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1

Breast and Ovarian Cancer Treatment: Facing Forward Women´s Health Care

Alice Laschuk Herlinger*, Klesia Pirola Madeira*,
Renata Dalmaschio Daltoé*, Ian Victor Silva,
Marco César Cunegundes Guimarães and Leticia Batista Azevedo Rangel
Federal University of Espírito Santo
Brazil

1. Introduction

In the last decades, the Oncology field has faced an era where the pace of biotechnological advances has promised improvements in cancer diagnosis and treatment in a truly impressive manner. In this context, the enlightenment of cancer biology and carcinogenesis mechanisms have enabled not only more accurate diagnosis of the disease, therefore guiding more specific and efficient therapeutic approaches, but also allowing the discovery of novel biomarkers to fight cancer with molecular targets. Regardless the referred progress in medicine, there is still low tumor responsiveness index to classic chemotherapy regimens, and an epidemiology scenario that shows an increase in cancer-related mortality rate over the years. According to American Cancer Society, in January of 2006, about 11.6 million living Americans had already developed cancer during lifetime. For the year of 2010, there are expected over 1.5 million new cancer cases diagnosis and about 1,500 cancer-related deaths daily in the USA. In the present chapter, the focus will be given to two major types of cancer affecting women's health care: breast cancer(BC) and ovarian cancer(OVCA). Whereas BC accounts for near 23% of all cancers diagnosed and 13.7% of cancer-related deaths in women, OVCA, although not very incident (approximately 3.7% of cancer cases among women), correlates to an extremely high mortality rate of affected women (approximately 4.2% of cancer related deaths among women).

2. Standard regimes for BC and OVCA treatment

Usually, BC diagnosis is based not exclusively on anatomic and pathological aspects of the tumor cells, but also on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) by the referred cells. Actually, tumor staging relies upon the TNM system, which considers the extent of the tumor (T), the extent of lymph nodes invasion (N), and the presence of distant metastasis (M). Besides, women's age and menopausal status at the disease diagnosis, and the nuclear grade of the primary tumor cells are taken into consideration (NCI, 2011; Simpson et al., 2000). Altogether, these

* These authors equally contributed to the elaboration of this chapter

parameters guide tumor treatment decisions, as well as the disease prognosis evaluation (Arnone et al., 2010). It is likely that BC classification may require revision, as a recent cDNA microarray gene expression profiling study has classified BC into 5 distinct subtypes based on variations in gene expression patterns (Haupt, 2010). These 5 subtypes are luminal A and luminal B, normal breastlike, HER2 overexpressing, and basal-like subtypes (Nielsenet al., 2004; Haupt et al., 2010).

BC treatment commonly follows combinatory schemes comprising surgery, radiotherapy, chemotherapy, and/or hormonotherapy. Surgical strategies of breast tumors vary according to the extent of the disease, which is evaluated as *in situ* carcinoma or invasive cancer. Lobular and ductal *in situ* carcinomas are treated, respectively, with excisional biopsy then prophylactic use of tamoxifen, or another hormonotherapy approach, for five years (depending on the tumor ER status), and mastectomy followed by radiotherapy. Partial mastectomy may also be considered. Although the discussion of BC surgery is beyond the scope of the present work, it is worthwhile to point that the decision to pursue with mastectomy, partial or radical, must consider that its curative benefit overpasses its mutilation impact on women's psychological health (Barros et al., 2009). On the other hand, invasive BC carcinomas are differentially treated depending on the tumor size, free surgical margins and residual post-surgical disease, skin damage, and the existence of metastasis. When BC is diagnosed as a tumor of 3 cm or less with free surgical margins, the recommendation is conservatory surgery, characterized by segmentar resection, followed by radiotherapy (Veronesi et al., 1995). Axillary linfadenectomy dissection is also advised whenever sentinel lymph node (SLN) tests positive for malignancy, as it indicates lymphoid drainage of the primary tumor micrometastasis (Fisher et al., 1997a). Nonetheless, invasive BC carcinomas larger than 3 cm at the disease diagnosis, both mastectomy and linfadenectomy are indicated. Breast reconstitution may be considered for patients presenting good clinical conditions (Barros et al., 2009).

Regarding the conventional pharmacologic control of BC, there are several multidrug regimens preconized for neoadjuvant, adjuvant, or palliative chemotherapy approaches. As for any other antineoplastic approach, BC chemotherapy combines drugs with distinct cytotoxic mechanisms of action aiming the avoidance of drug resistant phenotype development by cancer cells. In this context, current BC chemotherapy schemes include drugs classified as anthracyclines, alkaloid taxanes, nitrogen mustard alkylating agents, antimetabolic drugs, and hormonotherapeutic agents. Of interest, the relevant pharmacodynamic aspects of the cited drugs will be briefly addressed [Drugs mechanisms of action have been reviewed by Brunton (2010)].

Anthracyclines, which include doxorubicin and epirrubicin, are considered cytotoxic antibiotics that comprise a tetracycline ring coupled to a quinone or a hydroquinone ring by a daunosamine sugar. They form stable complexes with DNA and the enzyme topoisomarase II, therefore preventing the DNA double strand to be rebuilt, and subsequently inducing cellular apoptosis. Moreover, anthracyclines react with CYP 450 reductase in the presence of NADPH to form semiquinone radicals that, in turn, react with oxygen species. These free radicals can oxydate DNA nitrogen-bases, additionally resulting in cellular death. It is relevant to point that the reactive free radicals are also the cause of major cardiotoxicity, which can be cumulative and irreversible. Another important antineoplastic drug that inhibits topoisomerase II is etoposide.

The alkaloid taxane paclitaxel interact with β-tubuline within the cytoskeleton microtubules structure, stabilizing the polymer and preventing cellular division, thus inducing cellular

death. It has been also demonstrated that paclitaxel induces apoptosis through the interaction and further inhibition of the anti-apoptotic molecule Bcl-2. Vinorelbine is a synthetic alkaloid that also disrupts microtubule dynamics; therefore, inhibiting cellular division. The ultimate effect is cell cycle arrest; however, major peripheral neurotoxicity is also observed. Although not an alkaloid, a new drug that interferes with microtubule dynamics is the semi-synthetic epothilone B analog, ixabepilone: a 16-membered polyketide macrolide with a chemically modified lactam substitution for the naturally existing lactone that inhibits microtubule.

