Obesity as a Common Denominator in Breast Cancer and Cardiovascular Disease

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INTRODUCTION

OBESITY AS A MODIFIABLE RISK FACTOR FOR BREAST CANCER AND CARDIOVASCULAR DISEASE

There is a **link between increased body weight or amount of adipose tissue, and elevated cancer risk, especially in hormone-stimulated malignancies, such as breast cancer (BC).** In particular, excessive body mass has been associated with an increased risk of **postmenopausal BC**. Also, many women, who are overweight or obese at the time of BC diagnosis have elevated the risk of neoplastic recurrence, compared with women, who are lean. In addition, patients who gain weight after BC diagnosis can also be at increased risk of less favorable oncology and cardiovascular (CV) outcomes.

Simultaneously, **being overweight and obese are important risk factors for cardio-metabolic diseases**, such as **coronary heart disease (CHD), type 2 diabetes mellitus (T2DM), arterial hypertension (HTN), and dyslipidemia**. Furthermore, the adverse effects of some anti-cancer therapies can induce cardiotoxicity, and negatively impact prognosis, from both the oncology and cardiology point of view. This is particularly dangerous in women with human epidermal growth factor receptor 2 (HER2)-positive, and hormone receptor (HR) positive biological subtypes of BC. The relationships between obesity, HER2-positive BC, HR-positive BC, and cardiovascular disease (CVD) that are very complex, have been a subject of intense research investigation.

Cardio-oncology is a new **medical discipline, designed to provide the most optimal oncology treatment, without compromising the CV health** of the afflicted patients. Recently, cardio-oncology has grown significantly, because of the two main reasons:

- numerous patients with malignancies are now living much longer, and
- their oncology therapies have been greatly improved.

In addition, several new therapies for CVD have been evolving, as well. In this situation, the **key target populations for cardio-oncology** include

- patients, who are receiving anti-cancer treatments, and
- cancer survivors, who have received such therapies.

Since both cancer and CVD increase with age, in the older population, these two conditions represent competing causes of mortality.

Currently, more and more details have been known about **the subclinical toxicity of various anti-cancer treatments, including their impact on CV system**. For instance, in case of diastolic heart dysfunction, when patients are regularly examined by their clinicians, after taking commonly used chemotherapy regimens (e.g., based on anthracyclines), there is a linear progression of diastolic dysfunction, which could be due to these anti-cancer medications, or to some CV comorbidities or conditions (such as poorly controlled arterial blood pressure). It takes a dedicated, multidisciplinary team care to make comprehensive therapeutic decisions that will consider the benefits of the anti-cancer therapy and the risks for potential CV dysfunction, expressed in terms of the ejection fraction (EF) decline, or changes in cardiac biomarkers. Achieving a **proper balance between anti-neoplastic treatment and CV safety is essential in cardio-oncology management**. For example, if the breast tumor is very aggressive, then the most efficacious anti-cancer medications should be used, even if there is some cardiotoxicity related to that. At this point, a prompt cardiology evaluation and treatment, as well as close monitoring are required. In some cases, in which subclinical cardiotoxicity of an anti-cancer therapy can be suspected, it doesn't always mean that such a therapy has to be discontinued. In these circumstances, a treatment team should attempt to treat the patient, and then, make the most appropriate decisions, along the way. This vigilant and flexible approach should be most advantageous for each individual patient.

At present, **obesity, as a chronic illness, with its comorbidities (including BC and CVD) is growing exponentially, worldwide**, and thus, **comprehensive approaches to this challenge are urgently needed**.

In response to these unmet needs, this book is going to explain the role of obesity as an overlapping risk factor for BC and CVD, as well as to display

interrelations between excessive body/fat mass and outcomes among patients with BC and CVD. Furthermore, it outlines some ways of an early detection of the potential CV damage, due to standard anti-neoplastic therapies (e.g., via measuring cardiac biomarkers, using cardiac imaging techniques or clinical prediction algorithms). It also provides a concise summary of the cardiotoxic effects induced by common targeted anti-cancer therapies (e.g., for HER2-positive BC, or HR-positive BC), and outlines the recommended, easily available cardioprotective methods.

Moreover, some **multidisciplinary strategies**, aimed at **improving outcomes of BC and CVD**, combined with the **patient education, and effective communication with therapeutic teams** have been highlighted. Some important issues in cardio-oncology are displayed in a **patient-centered** manner so that oncologists and cardiologists can be encouraged to work together and to create a professional partnership with their patients. In addition, this book provides some **practical implications to the area of cardio-oncology, and primary care**, focusing on the key role of detecting, monitoring, and managing CV risk factors, and numerous concerns, which are encountered with standard anti-cancer treatments, and long-term follow-ups of BC survivors.

This book also addresses an **improvement of the quality of life of BC patients and survivors**, as well as reviews the **weight-loss interventions (focused on a synergy of well-balanced nutrition and regular physical activity)**, based on evidence from recent research studies. It emphasizes the impact of such supportive modalities on the overall therapeutic effects and survival. Finally, this book should be useful not only to the members of cardio-oncology teams, but also to many medical providers (e.g., primary care or family physicians, internists, nutritionists, psychologists, and rehabilitation therapists) taking care on a daily basis, of patients with BC, CVD, and obesity. The unique feature of this book is that it will help to motivate such patients to reduce their excess body/fat mass, and better control their response to stress, in face of BC, CVD, and various adversities (e.g., cardiotoxicity), associated with anti-cancer therapies.

