipher" the puzzle **of tumor heterogeneity**, *via* sampling the entire genome of the tumor [2]. In addition, it can be repeated over time, enabling long-term monitoring of the malignant tumor, together with its reactions to the applied antineoplastic therapies (Fig. **1**) [2].

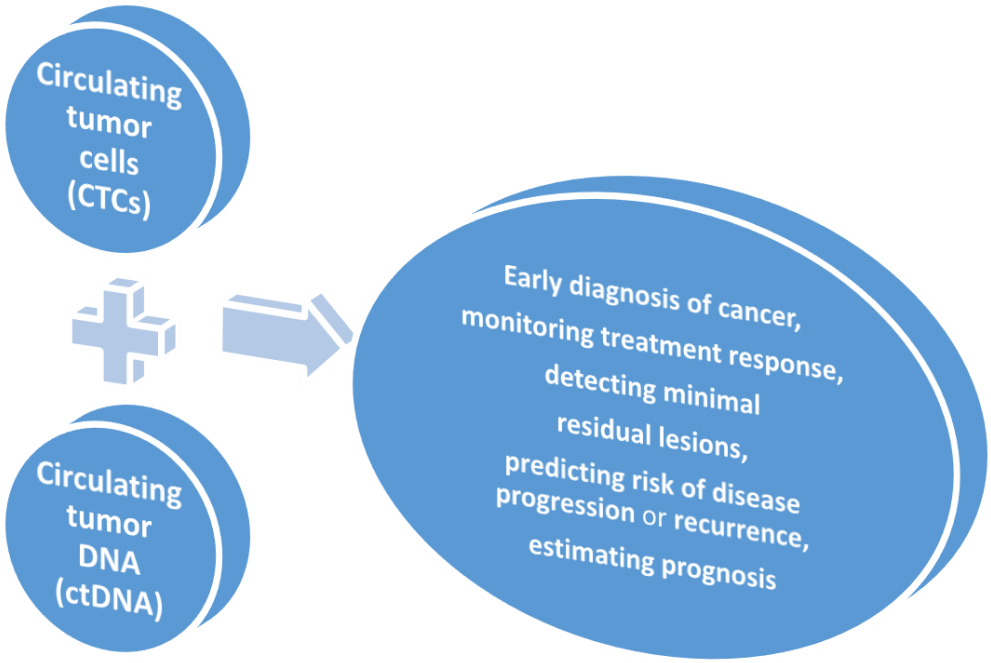

Fig. (1). Exemplary applications of liquid biopsy in the management of patients with cancer.

The aim of this chapter is to present the potential of **liquid biopsy** in patients with metastatic **BC** and explore its clinical applications (*e.g.*, for early **diagnosis, monitoring treatment response, detecting minimal residual lesions, predicting risk of disease progression** or **recurrence,** and **estimating prognosis**). In addition, this chapter compares a **liquid biopsy** with a **tissue biopsy**, and outlines **the benefits** and **limitations** of each of these procedures, for patients with metastatic BC. Moreover, it analyses the results from recent studies relevant to liquid biopsies in BC, focusing on **circulating tumor cells (CTCs)** and **circulating tumor DNA (ctDNA)**.

HOW LIQUID BIOPSY CAN BE USED IN MONITORING METASTATIC BC PROGRESSION AND TREATMENT?

Recently, the US **Food and Drug Administration (FDA**) approved the first companion diagnostic test, **Therascreen PIK3CA RGQ polymerase chain reaction assay,** for tissue and liquid biopsies [3, 4]. In short, the **therascreen PIK3CA RGQ PCR** is a laboratory test used to detect 11 mutations in the ***PIK3CA*** gene in tumor tissue or in the blood, obtained from patients with advanced or metastatic BC. In BC tissue, mutations in the *PIK3CA* gene create an

CHAPTER 4

Importance of Biomarker Conversions as "Road Signs" to Manage Women with Metastatic Breast Cancer: How To Use Them for Personalized Care of These Patients?

Abstract: During a metastatic progression of **breast cancer (BC**), and upon application of various antineoplastic therapies, the initial status of biomarkers can be altered. Awareness of changes in **hormone receptors (HR**) and **human epidermal growth factor receptor 2 (HER2)** is very important, because they may have an impact on patient management. However, the procedures for monitoring these changes in women with metastatic BC still remain unclear.

According to the guidelines for clinical practice from the **American Society of Clinical Oncology (ASCO),** the reevaluation of metastatic BC lesions, is of great importance, and it has been recommended that the biopsies of multiple metastatic lesions need to be performed.

The **aim** of this chapter is to highlight the role of **retesting receptor status in BC metastases** and the impact that this approach may have on the **selection of therapeutic strategies**, in the individualized **management plans for patients with metastatic BC**. In addition, this chapter concisely presents some novel biomarkers linked with targeted therapies for metastatic BC.

Keywords: Biomarkers, Breast cancer (BC), Estrogen receptor (ER), Hormone receptors (HR), Human epidermal growth factor receptor 2 (HER2), Progesterone receptor (PR), Triple-negative breast cancer (TNBC), Targeted therapies, Tumor heterogeneity.

INTRODUCTION

Systemic therapy is the basis of treatment for a majority of women with metastatic **breast cancer (BC)**. It is not considered to be curative, but some recent diagnostic and therapeutic efforts have ameliorated the patient survival (*e.g.*, a median **overall survival (OS)** has increased from about a year in 1985 to almost three years in 2016) [1].

Katarzyna Rygiel

In general, an effective systemic treatment of metastatic BC should be focused on improving patient's symptoms, **quality of life (QoL**), and survival, as well as minimizing toxic effects. Depending on the BC subtype, it includes traditional **chemotherapy (CHT), poly(ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors (ICIs), endocrine therapy (ET), small molecule signal transduction inhibitors, targeted monoclonal antibodies**, and **antibody-drug conjugates (ADCs)** [1]. It has been reported that during a **metastatic progression** of BC, and upon using different **anticancer therapies**, the initial status of BC **biomarkers** can undergo some specific **changes** [1].

It has been noted that changes in biomarker status in BC are not uncommon, and typically occur in an **undesirable** direction (*e.g.*, as a **negative conversion**) in the BC metastatic lesions [1, 2]. It should be highlighted that the awareness of such changes is clinically important, since it can influence many critical decisions relevant to the patient management. According to the guidelines for clinical practice from the **American Society of Clinical Oncology (ASCO**), the **reevaluation of metastatic BC lesions (including biomarkers**) is of great importance, and it has been recommended that the **biopsies of multiple metastatic lesions** should be performed [2].

The aim of this chapter is to explain the prognostic value of **biomarker's status re-evaluation** and the influence that this approach can have on the **selection of therapeutic strategies**, in the management of patients with BC. Moreover, this chapter highlights some features of **tumor heterogeneity**, with special emphasis on its pathologic findings. In addition, it provides insights into the clinical significance of molecular and cellular mechanisms of tumor heterogeneity. Furthermore, it concisely presents some novel **biomarkers** for the most adequate treatment tailoring in individual patients.

COMMON CONVERSIONS OF BIOMARKER'S STATUS IN METASTATIC BREAST CANCER

According to a recent article, approximately 15% changes in clinically meaningful receptors, such as **hormone receptors (HR**) (*e.g.*, **estrogen receptor [ER**] and **progesterone receptor [PR**]), as well as **human epidermal growth factor receptor 2 (HER2**) occur between primary and metastatic BC lesions [3]. In particular, **the negative conversion**, **from ER/PR-positive to ER/PR-negative** status (more frequent) usually signalizes that the present treatment is no longer effective, and requires an adjustment [1 - 3]. Also, a negative conversion of the **ER** status can indicate a worse patient's outcome. On the other hand, a **positive conversion** (less common) can indicate some new, **specific treatment directions**,

which should be followed [1 - 3]. For this with reason, it is **beneficial to timely re-assess changes in biomarker status** in women BC, for both prognostic and therapeutic purposes [1 - 3].

Since such alterations require new decisions about treatment strategies, a **tumor tissue biopsy** and **systemic biomarkers should be re-evaluated**, in the course of a patient's metastatic BC. This is particularly important in cases of ER-positive to ER-negative BC conversion, and in HER2-positive to HER2-negative, borderline or low HER2 expression [3]. However, there is no "predetermined" schedule, according to which, a follow-up test should be done. In fact, a **repeated biopsy** needs to be considered before making any new decision about the selection of therapeutic options [3].

ALTERATIONS OF THE BIOMARKER'S STATUS IN METASTATIC BREAST CANCER AND THEIR POTENTIAL ROLE IN THE PROGNOSIS AND THERAPY

It has been noted that some biomarkers, such as ***PI3K***, usually do not change over time. In practical terms, ***PI3K*** can predict therapeutic benefits of a ***PI3K*****-inhibitor, alpelisib [**4]. At present, only ***PIK3CA*** **mutations** have shown a **predictive value for treatment with α-selective and β-sparing PI3K inhibitors**, in females with the advanced BC [4]. Moreover, biomarkers, such as ***ESR1*** **mutations**, may serve as **predictors for lack of benefits from treatment with aromatase inhibitors (AI)** (*e.g*., a single-agent tamoxifen) [5].

It should be highlighted that clonal selection for hotspot ***ESR1*** mutations can occur at the early stages of both metastatic and locally recurrent BC. Such mutations may occur during or after an **adjuvant ET** or during **neoadjuvant ET** of primary BC lesions, possibly indicating a worse prognosis [5]. These findings carry some clinical implications for the future monitoring strategies to improve patients' outcomes [5]. Hopefully, further studies in the early recurrent BC phases will guide both researchers and clinicians how to provide the most suitable therapies in such patients.

Similarly, germline mutations of ***BRCA1*** and ***BRCA2*** genes are reliable **predictors for benefits with PARP inhibitors** [6]. In short, **PARP inhibitors** are the first FDA-approved **DNA damage response (DDR)-targeted** agents that have revolutionized treatment landscape for many patients with BC and ovarian cancer. **DDR deficiencies** represent a common factor that plays a key role in tumorigenesis. However, the **DDR deficiencies** are also a "weak spot" that can be "strategically " used as a therapeutic target [6]. Furthermore, there are some recent findings that **somatic** ***BRCA*** **mutations** may also predict some benefits from PARP inhibitors (Table **1**) [7]. In fact, the effectiveness of PARP inhibitors

CHAPTER 5

Putting It All Together: Clinical Pearls of Recently Approved Therapies for Triple-Negative Breast Cancer

Abstract: Three recently approved therapies for the treatment of **triple-negative breast cancer (TNBC**), including **poly(ADP-ribose) polymerase (PARP) inhibitors, immunotherapy**, and **antibody-drug conjugates (ADC**) have changed the management of several patients with advanced, metastatic, and even early-stage TNBC.

PARP inhibitors, such as **olaparib** and **talazoparib**, have been approved as therapies for ***BRCA*-mutated human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (BC**).

Immunotherapy has been approved for patients with **programmed death ligand 1** (**PD-L1)-positive, metastatic TNBC. Immune checkpoint inhibitors (ICIs)**, such as **atezolizumab** and **pembrolizumab** demonstrated a significant improvement in **progression-free survival (PFS)** (in combination with chemotherapy).

An **antibody-drug conjugate (ADC**), **sacituzumab govitecan (SG**) (that **targets trophoblast cell surface antigen 2** (**Trop-2**)), has shown efficacy and prolonged **PFS** and **overall survival (OS**) in patients with **metastatic TNBC.**

The goal of this chapter is to briefly review some of the most promising therapies available for the treatment of TNBC, including PARP inhibitors, ICIs, and ADCs. Considerations of choosing these therapeutic options and their sequence, in the context of the ***BRCA*** mutation and the **PD-L1 positivity**, in patients with TNBC have been discussed.

Keywords: Atezolizumab, Antibody drug conjugates (ADCs), Human epidermal growth factor receptor 2 (HER2), Immune checkpoint inhibitors (ICIs), Olaparib, Poly (ADP-ribose) polymerase (PARP) inhibitors, Pembrolizumab, Programmed death ligand 1 (PD-L1), Sacituzumab govitecan, Talazoparib, Triple-negative breast cancer (TNBC).

Katarzyna Rygiel

INTRODUCTION

Triple-negative breast cancer (TNBC) is more common in young women (*e.g*., under 40 years of age), premenopausal, those who are of African or Hispanic ancestry, and the ones, who harbor a germline mutation in the ***BRCA1*** gene [1]. **TNBC** is characterized by rapid growth, spread, and negative patient outcomes [1]. Also, **TNBC** has a higher risk of recurrence after therapy (*e.g*., especially for early-stage **TNBC)** and poor survival (*e.g*., for patients diagnosed with advanced and metastatic TNBC) [1].

Traditionally, **TNBC** has been defined by what it does **not express** (*e.g*., the **estrogen receptor (ER), progesterone receptor (PR**), and **human epidermal growth factor receptor (HER2**)) [1]. At present, this characteristic has been "enriched" by specifying what TNBC does express, such as ***BRCA1*** or ***BRCA2*** **gene mutations**, and **PD-L1** marker. Unfortunately, treatment options in TNBC have been limited, compared to some other forms of BC (*e.g*., hormone receptor (HR)-positive BC, and HER2-positive BC) [1].

However, it should be underscored that three recently approved therapies for the treatment of **TNBC**, including **PARP inhibitors, immunotherapy**, and **antibody-drug conjugates (ADCs**) have changed the management strategy for several patients with advanced, metastatic, and even early-stage TNBC [1].

For instance, inhibitors of **poly(ADP-ribose) polymerase (PARP**), such as **olaparib** and **talazoparib**, have been approved as therapies for patients with ***BRCA***-mutated **HER2-negative metastatic breast cancer (BC**) [2].

In addition, **immune checkpoint inhibitors (ICIs)** were initially explored in **TNBC** rather than in HR-positive BC. This is because, in contrast to the other BC subtypes, **TNBC** is more **immunogenic** (*e.g*., it has **a higher tumor mutational burden**, more abundant **tumor-infiltrating lymphocytes**, and higher **programmed death ligand 1 (PD-L1) expression**) [3]. In consequence, adding **immunotherapy** to chemotherapy **(CHT)** in patients with **TNBC**, who have tumors that are **PD-L1-positive** has shown beneficial effects [3].

Moreover, **antibody-drug conjugates (ADCs**) that **target trophoblast cell surface antigen 2** (**Trop-2)** have shown efficacy for patients with **metastatic TNBC**. In particular, an **ADC, sacituzumab govitecan (SG**), has revealed improved **progression-free survival (PFS)** and **overall survival (OS**) for women with **metastatic TNBC [**4].

The goal of this chapter is to briefly review some of the most promising therapies available for the treatment of TNBC, including PARP inhibitors, immune

checkpoint inhibitors (ICIs), and antibody-drug conjugates (ADCs). Considerations of choosing these therapeutic options and their sequence, in the context of the *BRCA* mutation and the PD-L1 positivity, in patients with TNBC are discussed.

A SPECIAL TASK OF PARP INHIBITORS: TARGETING ENZYMES THAT REPAIR DNA DAMAGE

To understand what are the **PARP inhibitors**, one has to first understand what the **poly (ADP-ribose) polymerase** (**PARPs**) is [2]. Simply put, **PARP** is a class of nuclear enzymes involved in the pathogenesis of various malignant tumors. In particular, **PARP1** and **PARP2** are the two most recognized members of this enzymatic family [2]. **PARP1** and **PARP2** are activated by DNA damage and can repair it (*e.g.*, single-strand DNA breaks). However, if **PARP1** and **PARP2** are suppressed, then the unrepaired single DNA base pairs degrade into double-stranded DNA breaks [2]. As a consequence, in patients who carry a ***BRCA*** gene mutation, the **PARP inhibitors** prevent the damaged cancer cells from the ability to repair their DNA breaks, leading to the ***BRCA*-**mutated cell death, and subsequently, to cancer's destruction [2].

WHO CAN BENEFIT THE MOST FROM PARP INHIBITORS? - GOOD NEWS FROM THE OLYMPIAD AND THE EMBRACA TRIALS FOR WOMEN WITH METASTATIC *BRCA*-POSITIVE TNBC

The **OlympiAD** trial has led to the approval of **olaparib** in **metastatic *BRCA*-positive BC** [5]. Patients included in this study had deleterious, **germline *BRCA* mutations** and **advanced HER2-negative BC** (**hormone receptor (HR)-positive** or **TNBC**). Previously, they received up to two lines of CHT for metastatic BC [5]. The participants of the **OlympiAD** trial were randomized to receive **olaparib (300 mg twice a day**) **or CHT of the physician's choice (capecitabine, vinorelbine, or eribulin**) [5]. The **PFS** was improved significantly in the olaparib group compared to the CHT. In addition, women with TNBC had the most beneficial effects from the olaparib therapy [5].

Concurrently, the **EMBRACA** trial examined **talazoparib** *vs.* CHT in women with deleterious, germline, *BRCA* mutation, with HER2-negative BC, who had received the previous CHT for metastatic BC [6]. They were randomized to receive **talazoparib** (1 mg a day) *vs.* **CHT of the physician's choice (capecitabine, vinorelbine, eribulin,** or **gemcitabine**). The women who received **talazoparib** had a better **PFS** [6].

The **TBCRC 048** examined the patients who had **somatic *BRCA* mutations** or **other germline mutations** (*e.g.*, ***PALB2*, *ATM,*** and ***CHEK2)***, to see whether or

CHAPTER 6

The Way Out From the Labyrinth of Anticancer Therapies for Patients with Breast Cancer: How Can We Improve Their Cardiac Safety and Quality of Life?

Abstract: Patients with **Breast cancer (BC**) often experience a spectrum of **adverse, anticancer therapy-related symptoms**, which deteriorate their **quality of life (QoL**). Therefore, effective strategies for BC are needed. Personalized medicine offers many therapeutic options (*e.g.*, targeted therapies) that can be tailored to the individual needs of a given patient.