Nitrogen mustards, as cyclophosphamide, are DNA-alkylating drugs. Specifically in the case of cyclophosphamide, the pro-drug is metabolized by CYP2B in the liver to acrolein and phosphoramide mustard. Whereas the former can cause hemorrhagic cystitis, the latter undergoes a series of reactions to ultimately alkylate DNA and disrupt its double strand structure, causing cellular apoptosis. In addition, the compound can cause cardiotoxicity, and hepatic vein occlusive disease. In brief, the bis-chloroethyl-amine undergoes an intramolecular cycling process to form the unstable ethylene-immonium structure that further transforms the tertiary amine into an unstable quaternary amine. Then, the ring opens to form the reactive carbonium ion that reacts majorly with the N7 of guanine within the DNA structure. It has been documented that the 7-alkyl-guanine confers lability to the imidazole ring that opens, inducing DNA depurination through the excision of guanine residues, and cellular death. Moreover, cellular apoptosis seems to be coupled to the tumor suppressor gene p53. Similar mechanism of action has been associated to the platinum-based compounds, as cisplatin and carboplatin.

The rational to develop antimetabolic drugs to control cancer progress relied on the idea that cancer cells have higher metabolic rates than the normal counterparts. The first antimetabolic drug to become available was methotrexate, which interacts with the catalytic site of the enzyme dihydrofolate reductase, thus decreasing the amount of tetrahydrofolate, and inhibiting the synthesis of thymidylate, purines, serine, and threonine. The critical event is the interruption of DNA, RNA, and protein synthesis, leading to cellular apoptosis. Similarly to the observation with the DNA-alkylating agents, methotrexate mechanism of action seems to be mediated by p53. Of clinical interest, methotrexate can cause dermatitis, pneumonia, nephrotoxicity, and neurotoxicity. Another antimetabolic drug used to control BC is 5-flourouracil. This is metabolized to 5-fluoro-2'-desoxyuridine 5'-phosphate that forms a stable ternary complex with the enzyme thymidylate synthetase; so, preventing RNA synthesis, and leading to cellular death. In addition, the drug can be converted in 5-fluorouridine, which incorporates into the RNA molecule, altering its processing and function, hence resulting in cellular apoptosis. Other important antimetabolic drugs are capecitabine, which is metabolized to 5-fluorouracil, and gemcitabine. The latter is metabolized to difluorodeoxycitidine diphosphate that inhibits ribonucleotide reductase, then preventing DNA synthesis, and difluorodeoxycitidine triphosphate, which is incorporated into DNA leading to precocious termination of the nascent molecule and cellular death.

Lastly, the well-established role of estrogen in tumorigenesis has corroborated with the use of modulators of the hormone interaction with its specific receptors or of its biosynthesis. The so called hormonotherapy consists on the use of ER antagonists, as tamoxifen, raloxifen, and lasofoxifen or aromatase inhibitors. Whereas the former class of drugs inhibits the estrogen-induced transcription of growth-regulating factors, as IGF-1, the latter blocking the conversion of adrenal androgens to estrogens by the enzyme CYP19 aromatase (Sikora et al.,

2009). In addition to the anti-estrogen action, hormonotherapy may also cause hot flashes, nausea, vomiting, menstrual irregularities, vaginal bleeding, hepatic and endometrial cancer (related to tamoxifen), thromboembolism, visual impairment, and osteoporosis. Despite the consequences, hormonotherapy is consensually prescribed to ER-positive and/or PR-positive BC carriers.

Neoadjuvant chemotherapy is a preoperative tumor-debulking strategy, usually recommended in the control of inoperable tumors, as well as in the treatment of operable ones, in which case it might enable more conservative surgery methods (Fisher et al., 1997b). Current neoadjuvant regimens include the anthracyclines doxorubicin or epirubicin, associated with taxanes or cyclophosphamide, and fluorouracil administered for 3 to 4 cycles, depending on the patients' responsiveness. It has been established that tumor resection by neoadjuvant chemotherapy serves as a predictor of patients' disease-free and overall survival rates (Bonadonna et al., 1998). Also of relevance, the success of breast conservation after preoperative chemotherapy depends on careful patient selection to receive neoadjuvant chemotherapy, and the achievement of negative surgical margins during the surgical process (Buchholz et al., 2008). In any event, the benefit of enrolling a BC patient in neoadjuvant chemotherapy schemes has been increasingly considered in routine clinical decisions.

On the other hand, adjuvant chemotherapy is prescribed to BC post-surgical patients, aiming the prevention of disease recurrence or the elimination of residual tumor. Tumor size is considered a major parameter in the guideline of BC adjuvant chemotherapy. With this regard, if the tumor is smaller than 1cm, there is an implicit low risk of axillary lymph node metastases occurrence; hence, leading some clinicians and investigators to argue against the routine axillary dissection in these women. In agreement, because the disease prognosis of these patients is generally favorable, regular prescription of adjuvant systemic therapy is considered unjustifiable by the same group of health professionals. Nonetheless, others have documented that some patients with apparent small tumors at BC diagnosis, thus considered to carry disease with low invasive potential, may actually present small invasive cancers that, indeed, may progress to axillary nodal involvement and/or metastatic disease (Chen & Schnitt, 1998). Despite the complexity of the matter, careful and methodical evaluation of each case should substantiate the patients eligibility to receive adjuvant chemotherapy, which might follow the specifications discussed thereafter. Conversely, BC patients with tumor size larger than 1cm at diagnosis might receive adjuvant polychemotherapy. In this context, different polychemotherapy regimens are recommended according to the status of axillary lymph node commitment, as: i) negative lymph node status: cyclophosphamide, methotrexate, 5-fluorouracil or 5-fluorouracil, doxorubicin, cyclophosphamide, or doxorubicin and cyclophosphamide, for 6 months; ii) positive lymph node status: docetaxel, doxorubicin, and cyclophosphamide (because the antracyclines-based regimens work better than cyclophosphamide and should be preferential indicated) (Barros et al., 2009). One important consideration should be made regarding the clinical value of taxanes in the treatment of lymph node-negative BC: whereas the actual risk/benefit of the drug remains unproven for these cases, some authors have found effectiveness in treating carriers with the docetaxel, doxorubicin, and cyclophosphamide scheme compared to the 5-fluorouracil, doxorubicin, cyclophosphamide regimen (Brunton, 2010).

As previously mentioned, adjuvant hormonotherapy is prescribed to ER-positive and/or PR-positive BC carriers and relies on two strategies: either selective modulators of ER (SERMs), as tamoxifen, raloxifen, or lasofoxifen, or aromatase inhibitors (AIs), including the third-generation nonsteroidal compounds anastrozole and letrozole, and the steroidal

compound exemestane (Sikora et al., 2009). Due to its peripheral action, aromatase inhibitors are not used in premenopausal women; rather is indicated exclusively to post-menopausal patients. In this context, AIs are becoming the hormonal treatment of choice for postmenopausal women with early BC, while tamoxifen can be used by pre- or postmenopausal women with or without the use of chemotherapy (Hortobagyi, 2002). Recent large, well-controlled clinical studies have established the efficacy and safety of initial adjuvant therapy with letrozole or anastrozole versus the previous standard of 5 years of adjuvant tamoxifen (20mg/day), and have supported the use of AIs following tamoxifen for 2-3 years (early 'switch' treatment) or 5 years (extended adjuvant treatment) (Bria et al., 2010). Therefore, these studies have indicated that initial therapy with AIs, which reduced early distant recurrence events, can be expected to improve long-term survival outcomes in elegible hormonotherapy BC patients (Bria et al., 2010).