CHAPTER ONE

OBESITY AND ITS LINKS WITH NEOPLASTIC AND CARDIO-METABOLIC COMORBIDITIES

Introduction

This chapter will present the relationships between obesity, cancer and cardio-metabolic diseases. Common pathways, by which obesity can increase the risk of malignant, cardiovascular (CV), and metabolic diseases will be discussed. The connection between obesity and breast cancer will be highlighted. In addition, the main areas of future research on obesity and cancer will be announced.

Relationships of obesity with cancer

An imbalance in the endocrine regulation of adipose tissue metabolism often leads to an abnormal fat accumulation, and an excess of the body mass, causing obesity. Commonly used **anthropometric markers of obesity** include

- **body mass index (BMI)** (weight (kg)/height (m2)),
- **waist circumference (WC)** (measured in cm), and
- **waist-to-hip ratio (WHR**) (the waist circumference divided by the hip circumference).

BMI categorizes individuals into the: underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9) or obese (≥30.0) class, and WHR reflects the distribution of the body adiposity (e.g., indicating whether more fat is located in the abdomen or the hips area) (Després, Lemieux 2006).

Research evidence that connects obesity to the risk of neoplastic diseases has mostly been derived from observational studies (e.g., cohort studies). However, the data from such studies are often difficult to interpret, since they cannot confirm whether or not obesity is a direct cause of cancer. This is due to the fact that the participating obese or overweight individuals can

be different from lean people in many ways, other than their adiposity. Moreover, these other differences or comorbidities could be responsible for the increased risk of malignancy. Regardless of the limitations of observational research designs, evidence exists that a larger amount of adiposity is related with elevated risk of several cancers (e.g., breast, endometrial, ovarian, esophageal, gastric, colorectal, liver, renal, pancreatic, thyroid, gallbladder, multiple myeloma, and meningioma) (Lauby-Secretan et al. 2016). Numerous studies have revealed that especially in postmenopausal women, an elevated BMI was related to increased risk of breast cancer (BC). For instance, obese postmenopausal women had a 20% - 40% increase in the risk of developing hormone receptor (HR)-positive BC, compared with normal-weight women (Munsell et al. 2014). In contrast, in premenopausal women, overweight and obesity were related with a 20% decreased risk of HR-positive BC (Munsell et al. 2014).

Common pathways by which obesity can increase the malignancy risk

Obesity can increase the risk of cancer via several mechanisms that are addressed below. It should be highlighted that the obese individuals can have **chronic low-level inflammation** that might cause some damage to DNA, leading to neoplastic lesions (Gregor, Hotamisligil 2011). Furthermore, adipose tissue produces an excessive amount of **estrogen** that has been related to an elevated risk of hormone-stimulated cancers, such as breast, endometrial, ovarian, and some other malignancies. In addition, obese individuals may suffer from **hyperinsulinemia, insulin resistance**, or pre-diabetes that represent disorders, which can precede the development of T2DM. They often have high blood levels of **insulin** and **insulin-like growth factor-1 (IGF-1)**, which may promote the development of breast, endometrium, colon, kidney, or prostate malignancies (Gallagher, LeRoith 2015).

Adipose cells produce **adipokines** (e.g., **leptin** and **adiponectin**) that are tissue hormones, which can stimulate or inhibit cellular growth or proliferation. In particular, in obese individuals, the level of leptin in the blood increases with growing body mass/fat, and the level of adiponectin (which has anti-proliferative effects) is lower, compared to people with normal body weight. Moreover, adipose cells can have direct or indirect effects on some **cell growth regulators**, such as a **mammalian target of rapamycin (mTOR)** and **AMP-activated protein kinase**. Some additional biological mechanisms that connect obesity and cancer risk include changes

in the immune response, alterations in the **nuclear factor kappa beta system**, and a higher level of the **oxidative stress** (Roberts et al. 2010).

The relationship between obesity and breast cancer

The relationship between obesity and BC is very complex. BMI has been established as a risk factor for BC, which influences the outcomes, mostly in postmenopausal women (Protani et al. 2010). In particular, it has been shown that **overweight and obese women with BC have elevated risk for distant metastases**, in comparison with patients, who have BMI within the normal range (Ewertz et al. 2011). Mechanisms connecting obesity and BC include the endocrine and metabolic effects of excess body mass and fat content, as well as the changes that they cause in molecular signaling pathways and endocrine communication (Ligibel 2011). A recent meta-analysis has found that each 5-kg increase in adult weight was correlated with an 11% increased risk of postmenopausal BC among women, who were not using the hormone replacement therapy (HRT). However, there was no similar relationship between obesity and BC in the case of premenopausal BC (Keum et al. 2015). Results of the NHS (Nurses' Health Study) and NHSII trials have revealed that excessive body mass and adiposity in childhood and adolescence were correlated with a 20% to 50% decreased the risk of BC, across the lifespan, regardless of menopausal status. However, the positive connection has been noted between a short-term weight gain, pre- and post-menopausal invasive BC, and types of hormone receptor status, after adjusting for pre- and post-menopausal BMI (Rosner et al. 2015). This correlation was stronger for premenopausal than for postmenopausal women. Furthermore, premenopausal short-term weight gain was more strongly associated in case of ER-positive/PR-negative BC, and ER-negative/PR-negative BC, as compared to ER-positive/PR-positive receptor status. This trial has shown the negative impact of short-term weight gain, especially among premenopausal females, after adjustment for BMI (Rosner et al. 2015). Increased risk of BC among postmenopausal women, who were lean in adolescence, was found in those, who had excessive weight gain during adulthood (Florath et al. 2016).