This chapter aims to briefly present typical **side effects of current anticancer treatments**, which often reduce the QoL of patients with BC and survivors. In particular, it addresses pain (including chemotherapy (CHT)-induced peripheral neuropathy (PN) and lymphedema), depression, cognitive dysfunction, premature menopause, and CHT-induced menopause. It focuses on the adverse effects of the BC therapies, such as **chemotherapy (CHT), immunotherapy (IT**), and some **targeted therapies.** In addition, several issues related to **cardiovascular toxicity** induced by anticancer treatments and **cardioprotective measures** for women with BC are addressed. This chapter also touches on the recent advances in precision medicine and provides some future directions, aimed at fulfilling unmet needs of patients with BC. The described approaches may be helpful in planning personalized treatment, facilitating the patient's tolerability of many available anticancer therapies, optimizing the medication selection, and improving the patient's QoL.

Keywords: Breast Cancer (BC), Chemotherapy (CHT), Cardiovascular toxicity, Cardioprotection, Cardio-oncology, Depression, Immunotherapy (IT), Pain, Peripheral neuropathy (PN), Personalized medicine approach, Precision medicine, Precision oncology, Quality of life (QoL), Targeted therapies.

INTRODUCTION

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),

Katarzyna Rygiel

and human epidermal receptor 2 (HER2)) detected in 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, radiation therapy (RT), endocrine therapy (ET) chemotherapy (CHT), some modern strategies, which influence the pathways of tumor signaling (*e.g.*, immunotherapy (IT) and targeted therapies), 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 targeted therapies and IT. In addition to the development of resistance to treatment, leading to patient relapses, the occurrence and severity of adverse effects of the standard and emerging anti-BC therapies often represent barriers to their application [4]. Risks for developing **long-term side effects post-BC treatments** are multifactorial, including the woman's age at the time of diagnosis, comorbid conditions with their therapies, and type, dose, and duration of the antineoplastic treatment [4]. In contrast to the "one size fits all" approach to patients with BC, individualized approaches should play the main role. In line with this concept, **precision medicine** presents strategies for the treatment and prevention of serious, chronic diseases (such as malignancies) that include the patient's genetics, cancer biological features, tumor microenvironment characteristics, patient's comorbidities, lifestyle, and quality of life (QoL) [5]. Furthermore, in **precision oncology**, the purpose 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]. At present, several commonly used anticancer therapies (*e.g.*, CHT) cause various, undesirable symptoms, which negatively influence the QoL of BC patients or survivors (Fig. **1**) [4, 6].

This chapter aims to briefly present typical side effects of current anticancer treatments, which often reduce the QoL of patients with BC and survivors. In particular, it addresses pain (including chemotherapy (CHT)-induced **peripheral neuropathy (PN)** and **lymphedema**), **depression, cognitive dysfunction, premature menopause,** and **CHT-induced menopause**. It focuses on adverse effects of BC therapies, such as chemotherapy (CHT), immunotherapy (IT), and some targeted therapies. Also, several issues related to **cardiovascular toxicity induced by anticancer treatments and cardioprotective measures** for women with BC are addressed. In addition, it touches on the recent advances in precision medicine and provides some future directions to novel therapies, aimed at fulfilling unmet needs of patients with BC. The described approaches may be

helpful in **planning personalized treatment**, facilitating the patient's tolerability of many available anticancer therapies, optimizing the medication selection, and improving the patient's QoL.

FREQUENT SIDE EFFECTS OF ANTICANCER TREATMENTS AND THEIR PERCEPTION IN PATIENTS WITH BREAST CANCER

Several patients with BC often experience treatment-related, unpleasant symptoms (Fig. **1**) [4, 6]. The effects of CHT on the QoL, among patients with BC and BC survivors, were assessed using the QoL evaluation forms (*e.g.*, physical and psychological parameters) at certain 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 post CHT). Based on this study's results, **pain, fatigue**, and **depressive symptoms**, were increased in the participating pre-and peri-menopausal women with BC at all stages of their therapeutic process [7]. In addition, many disturbing symptoms, as well as their adverse impact on the patient's functional status, corresponding with BC worse outcomes, were noted in these patients [8].

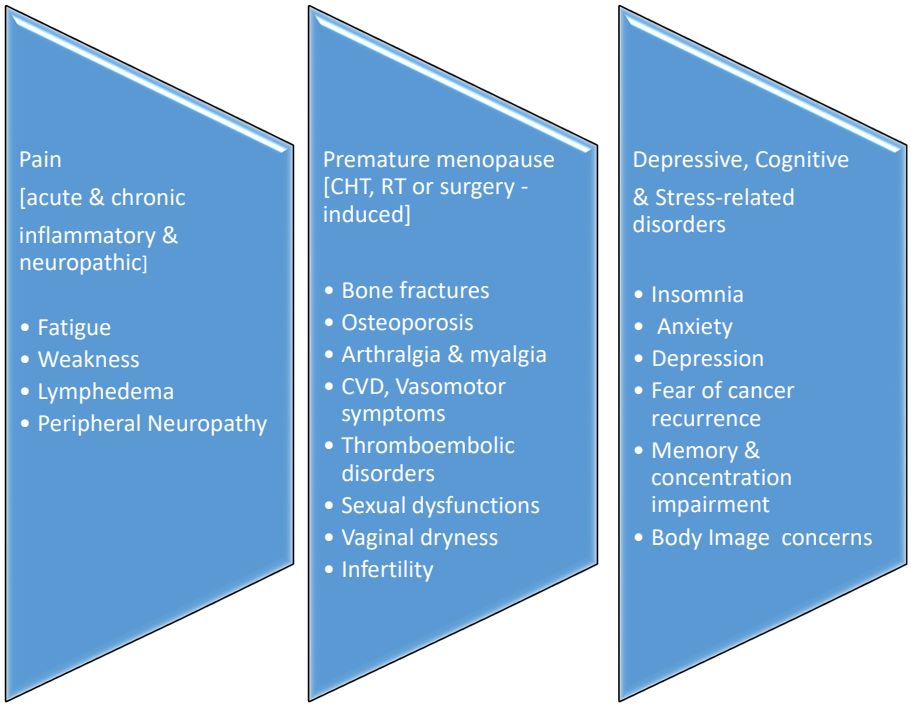

Fig. (1). Frequent adverse effects of breast cancer treatments that decrease the patients quality of life; CVD, cardiovascular diseases; CHT, chemotherapy; RT, radiotherapy.

CHAPTER 7

Can We Find A Noninvasive Tool of Precision Medicine That Can Always Be Used For the Individualized Treatment of Women With Breast Cancer?

Abstract: A constellation of specific personal characteristics of the patients have been described as **personomics**, which involves an individual patient's personality type, set of personal values, priorities, preferences, health-related beliefs, goals, economic status, and different life circumstances, which can affect when and how a certain disease (*e.g.*, breast cancer (BC)) can be manifested in a given woman.

As a consequence, **personomics** can be considered to be a **novel clinical instrument** that is helpful for making a **connection between the standard** and the emerging, more **individualized model of medical care**. This plays an essential role in patients diagnosed with the most aggressive and difficult-to-treat malignancies (*e.g.*, BC subtypes, such as triple-negative breast cancer (TNBC).

At present, many **biological properties** in the forms of different **"omics" platforms** (such as genomics, proteomics, transcriptomics, metabolomics, epigenomics, and pharmacogenomics) have emerged. They have been incorporated into **precision medicine**. However, to optimally tailor diagnostic and therapeutic approaches to a given patient, the biological characteristics need to be integrated with the personal ones.

This chapter aims to address some practical research ideas of personalized medicine, relevant to personomics that can incorporate individual patient issues into the comprehensive therapeutic plan.

Keywords: Breast cancer (BC), Precision medicine, Personomics, Patient-centered approach, Personalized medical care, Triple-negative breast cancer (TNBC).

INTRODUCTION

Evidence-based medicine (EBM) applies data from **randomized controlled trials (RCTs**) and formulates clinical practice guidelines for a variety of medical disciplines, including oncology [1]. Based on the EBM guidelines, the treatment

Katarzyna Rygiel

of patients with breast cancer (BC) has been mostly oriented on groups of women, who shared certain BC subtypes, in similar stages of progression [1]. However, the **EBM** guidelines have not included the patient's individual variability (*e.g.*, advanced age, multiple comorbidities, life experiences, psycho-social, or personal issues). In practice, these recommendations were usually based on data obtained from large groups of patients, with similar clinical and pathological characteristics. In this situation, many of the vulnerable women with BC could potentially receive some unnecessary therapies, leading to various adverse effects, not to mention about high medical costs [1]. At present, this approach has been changed, to some degree, with the advent of **precision medicine** and **personalized medicine** [2].

This chapter aims to address some practical research ideas of personalized medicine, relevant to personomics. It also presents how the personomics may facilitate the transition from the standard treatment to personalized medical management of individual women with the most difficult to treat BC subtypes.

The Goals and Tools of Precision Medicine

Simply put, **precision medicine** is the application of **modern medical sciences** for individual patients, based on their **unique biological characteristics** [2]. By using information from different biological "omics" platforms (*e.g.*, genomics, transcriptomics, proteomics, metabolomics, epigenomics, and pharmacogenomics), precision medicine creates the most optimally targeted diagnostic and therapeutic strategies, focused on the improvement of the treatment of various medical conditions (Fig. **1**) [2].

The objective of precision medicine in the oncology area is to individualize every patient's management, according to an assessment of the risk of cancer progression or recurrence [2].

Also, the whole malignancy course, including diagnostic work-up, treatment process, monitoring, and survivorship period should be approached in an individual manner, tailored to a given patient's clinical context [2].

AN EMERGING P4 MODEL: TRANSFORMATION FOR A NEW HEALTHCARE SYSTEM

To make measurable improvements in the patients' outcomes, the data from precision medicine needs to be integrated at multiple levels (*e.g.*, starting from the molecular level, through cells, tissues, organs, systems, and whole organisms, to the population level) [3]. At this point, systems biology needs to be used,

incorporating high throughput technologies to generate large data sets, which will contribute to expanding many interconnected aspects of human biology [3].

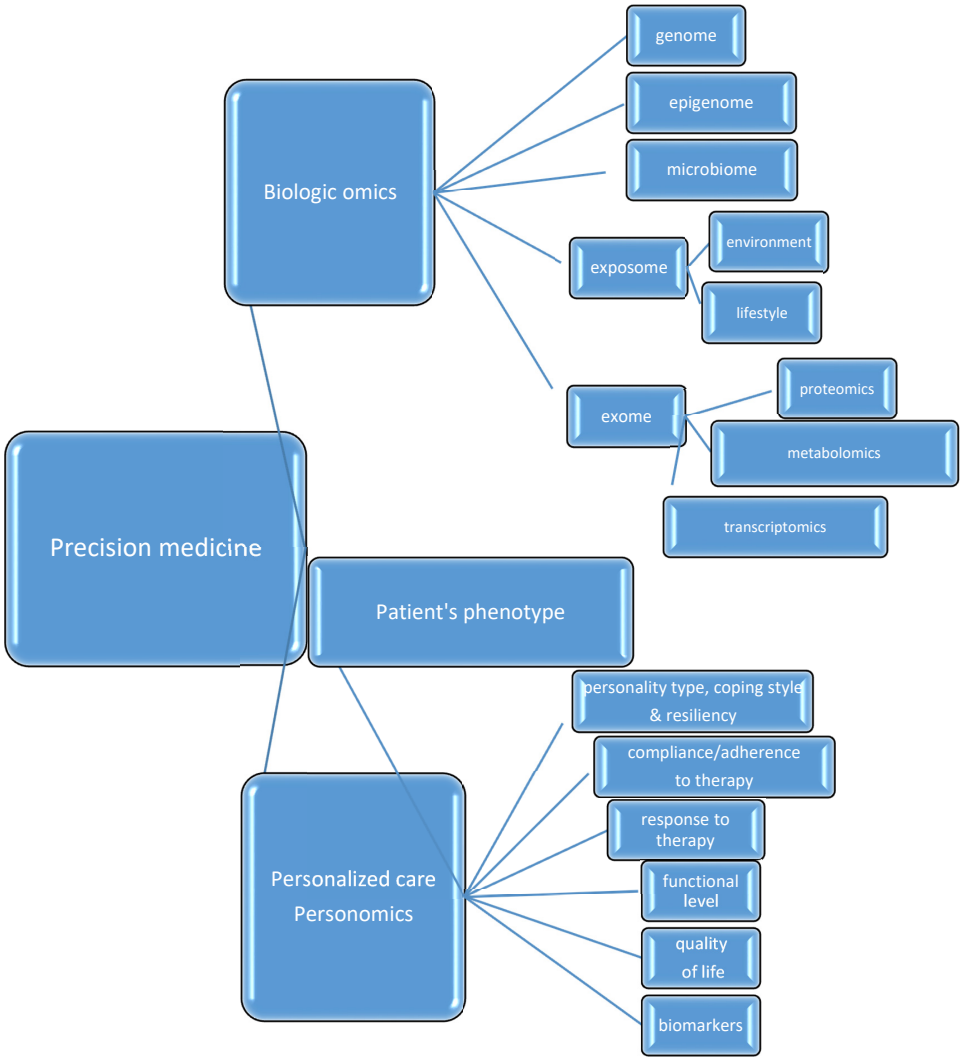

Fig. (1). Precision medicine and personalized model of care – the key interconnected components.

Furthermore, these data need to be disseminated, so that the **predictive, preventive, personalized**, and **participatory,** also known as **the P4 healthcare system,** can be developed and implemented in "real-life" circumstances, in the future (Fig. **2**) [3].

Part 2

The Role of Patient Education, Empowerment, and Communication with Medical Teams, and Psychological or Supportive Approaches in Advanced or Metastatic Breast Cancer (BC).

“You can’t stop the waves, but you can learn how to surf.”

Jon Kabat-Zinn

CHAPTER 8

Distress – Our "Internal Enemy": How to "Disarm" or Lessen its Negative Impact on the Psychophysical Condition of Women with Triple-Negative Breast Cancer?

Abstract: Stress is an inevitable part of life. It constantly bombards our lives, and these explosions range from minor daily frustrations to overwhelming fear brought on by the adverse prognosis of serious diseases, like triple-negative breast cancer (**TNBC)**. In patients with cancer, **distress** has been defined as "a **multifactorial unpleasant experience of a psychological** (*e.g*., cognitive, behavioral, emotional), social, spiritual, and **physical** nature that may **interfere with the ability to cope effectively with cancer**, its physical symptoms, and its treatment. However, even in such a difficult health-related situation, it is encouraging that some consequences of **distress** are not inevitable. Some natural questions for every woman with cancer (*e.g*., TNBC) are: "**What are the normal limits of distress?"** and "**What to do when distress becomes more serious?"**

This chapter will briefly address the above questions and will present some **t**ools that can be used to **measure distress**. In addition, a few simple **strategies** that are easily **accessible** and **effective in Distress Management** and its complications will be suggested (*e.g*., "**Do's** and **Don'ts**" list of recommendations).

Keywords: Cancer care team, Distress, Distress thermometer, Social services, Support.

INTRODUCTION

Women with cancer, especially as aggressive as **triple-negative breast cancer (TNBC**), and also, their families and friends can feel distressed after receiving a cancer diagnosis. Also, when cancer is treated and this "journey" undergoes dynamic changes, learning to cope with such a "moving target" is very difficult. Therefore, it's important to know some basic facts about the nature and manifestations of distress, and also, when, where, and how to receive help and support [1]. **Distress** is an unpleasant emotion, feeling, thought, condition, or behavior, and thus, it may influence the way how a person feels, thinks, or acts [1].

Katarzyna Rygiel

Moreover, **distress can impair a person's efforts to effectively cope with malignancy**, including managing its specific symptoms, therapies, and adverse effects [1]. In addition, distress may have a negative impact on decision-making (*e.g.*, therapeutic choices) and taking personal charge over one's health [1]. Since there are many stressful elements related to a malignant disease, some degree of distress is inevitable, and thus, considered "**normal** " (Fig. **1**) [1]. However, a transition of distress from the expected, controlled level, to the one that interferes with treatment (*e.g.*, decision-making, adherence to therapy, *etc.*) and makes it difficult to continue a usual daily functioning requires a proactive and individualized approach from the cancer care team (Fig. **2**) [2]. Furthermore, women who have limited access to health care due to language, medical insurance, or financial barriers, transportation problems, young children or elderly relatives at home, history of mental disorders, alcohol or drug abuse, usually have an increased risk for distress [2].

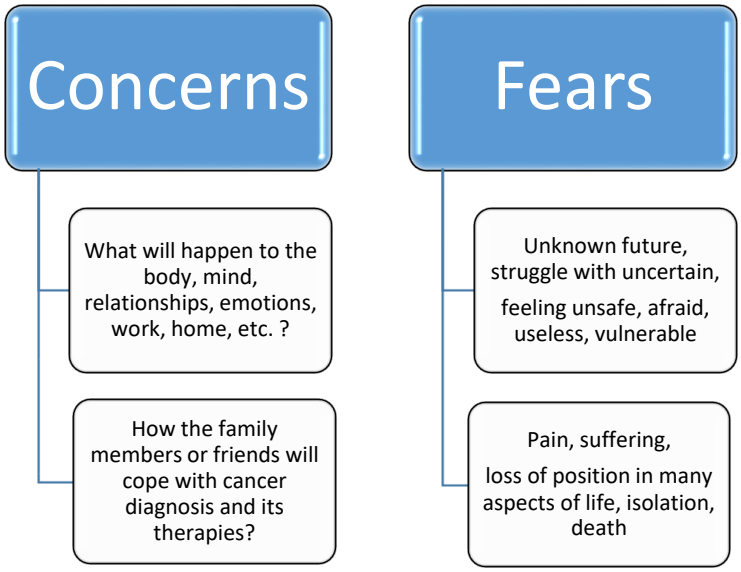

Fig. (1). Distress-related concerns and fears often experienced by patients with cancer.

Therefore, such vulnerable women should not be overlooked, since they need to receive immediate attention and help to be able to cope with different adversities [2]. This chapter will briefly address the issues linked with cancer-related distress and will present some **t**ools that can be used **to measure the distress levels**. In addition, a few simple **strategies** that are easily **accessible** and **effective in distress management** and its complications will be suggested (*e.g.*, in the form of "**Do's** and **Don'ts**" recommendations).