BC clinics have been dramatically impacted by newly classified triple-negative tumors, which are ER-negative; PR-negative, and HER2-negative. It is worthwhile to emphasize that triple-negative BC cases account for approximately 15% of all BC diagnosis, but rather correspond to a disproportionate share of mortality. Indeed, triple-negative BC is mostly characterized by an aggressive behavior with a poor prognosis course (De Laurentiis et al., 2010). Thus, to date, chemotherapy remains the only possible therapeutic option to control these tumors subtypes (Gluz et al., 2009). Given the lack of standard molecular targets, patients with triple-negative BC are unlikely to benefit from currently viable targeted therapy, such as endocrine or anti-HER2 agents. Therefore, the only systemic treatment option available for these patients is chemotherapy with standard cytotoxic agents. Fortunately, several studies have shown a marked chemosensitivity among these tumors, especially with regard to the neoadjuvant regimens. In fact, reports derived from diverse clinical trials, these subtypes of BC have demonstrated high response rates to neoadjuvant chemotherapy, including the schemes with anthracyclines and taxanes (Rouzier et al., 2005; Carey et al., 2007; Liedtke et al., 2008; Esserman et al., 2009). In these trials, the response of triple-negative BC is usually higher than those of other BC subtypes, but despite initial responsiveness, they show a poorer overall survival rate: such apparently surprising behavior is often referred to as "triple-negative BC paradox" (De Laurentiis et al., 2010). Last but not least, it seems that the triple-negative BC cases are extremely heterogeneous; thus, opening an intriguing avenue to investigate the distinct genomic signatures of the BC subtype carriers in an attempt to enlighten this challenge in the oncology field.

Notwithstanding the improvements in the early detection of BC, and the development of more effective adjuvant therapies to control the disease, the actual scenario remains fearsome. Indeed, epidemiology studies have revealed that about 30% of BC patients with early disease detection will relapse with distant metastases (Early Breast Cancer Trialists' Collaborative Group, 2005). In the meanwhile, metastasis BC is a heterogeneous disease presenting a variety of different clinical scenarios, ranging from a solitary metastatic lesion to diffuse and multiple organ involvement. Although the survival rate of patients with metastatic BC is gradually improving, many physicians believe that the disease remains largely incurable. In this context, another important aspect of cancer treatment has been explored: the palliative chemotherapy. The aims of palliative chemotherapy for metastatic BC are to prolong patients' survival rate while maintaining a good quality of life. However, clinical observations have clearly demonstrated that only in a minority of cases it is possible to obtain long-term survival (>5 years) using standard treatments (Iwata, 2010). The choice of drug, or drug combination in palliative therapy is determined by the subjective

symptoms of the patient, as well as by more objective parameters, such as patients age at diagnosis and general health status, localization of metastases, and aggressiveness of the disease, which is described by the necessity to achieve remission (Paepke & Kiechle, 2003).

The treatment options to prolong patients' survival rate, providing the best quality of life possible, in metastatic BC includes hormonotherapy, chemotherapy, radiotherapy, trastuzumab (a monoclonal antibody anti-HER2; to be discussed latter in this chapter) and bisphosphonates (Barrett, 2010). ER-positive and/or PR-positive, HER2-negative BC cases must always be treated with hormonotherapy, except in critical situations where there is an urge for rapid tumor response (Barros et al., 2009). In case of disease progression, the option is to move to a subsequent endocrine therapy with different class of medication, such AIs. If aggressive visceral metastasis is detected, the option is to interrupt hormonotherapy, and to promptly introduce chemotherapy. In some cases, however, initial treatment is already based on polytherapy, aiming a more rapid response, even though the most frequent recommendation is the use of drugs, alone or sequentially to each disease progression. The monotherapy treatment for metastatic BC is based on the following drugs: epirubicina, doxorubicina, paclitaxel, docetaxel, capecitabine, vinorelbine, ixabepilone or etoposide. On the other hand, current recommendations for patients with progressive or resistant disease include the combinations: capecitabine/docetaxel, gemcitabine/ paclitaxel, gemcitabine/docetaxel, ciclophosfamide/methotrexate, docetaxel/ doxorubicin, gemcitabine/cisplatin, cisplatin/vinorelbine, paclitaxel/ bevacizumab (to be further discussed in this chapter) (Rivera & Gomez, 2010).

The combination of anti-angiogenic drugs with standard chemotherapy has also increased both patients' objective response rate and median progression-free survival rate when compared with chemotherapy alone (Milano et al., 2007). At the time, blockade of growth factor receptors is the landmark of targeted therapy in metastatic BC. Monoclonal antibodies such as trastuzumab and bevacizumab represent the first generation of molecular-based therapies (Miller et al., 2007). HER2 inhibitors and the vascular endothelial growth factor antagonists have shown synergism with a broad spectrum of cytotoxins, thus being approved as the first-line treatment of metastatic BC in combination with taxanes (Bischoff & Ignatov, 2010).

More recently, tyrosine kinase inhibitors have been incorporated in the routine of BC clinics as an alternative approach for targeting HER2. This concurrent inhibition in ErbB1-expressing and ErbB2-overexpressing tumors blocks the activating signaling cascades in the MAPK and PI3K pathways, resulting in cellular growth arrest and/or apoptosis (Xia et al., 2001; Rusnak et al.,2001). A representative of tyrosine kinase inhibitors is lapatinib, an orally active small molecule (Xia et al., 2001; Rusnak et al.,2001), which reversibly inhibits both ErbB1 and ErbB2. The lapatinib effectiveness depends on the inherent biological profile of a tumor, since dependence on the EGFR and/or HER2 for cell proliferation and survival is the ideal target for lapatinib. Tumors with innate or evolved survival mechanisms which are not EGFR- and/or HER2- dependent are resistant or have reduced sensitivity to this therapy. Although lapatinib targets both EGFR and HER2, its effects on HER2 appear to be critical to its efficacy (Oakman et al., 2010). Lapatinib has demonstrated activity in trastuzumab-pretreated metastatic BC patients in combination with capecitabine (Walko & Lindley, 2005). Furthermore, chemotherapy-free regimens (trastuzumab or lapatinib plus AIs) have been identified as additional options for hormone receptor- negative and HER2-positive patients (Bischoff & Ignatov, 2010). An alternative is to substitute capecitabine by gemcitabine that is also an excellent agent in combination therapy with paclitaxel and trastuzumab (Suzuki et al., 2009)