In addition, in BC survivors, obesity can have an adverse influence on cancer recurrence, complications, and quality of life (Calle et al. 2003) (e.g., obesity predisposes to a higher risk of treatment-related lymphedema) (Paskett et al. 2012). It should be pointed out that the major RCTs in the BC area, such as the Combination Chemotherapy with or without Trastuzumab in Treating Women with HER2-Overexpressing Breast Cancer (the N9831)

trial, and the Doxorubicin and Cyclophosphamide Plus Paclitaxel with or without Trastuzumab in Treating Women with Node-Positive Breast Cancer That Overexpresses HER2 (the NSABP B-31) trial have revealed controversial data with regard to the association between the BC outcomes and obesity. According to the N9831 trial report, obese women had a worse disease-free survival (DFS), compared to the ones with BMI within the normal range. In contrast, the results of the NSABP B-31 trial did not demonstrate a significant difference in overall survival (OS), between the obese and non-obese patients. Similarly, based on the NSABP B-31 study findings, no increase in the relapse rate of BC was reported, in overweight or obese women, compared to those with normal weight (Perez et al. 2014). Furthermore, in the landmark Herceptin Adjuvant (HERA) trial, it was documented that the baseline BMI did not have a significant impact on the BC-free interval, disease specific-survival (DSS) and OS (Baselga et al. 2006).

The relationship between obesity and cardiovascular disease

Overweight and obesity represent risk factors of cardio-metabolic diseases, such as **type 2 diabetes mellitus (T2DM), arterial hypertension (HTN), and dyslipidemia**. Furthermore, the **adverse metabolic effects of excess body adiposity accelerate the progression of atheromatic lesions that in turn can lead to atherogenic CVD**, such as **coronary heart disease (CHD)**, stroke, or premature cardiac death (Mehta et al. 2018). Overweight and obesity (BMI of ≥25 and ≥30 kg/m2, respectively) represent important modifiable risk factors for CVD (Poirier et al. 2006). Moreover, excess body mass and central adiposity, that are often associated with physical inactivity, can augment the risk of CVD. In particular, class III obesity (BMI ≥40 kg/m2) can present a higher cardiovascular (CV) risk than class I (BMI 30-35 kg/m2) or class II (BMI 35-40 kg/m2) obesity, among postmenopausal women, across different ethnic populations (McTigue et al. 2014).

Furthermore, there is a link between obesity and thrombosis, including increased expression of the pro-thrombotic plasminogen activator inhibitor-1 (PAI-1) and tissue factor (TF). Also, some risk factors for venous thromboembolism, among patients with obesity involve inflammation, increased thrombin production, decreased fibrinolysis, and platelet's hyperactivity (Faber et al. 2009). Pro-inflammatory and pro-thrombotic factors can aggravate both atherogenic CVD and malignant lesions.

The main areas of future research on obesity and cancer

Some mechanisms, possibly connecting obesity with cancer, such as **microbial dysbiosis**, have currently been under investigation (Sheflin et al. 2014). It should be underscored that the microbiome (meaning microbes living in the gastrointestinal tract) plays a key role in obesity and T2DM. Both of these conditions have been related to dysbiosis that is an imbalance in the intestinal flora. In essence, the gut microbiomes of obese people are different from those of non-obese individuals. Furthermore, imbalances in the gut microbiota have been correlated with inflammation, metabolic derangement, and genotoxicity, which in turn, can be linked with malignancies (Banerjee et al. 2018). Emerging research considers some methods to alter the microbiota of cancer patients, in order to improve their outcomes, via anti-cancer immunotherapy (Sivan et al. 2015).

In addition, a new wave of exploration considers the role of **insulin receptor signaling** in cancer and obesity. This is based on assumptions that obesity alters inflammatory processes and insulin secretion. Moreover, several malignant cells express elevated levels of the insulin receptor-affinity (IR-A) for both insulin and insulin-related growth factors. Currently, the ways by which these factors can cause metabolic disorders and cancers are being explored in various research studies. Also, some possible innovative therapeutic targets, for future interventions to prevent obesity-related cancers, are undergoing investigation (Gallagher, LeRoith 2015).

Bariatric surgery and the risk of cancer – potential clinical implications

It has been established that overweight and obesity are associated with a higher risk for malignancy, and different lifestyle interventions, promoting weight reduction, have some beneficial impact on the risk of malignancy (Lauby-Secretan et al. 2016). However, bariatric surgery provides a unique opportunity to directly assess, whether or not the resulting weight loss is related to a decreased risk of malignancy. Such an assessment is more adequate, because the weight loss in these cases is mostly related to the operation itself, and not to some other interventions (e.g., a healthy nutrition, or regular physical activity, which can also decrease the neoplastic risk, to some degree). In fact, bariatric surgery reduced the risk of incident cancer rates (e.g., breast, uterus, colon, and pancreatic cancer) by approximately 45 % (Lauby-Secretan et al. 2016). It should be noted that

the strongest effects of bariatric procedures on the decreased risk for various types of malignancies have been reported among women, compared to men. This difference can be to some degree due to a reduction in levels of the circulating estrogens, after these procedures.