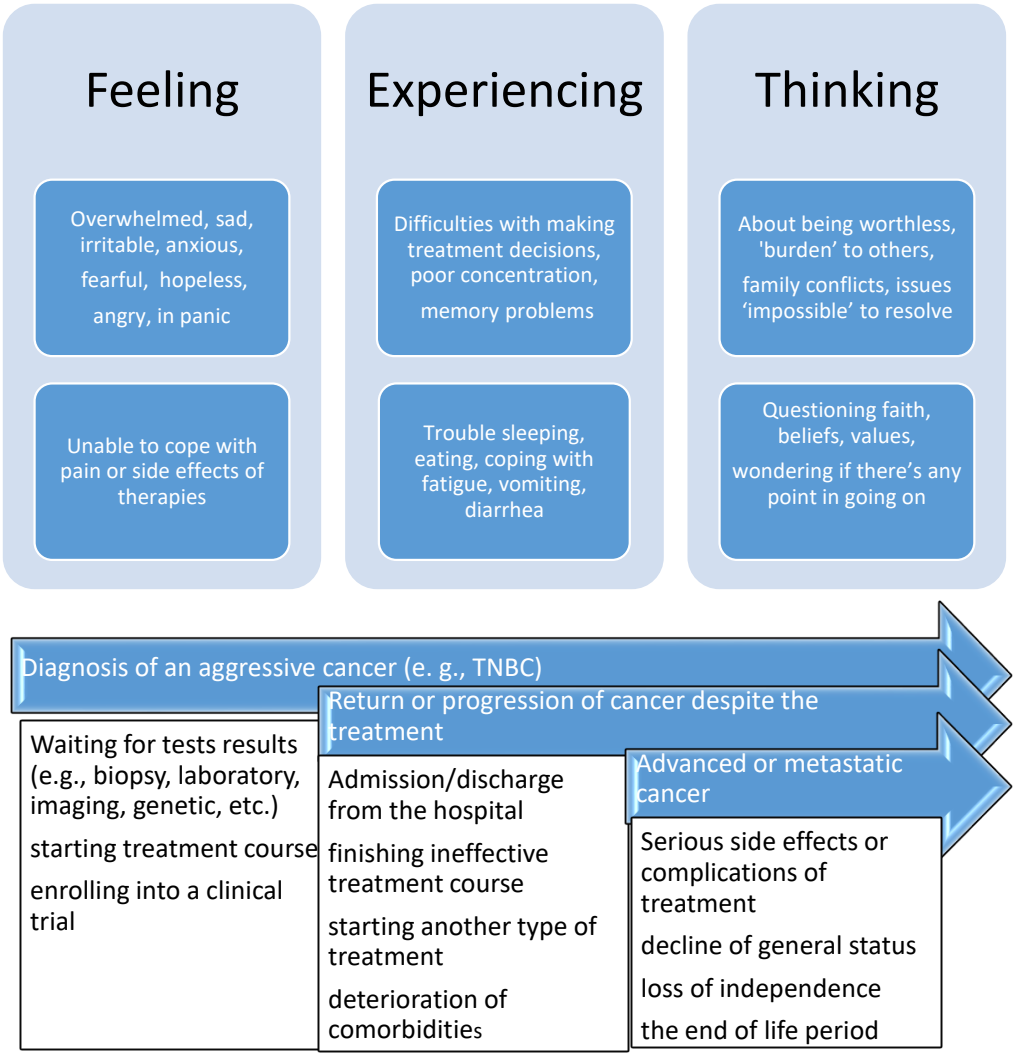

Fig. (2). Common challenging moments of the cancer journey, when the distress becomes very serious; TNBC, triple-negative breast cancer.

WHAT CAN PATIENTS WITH CANCER, CANCER CARE TEAMS, AND CAREGIVERS DO WHEN THE DISTRESS BECOMES VERY SERIOUS?

The distress can be particularly aggravated during some periods of the cancer journey. Since serious distress affects many key areas of one's life (*e.g.*, a patient has trouble sleeping, eating, or concentrating), it is critical to prepare the first line of defense as soon as possible. This means an ability to cope with distress, which can be triggered by various factors, together with **a cancer care team,**

CHAPTER 9

Teaching the Brain How to Counteract Distress: Practical Lessons About the Stress and Relaxation Responses for Women with Triple-Negative Breast Cancer

Abstract: In spite of a very difficult situation, women with triple-negative breast cancer (TNBC) need to realize that some consequences of the cancer-related **distress c**an be alleviated. Moreover, it is possible to counteract, to some degree, the damaging effects of this distress. In particular, the **relaxation response**, as the opposite, "**calming version**" of the "**typical" stress response** can be achieved by a given patient with cancer, with some simple, intentional, and conscious efforts.

In fact, modern s**tress management** offers a whole armamentarium of **tools** and **strategies** that are necessary to reduce negative results of stress-related reactions. Since many warning signs of stress are connected with certain activities of the **autonomic nervous system (ANS),** it should be beneficial to patients to learn some basic information about the ANS functions.

This chapter will explain how to elicit the **relaxation response** as the "**common denominator**" to counterbalance the "typical" stress response. It will also teach how to use **diaphragmatic breathing**, and the most **feasible to adopt elements of the mindfulness-based interventions,** as well as **cognitive-behavioral approaches,** to more effectively combat distress daily.

Keywords: Relaxation response, Stress response, Autonomic nervous system (ANS), Parasympathetic nervous system (PNS), Sympathetic nervous system (SNS), Diaphragmatic breathing, Cognitive-behavioral therapy (CBT), Acceptance and commitment therapy (ACT), Mindfulness-based interventions (MBI), Meditation.

INTRODUCTION

Despite an extremely difficult situation, women with triple-negative breast cancer (TNBC) should realize that some consequences of the cancer-related **distress c**an be alleviated, to some degree. In fact, it is possible to counteract the damaging

Katarzyna Rygiel

effects of this distress by calling upon the body's inherited potential for natural controlling mechanisms and healing processes [1].

In particular, the beneficial **relaxation response**, as the "**calming response**", which is opposite to the "**typical" stress-related response** can be achieved, with some intentional, conscious efforts of any woman with cancer, including TNBC. However, this pattern is not intuitive, and unfortunately, it is not on the front line of the therapeutic process. Therefore, it is necessary to educate both the patients in need and their cancer care teams about simple and easily accessible steps to prevent or combat some destructive consequences of undesirable **"stress response" [**1]. Moreover, the main goal of stress management is to help a person timely and correctly identify and interpret the warning signs of stress, which are manifested by certain activities of the **autonomic nervous system (ANS).** That's why this is of great importance to teach patients about ANS functions, so that they are able to recognize subtle changes, which may have a substantial impact on their overall psychophysical condition. Such a vigilant and noninvasive approach can bring some balance to an unstable, malignancy-related stressful situation. Since such distress can diminish a person's efforts to successfully cope with cancer, including managing its symptoms, therapies, and their adverse effects, as well as can impair decision-making abilities, it is crucial to explain what exact factors or behaviors can make some women more "stress-resistant", at least to some degree. Moreover, the simple and insightful s**tress management techniques** will help acquire skills, which are needed to neutralize the detrimental effects of distress and restore inner peace, stability, and confidence, especially for women with TNBC, who subjectively experience distress, such as feeling anxious, fearful, hopeless, concerned about cancer and also, about lost roles *(e.g*., as a mother, wife, grandmother, coworker, colleague, friend, *etc.)*, which they played at home, family, workplace, or a social group.

This chapter will explain how to elicit the **relaxation response** as the "**common denominator**" to counteract the "typical" stress response [1]. It will teach how to apply **slow, diaphragmatic breathing,** to more effectively combat distress on a daily basis. Furthermore, this chapter will encourage moderate **exercise, rest, relaxation,** and **social connections**. It will also provide some tips for the "informal" applications of **mindfulness-based interventions (MBI), cognitive and behavioral therapy (CBT),** and **acceptance and commitment therapy (ACT**) [2]. In essence, it will explore the key elements of these approaches, allowing making constructive changes to the "routine ways", in which many women with TNBC think, feel, and react to the stressful demands of the surrounding reality.

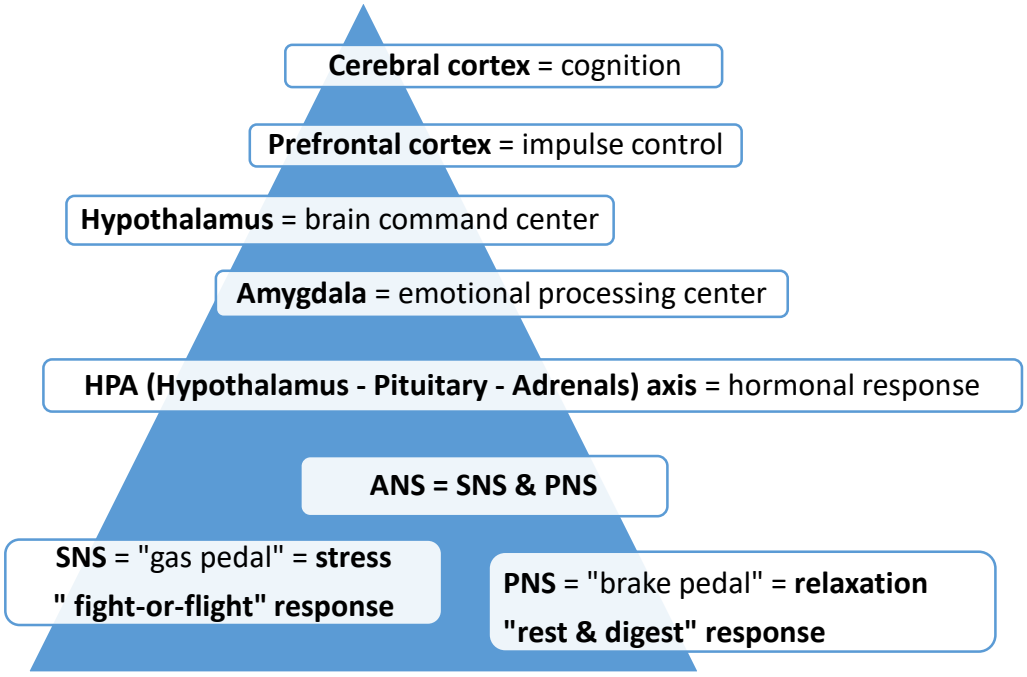

Fig. (1). Central, autonomic nervous system, and HPA axis - their roles in the perception or reaction to stress; ANS, autonomic nervous system; HPA, Hypothalamus - Pituitary -Adrenals; PNS, the parasympathetic nervous system; SNS, the sympathetic nervous system.

OPPOSITE PHYSIOLOGIC ACTIONS OF TWO PARTS OF THE AUTONOMIC NERVOUS SYSTEM (ANS) – THE SYMPATHETIC NERVOUS SYSTEM (SNS) AND THE PARASYMPATHETIC NERVOUS SYSTEM (PNS)

The nervous system consists of the **central nervous system (CNS)** which contains the brain and spinal cord, and t**he peripheral nervous system** which contains all the neurons outside of the **CNS (**Fig. **1**).

The **autonomic nervous system** (**ANS**) is part of the **peripheral nervous system** that consists of a collection of neurons, which affect the activity of various internal organs. The ANS has two parts: **the sympathetic nervous system (SNS)** which prepares the body to actively respond to changes or perceived threats (*e.g., via* activation of the "fight or flight" response), and **the parasympathetic nervous system (PNS)** is responsible for bodily functions at rest (*e.g., via* activation of the repair mechanisms) **(**Fig. **2**) [3]. Regulation of the internal environment is critical for maintaining homeostasis *(e.g*., relatively stable blood pressure, heart rate, respiratory rate, metabolism, temperature, *etc.)*. The main

CHAPTER 10

An Intersectional Neuroscience Approach for Disadvantageous Populations: Meditation Practice as a Possible Support Option for Women with Breast Cancer?

Abstract: Mindfulness and **compassion meditation** have a positive impact on cognition, mood, behavior, and general health, based on recent studies in neuroscience. However, the research methodology is still insufficient to **determine and measure different mental states during meditation**, especially **in minority populations.**

Intersectional Neuroscience, which is an innovative research model, may provide some solutions since it adapts modern research procedures to include **disadvantageous groups of participants (*e.g.*, ethnic minorities,** patients with **chronic diseases**, like **cancer, heart disease,** or **depression). Evaluating Multivariate Maps of BODY Awareness (EMBODY**) is a task designed to accommodate diverse neural structures and functions, using the **multi-voxel pattern analysis (MVPA**) classifiers, with **functional magnetic resonance imaging (fMRI**). The **EMBODY** task applies individualized **artificial intelligence** algorithms to the **fMRI** data, in order to identify mental states during **breath-focused meditation**, a **basic skill that stabilizes attention.**

This chapter describes a potential application of the Intersectional Neuroscience (IN) approach to developing useful metrics of meditation practice, including participants from disadvantageous groups. Hopefully, these findings can be explored in-depth, and possibly applied to **patients with triple-negative breast cancer** (**TNBC**), in the future.

Keywords: Breath-focused meditation, Community-based participatory research (CBPR), Compassion meditation, Functional magnetic resonance imaging (fMRI), Intersectional neuroscience (IN), Mindfulness, Mindfulness-based interventions (MBI).

INTRODUCTION

Meditation is considered to be a part of **integrative medicine** since it connects the traditional, 7,000-year-old practice of **mindfulness** that is focused on paying close attention to the present moment ("**here and now**"). Nonjudgmental accep-

Katarzyna Rygiel

tance of whatever arises in the awareness is a cornerstone of **mindfulness,** according to modern neuroscience and psychology (Fig. **1**) [1]. **The main approaches to meditation practice i**nclude focused attention, breath-focused, compassion, and movement-based practices so that a patient can choose the one that is most convenient for her [1].

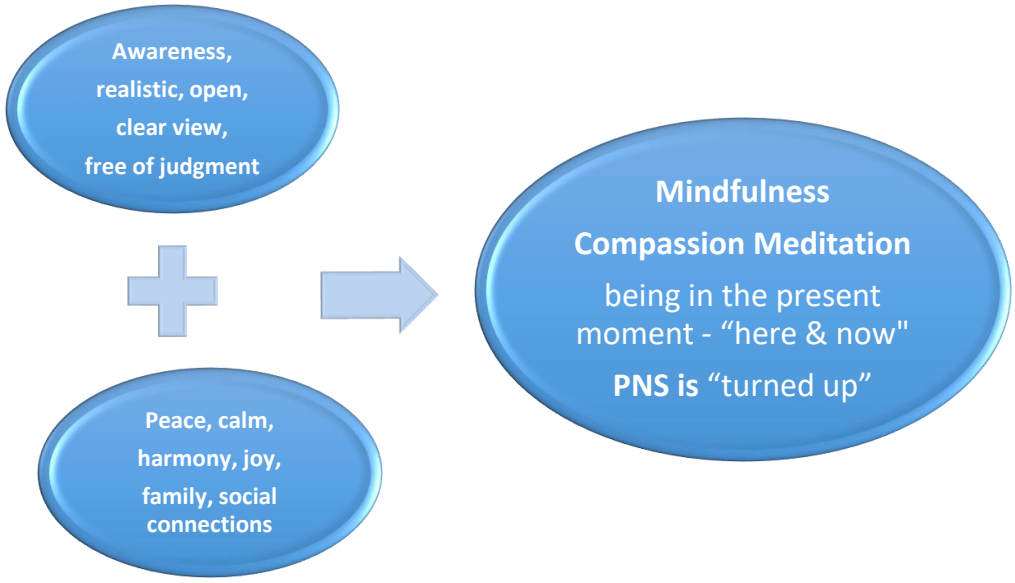

Fig. (1). Important Components of Mindfulness and Compassion Meditation; PNS, parasympathetic nervous system.

During meditation, a **sympathetic nervous system** (**SNS**) (responsible for arousal, stress-response, and stressful feelings) is "turned down". Simultaneously, a parasympathetic nervous system **(PNS**) (responsible for the relaxation response, rest, and repair) is "turned up" [2]. This allows the heart rate, blood pressure, and respiratory rate to return to physiological ranges [2].

Mindfulness and **compassion meditation** represent **contemplative practices** that may increase [3] the **neuroplasticity of cerebral communication pathways,** relevant to **emotional regulation** and **empathy** [3, 4]. The roots of contemplative research originate from a dynamic exchange between meditation practitioners and scientists, and this interaction has a unique potential for promoting social and behavioral skills in a multicultural environment.

Moreover, in the face of suffering due to common somatic and mental health problems (*e.g.*, a chronic disease, such as TNBC with comorbidities), especially in the ethnic minority groups of women, contemplative interventions (*e.g.*,

mindfulness or compassion training) may decrease stress-related reactions to these adversities [5]. Unfortunately, in the contemplative research field, many ethnic minorities are under-represented in the studies of **mindfulness-based interventions (MBI**) [6] Moreover, participation rates of patients from minority groups in neuroscience studies focused on meditation and using **functional magnetic resonance imaging (fMRI**) methodologies, still remain low. As an attempt to address this challenge, an **Intersectional Neuroscience** model has been designed, to be used in the context of contemplative neuroscience [7].

This chapter describes a potential application of the Intersectional Neuroscience approach to developing useful metrics of meditation practice, including disadvantageous groups of participants. Perhaps, after further exploration, these findings may be applied to patients with aggressive subtypes of breast cancer (BC) (*e.g.*, triple-negative breast cancer (TNBC)).

Intersectional Neuroscience (IN) - A Novel Research Model That Can Help Determine Mental States during Meditation in Diverse Populations of Participants

A new research model, known as **Intersectional Neuroscience (IN**), may offer some helpful solutions to this challenge. **IN** adapts research procedures to include some minority or disadvantageous groups of participants, so that, they can be properly represented [7]. Moreover, **IN** incorporates some inclusive processes into research study designs, based on community engagement with diverse populations of participants [7]. Simultaneously, some individualized multivariate neuroscience methods to accommodate individual neural diversity are also introduced [7].

Recently, the feasibility of this framework was tested with a meditation center, in the US, using a small focus group [7]. The **functional magnetic resonance imaging (fMRI**) screening and recruitment procedures were adapted to be inclusive of participants from various under-represented groups, including ethnic minorities, people with disabilities, neuropsychiatric disorders, and low-income [7].