Multitarget tyrosine kinase inhibitors have the potential to inhibit several signaling pathways involved in BC-related angiogenesis. Until now, they have failed to show a clear benefit in metastatic BC. On the other hand, poly (ADP-ribose) polymerase (PARP) inhibitors, represent an exciting new therapeutic direction in oncology. The rational behind PARP inhibitors design is targeting tumor-cell vulnerability during DNA repair (Care & Sharpless, 2011). These new strategies are being rapidly developed and approved by the health vigilance agencies, due to the exciting preliminary clinical studies, in which their activity as single agents in the control of BRCA mutation-associated BC, and in combination with chemotherapy in triple-negative BC has been demonstrated (Telli & Ford, 2010). There is an enormous expectation that these treatments might offer hope for patients with refractory BC (Ellisen, 2011).

Future directions of research, particularly in HER2-positive BC, focus on the evaluation of novel antibodies (pertuzumab, T-DM1), and irreversible tyrosine kinase inhibitors (neratinib, BIBW 2992), as well as inhibitors of HER2-related downstream signaling molecules (mTOR, TORC 1/2, PI3K/Akt), and of receptor cross-talks (IGFR) (Bischoff & Ignatov, 2010).

Regarding OVCA treatment, cytoreductive surgery and chemotherapy platinum-based (an alkylating agent) are the basis of conventional treatment. Surgical evaluation is indicated for most women with known or suspected OVCA. Surgery is generally recommended, provided there are no medical contraindications, and the distribution of disease is deemed resectable on preoperative evaluation. The goals of the initial surgery are to obtain pathologic diagnosis, accurately determine the extent of the disease and, when feasible, optimally cytoreduce the OVCA. According the Gynecologic Oncology Group (GOG), optimal surgical cytoreduction is defined as residual tumor less than 1cm. Treatment is often driven by the surgical stage, as expressed by the International Federation of Gynecology and Obstetrics (FIGO) staging system. Precise surgical staging is critical for the patient in terms of both therapy and prognosis guidance (Ramirez et al., 2011).

In patients with early disease (FIGO stage I–II), apparently confined to the pelvis without extra-abdominal metastatic disease, the recommendation is total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy, peritoneal washing, peritoneal biopsies, evaluation of the entire abdominal cavity and retroperitoneal assessment that involves both the pelvic and para-aortic area. In selected patients who desire to preserve their childbearing potential, unilateral salpingo-oophorectomy with adequate staging may be performed after proper counseling (Colombo et al., 2010).

Adjuvant chemotherapy for early stage OVCA remains a controversial topic. Meta-analysis of three trials with adequate data, assessing 1,008 women, indicated that women who have received adjuvant platinum-based chemotherapy had better overall survival (OS) rates than those who did not received the treatment (hazard ratio (HR) 0.71; 95% CI 0.53 to 0.93). Likewise, meta-analysis of four trials with adequate data, assessing 1,170 women, has indicated that women who have received adjuvant chemotherapy had better progression-free survival (PFS) rate than those who did not get the treatment (HR 0.67; 95% CI 0.53 to 0.84) (Winter-Roach et al., 2009). To evaluate the clinical benefit and toxicity of two regimens used to treat early epithelial ovarian cancer, single agent carboplatin and a carboplatin/paclitaxel combination, a retrospective review including women treated with adjuvant chemotherapy between 2002 and 2005 has been performed. Five year OS rate was 62% (95% CI 44-81%) for carboplatin, and 73% (95% CI 61-85%) for carboplatin plus paclitaxel (P = 0.316). For the subgroup with stage I disease and good performance status 5-

year OS rate was 80% (59-100%) for carboplatin, and 79% (63-95%) for carboplatin plus paclitaxel (P = 1.0). For those patients with stage 2 disease, 5-year OS rate was 29% (95% CI 0-62%) for carboplatin, and 63% (95% CI 44-82%) for carboplatin plus paclitaxel (P = 0.025). Recurrences of the disease and patients death rates have been proven similar in both cohorts. It is clear that well-designed trials are needed to identify the optimum chemotherapy regimen to control OVCA (Adams et al., 2010). With this regard, the European Society for Medical Oncology, based on a meta-analysis data evaluation, has recommend six cycles of single-agent carboplatin as the adjuvant treatment in patients with intermediate and high-risk early stage OVCA. Low risk of recurrence includes stage IA–IB grade 1 tumor; medium risk includes stage IA and IB grade 2; high risk includes stage IC all grades, IB or IC grades 2 and 3, clear cell histology (Colombo et al., 2011).

For advanced OVCA (FIGO-Stage III and IV), on the other hand, the standard initial treatment consists of cytoreductive surgery followed by a combination platinum-based chemotherapy. Since 1996, the combination of platinum plus paclitaxel has become the standard treatment for the disease (Colombo et al., 2010). A study conducted by GOG (GOG 111) has demonstrated a survival benefit of the combined regimen with cisplatin and paclitaxel in comparison to cisplatin and cyclophosphamide. The authors have observed that the PSF was significantly longer in the cisplatin-paclitaxel group than in the cisplatin-cyclophosphamide group (median, 18 versus 13 months). OS has been also significantly longer in the cisplatin-paclitaxel group when compared to the cisplatin-cyclophosphamide group (median, 38 versus 24 months) (McGuire et al., 1996). In the study denominated GOG 158, the investigators have demonstrated that patients with advanced ovarian cancer would benefit from the chemotherapy regimen consisting of carboplatin plus paclitaxel, due to lower systemic toxicity when compared to the scheme with cisplatin plus paclitaxel. Besides, the former is at least as effective as cisplatin plus paclitaxel (Ozols et al., 2003).

The phase III Gynecologic Cancer Intergroup (GCIG) trial (GOG 0182-ICON 5) has been established to determine if additional cytotoxic agents in the front-line setting against OVCA would further extend patients PFS or OS. Each arm of the trial have included 8 cycles of triplet (carboplatin–paclitaxel–gemcitabine and carboplatin–paclitaxel–pegylated liposomal doxorubicin, or sequential-doublet chemotherapy, which provided a minimum of 4 cycles with the experimental treatments (carboplatin–topotecan and carboplatin–gemcitabine) while maintaining at least 4 cycles with carboplatin and paclitaxel, or 8 cycles of standard treatment (carboplatin–paclitaxel). Compared with standard paclitaxel and carboplatin, addition of a third cytotoxic agent provided no benefit in patients PFS or OS after optimal or suboptimal cytoreduction (Bookman et al., 2009). Paclitaxel plus carboplatin remains the standard front-line intravenous therapy in the fight against OVCA.