Summary - points to remember

- Basic **anthropometric measurements of obesity** include **BMI**, and **WC** or **WHR** (that reflect the distribution of body adiposity).
- In comparison with individuals of normal body mass, those who are overweight or obese are at greater risk for CVD, T2DM, HTN, stroke, and various types of cancer.
- **Obesity is a chronic disease that can increase the risk of cancer via** several mechanisms, such as **chronic low-level inflammation** (which can damage DNA, leading to malignant lesions) or **hormone imbalance**.
- **Adipose tissue produces an excessive amount of estrogen**, which can contribute to an elevated risk of **hormone-stimulated cancers (e.g., breast, endometrial, ovarian, and colon).**
- Obese patients often have high blood levels of **insulin** and **insulin-like growth factor-1 (IGF-1)** that can promote the development of breast, endometrium, and colon cancer.
- Adipose cells produce **adipokines** (e.g., **leptin** and **adiponectin**), which are tissue hormones that may influence cellular growth or proliferation.
- Mechanisms linking obesity and BC involve the endocrine and metabolic effects of excess adipose content.
- The changes caused by deranged hormonal communication and abnormal molecular signaling pathways can often lead to BC.
- Patients who gain weight after BC diagnosis may be at higher risk of less favorable oncology and CV outcomes.
- Obesity has been associated with an increased risk of postmenopausal BC.
- Excessive body and fat mass have an impact on cancer progression, recurrence, complications, comorbidities, and quality of life.
- Adverse metabolic effects of excess body adiposity accelerate the progression of atheromatic lesions that may lead to atherogenic CVD, such as CHD.
- Avoiding excessive weight gain in the first place is a proactive way of cancer prevention.

- Even **moderate weight loss reduces the risk of cancer among women with overweight and obesity**.
- Lifestyle interventions, promoting weight reduction and physical activity may decrease the risk of malignancy.
- Bariatric surgery decreases the risk for breast, uterus, or colon cancer in women, and this is partially related to a reduction in levels of circulating estrogens, after the procedure.

CHAPTER TWO

BREAST CANCER: A BRIEF OVERVIEW OF DIAGNOSTIC WORK-UP AND TREATMENT

Introduction

This chapter will briefly summarize the main diagnostic steps and therapeutic considerations in patients with BC. It will focus on adjuvant chemotherapy (CHT), endocrine therapy, and targeted therapy, especially for HER2-positive, or HR-positive BC. In addition, a concise overview of biological subtypes of BC, as well as common treatment modalities and outcomes in women with BC will be addressed.

Key diagnostic steps in evaluation of patients with breast cancer

After detecting a suspicious mass via breast self-examination, or by screening mammogram, the healthcare team proceeds with several diagnostic tests, such as a diagnostic mammogram (more extensive than the screening one) or ultrasound.

Biopsy

A biopsy is taken to perform **a pathology examination of some breast tissue suspicious areas** (e.g., using a thin needle), and ultrasound, magnetic resonance imaging (MRI), and X-rays can be applied to guide the needle placement. In addition, a surgical procedure may be necessary to perform a core biopsy, when access to a suspicious breast mass is difficult.

Based on the biopsy, **the biological subtype** (**Table 3**) is being determined (e.g., **ductal** or **lobular**). Similarly, **a histological grade**, indicating whether or not the cancer cells still appear close to normal (grade 1), have characteristics of both normal and abnormal cells (grade 2), or are abnormal

and fast-growing (grade 3) is being assigned (**Table 3**) (Knuttel et al. 2016). The following molecular characteristics of the cells: 1) **estrogen** and **progesterone receptors**, and 2) overexpressing **HER2** are also being assessed. Determining the expression of these receptors is crucial in planning therapy, since some treatments target these receptors and their signaling pathways (**Table 3**).

Prognosis and staging

After establishing a diagnosis, it is necessary to assess the size of the primary tumor and its potential spread. **Table 1 (Stages of Breast Cancer (BC))** contains a description of BC stages I-IV (Davidson 2016). Furthermore, some blood tests may indicate if the liver or the bones have been affected by a metastatic spread. In case of metastases, or associated symptoms (e.g., pain) a bone scintigraphy, or a computed tomography (CT) scan, MRI, or ultrasound examination (to assess the abdomen, chest, or pelvis area) need to be performed.

Molecular and genetic tests

BC stage, hormone receptor (HR) status, and biological subtype provide information on a patient's prognosis that will guide therapeutic decisions. In addition, some novel molecular tests have been available (Gyorffy et al. 2015; Nicolini et al. 2017). They include the **MammaPrint** that examines the expression levels of 70 genes in the tumor, and classifies patients into high-risk and low-risk categories, and the **Oncotype DX** test that examines 21 genes, and classifies patients into low-risk, intermediate-risk, and high-risk groups (facilitating clinical decisions, and indicating which patients should receive CHT post-surgery). **Table 2** presents **molecular tests for BC and their prognostic implications.**