EVALUATING MULTIVARIATE MAPS OF BODY AWARENESS (EMBODY) - THE INNOVATIVE TASK TO "DECIPHER" MENTAL STATES DURING THE BREATH-FOCUSED MEDITATION

In a recent study, the participants completed the **Evaluating Multivariate Maps of BODY Awareness (EMBODY**) task, which applies individualized machine learning algorithms to fMRI data, in order to identify mental states during **breath-focused meditation**, a **basic skill that stabilizes attention** to support **interoception** and **compassion** [7].

CHAPTER 11

May We Adjust the "Third Wave" of Cognitive and Behavioral Therapies (CBT) and Psychological Processes of Change for Women with Breast Cancer?

Abstract: To emphasize on the suffering of women with breast cancer (BC), it is necessary to identify and deeply understand many aspects of BC etiology, development, and complex management. However, the strategies for achieving these goals for individual patients often need to be refocused, or redirected, based on personal expectations, needs, and circumstances that can differ considerably among women with very aggressive BC, such as triple-negative breast cancer (TNBC). The main goal of cognitive-behavioral interventions is to change some specific thoughts, emotions, and behaviors and teach constructive coping skills and behavioral modifications, which will aid in building an individual activity plan, coordinated with cancer-related therapies.

This chapter will present the concept of the "**third-wave" cognitive and behavioral therapies (CBT)** and the importance of **psychological processes of change**, in supportive care interventions, for patients with TNBC. Adding such processes of change should facilitate the development of personalized care solutions for better outcomes for many patients suffering from BC, despite their poor prognosis. This should encourage the patients, caregivers, and their medical care teams to learn, and then, apply these safe interventions in their individualized contexts.

Keywords: Acceptance and commitment therapy (ACT), Cognitive and behavioral therapies (CBT), Psychological processes of change, Psychological flexibility, Mindfulness-based cognitive therapy (MBCT).

INTRODUCTION

Traditionally, **cognitive and behavioral therapies (CBTs**) have been studied in **randomized controlled trials (RCTs**) for specific psychiatric syndromes. However, the **RCTs** have often failed to pay attention to the **processes of change**, which play a critical role in the survival of many women, who struggle with breast cancer (BC). In order to rectify this problem and to effectively help individual patients with BC achieve their functional goals (often in the face of adverse prog-

Katarzyna Rygiel

nosis) a new solution is needed, in which, person-oriented, feasible, and effective methods should be applied [1]. It appears that the "**third-wave" CBTs** attempts to offer a reasonable solution to this challenge. It should be highlighted that in the "**third wave" of CBTs**, the cognitive and behavioral components began with **a person-oriented focus**, which represents a **transition** from rather "static" classical therapeutic models to much more dynamic **processes of change** [1]. Since many mental disorders or psychosomatic diseases (*e.g.*, BC associated with distress or depression) cannot be simply classified into predefined, "formal" categories, the new CBT methods may be more suitable to target some processes of change [1].

This chapter will briefly describe the concept of the "t**hird-wave" CBT** and the **psychological processes of change**, and their role in supportive interventions, for patients with triple-negative breast cancer (TNBC). This should encourage the patients, their caregivers, and medical care teams to learn and then apply these safe interventions in their individualized contexts.

AN ADVENT OF THE "THIRD-WAVE" COGNITIVE AND BEHAVIORAL THERAPIES AND PROCESS-BASED APPROACHES TO PATIENTS WITH BREAST CANCER

The main innovative features of the **"third-wave" CBTs** involve **focusing on the context and function**, as well as on applying a concept of **psychological processes of change** to the patients and their clinicians or care teams [1]. In this way, such new CBT methods can be considered as a well-organized approach to process-based functional analysis [1]. **Psychological processes of change** can be structured in six domains, including cognition, affect, attention, self, motivation, and behavior (Fig. **1**) [1].

Moreover, the **"third-wave" processes** are characterized by **psychological flexibility**, which combines the concepts in each of the above six dimensions, and enriched them by adding a perspective-taking sense of self, and personal values as motivating factors [1].

In addition, the **psychological processes of change** are adaptable and can harmoniously blend two or more of the six domains. Subsequently, matching the safe, simple, and accessible psychological intervention strategies, to target the appropriate goals for individual women with TNBC, may represent an important step forward in the direction of personalized care (Fig. **2**) [2].

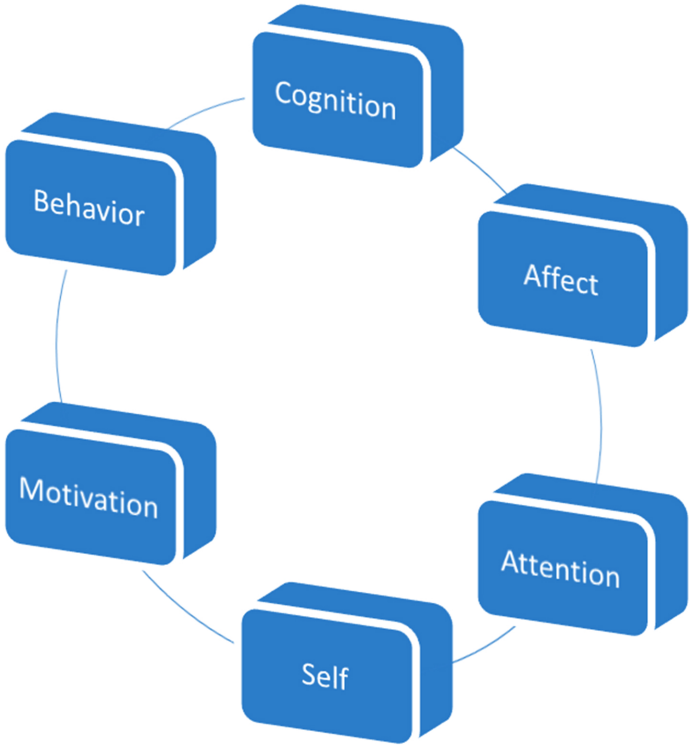

Fig. (1). The "third-wave" CBT - psychological processes of change organized in six domains; CBT, cognitive and behavioral therapy.

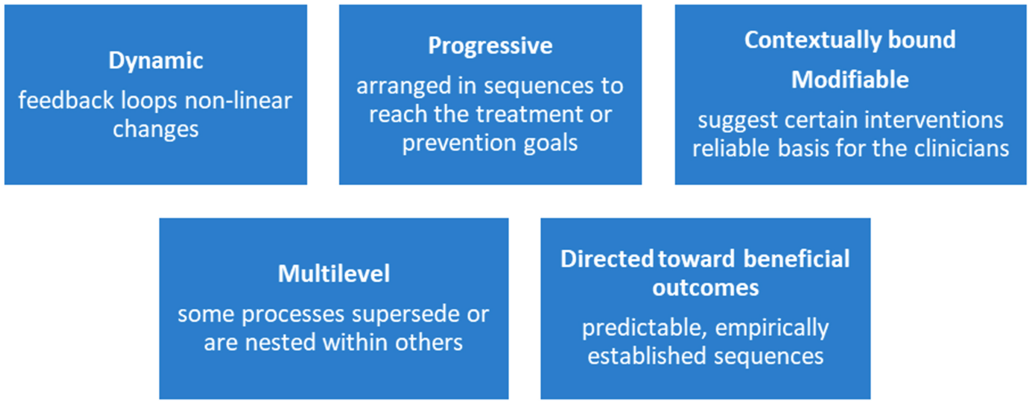

Fig. (2). Common mechanisms involved in the psychological processes of change in the new cognitive and behavioral therapy (CBT).

CHAPTER 12

Exceptional Responders: Exploring the Molecular "Make-up" of Patients with Cancer Who Experienced Recovery

Abstract: Patients with cancer, who have achieved an unexpectedly **favorable** and long-term clinical **response** are commonly known as **exceptional responders (ER)**. Such patients have often experienced extraordinary responses to some oncology therapies, which have been ineffective for other individuals with similar malignancies.

These unusually positive responses may be partially due to some unique genetic and molecular mechanisms, which can be further studied. This, in turn, could provide some directions to a better understanding of why the specific therapy works for only a small number of patients with cancer, but not for everybody. To further elucidate these issues, the **National Cancer Institute (NCI**) has been conducting various research projects to explain biological processes, which can be responsible for these remarkable responses.

A recent pilot study, known as the **Exceptional Responders Initiative (ERI),** has evaluated the feasibility of identifying exceptional responders retrospectively, by obtaining pre-exceptional response treatment tumor tissues and analyzing them with modern molecular tools. The promising findings of this study can inspire many women with breast cancer (BC) and their medical teams.

This chapter presents a synopsis of the **ERI**. It suggests some possibilities to adjust this concept for patients with breast cancer (BC) (*e.g*., advanced or metastatic triple-negative breast cancer (TNBC)).

Keywords: Actionable mutations, Exceptional responders, Exceptional responses, Integrated studies, Next-generation sequencing (NGS), Precision oncology.

INTRODUCTION

Patients with cancer, who have achieved **unexpectedly beneficial** and **long-standing clinical responses to therapy** are commonly known as **exceptional responders (ER)** [1]. Such patients have demonstrated an extraordinary response to some anticancer treatments, which have been ineffective for others with similar types of cancers [1].

Katarzyna Rygiel

These **exceptional patient cases** are very interesting and challenging to many researchers and clinicians, who want to find out what exactly they have been doing to recover from cancer, despite the adverse prognosis. Initially, casual examples of remarkable outcomes of chemotherapy (CHT) or targeted therapy were rather informal observations, because the clinicians' ability to identify the molecular mechanisms underlying relatively rare responses has been limited. However, currently, with a growing interest in this area, the situation has changed. It is conceivable that such unusual responses can be attributed, to some degree, to individual genetic and molecular mechanisms, which may offer valuable directions to a better understanding of why the specific therapy works for only a small number of patients, but not for a majority of them. Recently, the **National Cancer Institute (NCI**) has been conducting research projects, trying to explain complex biological processes that are potentially responsible for these unusually positive clinical responses [1, 2].

This chapter briefly presents a synopsis of the **Exceptional Responders Initiative (ERI).** It suggests some possibilities to adjust this concept to patients with breast cancer (BC), in particular with aggressive subtypes (*e.g.*, triple-negative breast cancer (TNBC)).

The Exceptional Responders Initiative (ERI) – New Hopes and Challenges Uncovered by a Pilot Study

The **exceptional response** has been defined as a **partial response (PR**) or **complete (CR) response** to systemic anticancer treatment with a population PR or CR rate less than 10% or an unusually lengthy response (*e.g.*, duration three times higher than the median) [2].

The **NCI** has recently conducted a **pilot study** that retrospectively evaluated **clinical data** and **tumor samples** from over one hundred cases of patients with cancer [2]. To test the feasibility of collecting the archival tissues from **exceptional patients** and conducting subsequent molecular profiling, **NCI** introduced a protocol for the **Exceptional Responder Initiative (ERI**) study [2].

Molecular profiling technology, including **next-generation sequencing (NGS**), has transformed the development of oncology therapies, especially in the early phases of clinical trials, with efforts to select patients, depending on molecular aberrations. The **ERI** tumor material, collected from several cancer types, provided by the participated oncologists, was profiled [2]. These cancer cases usually involved patients undergoing targeted therapies. However, these **patients were treated without knowing their tumor's genomic alterations**. Post-treatment, when it was revealed that some of them had specific genomic changes, which could have made their tumor particularly sensitive to blocking of a driving

pathway by a given targeted agent, this "puzzle" of better clinical effects (than expected initially) was at least partially solved [2].

The next step to elucidate this topic was to determine the exact molecular causes and precise reasons why some tumors responded to targeted therapies or to standard chemotherapies (CHT). Finding correct answers to this question would potentially allow adjusting the therapeutic options to patients, who have the highest probability to respond to certain therapies. For instance, in the **ERI** pilot study, including over one hundred cases of exceptional responders, about 70% of participants were treated with combination CHT regimens, almost 30% had received anti-angiogenesis agents, and a few patients had been treated with immune checkpoint inhibitors (ICI) [2]. Moreover, clinically relevant germline mutations were identified in six tumors, including pathogenic ***BRCA1*** or ***BRCA2*** mutations, which were found in two women with BC. For instance, one patient with BC had a pathogenic *BRCA1* germline mutation, and another had a germline mutation in ***CHEK2***. In addition, a patient with lung cancer, who had a history of BC, had also a ***PALB2*** mutation [2].

Molecular mechanisms are crucial, but other factors (*e.g*., comorbidities, use of medications, complementary approaches, and lifestyle components) can also contribute, often in unpredictable ways, to eliciting an **exceptional response** [2]. Therefore, a future gathering of such variables would allow adequately presenting the findings, in order to design concepts about molecular and other reliable predictors of response or resistance to anticancer treatment.

In summary, in the **ERI** pilot study, **ER cases** represented different types of cancers and treatment strategies, such as standard cytotoxic chemotherapy (*e.g*., single or multi-agent CHT), CHT/radiation combinations, or investigational therapeutics (*e.g*., modern targeted therapies) [2]. Several cases with exceptionally durable PRs (*e.g*., over 100 months) may represent actual CRs or tumors with an indolent clinical course. Prolonged responses may suggest favorable immune system influence. In this analysis, creating clusters of patients, who were treated with medications, which have similar mechanisms of action could increase confidence in reported associations between molecular alterations and responses to anticancer agents within a particular pharmaceutical class [2].

Unfortunately, the **ERI study was limited**, since there was no molecular analysis of tumors from patients, who responded poorly to the same treatment that was administered to the ER patients. In fact, for an adequate comparison, clinical characteristics of non-responders to the same therapy regimen would have to be matched (*e.g*., primary tumor, performance status, medications for comorbidities, and line of treatment) to those in the **ER** group [2].

CHAPTER 13

Radical Remissions: Unique Lessons from Patients with Cancer Who Were Able to Defy the Odds and Recover

Abstract: Many women with aggressive BC subtypes are devastated, due to metastatic spread, resistance to therapy, and poor prognosis. However, there is a growing body of scientific evidence that some patients have been able to defy the odds of advanced malignancy and recover, in spite of their fatal prognosis and dismal oncology statistics. Also, these "**better than expected" clinical effects** were not totally rare.

To explore this fascinating subject, future research is undoubtedly necessary. In line with this challenge, the innovative "**Radical Remission Project**" was created, which allows collecting cases of Radical Remissions for research studies. It also connects survivors with patients, who actually struggle with aggressive cancers. Since there is a **concern about giving false hope** to patients with advanced malignancies, they need to be professionally informed that the cases of Radical Remissions must be first explored in detailed research studies, before making any conclusions about their potential applicability to patients with similar prognoses. This is necessary to protect the most vulnerable patients, who must not be given any false expectations, and the practical **communication** skills of the cancer care teams are crucial to accomplish it.

In addition, **Complementary** and **Integrative Medicine** (**CIM**), which manages the physical, mental, emotional, and spiritual needs of patients with cancer, **regardless of their prognosis**, appears to be helpful in an attempt to meet these needs. CIM is gradually becoming a part of each stage of the cancer journey, from active to supportive and palliative oncology care. Similarly, **integrative oncology** that uses **evidence-based**, lifestyle modifications, mind-body techniques, and specific natural products in combination with conventional anticancer treatments is in line with patients' safety.

This chapter briefly addresses some universal factors, which can make a genuine difference to help in recovery from cancer, based on the **Radical Remission Project** and **CIM**-related research. It focuses on the role of open and precise **communication** between patients and cancer care teams. The ongoing **Radical Remission Project** can inspire many women with breast cancer (BC) and their medical teams to consider introducing some safe and useful approaches to their standard oncology management.

Keywords: Complementary and integrative medicine (CIM), Communication, Decision-making, Integrative oncology, Radical remissions, Supportive care.

Katarzyna Rygiel

INTRODUCTION

It should sound optimistic for some women with aggressive BC subtypes, who are often overwhelmed, due to metastatic spread and poor prognosis) that there is a growing body of research evidence that some patients were able to defy the odds, and recover, in spite of their adverse prognosis and dismal oncology statistics [1]. These individuals have often been diagnosed with incurable malignancies, but their experiences have been atypical or uncommon, in a positive sense. Moreover, these "**better than expected" clinical outcomes** were not totally rare. In fact, there are numerous patients with cancer, who have extended their survival far beyond the upper limits of the median, or who recovered, after having received a terminal prognosis, based on the standard oncology approach [1, 2].

On the other hand, however, there is a real **concern about giving false hopes** to patients with advanced malignancies [2]. It should be underscored that such patients need to be clearly informed that the cases of r**emissions** must be first explored in detail, according to strict research procedures, before making any conclusions about their potential applicability to patients with similar prognoses. Also, it should be emphasized that navigating through false hope (often promoted in the media) is very difficult, and the patients should be protected, and not be given false expectations. Therefore, any extraordinary remissions cases need to be discussed with caution and analyzed in the individual patient's context. Of course, studying long-term survivors should be a high priority, for both clinicians and researchers [2].

In line with these goals is **Complementary** and **Integrative Medicine** (**CIM**), which gradually becomes a part of each stage of the cancer journey, and in particular, supportive and palliative oncology care [3]. **CIM** manages the physical, psychological, emotional, and spiritual needs of patients with cancer, **regardless of their prognosis** [3]. Similarly, **integrative oncology** uses **evidence-based**, safe lifestyle modifications, mind-body practices, and specific natural products in conjunction with conventional anticancer treatments [4]. Effective **communication** about applying the most appropriate **CIM** or **integrative oncology** interventions requires multidisciplinary skills from the cancer care team members.

This chapter briefly addresses some universal factors, which can make an actual difference to help with recovery from cancer, based on the **Radical Remission Project** and **CIM**-related research. It also focuses on the remarkable role of **communication** between patients and providers. Recent reports of the ongoing **Radical Remission Project** can inspire many women with breast cancer (BC) and

their medical teams to consider incorporating some safe and useful approaches to their standard oncology management.

"The Radical Remission Project"-Directions for Future Research and Navigation Through the Labyrinth of False Hope

"The Radical Remission Project" offers an innovative website (www.RadicalRemission.com) that allows collecting cases of Radical Remissions for research studies [5]. In addition, this project connects Radical Remission survivors with patients, who actually struggle with various types of aggressive cancers [5]. According to a detailed analysis of numerous cases, documented in this project, some common factors that can make a real difference to help achieve recovery from cancer were reported, involving universal psychosocial (mental or emotional) and nutritionally-related domains (Fig. **1**) [5].