Concurrent with the development of intravenous treatment approaches, intraperitoneal treatment has also been shown to be a valuable strategy against OVCA, as it offers the possibility of targeting the therapy to the site of disease while minimizing systemic toxicities. In this context, the GOG 172 study has shown that the intraperitoneal therapy is associated with longer survival rate in surgically treated patients added to intravenous therapy as compared with intravenous therapy alone (65.6 versus 49.7 months of median survival with a 21.6% reduction in death). However, only 42% of patients were able to complete 6 cycles of intraperitoneal treatment, because toxicities were higher in the intraperitoneal treated group than in the intravenous-treated group (Armstrong et al., 2006).

Then, the following drug combination has been recommended as initial chemotherapy for epithelial OVCA in advanced stages, intravenously: i) paclitaxel is given over a 3-hour

intravenous infusion followed by carboplatin over a 1-hour intravenous infusion on day 1. This combination is given every 3 weeks for a total of 6 cycles; ii) paclitaxel is given over a 1-hour intravenous infusion on days 1, 8 and 15 plus carboplatin over a 1 hour intravenous infusion on day 1 only. This combination is given every 3 weeks for a total of 6 cycles. Intraperitoneal chemotherapy may be used in combination with intravenous drug therapy in the following regimen: paclitaxel continuous intravenous infusion over 24 hours on day 1 followed by intraperitoneal cisplatin on day 2, and intraperitoneal paclitaxel on day 8. This combination is given every 3 weeks for a total of 6 cycles (National Comprehensive Cancer Network, 2010).

As stated earlier, for patients with suspected advanced OVCA, the general recommendation is primary surgical cytoreduction followed by chemotherapy. However, some patients are too medically ill to initially undergo any type of abdominal operation, whereas others have disease that is obviously too extensive to be resected by an experienced ovarian cancer surgical team. In these circumstances, neoadjuvant platinum and taxane-based chemotherapy is routinely used. Following a few courses of treatment, the feasibility of surgery can be reassessed (Schorge et al., 2010). In some cases, neoadjuvant therapy followed by interval tumor debulking has demonstrated comparable survival outcomes to those reported for primary surgery. In a study conducted by Schwartz et al. (1999), no statistical difference has been observed in OS ($P = 0.1578$) or in PFS between the group treated with neoadjuvant chemotherapy and the conventionally treated group ($P = 0.5327$), despite neoadjuvant chemotherapy patients being statistically older (median age 67 years [range 44 to 85 years] versus a median age of 60 years [range 19 to 79 years] for conventionally treated patients; $P < 0.001$), and having a statistically poorer performance status ($P < 0.001$) than the conventionally treated group.

Regardless the initial response to treatment (~80%), approximately 70% of OVCA cases will relapse after receiving the first-line platinum-based chemotherapy (even in combination with paclitaxel) (Galic et al., 2011; Ozols et al., 2003; Pfisterer et al., 2006). Platinum-sensitive OVCA cases are the ones that remain in remission for at least 6 months after completing the primary treatment regimen, whereas platinum refractory or resistant OVCA cases progress in less than 6 months from completion of the primary treatment scheme. Patients experiencing a durable response to platinum-based chemotherapy have a high probability of responding again to platinum-containing compounds. Then, patients with recurrent platinum sensitive OVCA have been retreated with platinum-based chemotherapy, often in combination with another chemotherapeutic agent. The preferred drug combination regimens to treat OVCA platinum-sensitive cases are: carboplatin and paclitaxel, carboplatin and docetaxel, carboplatin and gemcitabine, carboplatin and pegylated liposomal doxorubicin, cisplatin and gemcitabine (National Comprehensive Cancer Network, 2010).

In general, OVCA patients relapsing after receiving the first-line platinum–paclitaxel therapy are at risk of significant neurotoxicity when retreated with the same regimen within up to 12 months from the end of first chemotherapy round, due to the cumulative neurotoxicity of both carboplatin and paclitaxel. Therefore, combinations of other drugs with platinum have been explored. Among these possibilities are pegylated liposomal doxorubicin, epirubicin, ifosfamide (an alkylating agent), gemcitabine, topotecan, docetaxel, irinotecan (a topoisomerase I inhibitor), etoposide, hexamethylmelamine (an alkylating agent), vinorelbine, fluorouracil, capecitabine, pemetrexed (an antimetabolic drug that acts similarly to methotrexate), oxaliplatin (an alkylating agent), vinorelbine, tamoxifene or bevacizumab (National Comprehensive Cancer Network, 2010; National Cancer Institute, USA, 2011).

In patients with relapsed OVCA, the objectives of salvage therapy are considered aiming the maintenance of patients' quality of life, and prolongation of patient survival. Salvage chemotherapy in platinum-refractory patients typically results in low response rates and short survival, and the main goal of salvage therapy in this group of patients is palliation. Rechallenge with platinum-based treatments produces a response rate of approximately 10% and the response rate of drugs mentioned above with antitumor activity in paclitaxel–platinum-refractory disease is also of approximately 10% (Colombo et al., 2010).
The role of cytoreductive surgery at disease recurrence is controversial and guidelines are not standardized, but surgical management of recurrent ovarian cancer has been demonstrated to improve patients' survival in optimal surgical candidates, and several studies have suggested the importance of cytoreductive surgery prior to the initiation of second-line chemotherapy (Revised in Burton et al., 2010). Unfortunately, the conclusion is that OVCA remains a lethal disease for which improved screening and treatment strategies are urgently needed.