Genetic testing for *BRCA1* and *BRCA2* mutations

BRCA1 and ***BRCA2*** are genes that code for proteins, which suppress tumors. These proteins are able to repair damaged DNA and protect the genome stability (Toland, Andreassen 2017). When *BRCA1* or *BRCA2* don't function correctly, the resulting cellular alterations augment the risk of BC, ovary and some other cancers (Davidson 2016). *BRCA1* and *BRCA2* mutations (that can be inherited from mother or father) play a role in only about 30% of heritable BC (Valencia et al. 2017). Furthermore, in a population of younger women (below 40 years of age), inherited changes in

a protein ***PALB2*** (that interacts with *BRCA2)* can increase the risk of BC nine-fold over the usual risk (Erel et al. 2014). Women should undergo genetic testing if their family history is positive for an increased risk of BC or ovarian cancer (Davidson 2016). In addition, a consultation with a genetic counselor is strongly recommended. Positive test results for genetic mutations would facilitate screening and therapeutic plans in such patients (Paterson, Phillips 2017).

Therapeutic options for patients with BC

Since every patient with BC and each treatment plan are unique, all members of the oncology treatment team (e.g., surgeon, radiation oncologist, and medical oncologist) have to coordinate all aspects of therapy (e.g., decisions on what type of treatment should be applied, and when it should be delivered). Based on the results of staging, hormone receptor (HR) status, HER2 status, and genetic testing (if available), an individual treatment plan should be developed. **Table 3** presents an overview of **biological characteristics, common treatments, and outcomes in patients with BC.**

Treatment considerations for patients with BC

Treatment for stages I, IIA, IIB, or IIIA (T3N1M0) of BC includes the following options:

- Surgery,
- Radiation therapy (RT) (in most cases),
- Adjuvant chemotherapy (CHT), endocrine therapy, targeted, or biologic therapy (in selected cases).

Surgery is considered to be the primary treatment for early-stage BC. The goals of BC surgery include complete resection of the primary tumor with negative margins, in order to reduce the risk of local recurrences.

Surgical options include as follows:

- Lumpectomy to negative margins, plus RT,
- Mastectomy,
- Mastectomy with reconstruction, and
- Axillary dissection (which is considered in cases of node-positive BC; axillary assessment is usually performed with sentinel node biopsy).

Considerations regarding BC surgery

Many patients with BC start their treatment with surgery to remove the tumor and involved lymph nodes. For many patients with stage I or II BC, **a breast-conserving surgery (a lumpectomy)** is often recommended, while some patients receive CHT prior to surgery, to shrink the tumor (to facilitate its subsequent removal).

A **mastectomy** (a surgery, which completely removes the breast) can be required, depending on the size or location of the tumor, as well as associated risk factors. If, for instance, a patient with BC has a family history of BC, or a *BRCA1* or *BRCA2* mutation, bilateral mastectomy can be recommended (Eisemann, Spiegel 2018). Since a mastectomy is a longer procedure than a lumpectomy, a recovery is slower, and the procedure leaves a larger scar. Breast reconstruction can be performed post-surgery (Platt, Zhong 2018). During a lumpectomy or mastectomy, a routine check of lymph nodes for cancer is performed. In an axillary lymph node dissection, 10 or more lymph nodes are usually being checked for malignancy. Removing the lymph nodes may cause lymphedema that can be managed with physical therapy, massage or compression sleeves.

In case of no lymph node enlargement, **sentinel lymph node biopsy (SNB)** is performed (a dye is used to determine which lymph node the tumor drains to) (Esposito et al. 2017). Subsequently, only that node is dissected and examined for malignant cells.

In patients with large, clinical stage IIA, IIB, or IIIA (T3N1M0) breast tumors, preoperative CHT should be considered, if they have any of the following:

- T3-T4 disease,
- Node-positive disease,
- ER-negative BC,
- HER2-positive BC, or
- Tumors that require downsizing prior to surgery.

If the patient has clinically negative axillary nodes, then a sentinel node biopsy (SNB) is considered. If the patient has clinically positive axillary nodes, a core biopsy or fine-needle aspiration (FNA) is performed. For HER2-positive BC, the neoadjuvant chemotherapy (CHT) regimen has been recommended.

Considerations regarding adjuvant chemotherapy (CHT) for HER2-positive, localized BC (stage I, IIA, IIB, or IIIA) (T3N1M0)

Anti-HER2-positive targeted therapy (e.g., trastuzumab, or neratinib) is indicated for use in combination with CHT in patients with HER2-positive BC. HER2 overexpression occurs in about 15-20% of cases of localized BC. It is related to a higher risk of recurrence, and also, it allows to detect patients, who will benefit from adjuvant anti-HER2-positive directed therapies.

First-generation CHT regimens

First-generation CHT regimens are considered less effective than second- or third-generation regimens. However, they still play a role in certain clinical scenarios. For instance, CMF (Cyclophosphamide plus methotrexate plus 5-Fluorouracil) regimen can be an appropriate consideration for women, who have contraindications to anthracycline (e.g., due to CVD) or taxane therapy. Similarly, AC (Adriamycin plus Cyclophosphamide) regimen can be a right option for patients with contraindications to taxane therapy (e.g., due to neuropathy). These regimens are presented in **Table 6.**

Second-generation CHT regimens

Second-generation CHT regimens are usually more effective than other regimens (e.g., CMF) (**Table 6**).