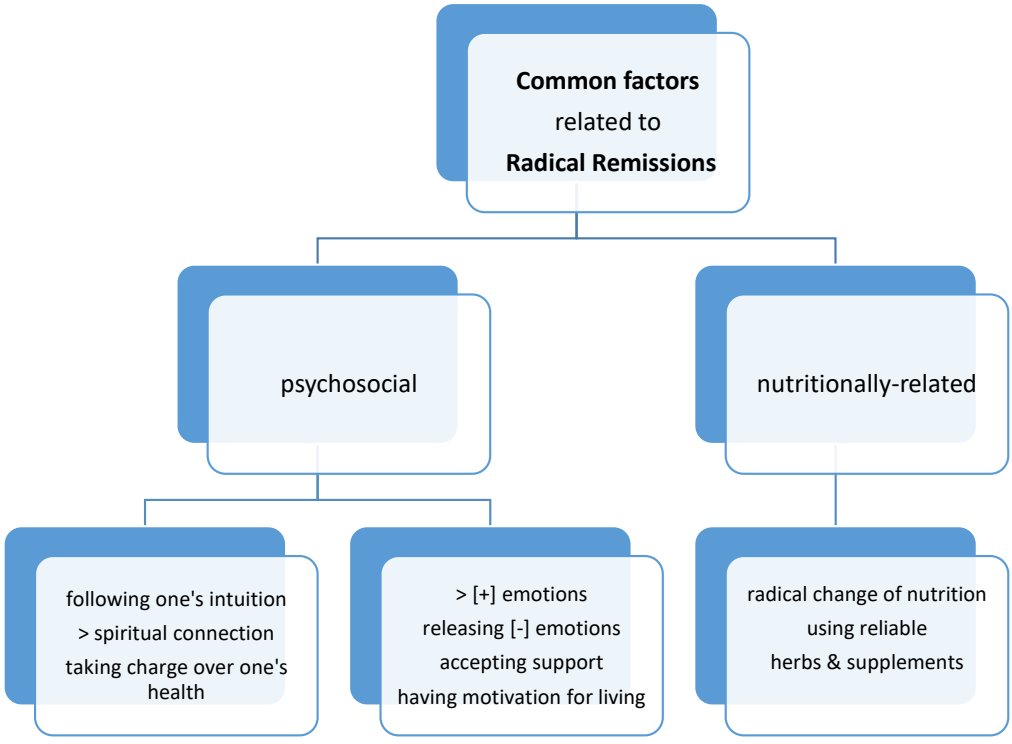

Fig. (1). Common Lifestyle-related Factors Reported in Radical Remission Cases.

CHAPTER 14

How Can We Redefine Hope and Gratitude to Help Patients with Breast Cancer Build Their "New Life"?

Abstract: There is a need to practically **redefine the future way of life**, among numerous patients with breast cancer (BC). In fact, **spirituality, hope,** and **gratitude** may play a remarkable role in a possible transformation into a **"new life**". Also, these invisible, positive "forces" recognize patients as individual human beings, which should be connected with their families, caregivers, friends, and medical professionals, as functional "units".

This chapter provides some suggestions for practical approaches to help **design a functional "new life**", especially for women with aggressive BC (*e.g*., triple-negative breast cancer (TNBC)). In addition, medical care teams may consider incorporating such supportive modalities into the main therapeutic oncology plan.

Keywords: Breast cancer, Gratitude, Hope, Medical professionals, Patients with cancer, Spirituality.

INTRODUCTION

Many women with **newly diagnosed breast cancer** (**BC**) or those, who already encountered a disease **crisis** (*e.g*., due to advanced, recurrent, or **metastatic BC**) often wonder what their life is going to be like during and after anticancer therapies. At that time, they frequently re-evaluate some past experiences and worry about what the future will bring. Some patients are searching for stability or so-called "normal" life. However, they typically experience serious emotional "turbulences" associated with symptoms of **distress, anxiety,** and **depression** relevant to BC.

During the cancer journey, when a "**new reality**" sets in, what was once crucial in life can momentarily change. Some women struggle harder to hang onto who they were, while others are able to simply allow "letting go" and give a chance to the **"new normal**" scenario. This approach often permits them to **discover new meaning in life** that subsequently enables them to move forward, despite experi-

Katarzyna Rygiel

encing many disturbing symptoms or negative emotions. At this point, **mindfulness-based stress reduction (MBSR**), which offers **mindfulness meditation** to decrease symptoms of **distress, anxiety,** and **depression**, can be extremely helpful in different populations of patients with BC [1]. For instance, according to recent study findings, the psychological symptom reduction reported after the MBSR intervention was clinically significant and meaningful for many patients [1]. In addition, such results have indicated that the reliable improvements on each measurement scale (*e.g*., worry, depression, anxiety, and distress) can be conveniently assessed and precisely monitored for each involved patient [1].

Many patients with BC grieve the **loss of** the specific "**roles**", they played in life. One of the crucial elements is to help them realize that although BC may occupy a "central" place in their present situation, with time, this can eventually become only a "peripheral" part of their life. This particular view has a remarkable potential to "**open the door**" to new possibilities in the future. At this point, cancer care teams and their patients with BC might be encouraged to know that MBSR alleviates different psychosomatic symptoms, often contributing to meaningful, long-term changes in patients' ways of thinking, feeling, and approaching numerous obstacles related to BC or its therapies [1]. Moreover, women with BC could be reminded of the significance of **hope** and **gratitude** in a daily life struggle to reclaim internal balance and strength to go forward [2].

This chapter outlines some suggestions (according to recent studies) for useful approaches to help **design a functional "new life**", especially for women with aggressive BC (*e.g*., triple-negative breast cancer (TNBC)). In addition, medical professionals may consider to incorporate such supportive modalities into the main therapeutic oncology plan.

PRECIOUS "SECRETS" OF LONG-TERM SURVIVORS OF BREAST CANCER

Positive emotions can serve as building blocks for **resilience**, especially at stressful times, like those, experienced by women with BC. Moreover, some positive emotions, such as **gratitude**, may play an adaptive role under such adverse circumstances. Based on a study that examined a group of women with metastatic BC, it has been revealed that grateful responding to received benefits predicted an increased perception of social support (especially in patients sensitive to positive emotions) [2].

Moreover, according to a qualitative study, long-term survivors of BC were "going through" distinct stages of the survival process, such as analyzing the BC diagnosis and its consequences, confronting a possible death, reprioritizing values

in life, moving forward, and flashing back (similar to posttraumatic stress disorder (PTSD)).

It should be underscored that several study participants reported that they emerged from their BC experiences with more **gratitude for the gift of life**, a clear sense of self, confidence, and internal power to overcome future health crises. These findings suggest that cancer care team members could incorporate the individual context of a given patient's life to augment the beneficial effects of integrative oncology management [3].

A "FRESH LOOK" AT HOPE, GRATITUDE, AND SPIRITUALITY CONCEPTS IN THE CONTEXT OF PATIENTS WITH BREAST CANCER

Hope and **gratitude** represent an important step in **redefining the future way of life** for numerous women with BC (Fig. **1**) [2, 3]. It should be underscored that cancer care teams are in a unique position to teach their patients with BC to practically apply **hope** and **gratitude** during the most **challenging moments of the cancer care journey**, in agreement with the patient's personal beliefs, family, or social values, and cultural traditions. In fact, despite many sociocultural differences, patients have usually displayed **similar coping mechanisms** [2, 3]. However, their **points of view on cancer-related situations** can be different. Nevertheless, some **universal tools** can be used to aid in surviving many critical situations, and then, practical lessons about **hope** and **gratitude** can **help** them **reclaim a new, functional way of life** [2, 3].

It has been commonly known that patients with BC can use different **coping strategies** for **stress, trauma,** and **adversity**. Unfortunately, some of them are destructive (*e.g*., alcohol, nicotine, or substance abuse), since they mostly create a temporary illusion, and in reality, augment existing problems or create a harmful "escape" from them. Similarly, denial can go a long way to providing respite from trauma, but cannot resolve difficult, chronic, BC-related problems.

However, some other strategies are productive (*e.g*., moderate physical exercise, social engagement, or mindfulness meditation), since they are focused on confronting the unavoidable challenges and building resilience to survive cancer itself and its therapies [1 - 3]. In addition, the constructive techniques focused on being hopeful and grateful may also serve as effective **tools for letting go of negative emotions** (*e.g*., anger, fear, guilt, anxiety, and sadness). Patients who lose their coping skills can often regress into depression, anxiety, and hopelessness. They can lose interest in what was pleasing them in the past, and find out that cancer has "stolen" their joy of life. Moreover, they can lose their sense of identity, which often raises concerns among family members or friends,

CHAPTER 15

The Self-kindness Component of Mindfulness Meditation: A Helpful Strategy to Enhance Emotion Regulation and Reduce the Depression and Distress Symptoms in Women with Breast Cancer

Abstract: It has been demonstrated that one of the components of **mindfulness meditation,** called **self-kindness**, plays a prominent role in **alleviating distress perception**, and **reducing depressive symptoms,** especially among **younger women with breast cancer** (**BC)**, who represent a particularly vulnerable patient population, often struggling not only with a serious illness but also with numerous family and work-related obligations.

This chapter will describe in detail **self-kindness** as a technique to help **ease distress, anxiety,** and **depressive feelings,** as well as **enhance resilience** and establish objective health-related expectations or goals for **patients with cancer,** including women with an aggressive subtype of BC, such as **triple-negative breast cancer** (**TNBC)**.

Keywords: Anxiety, Distress, Depression, Emotion regulation, Mindfulness meditation, Mindful awareness practice (MAP), Mindfulness-based interventions (MBI), Resilience, Rumination, Self-kindness.

INTRODUCTION

The essence of **mindfulness** is the practice of **focusing attention** on the "**here and now**" and accepting whatever arises in the awareness, with curiosity, and without judgment. However, some mechanisms for effective interventions, which can be translated into daily practice, still need to be elucidated in more detail.

A recent study examined some **emotion regulation strategies,** as factors that influence the effects of **mindfulness meditation** among young women, undergoing treatment for BC, in whom risks of psychological distress and depression are considered high. In fact, degrees of perceived **distress or depression** at **breast cancer (BC)** diagnosis, and then, during many critical

Katarzyna Rygiel

moments of the BC progression, or in the treatment process are usually higher in younger females, than in their older counterparts [1]. This is pertinent to **patients with triple-negative breast cancer** (**TNBC)**, who often receive a diagnosis of this aggressive malignancy at a younger age.

It has been noted that **Mindfulness-Based Interventions** (**MBI)** can decrease psychological distress and depressive symptoms in patients with cancer, cancer survivors, and many other populations (*e.g*., patients with chronic psychophysical diseases) [2, 3]. **It seems that** women with TNBC would be a good target population for **MBI**, and in particular, for the selected, **"**patient-friendly" components, such as the **self-kindness** approach, which could be translated into a daily routine.

This chapter will describe in detail s**elf-kindness** as a technique to help **ease distress, anxiety,** and **depressive feelings,** as well as **enhance resilience** and establish realistic health-related expectations and goals for **patients with cancer,** including women suffering from **TNBC**.

THE SELF-KINDNESS – A BASIC COMPONENT OF MINDFULNESS MEDITATION THAT CAN IMPROVE EMOTION REGULATION, DECREASE DISTRESS PERCEPTION AND INCREASE RESILIENCE

Self-kindness, as an **emotion regulation strategy**, can play a unique role in reducing distress in younger women with BC [3, 4]. Although **self-kindness** still requires further studies, to assess its effects in different age groups of women with BC, it is considered a safe, feasible, and beneficial approach, and thus, it appears suitable for **women with BC** (*e.g.*, TNBC), who are frequently in the younger age category [5].

It has been suggested that **Mindfulness-Based Interventions** (**MBI)** reduce distress *via* better **emotion regulation.** Moreover, **MBI** can "operate" through the "channels", by which it is possible to change the patterns of experiencing and expressing emotions [3, 4]. Notably, impaired emotion regulation has been connected to higher degrees of perceived distress [3, 4] and depression [3 - 5]. This can have particularly deteriorating consequences in patients with TNBC. In a recent clinical study, two contrasting **emotion regulation** processes, namely: **self-kindness** and **rumination,** were addressed by using a standardized intervention, in the form of the **Mindful Awareness Practice (MAP)** [6]. The study results have shown that the **MAP** reduced the feelings of perceived distress and depressive symptoms in a younger group of BC survivors [5 - 7].

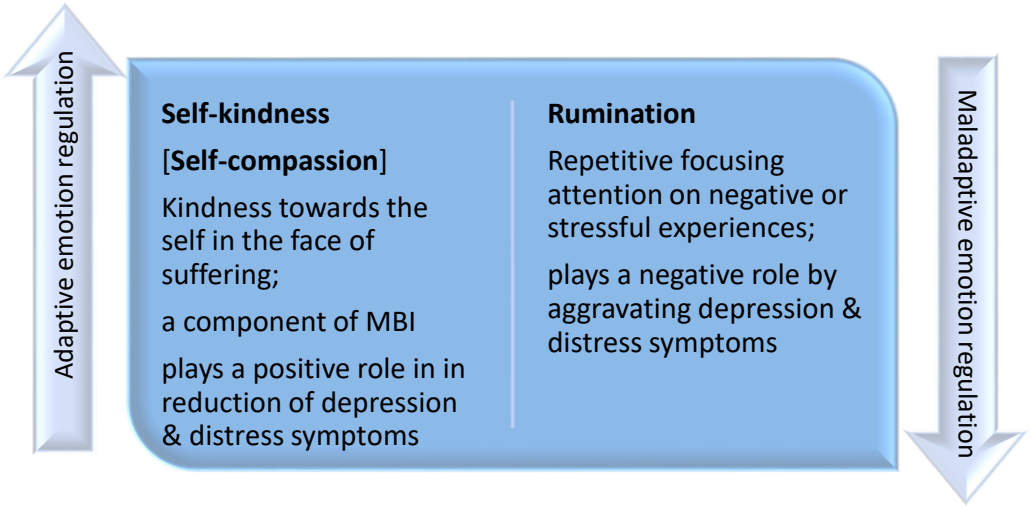

Fig. (1). The main characteristics of two emotion regulation processes linked to depression and distress - self-kindness and rumination; MBI, Mindfulness-Based Interventions.

These encouraging study findings would merit further exploration and possible implementation, as one of the supportive care options, for women suffering from TNBC.

TWO OPPOSITE DIRECTIONS OF THE EMOTION REGULATION - SELF-KINDNESS STRATEGY AND RUMINATION PROCESS

In brief, **self-kindness** is an **adaptive emotion regulation strategy**, which includes the generation of **kindness towards the self in the face of personal suffering** (Fig. **1**) [8]. **Self-kindness (**or **self-compassion)** is one of the components of a multi-dimensional construct, related to lowering the negative impact of depressive symptoms on the psychosomatic condition [8]. As an illustration of this view, in a study focused on depression, it was reported that directing kind thoughts toward the self was equally effective to a cognitive reappraisal, for a successful decrease of a negative mood, in the depressed participants [9].

In opposition to that, **rumination** is a maladaptive emotion regulation process that includes passive, repetitive **focusing attention** on the causes and consequences of **negative or stressful experiences** (Fig. **1**). Rumination often predicts the onset of depression and the persistence of its symptoms [10]. Unfortunately, women who are diagnosed with BC are also more prone to **depression,** often associated with insomnia, anxiety disorders, or other mental problems [10].

CHAPTER 16

Compassion-Focused Therapy (CFT): Introducing a Process-based System of Psychotherapy to Help Patients with Breast Cancer

Abstract: Compassion-focused therapy (CFT) integrates techniques from cognitive-behavioral therapy with concepts from psychology and neuroscience. The main objective of **CFT** is to use compassionate mind training to help individuals develop and maintain the experiences of inner warmth and stability, through the cultivation of compassion (including **self-compassion**).

This chapter will describe in detail **self-compassion** as a technique to help ease distress, anxiety, or depressive feelings, as well as enhance resilience and establish objective health-related expectations and goals for patients with serious chronic diseases, such as cancer, including triple-negative breast cancer (TNBC).

Keywords: Behavioral practices, Compassion-focused therapy (CFT), Negative emotions, Psychoeducation, Self-compassion.

INTRODUCTION

Compassion is an important derivative of the **biopsychosocial** process of care, which was developed to assure protection, safety, and support of the most vulnerable patients [1].

Moreover, **compassion** can offer encouragement and guidance for learning how to regulate threatening emotions, which are overwhelming or destructive [1]. In this constantly evolving **process** of psychotherapy, one of the main universal components is **Compassion-Focused Therapy (CFT)**, which is a system that integrates techniques from cognitive-behavioral therapy with concepts from psychology, and neuroscience [1]. The main purpose of **CFT** is to use compassionate cognitive training to help individuals develop and maintain the experiences of inner warmth or safety, through the cultivation of an attitude of compassion (including self-compassion) [2].

Katarzyna Rygiel

Such a concept of **compassion**, as an **innovative therapeutic option**, is based on internal **wisdom** and **courage that might characterize many** patients with cancer or other serious, chronic diseases. Moreover, compassion is viewed as a **constellation** of different **abilities, insights, motivations,** and **competencies**, which can be flexibly applied as potential **therapeutic modalities** for many types of psychosomatic problems [1, 2].

CFT can be delivered as a practical educational **course**, during which a **functional analysis** of common **safety behaviors** used by many patients can be conducted [2]. This **analysis** can subsequently be compared to the functional model of caring behavior and compassion. During this **process,** finding some specific points for a potential **compassionate self-correction** may serve as a very helpful solution to many difficult problems, which are often encountered by chronically ill patients (*e.g.*, including those with advanced or metastatic triple-negative breast cancer (TNBC) and its comorbidities).

In addition to the usual caring, which provides protection and support, **compassion** offers some unique ways of **regulating negative emotions**. Most importantly, it should be underscored that negative emotions often contribute to the patient's psychosomatic destabilization. As a counterbalance to that, the compassionate style of reasoning, imagining, and acting can be learned, exercised, and possibly introduced into a daily routine. Therefore, it would be beneficial to teach, guide, and encourage patients to use these simple techniques, as a part of the multidisciplinary supportive therapy.