3. Cancer immunotherapy

3.1 Monoclonal antibodies in oncology

The idea of using specific antibodies to target tumors back over 100 years, when Paul Ehrlich hypothesized that "magic bullet" could selectively target a given disease. Nevertheless, it would only became possible with the development of the hybridoma technology by Kohler & Milstein (1975). This technology enabled the production of murine monoclonal antibodies (mAbs) with high specificity to a target. However, the applicability of these murine mAbs to human therapy was questioned, mainly because of their immunogenicity. The first studies involving cancer patients who received murine mAbs showed the production of human anti-globulin antibodies (HAGA) and human anti-mouse antibodies (HAMA). Among patients with solid tumors, 50-70% of them developed HAMA after the exposure to the Abs. The main problem from these responses was the implications it had on the effectiveness of the therapy (DeNardo et al., 2003), since subsequently administrated mAbs had different biodistribution patterns as well as altered pharmacokinetics. To overcome this curb, researches started looking for alternatives that would reduce this adversity. Actually, this has been accomplished by the development of chimeric and humanized mAbs, which carry the human Fc backbone and the murine variable region (or a part of it). More recently, modifications had been incorporated to the chimeric or humanized mAbs, so that they have an increased ability to bind to their targets or to recruit the immune system effectors components. These mAbs, also called "next generation mAbs" are still under development, and are expected to have a higher ability to penetrate solid tumors than the previous ones (Adams & Weiner, 2005).
Chimeric and humanized antibodies differ from each other by the extension of the murine segment that is incorporated to the human Fc portion: While chimeric antibodies contain the full murine variable region, humanized antibodies contain only the complementarity-determining regions (CDR) from mice. Besides diminishing the immunogenicity by assembling a chimeric or humanized mAb, this approach also enables choosing the IgG isotype according to the desired function. Antibodies designed to act by Fc domain-based functions, such as antibody-dependent-cellular citotoxicity (ADCC), are produced as IgG1 or IgG3 antibodies. On the other hand, when antibody is expected to act by steric inactivation of its target, without recruitment of the immune system, they are usually IgG2 (Adams & Weiner, 2005).

As for the molecular target of therapeutic Abs, they could be an antigen presented in the cancer cell surface, or molecules presented in the cancer microenvironment. Cancer cell surface targets can be cancer-specific antigens or proteins that are overexpressed in the tumoral tissue. Antigens presented in the tumoral microenvironment, in turn, are usually growth-factors or molecules necessary for the tumor progression. The state-of-the art immunotherapy of cancer has revealed a remarkable progress in controlling cancer with monoclonal antibodies. Additionally, it has stimulated investigators worldwide to pursue with molecular studies aiming the identification of novel tumor markers that could ultimately serve as antigen to the development of other therapeutic antibodies (Adams & Weiner, 2005).

Mechanisms elicited by monoclonal antibodies against tumor are normally characterized by cytotoxic effects. Most of them are associated with ADCC or complement dependent cytotoxicity (CDC), both leading to the cytolysis of tumor cells (Adams & Weiner, 2005). ADCC happens after antibodies bind antigens on tumor cells, and the antibody Fc domain engages Fc receptor (FcR) on the surface of immune effector cells, principally natural killer (NK) cell, although neutrophils and eosinophils can also mediate ADCC. On the other hand, DCC is triggered by antibodies and complement system to induce cell killing. In addition to these classical methods, monoclonal antibodies can be used to target toxins or radioisotopes to kill tumor cells (Adams & Weiner, 2005; Challacombe et al, 2006; Rivolti et al, 1993).

Despite the optimism to fight cancer with molecular targets using antibodies, the therapeutic success is critically dependent on the proper selection of the antigen to be target. The current issue is related to the way that tumor-associated antigens (TAA) are expressed. Apart from the issue that some of them are not exclusive of the malignant cells, the ideal tumor targets need to be easily accessible, homogeneous, expressed in a vast majority of cancer cells, and would also need to be stationary. Although this may sound as utopia, in fact, up to now mAbs have been proven more effective against hematologic cancers than solid cancers, what is partially justified by the former best cellular accessibility (Nyberg, 2007). Nonetheless, an impressive progress in solid tumor control using antibodies has been noted. Therefore, important features of anti-tumor antibodies against BC and OVCA are herein presented, focusing on the current strategies and perspectives of new antibodies.

Since 1986, many platforms of antibodies have begun to be developed aiming the activation of effector pathways of immune response while avoiding immunogenicity. As a result, in 1997, the Food and Drug Administration (FDA) has approved the mAb rituximab, a chimeric IgG1 mAb developed to treat B cell non-Hodgkin lymphoma resistant to other chemotherapy regimens (Scott, 1998). This antibody binds CD20 protein, primarily found on the surface of B cells, and triggers cellular death by eliciting ADCC mechanisms.

In the next year, 1998, FDA approved trastuzumab, a recombinant humanized IgG1 antibody targeting HER2 (also known as Erb-2) encoded by the ERBB2 gene. This receptor belongs to the epidermal growth factor receptor (EGRF) family of receptors tyrosine kinases, which are involved in the control of gene expression of angiogenic factors. HER2, as well as HER1 and HER3, activation occurs by ligand binding followed by receptor dimerization and intracellular signaling initiation, leading to cellular proliferation. By binding to HER2, trastuzumab inhibits endogenous growth factor interaction, which, in turn, prevents the receptor dimerization and the activation of downstream proliferative pathways. The expression profile of HER2 has been widely studied in BC samples, and has been proven to be overexpressed in approximately 20 to 30% of invasive breast carcinomas. Besides, it has been observed that HER2-positive BC corresponds to poor prognosis disease when

compared to the HER2-negative counterpart (Hudis, 2007). Indeed, it has been well documented that the former presents a lower OS rate as well as different responses to chemotherapy and hormonal agents when compared to the later. Of clinical relevance, HER2 has been found to be overexpressed in several other tumor, including OVCA, in which case the profile has been observed in 11 to 16% of carriers. Also of interest, as noted for BC carriers, HER2-positive OVCA also correlates to poor prognosis disease (Hogdall et al., 2003; Camilleri-Broet et al., 2004). Importantly, trastuzumab has described synergistic and additive effects with several chemotherapeutic agents, including platinum, taxanes, cyclophosphamide, and anthracyclines, when treating BC (Florescu et al., 2011). Actually, the combination of trastuzumab and paclitaxel is recommende by FDA to treat patients with metastatic BC whose tumors overexpress HER2 protein.

More recently, bevacizumab has been also approved by FDA as the first therapeutic antibody targeting pro-angiogenic factors (Eskander & Randall, 2011). Among them, vascular endothelial growth factor (VEGF) deserves consideration. It acts by binding to the VEGF receptors VEGFR-1 and -2, eliciting biological effects that include induction of cellular proliferation and migration, remodeling of the extracellular matrix, increase of vascular permeability and contribution to newly formed blood vessels survival. Regarding its role in tumorigenesis, it is well known that VEGF is overexpressed in most of the human cancers, and increased levels of this growth factor is correlated with higher microvessels density and advanced disease stages. Bevacizumab recognizes the biologically active isoforms of VEGF and sterically inhibits their binding to the receptors, thus preventing angiogenesis. Originally, bevacizumab has been approved to treat metastatic carcinoma of the colon and rectum (Ferrara et al. 2004). Latter, its application has been expanded to other types of cancer including HER2-negative BC, and, in 2008, the combination of this hmAb with paclitaxel has been approved as a first-line metastatic BC treatment (Miller et al., 2007). Since then, many controversial data concerning the clinical benefits of bevacizumab-based treatment brought forth discussion whereas FDA approval should be kept or withdrawn. In 2010, the Office of New Drugs from the FDA decided for the withdrawn of bevacizumab as the first-line metastatic BC treatment, and has already started the removal of this indication from bevacizumab label (Jefferson, 2010). Regarding the bevacizumab use for OVCA treatment, several clinical trial are currently under development. Data from several phase II studies had shown 15 to 20% response rated with up to 50% PFS in 6 months, and some preliminary data from phase III studies had also indicated an increase in PFS when bevacizumad is combined with other treatments (Eskander & Randall, 2011). However, this hmAbs has not been FDA-approved to treat OVCA.