Third-generation CHT regimens

Third-generation CHT regimens are more effective than some second-generation regimens, and contain both anthracyclines and taxanes (**Table 7**). It should be underscored that adjuvant treatments in patients with BC are designed to treat micrometastatic disease (e.g., BC cells, which have escaped from the breast and regional lymph nodes, prior to forming identifiable metastasis). Such treatments include radiation therapy (RT) and systemic therapy (e.g., different kinds of chemotherapy (CHT), endocrine therapy, and biologic medications) (Tables 3, 4, 5, and 8). In patients with stage 0, I, II, or III BC, the main goal is to remove the tumor surgically. In addition, treatments such as CHT, endocrine therapy, and RT should be considered, depending on the individual clinical context. In patients with metastatic BC, endocrine therapy, surgery, and RT are usually being used for long-term symptomatic control, and improvement of the quality of life (QoL) (NCCN 2017 a).

Considerations regarding CHT and HER2 inhibitors in patients with BC

Some patients are treated with CHT before surgery (neoadjuvant treatment) to shrink the tumor, or after surgery (adjuvant treatment) to destroy any remaining malignant cells. CHT can reduce the likelihood of BC recurrence. The selection of CHT (e.g., medications and dosing schedules) is determined by several factors, including the size of the tumor, its histological type, and molecular test results. CHT medications are usually given in combinations to target neoplastic cells in different ways, and to reduce the development of resistance (Curigliano, Criscitiello 2017). **Anthracyclines** (e.g., **doxorubicin (Adriamycin),** and **epirubicin (Ellence)), taxanes** (e.g., **docetaxel (Taxotere),** and **paclitaxel (Taxol)), 5-fluorouracil (5-FU), cyclophosphamide (Cytoxan) vinca alkaloids (**e.g., **vinorelbine (Navelbine)), and carboplatin (Paraplatin)** represent the common chemotherapeutics (Davidson 2016). **Monoclonal antibodies: trastuzumab (Herceptin)** and **pertuzumab (Perjeta)** bind to HER2, and in this way, prevent molecular signaling in BC overexpressing HER2. **Trastuzumab emtansine (Kadcyla)** is a novel version of trastuzumab (Baselga et al. 2017). Four consecutive **Tables (4-7)** concisely summarize common CHT regimens in patients with BC as follows: **Table 4. Adjuvant trastuzumab chemotherapy regimens for patients with HER2-positive BC, Table 5. Adjuvant non-trastuzumab chemotherapy regimens for patients with BC, Table 6. First- and second- generation chemotherapy regimens for patients with BC,** and **Table 7. Third-generation chemotherapy regimens for patients with BC**.

Adverse effects differ, depending on the CHT regimen that was used. They commonly include gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea), anemia, leukopenia, thrombocytopenia, immunosuppression, fatigue, hair loss, and cardiotoxicity (this monograph mostly focuses on cardiotoxic effects and their prevention). Side effects can often be managed pharmacologically.

Radiation Therapy (RT) in patients with BC – general remarks

Radiation therapy (RT) uses high energy rays to damage the DNA inside the cell nucleus. An RT has usually been applied after CHT, or for patients not treated with CHT, soon after surgery (Boyages 2017). Modern RT techniques direct the radiation to malignant cells and attempt to minimize damage to healthy tissues. For instance, in patients post lumpectomy, RT is targeted to a part or all of the breast, or can also target lymph nodes

(depending on the risk of BC recurrence) (Kim, Algan 2017). In patients post mastectomy, RT is targeted to the chest wall and adjacent lymph nodes (Recht et al. 2016).

An external beam radiation therapy (EBRT) represents the main type of the RT for BC. In addition, a newer RT delivery approach, known as **intensity-modulated radiation therapy (IMRT),** uses much smaller radiation beams, calculated to deliver the optimal dose of the RT, targeted to the neoplastic lesion, and spearing the surrounding healthy tissues (Chan et al. 2017). At the end of RT, patients can receive a higher dose of RT (a radiation boost) to the lodge of the tumor (Kindts et al. 2017). This boost can be delivered by EBRT or internal radiation (e.g., brachytherapy) (Deng et al. 2017), using small radioactive seeds implanted in the breast tissue. RT for patients with BC can cause several adverse effects (e.g., skin injury and pain of the irradiated field, fatigue, and damage to the heart or lungs) (Kole et al. 2017**;** Taylor et al. 2017).

Endocrine therapy in patients with BC - general remarks

BC often overexpresses receptors (R) for female hormones, such as estrogen (ER) and progesterone (PR) (Davidson 2016; Howlader et al. 2014). Abnormal signaling via these receptors gives the cancer cell messages to grow and divide indefinitely. Endocrine therapies disrupt such signaling pathways, and thus, have been recommended for the majority of patients with ER-positive BC. The exact kind of endocrine therapy, recommended to a given patient, usually depends on her menopausal status, and individual clinical parameters. Ovarian suppression reduces the levels of female sex hormones in premenopausal women, by using **luteinizing hormone-releasing hormone (LHRH) agonists** (e.g., **goserelin (Zoladex)** and **leuprolide (Lupron))** (Burstein et al. 2016). Also, a surgical removal of the ovaries (ovariectomy) can be performed in some women. Both premenopausal and postmenopausal patients can be treated with an antiestrogen agent, such as **tamoxifen**, which binds to the ER to inhibit estrogen signaling (Jameera Begam et al. 2017). Postmenopausal women can also be treated with **aromatase inhibitors (AI),** such as **anastrozole (Arimidex), letrozole (Femara),** and **exemestane (Aromasin)**, which block the conversion of testosterone to estrogens (Davidson 2016). Hormone therapy should be continued for a long period since BC diagnosis. A recent meta-analysis, which showed that after 5 years of endocrine therapy BC may still recur (Pan et al. 2017), underscores the importance of this continuation. If BC recurs or becomes resistant to endocrine therapies, then **everolimus (Afinitor)** can be helpful (Steelman et al. 2016). During