This chapter will describe **self-compassion** as a technique to help ease distress, anxiety, or depressive feelings, enhance resilience, and establish realistic health-related expectations and goals for patients with serious chronic diseases, such as cancer, including TNBC.

A CONCEPT OF COMPASSION AS AN INNOVATIVE THERAPEUTIC MODALITY USING BEHAVIORAL APPROACHES - POSSIBLE BENEFITS OF CFT FOR THE PATIENTS WITH BREAST CANCER

The CFT can help patients **depersonalize** and **decenter from their inner experiences**, which are undesirable. At this point, it would be useful for patients to recognize that they naturally have a particular type of consciousness, which is free of content [2]. The content is usually created from genetic predispositions and social or environmental exposures that are, in fact, random experiences of consciousness. Moreover, such knowledge and insights can play a crucial role in reducing many destructive effects of suffering from isolation, distress, despair, marginalization, shame, or irrational self-criticism, among many vulnerable patients with breast cancer (BC) [2].

Furthermore, subsequent **empathy training** can help such patients recognize that they may unintentionally arrive at some "unnecessary" states of suffering (for themselves or others, like caregivers or family members). Therefore, teaching them how to "reorganize" their internal "software" can possibly help them find some "hidden obstacles" within themselves so that they can override them, to be able to function at a more acceptable or comfortable level. Also, it should be highlighted that **CFT** may help patients recognize that practicing several forms of **mindfulness** can increase their sensitivity to different states of mind [2]. This, in turn, may allow them to be aware of specific motives and emotions that they experience during their disease and therapy journey. Furthermore, **mindfulness** is one of the pillars of CFT, which can help detect when exactly one should **switch the attention, thoughts, emotions, and motives away from the unhelpful or unacceptable, toward the most helpful or acceptable patterns** (Fig. **1**) [2, 3].

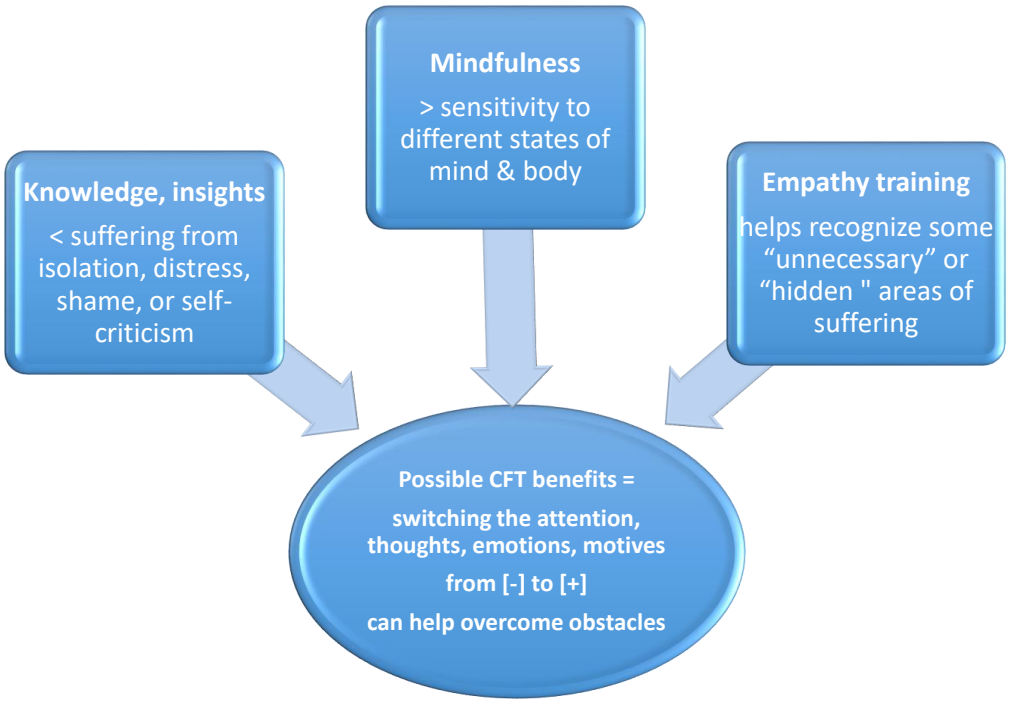

Fig. (1). Possible benefits of CFT for patients with breast cancer; CFT, Compassion-Focused Therapy.

ACCESSIBLE TECHNIQUES FOR ENHANCING THE BIDIRECTIONAL MIND AND BODY CONNECTIONS

Concurrently, the **CFT** may allow patients to refine their mental awareness and abilities to distinguish between complicated motives, dynamic emotions, and

CHAPTER 17

How Can Medical Professionals Maintain Compassion for Their Patients with Breast Cancer?

Abstract: Compassion in the medical field differs from its traditional meaning in daily life. In medicine, **compassion includes a desire to understand an individual's suffering, together with a wish to relieve it**. In essence, **compassion** offers a unique concept, according to which, the modern science of compassion can be practically applied to suffering people, in many circumstances. This is particularly important for some vulnerable groups of patients (*e.g*., ethnic minorities), such as women with **breast cancer (BC**) (*e.g*., in advanced or metastatic stages, with comorbidities and socioeconomic problems).

This chapter presents some suggestions (based on recent research reports) for helpful **strategies that medical professionals can use** daily, **to help maintain compassion** for their patients with serious diseases, including some aggressive **cancers** (*e.g*., Triple-Negative Breast Cancer (TNBC)).

Keywords: Breast cancer (BC), Compassion, Empathy, Medical professionals, Patients with cancer, Sustainable compassion training (SCT), Transactional model of compassion (TMC).

INTRODUCTION

Compassion is one of the most important **ingredients of healthcare**, certainly desired by patients and their families. Unfortunately, in the past, research was mainly focused on **compassion fatigue** or **burnout**, and not on the **beneficial role of maintaining compassion for patients** by the medical teams in charge of their care [1]. In medicine, **compassion includes a desire to understand an individual's suffering, together with a sincere wish to relieve it** [2]. Naturally, compassion involves awareness and sensitivity to recognize physical or emotional suffering, feeling for the suffering person, tolerating some degree of discomfort (relevant to another individual's suffering), as well as motivation to actively relieve suffering [3].

Katarzyna Rygiel

The desire to alleviate suffering is the main attribute that differentiates compassion from empathy or sympathy [2, 3]. Simply put, **empathy** is the capacity to understand or feel what another person is experiencing. That means the ability to place oneself in another's position. Empathy includes a range of cognitive, emotional, and social processes, mostly concerned with understanding others, and thus, different types of empathy can be distinguished (Fig. **1**).

This chapter presents some suggestions (based on recent research reports) for helpful **strategies that medical professionals can use** daily, **to help maintain compassion** for their patients with serious diseases, including **cancer** *(e.g.*, Triple-Negative Breast Cancer (TNBC)).

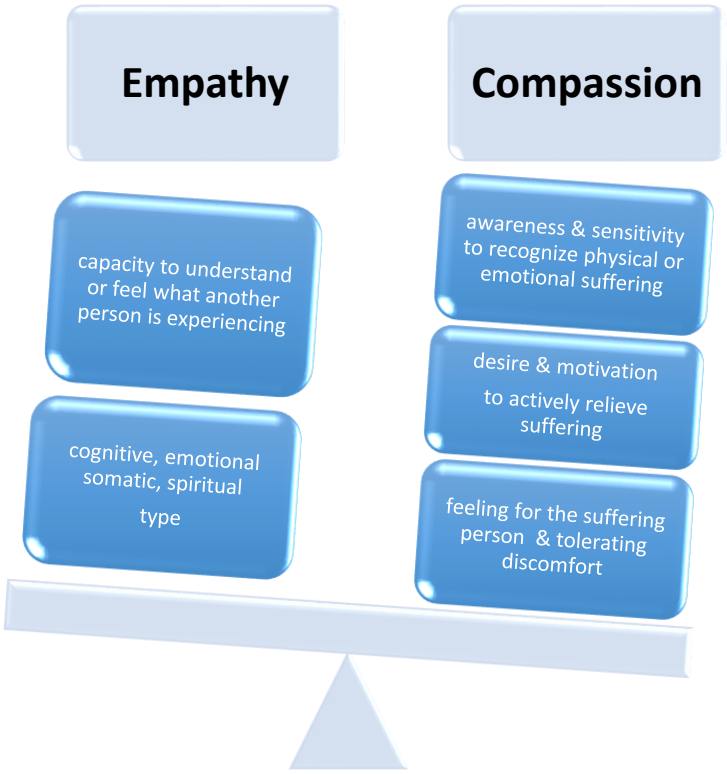

Fig. (1). A comparison of compassion and empathy.

WHY COMPASSION AND EMPATHY ARE SO CRUCIAL TO DELIVERING THE HIGH-QUALITY HEALTHCARE?

In an attempt to answer this question, some basic facts need to be considered, as follows:

1). **Compassion** and **empathy** are extremely important, due to their documented **correlations with beneficial patient outcomes** (*e.g*., decreased anxiety), increased patient satisfaction, reinforced patient-doctor relationships, decreased **posttraumatic stress disorder (PTSD)** after medical emergencies or disasters, and improved overall health outcomes [4].

2). **Compassion** is associated with **positive consequences for physicians** or nurses (*e.g*., greater work satisfaction or patient retention), and financial compensation, not to mention economic advantages for health care systems, due to fewer medical errors or malpractice lawsuits [5].

3). **Compassion** among physicians can **counterbalance** some harmful **stress-related reactions** [5].

Therefore, based on this evidence, compassion is a professional duty of physicians and nurses, and also, one of the patient's rights [6]. Moreover, this is an essential component for effective healthcare delivery in any setting. Therefore, discussing some feasible **strategies** that medical professionals can use to maintain **compassion** in the healthcare environment would be beneficial to the patients and to their medical providers [4, 6].

HOW THE HEALTHCARE PROFESSIONALS COULD MAINTAIN THEIR COMPASSION OR EMPATHY IN A DAILY PRACTICE?

According to a recent small study, focused on mental health, conducted among the nursing personnel and patients under their care, it was reported that **asking patients questions** and **reflecting on their individual difficulties** were the most commonly documented strategies when trying to apply an **empathic or compassionate approach** into daily medical practice [7]. Furthermore, psychological writings indicate that **mindfulness meditation**, **self-compassion**, and **connecting with patients** can help establish empathic, trustworthy relationships [8, 9].

It should be highlighted that **empathy** can offer a helpful **"window" to compassion**. However, there are some subtle differences between these two terms, mostly with regard to certain healthcare structures or contexts. Nevertheless, the **way how healthcare professionals maintain their compassion or empathy**, and which strategies are the most effective in particular circumstances, still remain unknown and deserve exploration in further clinical studies.

APPENDIX

METASTATIC BREAST CANCER

This **appendix** provides practical information, definitions of professional medical terminology, and **lists of common questions** about **metastatic BC, its diagnosis, and multidisciplinary therapy,** to help patients effectively communicate with their medical providers and caregivers.

The main purpose of this **appendix** is to educate and empower women suffering from BC to be able to openly **discuss their goals, needs, expectations,** and **concerns** before selecting the most optimal **treatment or supportive care options** for their individual clinical and personal context (based on the main reference: https://www.nccn.org/patientresources/patient-resources/metastatic-breast-cancer-2020).

HIGHLIGHTS FOR PATIENTS WITH BREAST CANCER TO REMEMBER & PRACTICAL QUESTIONS TO ASK

Where does Breast Cancer (BC) Start?

Breast cancer (BC) starts in the cells of the breast

• Almost all BCs are carcinomas (cancers originating from the cells, which line the inner or outer surfaces of the body).

• Cancer cells behave differently than normal cells (*e.g.*, unlike healthy cells, cancer cells can spread and form tumors (metastases) in other body parts).

Origins of BC:

1. Ductal BC

Starts in the cells that line the milk ducts (tubes that carry milk from the lobules of the breast to the nipple; the most common type of BC.

2. Lobular BC

Starts in the lobules (milk glands) of the breast (Fig. **1**).

How does BC Spread in the Body?

Primary BC, or primary tumor – is a local mass formed by cancer cells.

Invasive BC – is the one that has spread from the milk ducts or lobules into the surrounding breast tissue or nearby lymph nodes (LN).

Metastatic BC – is a cancer that has spread from the primary breast tumor into other parts of the body.

In this process, cancer cells break away from the primary tumor and travel through blood or lymph vessels to distant areas. Once in other sites, cancer cells may form secondary tumors (metastases) (Fig. **2**).

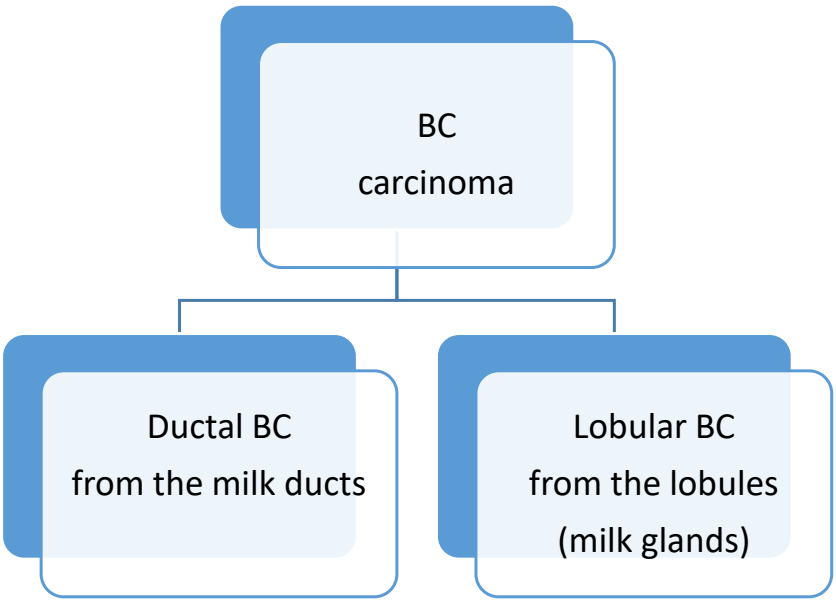

Fig. (1). Origins of breast cancer (BC).

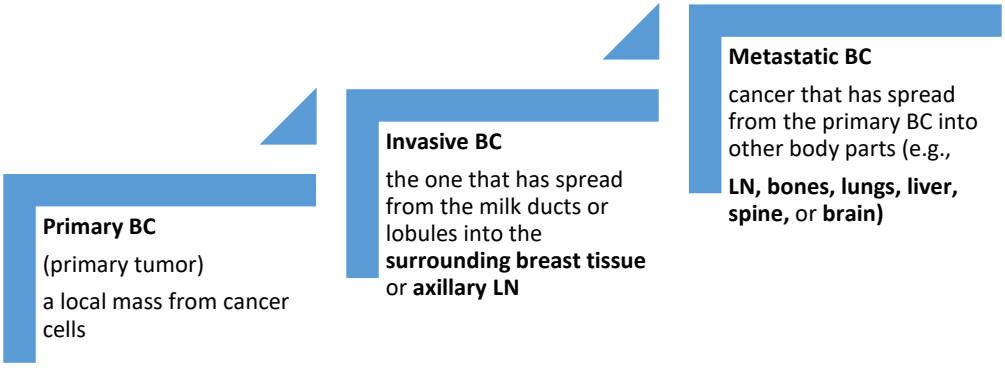

Fig. (2). Spread of breast cancer (BC). LN, lymph nodes.

Cancer that has spread to a nearby body part, such as the axillary lymph nodes, is called a **local metastasis**. It might be referred to as a **local/regional disease, invasive,** or **locally advanced.**

Cancer that has spread to a body part far from the primary tumor is called **distant metastasis**. BC can metastasize to the **bones, lungs, liver, spine,** or **brain**.

HOW DO YOU CHOOSE AN OPTIMAL TREATMENT PLAN FOR A WOMAN WITH TRIPLE-NEGATIVE BREAST CANCER (TNBC)?

In general, choosing a treatment plan that is optimal for a given woman with BC requires (in addition to standard diagnostic medical work-up) **testing for estrogen, progesterone**, and **HER2 (ER, PR,** and **HER2) receptors** since these important components of hormonal and molecular signalization pathways contribute to the growth and spread of BC.

In the case of **TNBC,** receptors for estrogen, progesterone, and HER2 are not found, meaning that the BC cells have tested negative for estrogen hormone, progesterone hormone, and HER2 receptors. Therefore, since there are:

• No estrogen or progesterone **hormone receptors (HR**), **endocrine therapy (ET) is not an option,**

• No HER2 receptors, **anti-HER2-targeted therapy is not an option**.

As a result, without any of these receptors, TNBC is more challenging to treat, and usually, **systemic therapy** is used, including multiple lines, which are given:

• Until TNBC progression occurs or

• Unacceptable toxic effects develop (that create serious health risks for a patient).

Usually, TNBC

• Has a more **aggressive behavior,**

• Is more **likely to metastasize,** and

• Often returns after treatment - **resistance** develops when TNBC stops responding to therapy.

In consequence, selecting a treatment plan that is most appropriate for a given woman with TNBC is difficult, and requires continuous, effective communication, and cooperation between a patient and her Treatment Team members.

What is the Role of Monitoring in Patients with TNBC?

The main goal of monitoring is to determine whether or not treatment provides benefits (keeping BC stable), what adverse effects are present, and how effective is their control (*e.g.*, watching for symptoms caused by BC, including pain from bone metastases).

Monitoring usually includes

• physical exams.

• laboratory blood tests.

• radiology imaging scans, and

• tumor, lymph nodes', or tissue testing (*e.g.*, biopsy).

Monitoring has been used to determine if BC is responding to treatment, or if it is resistant, and progressing.

For instance, if the bone disease is present, a patient often needs to be treated with preparations of calcium, vitamin D, and either denosumab, zoledronic acid, or pamidronate.

Also, a stomatology consultation prior to starting any of the bone-targeted agents is recommended. If an anticancer treatment is not helping any more, and it is making a patient feel worse, then it might be the moment to consider its termination, while continuing palliative and supportive care.

What are some Recommended or Preferred Options in the Systemic Therapy for HER2-negative BC?

Recommended or preferred options in the systemic therapy for **HER2-negative BC** often include different combinations of pharmacotherapy agents (Tables **1** and **2**).