Also in 2004, FDA has approved the use of cetuximab for coloretal cancer which had spread to other tissues. This is a chimeric mAb which targets the epidermal growth factor receptor-1 (EGFR-1), a cell membrane receptor closely related to HER2. Activation of EGFR-1 occurs by ligand biding, leading to a signalization cascade that culminates with cell proliferation induction (Warksal, 1999). Similarly to what is observed with HER2, EGFR-1 has been found overexpressed in many tumor cells, including both OVCA and BC, among others. This antibody has recently been under clinical trials as a single agent and in combination with platinum-based chemotherapy regimes. Although these trials had shown quite modest results, with relatively low clinical relevant responses and some serious associated side-effects, it is believed that maybe OVCA with lower EGFR-1 expression could be more responsive to this treatment (Frederick et al., 2009).

Other therapeutic mAb that is currently under study is oregovomab, which targets cancer antigen 125 (CA-125). This is a surface glycoprotein antigen, known as a clinical relevant biomarker to OVCA, being elevated in 95% of patients with stage III and IV OVCA (Bast et al., 1983). However, CA-125 can also be found up-regulated in other malignancies, including BC, and in benign tumors and other inflamatory diseases. Oregovomab is a murine mAbs and its binding to CA-125 constitutes a complex that is recognized by the immune system as being foreign. Thereby, producing anti-mouse specific antibodies, anti-idiotype antibodies, and antibodies specific to CA-125, inducing a humoral response to CA-125. A phase II clinical trial with 20 recurrent OVCA patients has evaluated the clinical value of the combination of ovregovomab with citotoxic chemotherapy (Gordon et al., 2004). Patients who have received the combined therapy have shown a good tolerance, presenting only mild side effects. Moreover, a significant longer survival span has been observed in patients who had develop a specific immune response. A randomized, double-blind, placebo-controlled stage III/IV clinical trial with stage III/VI OVCA patients has also been performed (Berek et al., 2008). Initially, the study failed to show a clinical advantage of oregovomab administration, once the median time to relapse (TTR) was unaltered between both groups of patients. However, a subgroup of patients with better prognosis features could be identified, and these, indeed, had a significative shorter TTR than other patients. On the other hand, patients who have received oregovomab and have failed to mount a specific immune response also had a worse prognosis than the placebo group. With respect to the 5-year disease-free survival, oregovomab-based treatment has lead to a mean increased survival time of 58 months compared to 49 month among patients who received the placebo. Currently, oregovomab has not been FDA-approved yet, and it has the status of orphan product.

3.2 Perspectives for BC and OVCA immunotherapy

3.2.1 Cancer vaccines and cytokines

Whereas the use of Abs as therapeutic agents for OVCA and BC has already proven to be of remarkable clinical relevance, analog assessment has not become available as far as the utilization of vaccine- and cytokine-based strategies are concerned. Currently, no cancer vaccine has been approved by FDA, neither for BD, nor for OVCA; but results from many clinical trials using different vaccination approaches and immunogens have shown promising data towards the use of such therapeutic approaches for BC and OVCA (Floresco et al., 2010; Liu et al., 2010).

Many immunogens and vaccine compositions can be considered for cancer therapy. Firstly, it is possible to name vaccines using tumor antigens. A phase I/II study performed with BC, OVCA and lung cancer patients using a HER2 peptide-based vaccine showed that 92% of patients developed immunity to both HER2 peptide and protein (Disis et al., 2002). Besides that, several phase I trials of vaccination against HER2 have demonstrated safety and immunogenicity, with only rare grade 3 toxicity reports (Disis et al., 2004; Wiltschke et al., 2008).

Professional antigen-presenting cells challenged with tumor antigens or fused to tumor cells also represent a vaccination option against cancer. Two small phase I studies have provided some promising data on a HER2 dendritic cell (DC) vaccine, lapuleucel-T (Peethambaram et al., 2009; Park et al., 2007); and a HER2-target DC vaccine could be used to eliminate HER2-overexpression cells in patients with ductal carcinoma in in situ lesions (Czerniecki et al., 2007). In a similar study, patients with advanced BC or OVCA received autologous DCs

pulsed with HER2- or MUC1-derived peptides. After vaccination, 50% of patients developed peptide-specific citotoxic T lymphocites (Brossart et al., 2000).
Other approach for immunotherapy is the combinatory vaccination with the desired antigen and plasmid DNA (pDNA). The first induces antigen-specific antibody production, while the former efficiently promotes the generation of antigen specific T-cells, as well as antibody production (Donnelly et al, 1997). Encouraged by this scenario, some researchers have observed that HER2-pDNA vaccination in combination with cytokines granulocyte macrophage colony stimulating factor (GM-CSF) and interleukin (IL)-2 administration is safe, well tolerated and can induce long-lasting cellular and humoral immune responses against HER2 in patients with advanced BC (Norel et al., 2010). Yet, some studies, targeting metastatic BC, found evidence that vaccination with Mage-b DNA was effective against metastases in various metastatic mouse breast tumor models (Sypniewska et al., 2005; Gravekamp et al., 2008). Mage is an attractive tumor-associated antigen because it is expressed in >90% of all BC but not in normal cells (Park et al., 2002). To further improve the vaccine efficacy of Mage-b, investigators have used an attenuated Listeria monocytogenes (LM) as DNA delivery system. LM is an intracellular pathogen that delivers the vaccine antigen directly into APCs, such as macrophages, with high efficiency (Paterson & Maciag, 2005). Regarding OVCA, a phase II study has evaluated the toxicity of carboplatin, GM-CSF and recombinant interferon γ1b in patients with recurrent, platinum sensitive ovarian, fallopian tube and primary peritoneal cancer. This study has revealed an overall reasonable response and improvement in patients' quality of life (Schemeler et al., 2009).

3.2.2 Novel targets

The identification of novel biomarkers and tumor associated antigens is a promising approach for the effective therapy of cancer. Nowadays, researches are looking for both the antigens and auto-antibodies to the tumoral tissue. The search for antigens can be done in many levels, using high throughput technologies that allow the identification of variations in the expression profile of either mRNA or protein; whilst the search for natural antibodies has been done base on display technologies and combined proteomic and immunological approaches.