hormone therapy, some malignant cells find certain pathways to proliferate, independent of hormone signaling (Fan et al. 2015). Everolimus inhibits some of them, and in this manner, reverses this resistance (e.g., the neoplastic cells become again reliant on hormone signaling) (Royce, Osman 2015). In particular, everolimus in combination with the aromatase inhibitor (AI) - exemestane (Aromasin) was shown to improve progression-free survival (PFS) (Baselga et al. 2012). Endocrine therapies can cause adverse effects resembling menopausal symptoms (e.g., hot flashes, vaginal dryness, and mood instability). In addition, tamoxifen may increase the risk of blood clots and uterine cancer (Antimisiaris et al. 2017). AI may cause increased levels of serum cholesterol, and elevate blood pressure (Foglietta et al. 2017), as well as reduce bone mass (Kristensen et al. 2017). To protect patients from osteoporosis and bone fractures, a treatment with bisphosphonates or denosumab (Xgeva), combined with calcium preparations, and vitamin D3 has been recommended (Tremblay et al. 2018).

New therapeutic options for patients with BC – Cyclin-Dependent Kinase (CDK 4/6) Inhibitors

Cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) are signaling proteins that can help to proliferate some malignant cells, which are resistant to hormone therapy. **CDK 4/6 inhibitors** such as **palbociclib (Ibrance), ribociclib (Kisqali**), and **abemaciclib (Verzenio)** work in combination with endocrine therapy (Kwapisz et al. 2017). Patients with advanced BC, who use both the CDK 4/6 inhibitor - palbociclib and the endocrine agent - **fulvestrant (Faslodex)** had their median PFS much longer than the ones, taking fulvestrant and placebo (e.g., 9.2 months vs. 3.8 months, respectively) (Turner et al. 2015). Moreover, palbociclib and ribociclib have been approved for the metastatic BC, in combination with endocrine therapy (de Groot et al. 2017).

Treatment of bone metastases in patients with BC - general remarks

Among patients with metastatic BC, over one half has bone metastases (Body et al. 2017). When BC has spread to the bone, the osteoclasts become overactive, and cause bone loss, leading to pain, osteoporosis, and fractures. To reduce the risk of fractures, medications such as **bisphosphonates** (e.g., **zoledronic acid (Zometa)** and **pamidronate (Aredia)**), and the monoclonal antibody **denosumab (Xgeva)** have been recommended (O'Carrigan et al. 2017).

Breast reconstruction in patients with BC - general remarks

For many women, restoring their breasts after cancer surgery is important. Reconstructive surgery can either rebuild breasts after mastectomies or restore the appearance of breasts after lumpectomies. Recent studies have demonstrated that reconstruction can relieve feelings of stress and anxiety in some women (McCarthy et al. 2017). A breast reconstruction procedure can be done at the same time as a total mastectomy, or after treatment is completed (Thamm, Andree 2018).

Summary - points to remember

- Based on the biopsy results, the **biological** subtype of BC is determined (e.g., **ductal** or **lobular**), the **molecular characteristics of the tumor cells** (e.g., **estrogen** and **progesterone receptors**, **overexpression of HER2**) are assessed, and a **histological grade** (1-3) is assigned.
- The **size of the BC primary tumor** and its **spread** are assessed in **stages I-IV**.
- **BC stage, hormone receptor (HR), HER2 status**, and **biological subtype** provide baseline information on a patient's prognosis, and **guide therapeutic decisions**.
- ***BRCA1* and *BRCA2* mutations increase the risk of BC**, **ovarian cancer**, and some other cancers.
- In younger women, inherited **changes in a protein *PALB2* can increase the risk of BC** nine-fold over the usual risk.
- **Molecular tests** (e.g., MammaPrint, and the Oncotype DX) can **facilitate clinical decision-making** (e.g., who needs to receive CHT post-surgery).
- According to the results of **BC staging, hormone receptor (HR) status, HER2 status, and genetic testing, an individual treatment plan should be developed** and carried on.
- Treatments for stages I, IIA, IIB, or IIIA (T3N1M0) (localized) of BC include the following considerations: surgery, radiation therapy (RT) (in most cases), adjuvant chemotherapy (CHT), endocrine therapy, targeted, or biologic therapy.
- CHT can be administered before surgery (neoadjuvant treatment) to shrink the tumor, or after surgery (adjuvant treatment) to destroy the remaining malignant cells.
- CHT reduces the probability of BC recurrence.