Table 1. Recommended or preferred options in the systemic therapy for **HER2-negative BC**.

Recommended Pharmacotherapy Options	Pharmacotherapy Agents
Anthracyclines	doxorubicin or liposomal doxorubicin
Taxanes	paclitaxel
Anti-metabolites	capecitabine or gemcitabine
Microtubule inhibitors	vinorelbine or eribulin
For *BRCA1* or *BRCA2* mutations - PARP inhibitors	olaparib or talazoparib
For *BRCA1* or *BRCA2* mutation - platinum agents	carboplatin or cisplatin
For NTRK fusion	larotrectinib or entrectinib
For MSI-H/dMMR	pembrolizumab
For PD-L1 expression of more than 1% - ICI	atezolizumab + albumin-bound paclitaxel
Other options	Cyclophosphamide
	Docetaxel
	Albumin-bound paclitaxel
	Epirubicin
	Ixabepilone

Table 2. Additional combinations therapies used in some cases of **HER2-negative BC**.

Combination Therapy	Pharmacotherapy Agents
AC	doxorubicin + cyclophosphamide
EC	epirubicin + cyclophosphamide
CMF	cyclophosphamide + methotrexate + fluorouracil
GT	gemcitabine + paclitaxel
Other options	gemcitabine + carboplatin
	paclitaxel + bevacizumab
	carboplatin + paclitaxel or albumin-bound paclitaxel
	docetaxel + capecitabine

Multiple lines of systemic therapy are often given until BC progression or unacceptable toxicity (a serious risk to a woman's overall health) occurs.

How BC Progression can be Manifested?

BC progression can be manifested by various symptoms experienced by patients and changes or new abnormal findings documented by different tests (Fig. **3**).

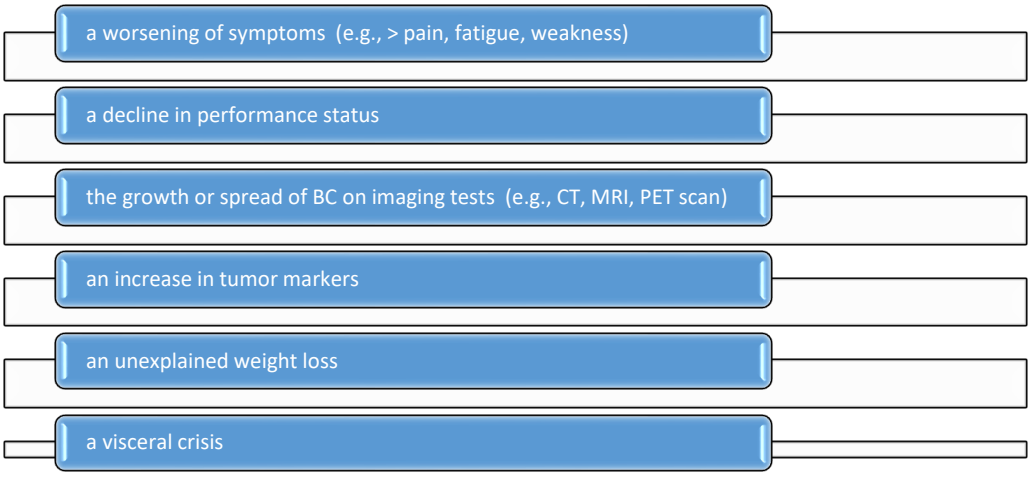

Fig. (3). Examples of subjective and objective manifestations of BC progression. BC, breast cancer; CT, MRI, PET.

WHAT ARE THE MAIN TOPICS THAT A PATIENT WITH BC AND HER PHYSICIAN NEED TO DISCUSS BEFORE CONSIDERING AN APPLICATION OF THE NEW LINE OF SYSTEMIC THERAPY?

Before a new line of systemic therapy is applied, a patient with BC and her physician need to discuss the patient's individual condition from her personal point of view, in agreement with medical recommendations for her management (Fig. **4**).

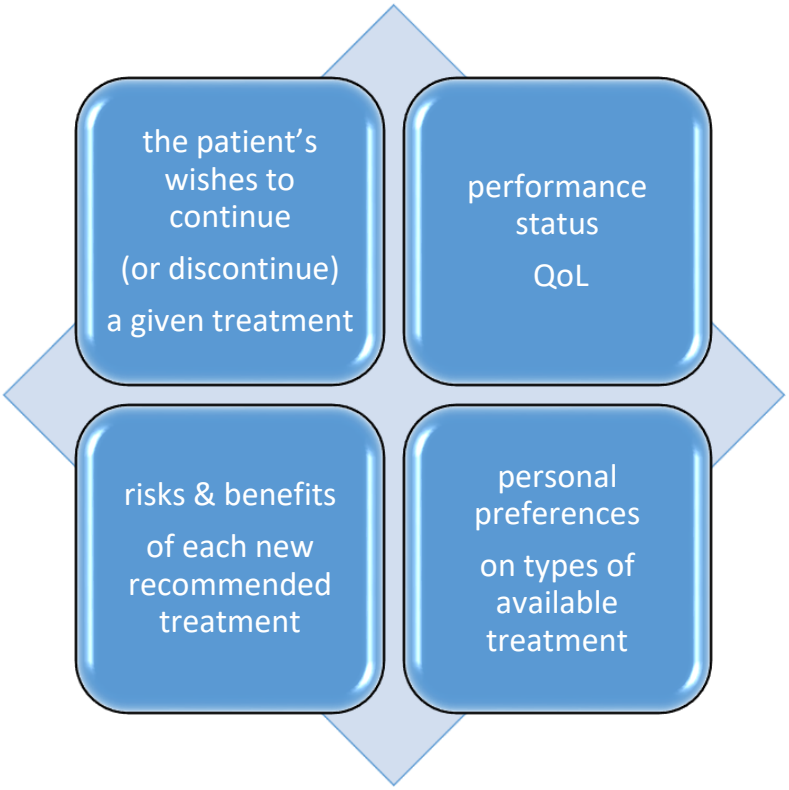

Fig. (4). Points to consider before a new line of systemic therapy for BC is applied, during a discussion between a patient and her physician. BC, breast cancer; QoL, quality of life.

After multiple lines of systemic therapy, it might be time to consider stopping systemic therapy and focusing on supportive care, especially when

• the possible adverse effects (AE) of continuing with another line of systemic therapy would most probably outweigh the benefits.

• a patient strongly prefers palliative care.

What are the most Important Steps in Shared Decision-making?

In shared decision-making, a patient and her doctor share medical information, analyze the diagnostic and therapeutic options and agree on a certain treatment plan (Fig. **5**).

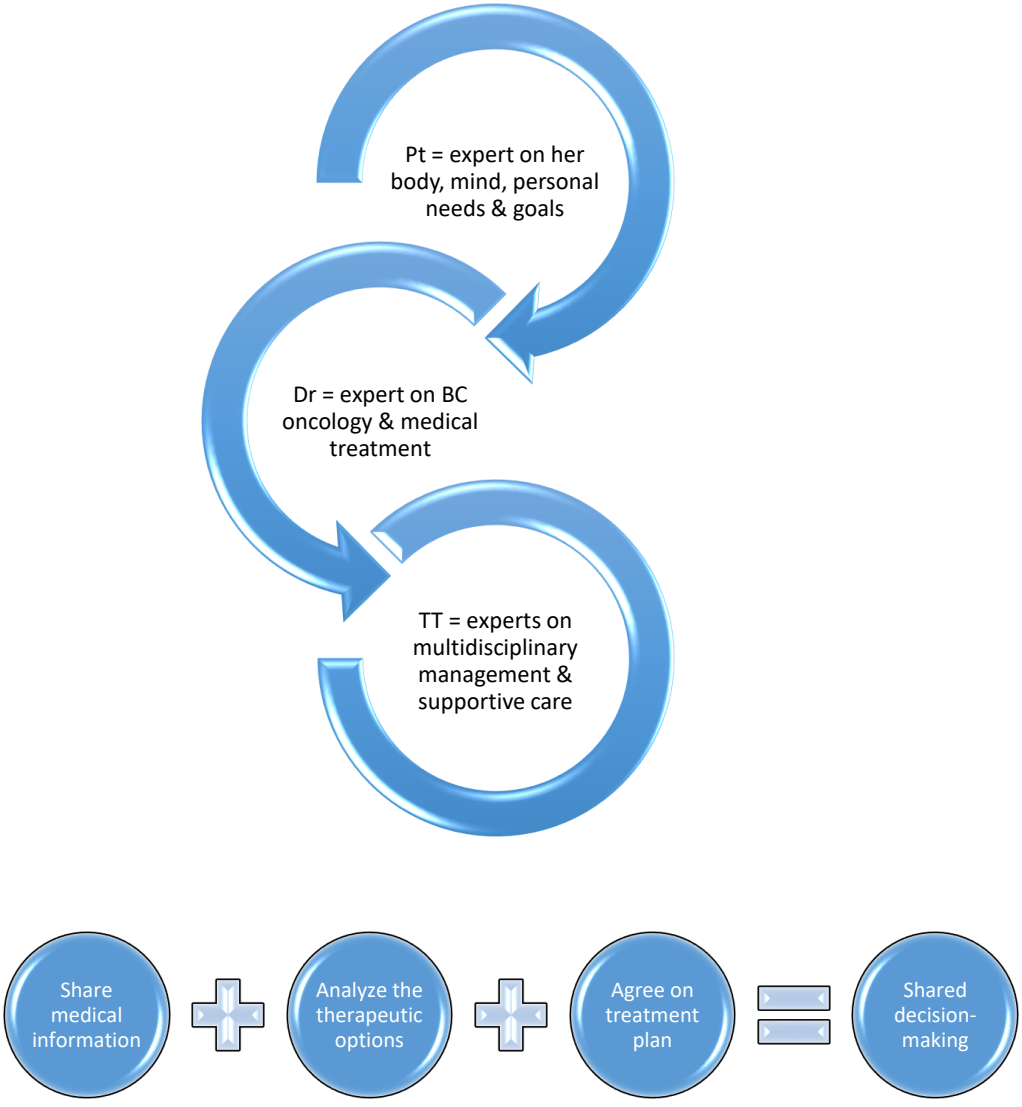

Fig. (5). Shared decision-making between a patient with BC and her doctor. BC, breast cancer; Pt, patient; Dr, doctor; TT, therapeutic team.

Such decisions should consist of an exchange between a patient's personal needs and her doctor's professional medical expertise.

WHICH FACTORS USUALLY PLAY A ROLE IN THE PERSONAL OR SHARED DECISION-MAKING OF PATIENTS WITH BC?

A patient's opinions, beliefs, and feelings about different types of therapies, their complications, side effects, and their impact on daily functioning are usually very important in personal or shared decision-making (Fig. **6**).

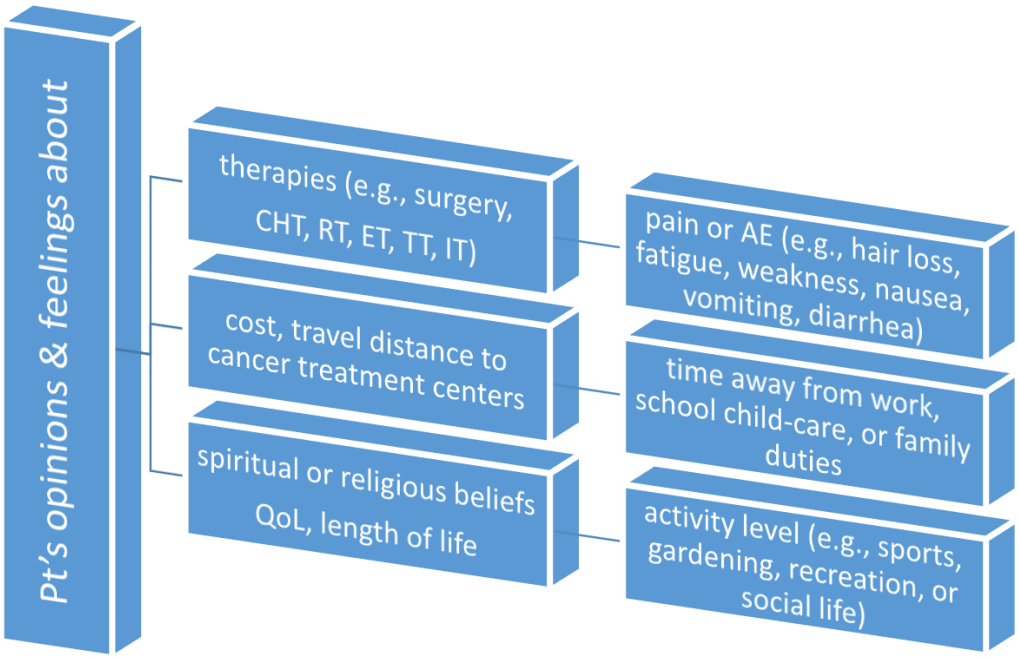

Fig. (6). Common factors which can play a role in personal or shared decision-making. AE, adverse effects; CHT, chemotherapy; RT, radiotherapy; ET, endocrine therapy; TT, target therapy; IT, immunotherapy; QoL, quality of life;.

It's important for every woman with BC to feel comfortable with the anticancer treatment of her choice. This starts with having an open conversation between a patient and her doctor. During this honest conversation, a woman should not be afraid to clearly express what she expects or wants from a particular anticancer treatment approach (Fig. **7).**

IN WHICH WAY A SECOND OPINION CAN BE HELPFUL FOR A WOMAN DIAGNOSED WITH BC?

It is natural and appropriate to wish to begin anticancer immediately. However, it may be prudent to have another oncology expert review a patient's clinical scenario and test results, in order to express an independent professional, second opinion in the form of a proposed treatment plan.

Preparation for the second opinion involves

• verification rules on second opinions with an insurance company.

• copies of all medical records to be sent for a second opinion.

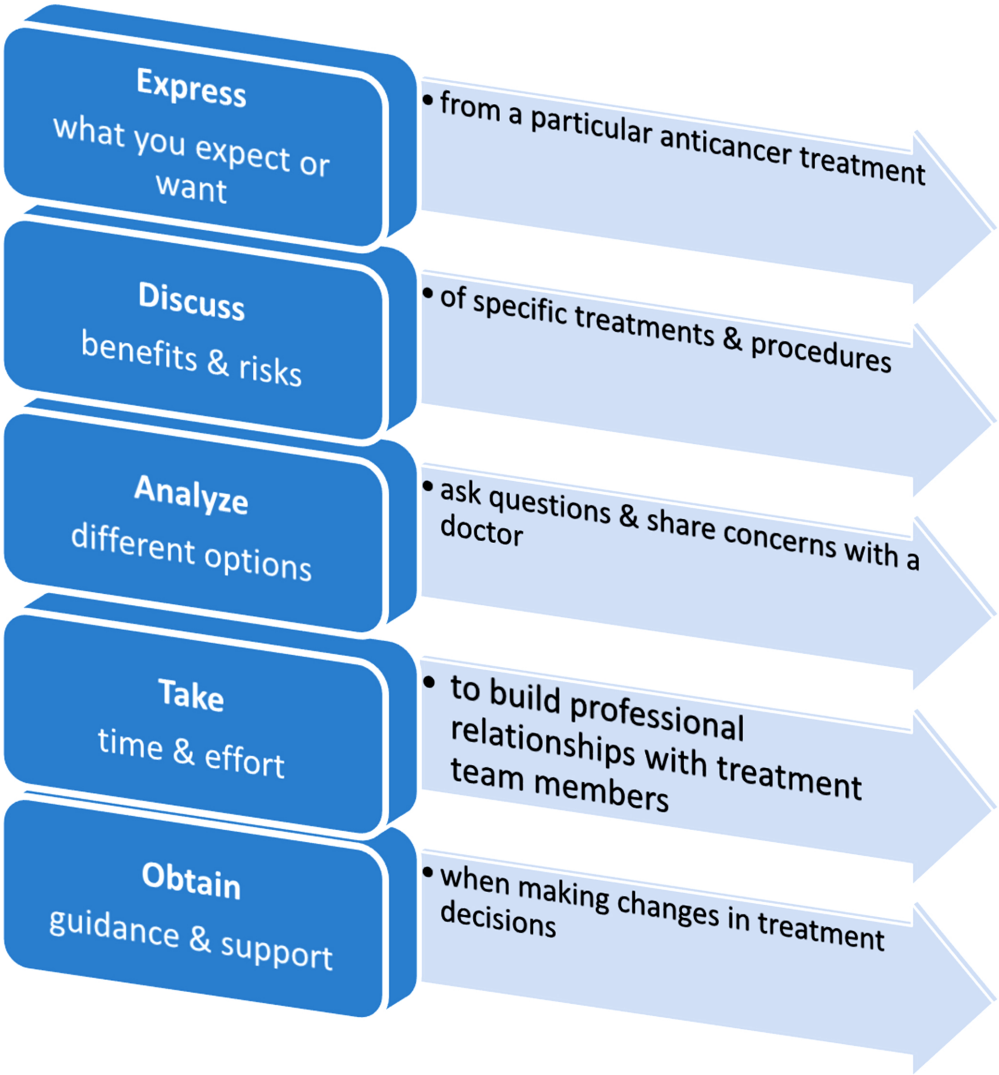

Fig. (7). EDATO – an approach to shared decision-making while discussing any anticancer treatment option.

WHAT ARE THE MAIN BENEFITS OF ATTENDING SUPPORT GROUPS?

Support groups are useful since they usually involve a broad spectrum of patients at different stages of anticancer treatment (*e.g.*, from women newly diagnosed with BC to the ones who completed treatment). This allows us to ask many "burning" questions and exchange experiences in a friendly and stimulating atmosphere.

If a given hospital, cancer treatment center, or community doesn't offer support groups for patients with BC, such services can be available on the websites (listed under references).

POSSIBLE QUESTIONS TO ASK DOCTORS ABOUT BC DIAGNOSIS, PROGNOSIS, AND TREATMENT OPTIONS

Helpful for making treatment decisions, considering a patient's goals and expectations from various treatments.

1. General questions about BC diagnosis & prognosis (Fig. **8**).

2. "Decalogue" of practical questions about BC treatment options (Fig. **9**).