Type IIb sodium-phosphate cotrasporter (NaPi-IIb)

A correlation between NaPi-IIb and OVCA has been demonstrated even before either the protein or the gene that encodes it (SLC34A2) have been characterized. Latter on, both the gene and the protein have been found overexpressed in OVCA when compared to normal ovarian tissue; and a difference has been found among the histological OVCA types, and according to the differentiation grade of the tumor (Rangel et al., 2003; Yin et al., 2008; Gryshkova et al., 2009). Nowadays, NaPi-IIb is no longer considered an OVCA-specific marker, since differences in its expression profile have been observed in non-small cell lung cancer, papillary thyroid cancer and BC (Kopantzec et al., 2008; Jarbaz et al., 2005; Kim et al., 2010; Chen et al., 2010). With respect to BC, the same overexpression pattern described to OVCA has been observed, however no correlation between the NaPi-IIb expression level and the differentiation grade of the tumors have been established. Therefore, owing to the high specificity and differential expression patterns showed in cancer, SLC34A2/NaPi-IIb has been pointed as a clinical relevant tumoral biomarker thus representing a potential target for cancer immunotherapy.

Claudins

Claudins are a family of proteins encoded by the claudin gene (CLDN). These proteins are transmembrane proteins with crucial role in the formation and function of tight junctions (Lal-Nag & Morin, 2009). Several analyses had shown that the members of this family have their expression profile altered in various types of cancer. For instance, CLDN3 and CLDN4 have been found to be up-regulated in OVCA and BC, among others. Intriguingly, CLDN16 is up-regulated exclusively in OVCA (Rangel et al., 2003). Moreover, CLDN7 and CLDN1 are down-regulated in BC among others (Morin, 2007). The precise role of claudins in cancer is still unclear; however, it has been hypothesized that the lost of claudins and other tight junction proteins expression could be an important step in the progression of cancer to metastases, since it would lead to loss of cell adhesion. In OVCA, CLDN overexpression has been related to increased invasion, motility and cell survival, all important characteristics to metastasis, thus playing a positive effect on tumorigenesis (Agarwal et al., 2005). Due to the specificity of claudin expressions patterns in cancer, as well as its membrane localization, it has been suggested that members of this family of proteins can represent useful targets to cancer therapy.

4. Nanothecnology and the development of novel drugs

By the end of the last century, Nanomedicine has become a recurrent expression on medical literature, and conjures up the use of Nanotechnology has brought impressive advances in medicine, both in diagnosis and therapy. As for therapeutic exploitation of Nanothecnology, the focus of this chapter, one of the main advances in this area is the use of nanoproducts as carriers of chemotherapy agents, producing nanodrugs. These carriers may be of different origins, but one the most used ones for drug delivery are the lipid nanocarries, which include liposomes and multilamellar, multivesicular liposomes, nanostructured lipid carries and solid lipids (Cattaneo et al., 2010). Yet, the carriers themselves may have some modifications to avoid the immune system, enhancing the drug availability to the organism. This encapsulation of drugs brings many advantages such as lowing systemic toxicity, enabling drug targeting, and prolongation of drug half-life; also overcoming the issue of drug solubility, among others (Jain, 2010).

These presented characteristics theoretically oppose to the main disadvantages of classical chemotherapy (low or no specificity to cancer cells; low accumulation of the drug at the tumor site and high systemic toxicity). Thus, the use of nanodrugs in oncology may be considered as one of the most significant breakthroughs in cancer therapy, bringing new alternatives for the treatment of advanced, refractory and relapsing tumors. Additionally, tumors also present some unique features that facilitate drug targeting by nanodrugs, namely the presence of cancer cell-specific and tumor vasculature markers.

Currently there are about 150 nanotechnology-based drug in development, and some of them had already been approved by FDA (Ruoslahti et al., 2010). Among these, two nanodrugs are indicated by FDA for the treatment of OVCA and/or BC.

Abraxane® (Abraxis Bioscience) is a paclitaxel albumin-bound injectable particle suspension approved by FDA in 2005 for the treatment of metastatic BC which failed to respond to combined chemotherapy or that relapse within 6 moths of adjuvant chemotherapy. This is a novel solvent-free formulation of paclitaxel in which it is bound to albumin forming 130 nm stable particles. The classical solvent to paclitaxel, Cremophor-EL, causes severe hypersensitivity reaction, thus this new formulation eliminates solvent-related toxicity. The

approval of Abraxane® was performed based on a comparative trial versus taxol with a group of metastatic BC patients. In this study, patients who have received Abraxane® had better response and progression rates. Currently, the use of Abraxane® for the treatment of other solid tumors is under evaluation, and some beneficial effects of these treatments has been reported to treat refractory metastatic OVCA.

Doxyl®/Caelyx® (Ortho Biotech) is a doxorubicin hydrochloride (HCl) encapsulated in pegylated liposomes for intravenous administration. The liposomes used to encapsulate this drug are modified (pegylated) to avoid liposomes to be identified by the mononuclear phagocity system, thus increasing the compound half-life in the organism. It is hypothesized that this nanocapsules are able to penetrate the tumor vascular system, but not the normal one, due to its small diameter (approximately 100 nm). Because of this, Doxil® is much more specific to tumor tissues, and thus presents a lower cardiotoxic activity when compared to doxorubicin alone. Doxil is approved with 3 indications, including the treatment of OVCA patients whose disease has progressed or relapse after platinum-based chemotherapy. In 2009, Ortho Biotech requested the indication of Doxil® in combination with docetaxel for the treatment of locally advanced or metastatic BC based on the results from 3 large, international, randomized, controlled studies that enrolled more than 1,500 patients. Even though the conclusion of this studies were that patients with advanced BC would clinically benefit from Doxil® therapy with a favorable risk benefit rate, FDA has not stated its decision about this new application to Doxil®.

5. Conclusion

To put it briefly, the present chapter has compiled the state-of-the-art information regarding BC and OVCA treatment. Women's health matters remain a priority in public and private care systems, as female cancers remain lethal diseases for which improved screening and treatment strategies are urgently needed.

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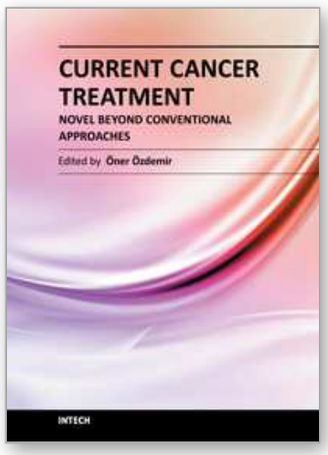

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Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

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