- CHT medications are usually given in combinations to "attack" the neoplastic cells in different ways, and to reduce the development of resistance to therapy.
- Commonly used chemotherapeutics include **anthracyclines** (e.g., doxorubicin, epirubicin), **taxanes** (e.g., docetaxel, paclitaxel), **5-fluorouracil, cyclophosphamide, vinca alkaloids** (e.g., vinorelbine), and **carboplatin**.
- Monoclonal antibodies: trastuzumab and pertuzumab bind to HER2, and in this way, prevent molecular signaling in the case of BC overexpressing HER2.
- **Anti-HER2-positive targeted therapy** (e.g., **trastuzumab**) is indicated for **use in sequence, or in combination with CHT, for HER2-positive BC**.
- **HER2 overexpression occurs in about 15-20% of cases of localized BC**, and it is related to a **higher risk of recurrence**.
- **Hormone therapies** (depending on the menopausal status) are **recommended for the majority of patients with ER-positive BC**.
- When BC becomes resistant to endocrine therapies, then everolimus (reversing such a resistance) can be useful.
- **Everolimus in combination with the aromatase inhibitor (AI) - exemestane can improve progression-free survival in patients with BC**.
- **CDK 4/6 inhibitors** (e.g., **palbociclib**, and **ribociclib**) are approved for the **treatment of metastatic BC, in combination with hormone therapies**.
- **Endocrine therapies can cause adverse effects similar to the menopausal symptoms** (e.g., hot flashes, vaginal dryness, and mood instability), osteoporosis, and bone fractures.
- Tamoxifen may increase the risk of venous thrombosis, CV events, and uterine cancer.
- If metastatic BC has spread to the bone, **bisphosphonates (zoledronic acid** and **pamidronate**), or the **monoclonal antibody (denosumab)** are **recommended for decreasing the risk of osteoporosis and fractures**.

CHAPTER THREE

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2)-POSITIVE, AND HORMONE RECEPTOR (HR)-POSITIVE BREAST CANCER

Introduction

This chapter will focus on the HER2-positive BC that is characterized by a very aggressive behavior. Targeted anti-HER2 therapies, from the class of monoclonal antibodies (e.g., trastuzumab) will be presented, including their benefits, and adverse effects, such as cardiotoxicity. Hormone receptor (HR) (estrogen and progesterone)-positive BC will be discussed, including the use of endocrine therapy, depending on premenopausal or postmenopausal status, and some other, important clinical criteria. Furthermore, the concept of concurrent hormonal therapy and anti-HER2-targeted therapy or CHT, for patients with HER2-positive and HR-positive BC will be explained.

The main biological subtypes of BC and targeted therapeutic approaches

There are different subtypes of BC, based on the overexpression and/or gene amplification of human epidermal growth factor receptor 2 (HER2), and expression of hormone receptors (HR) for estrogen and progesterone **(Table 3) (**Tripathy et al. 2013). About 15-20% of BC is characterized by HER2-positive status, and approximately 10% of HR-positive BCs are HER2-positive, while 50% of patients with **HER2-positive** status are also HR-positive (Tripathy et al. 2013). In practical terms, the expression of HRs and overexpression of HER2 have been related to the BC prognosis and specific therapeutic implications (**Table 3).**

An overexpression (or gene amplification) of HER2 (the main member of the HER family of four receptors) is indicative of a very **aggressive behavior of the neoplastic lesions** (Nicolini et al. 2017). This is due to the mechanism, through which the activated homo- and heterodimers of HER

family organize a complex downstream signaling network that regulates cell metabolism, proliferation, and metastatic spread. Currently, a growing number of patients have been diagnosed with HER2-positive BC (Nicolini et al. 2017). The **greatest therapeutic** progress has occurred in this BC subtype, mostly due to the introduction of **targeted anti-HER2 therapies**, such as **trastuzumab, pertuzumab**, or other **agents from the class of monoclonal antibodies.** These antibodies are designed to react against specific antigens on malignant cells, augmenting the patient's immune response, and inhibiting the neoplastic cell growth (Swain et al. 2015).

Trastuzumab is a monoclonal antibody, which has significantly improved the outcome of patients with HER2-overexpressing BC (Cameron et al. 2017). Trastuzumab targets abnormal expression of HER2 in tumors that are "addicted" to HER2 activation. In consequence, its treatment effects have been attributed to inhibiting some intracellular signaling pathways. Moreover, since the immune system is involved in the beneficial therapeutic effects of monoclonal antibodies, trastuzumab can be considered for a large population of patients with an early-stage HER2-positive BC, in the neoadjuvant (pre-surgical) setting (except from small tumors, without spread to lymph nodes), adjuvant (post-surgical) setting, and metastatic BC. It should be highlighted that the progression of BC can be associated with different ways of resistance to anti-HER2 therapies in HER2-positive tumors (De Melo Gagliato et al. 2016). This can be due to the crosstalk between molecular signals reaching the ERs and HER2, or receptors of some other members of the EGFR family. This abnormal molecular communication can be attributable to BC progression, or therapeutic resistance to targeted or endocrine therapies (Mehta et al. 2014).

A concept of concurrent hormone therapy and anti-HER2-targeted therapy in HER2-positive and ER-positive BC

It has been established that targeting the ER by using the **selective ER modulators** (e.g., **tamoxifen**), **aromatase inhibitors** (**AI**) (e.g., **anastrozole** or **letrozole**) or **ER downregulating agents** (e.g., **fulvestrant**) represent effective therapeutic options.

Tamoxifen is a selective ER modulator that blocks estrogen binding to the ERs in breast tissue. Due to its property of inhibiting estrogenic stimulation of malignant cells, tamoxifen has been established as a baseline hormone therapy for women with hormone-sensitive BC (e.g., as the standard