3. Specific questions about various treatments for BC (Fig. **10**).

AE, adverse effects; RT, radiation therapy; CHT, chemo therapy; ET, endocrine therapy; TT, target therapy; IT, immune therapy; QoL, quality of life;

4. Questions about clinical trials (Fig. **11**).

5. Questions about the side effects of BC treatment (Fig. **12**).

• Making treatment decisions is a patient's choice, on the basis of professional medical recommendations, in an individual clinical & personal context.

• It should be kept in mind that supportive care will always be provided.

• The therapeutic modalities for patients with invasive or metastatic BC are often complex and diversified.

• Usually, the evaluation, treatment, and follow-up recommendations in the standard oncology guidelines are based on the results of clinical trials.

• However, to optimize the treatment of BC (*e.g.*, maximize cure or minimize toxicity), participation in prospective clinical trials will allow patients in different clinical situations to receive the most appropriate anticancer treatment.

• This might also contribute to better treatment outcomes in the future.

Fig. (8). Helpful general questions to ask about BC diagnosis & prognosis. BC, breast cancer.

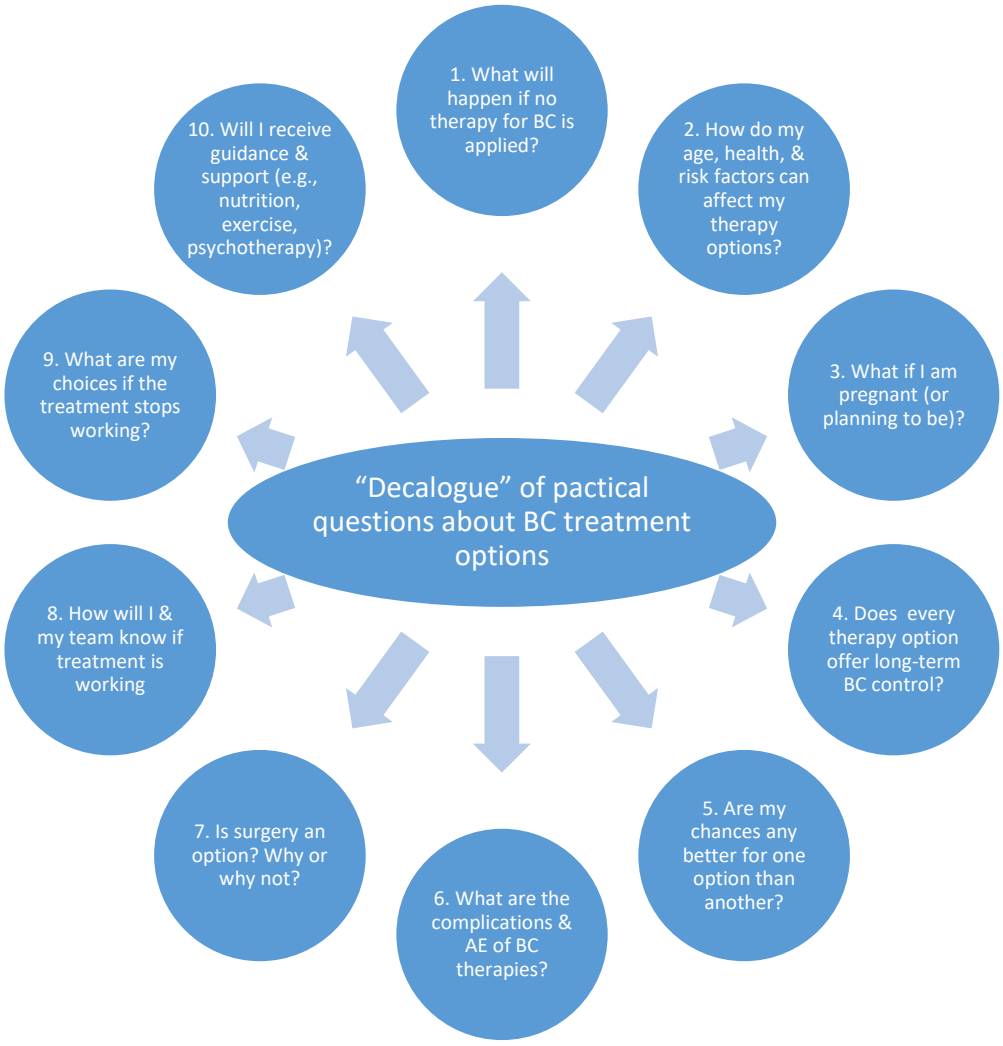

Fig. (9). Practical questions to ask about possible BC treatment options. BC, breast cancer.

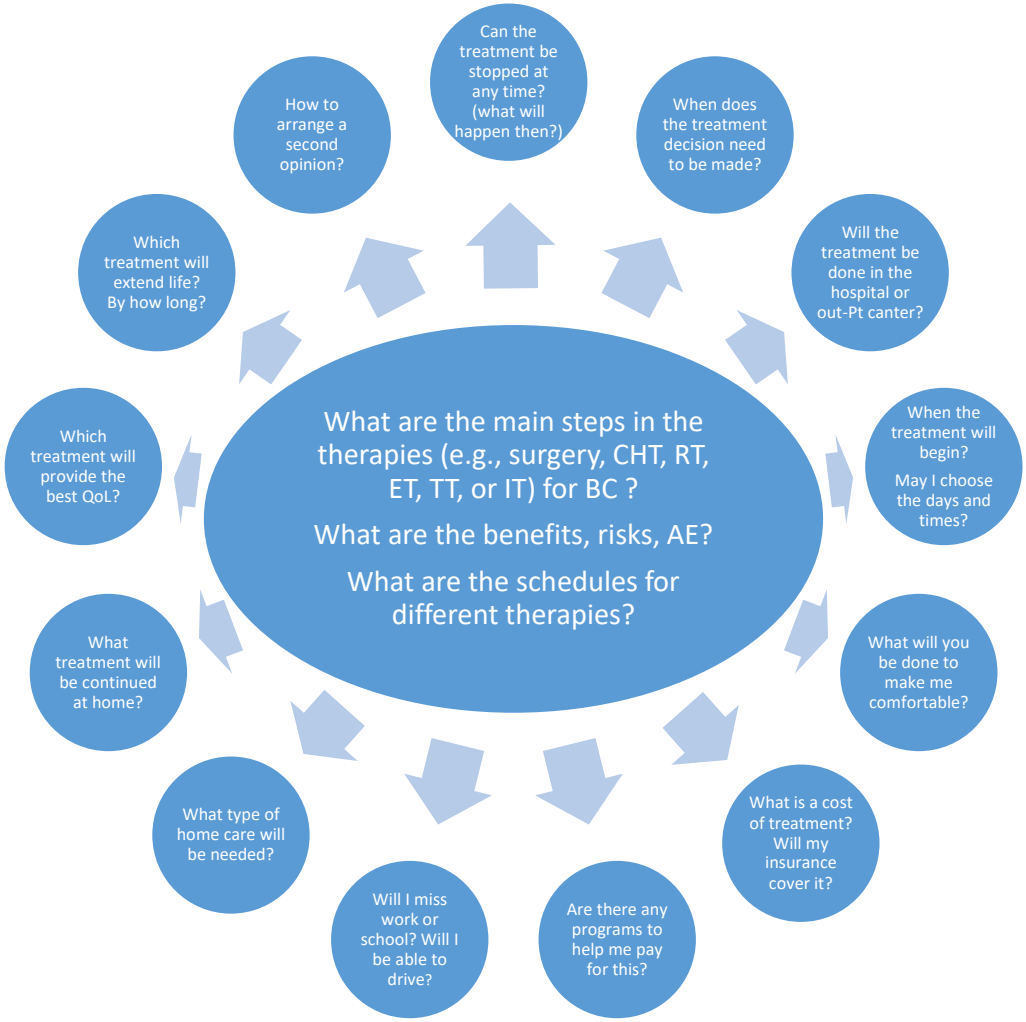

Fig. (10). Specific questions to ask about various treatments for BC. BC, breast cancer.

Fig. (11). Questions to ask about clinical trials. RCT, randomized control trial; BC, breast cancer; AE, adverse effects;.

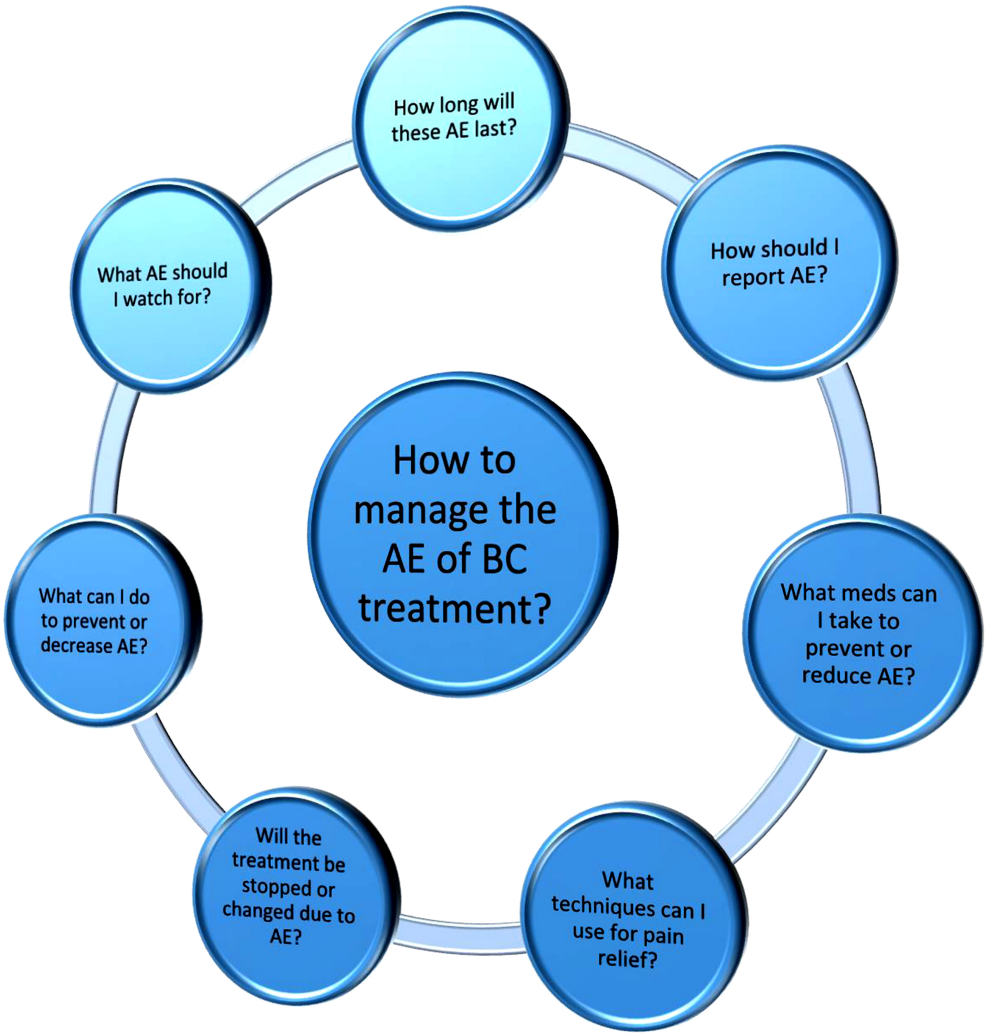

Fig. (12). Questions to ask about side effects of BC treatment; AE, adverse effects; BC, breast cancer; meds, medications;.

REFERENCES & RESOURCES

www.cancer.org/treatment/understanding-your-diagnosis/what-is-cancer.html

www.cancer.org/cancer/breast-cancer/non-cancerous-breast-conditions.html

www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer diagnosis/breast-cance--hormone-receptor-status.html

www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer diagnosis/breast-cance--her2-status.html

www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer diagnosis/breast-cance--grades.html

American Cancer Society – www.cancer.org/cancer/breast-cancer

Breast Cancer Alliance – www.breastcanceralliance.org

Breastcancer.org - breastcancer.org

Breast Cancer Trials - breastcancertrials.org

DiepCFoundation - diepcfoundation.org

FORCE: Facing Our Risk of Cancer Empowered - facingourrisk.org

Living Beyond Breast Cancer (LBBC) - lbbc.org

National Cancer Institute (NCI) - cancer.gov/types/breast

Sharsheret - sharsheret.org

Young Survival Coalition (YSC) - youngsurvival.org

Information for Finding a Clinical Trial

• Search the National Institutes of Health (NIH) database for clinical trials

(*e.g.*, whom to contact, and how to enroll).

Look for an open clinical trial for your specific type of cancer - Go to ClinicalTrials.gov.

• The National Cancer Institute's Cancer Information Service (CIS) provides up-to-date information on clinical trials (call 1.800.4.CANCER (800.422.6237) or go to cancer.gov.)

HELPFUL MEDICAL TERMINOLOGY

Aromatase Inhibitor (AI) - a medication that lowers the level of hormone estrogen in the body.

Axillary Lymph Node (ALN) - a lymph node located near the armpit.

Bilateral oophorectomy - a surgical procedure that removes both ovaries.

Biopsy - removal of small amounts of tissue or fluid to be tested for disease (*e.g.*, BC).

Cancer stage - rating of the growth and spread of neoplastic tumors.

Carcinoma - cancer that starts in cells that form the lining of organs and structures in the body.

Clinical trial – a research study on a test or treatment to evaluate its safety (*e.g.*, any possible side effects) and efficacy (*e.g.*, how well it works for the treatment of disease, such as BC).

Complete Blood Count (CBC) - a lab test that includes the numbers of blood cells (BC) (*e.g.*, WBC – white BC, or leukocytes, RBC – red BC, or erythrocytes, and platelets)

Computed Tomography (CT) –an imaging radiology test that uses x-rays from many angles to make a picture of the inside of the body organs and tissues.

Connective tissue - supporting and binding tissue that surrounds other organs and tissues.

Contrast - a substance put into the body to make clearer pictures during imaging tests.

Duct - a tube in the breast that drains breast milk.

Endocrine Therapy (ET) or Hormone Therapy (HT) - a treatment that stops making or inhibits the action of hormones in the body.

Estrogen (E) - a hormone that develops female body traits (*e.g.*, breast).

Estrogen Receptor (ER) - a protein inside of cells that binds with estrogen.

Fertility - the ability to become pregnant and have a child.

Genetic counseling – a discussion with a medical expert about the risk for a disease (*e.g.*, TNBC) caused by changes in genes (*e.g.*, *BRCA1/2*).

Hereditary breast cancer - Breast cancer (BC) that was likely caused by abnormal genes passed down from mother to daughter.

Hormone – a chemical in the body that activates cells or organs.

Hormone Receptor–negative (HR-) cancer - cancer cells that don't use hormones to grow or spread.

Hormone Receptor–positive (HR+) cancer - cancer cells that use hormones to grow or spread.

Human Epidermal Growth Factor Receptor 2 (HER2) - a protein on the edge of a cell that sends signals for the cell to grow.

Immunohistochemistry (IHC) - a lab test of cancer cells to find specific cell traits involved in abnormal cell growth.

Invasive breast cancer - cancer cells have grown into the supporting tissue of the breast.

Kinase inhibitor – an anticancer agent that blocks the transfer of phosphates.

Liver function test - a test that measures chemicals made or processed by the liver.

Lobule - a gland in the breast that makes breast milk.

Luteinizing Hormone-Releasing Hormone (LHRH) - a hormone in the brain that helps control the production of estrogen by the ovaries.

Lymph - a clear body fluid that contains white blood cells.

Lymph Node (LN) – a small clusters of specialized disease-fighting cells located throughout the body.

Magnetic Resonance Imaging (MRI) - a test that uses radio waves and powerful magnets to make pictures of the internal organs and tissues of the body.

Medical oncologist - a doctor who's an expert in anticancer pharmacologic therapies.

Menopause - the interval of time in a woman's lifecycle, when menstrual periods end.

Metastasis - the spread of cancer beyond the breast and nearby lymph nodes to distant sites like bone, lung, liver, or brain.

Mutation - an abnormal change in the genetic instructions in cells for making new cells and controlling their behavior.

Noninvasive breast cancer - cancer cells have not grown into the supporting tissue of the breast.

Ovarian ablation – a group of methods used to stop the ovaries from making hormones.

Ovarian suppression - a group of methods used to lower the amount of hormones produced by the ovaries.

Pathologist - a doctor who's an expert in testing cells and tissue to find disease.

Performance status - a rating of general health.

Premenopause - the state of having regular menstrual periods.

Positron Emission Tomography (PET) – the use of radioactive material to see the shape and function of different body parts.

Postmenopause - the state of the end of menstrual periods.

Primary tumor - the first mass of cancer cells in the body.

Progesterone – a female hormone that is involved in sexual development, menstrual periods, and pregnancy.

Prognosis - the expected pattern and outcome of a disease based on laboratory and radiology tests.

Radiation Therapy (RT) - the use of high-energy rays to destroy cancer cells.

Selective Estrogen Receptor Down-Regulator (SERD) - anticancer agent that blocks the effect of estrogen.

Selective Estrogen Receptor Modulators (SERM) - anticancer agent that blocks the effect of estrogen.

Side effect or Adverse effect (AE) - an unhealthy physical or emotional response to treatment.

Supportive care – a treatment for the symptoms or health conditions caused by cancer or cancer therapy.

Systemic therapy – a treatment of cancer throughout the body.

Triple-Negative Breast Cancer (TNBC) – a breast cancer that is not hormone-positive or HER2-positive.

SUBJECT INDEX

A

B

C

Katarzyna Rygiel

D

E

F

G

H

I

L

M

N

O

P

Q

R

S

T

V

W

Katarzyna Rygiel

Dr. Katarzyna Rygiel, M.D., Ph.D., has a background in primary care and medical research/education. She is a graduate of the Medical University of Silesia (SUM) in Poland, and she holds a certificate in Clinical Trials Design and Management from the University of California (UCSD) in the U.S., where she completed her research training. Her professional interests are focused on cardio-oncology, immuno-oncology, psycho-oncology, cardio-metabolic diseases, psychosomatic diseases, stress management, lifestyle modification, human aging, quality of life, patient education, and interdisciplinary team collaboration. She authored over 60 articles in various international medical journals, three book chapters, and four books.