Breast cancer is the most common cancer affecting women worldwide. Over 100 years ago, Beatson (1) discovered that an oophorectomy in a premenopausal patient resulted in regression of her breast cancer. Since then, estrogen deprivation has become widely used, both in the adjuvant and advanced setting, even in healthy women at high risk of developing breast cancer addressing the issue of prevention. More than 20% of all breast cancers occur in women younger than the age of 50, and 60% of these are ER-positive, in comparison to 80% of ER-positive women older than the age of 50 (2). Among them, three endocrine responsiveness categories were defined. Highly endocrine responsive: tumors express high levels of both steroid hormone receptors in a majority of cells identified with proper immunohistological methods. Incompletely endocrine responsive: some expression of steroid hormone receptors but at lower levels or lacking either ER or PgR. Endocrine non-responsive: tumors having no detectable expression of steroid hormone receptors (3).

The discovery and use of tamoxifen represented major breakthrough and it has now been in use for more than 30 years. Initially thought to be valuable only in postmenopausal setting, it acts as a selective estrogen receptor antagonist, competitively blocking receptors in breast tissue, both in the pre- and postmenopausal women. Tamoxifen has been the gold standard in the adjuvant endocrine therapy of both premenopausal and postmenopausal breast cancer for more than two decades. It was first shown to reduce recurrence and mortality in a series of definitive trials in the early 1990s (4). Adjuvant tamoxifen is typically administered for 5 years. The overview showed that 5 years is significantly more effective than 2 years, with a further 18% reduction in the annual recurrence rate and a 2% reduction in the annual mortality rate. More than 5 years has for some time been considered inappropriate mainly on the basis of the NSABP-B14 trial. No advantage beyond 5 and the optimal duration of tamoxifen in premenopausal women remains an open question. The Overview shows that the incidence of uterine cancer increases with duration of treatment. Two large trials of tamoxifen duration are still ongoing (5).

Adjuvant surgical oophorectomy was first proposed in 1889 and was shown to be effective in the first randomized trial in breast cancer started almost 60 years later in 1947 (6). The overview showed no significant difference in efficacy between ovarian ablation and ovarian suppression, but there was a trend against the LHHR analogs. A meta-analysis of 16 trials involving 9,002 women with hormone receptor-positive early breast cancer treated with adjuvant LHHR agonists have shown that there was an insignificant trend towards reduction in risk of recurrence and a similar insignificant trend in risk of death. Most of the trials have used 2 years of treatment, with a range of 18 months to 5 years (7).

In recent years, the success of tamoxifen has been superseded by the recognition of aromatase inhibitors (AI) as a potentially superior form of treatment. These agents block the conversion of androgens to estrogens in peripheral, breast and other tissues by inhibiting the cytochrome P450 enzyme aromatase. By this mechanism AI lowers both the circulating estrogen and also local estrogen production in the breast tumor. Aminogluthimide and formestane, first- and second-generation AI, respectively, have been restricted by unacceptable toxicities. Third-generation AI has improved the greatest impact, namely anastrozole, exemestane and letrozole (8). The so-called third-generation aromatase inhibitors have shown a moderate but consistent improvement over tamoxifen in premenopausal women whether given up-front or sequentially. They are contraindicated in premenopausal patients because the suppression of peripheral aromatase results in reduced feedback to the hypothalamus and an increase in ovarian stimulation (2).

Based on these findings, a few expert groups and Consensus Panel developed evidence-based guidelines for early-stage breast cancer treatment (9,10). Despite the overwhelming trial data on activity and tolerance, it is not yet possible to define when and for how long, AI should be initiated. There remains a degree of uncertainty regarding the role of AI in the upfront, ‘switch’ and extended-therapy settings. In addition, we still need to clarify which group of patients should receive adjuvant therapy beyond 5 years. After 5 years of hormone therapy, there remains 1.5–2% annual risk of recurrence during the 5–to 15-year period after diagnosis and treatment. Aromatase inhibitors are clearly efficacious, but also have potential long-term adverse effects. The optimal treatment regimen should attempt to gain the maximum benefit from both. A further area of controversy surrounding the initiation of aromatase inhibitors is predicting which subgroups of patients are tamoxifen resistant yet AI sensitive. The future emphasis needs to be on designing therapy for specific patients and assuming a more individualized treatment strategy.

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Adjuvant therapy of women under 35 years of age is an important focus in the treatment of early breast cancer. This age group of population is rarely affected with breast cancer (only 2% to 4% of all cancer diagnoses). It has been known that women under 35 years of age with breast cancer have poorer disease prognosis than women of older age. As compared to other factors, the age under 35 years is an independent risk factor. The patients are under a higher risk to develop disease recurrence and death. Tumors in younger women are biologically more aggressive, they are associated with higher histopathological grade and index of proliferation, more vascular invasion, and frequent appearance of local recurrences. Nodal status, positive HER2, and negative ER/PR status is more frequent in patients of 30 to 35 years of age and it is associated with higher risk to develop recurrence and poorer survival prognosis. However, patients under 30 years of age with positive receptor status form a group of young patients with better prognosis.

Patients’ quality of life and their concern related to fertility, sexuality, and signs of premature menopause are an important segment of adjuvant treatment of breast cancer. Pregnancy of breast cancer patients during and after the treatment of the disease has been an interesting topic of numerous discussions but also of numerous prejudices. Literature data report that pregnancy after the treatment of early breast cancer does not influence total survival rate.

All stated parameters are important in making decision about adjuvant systemic treatment and application of adjuvant chemotherapy and/or hormonal therapy. Boost radiotherapy reduces the risk of disease recurrence. Decision about the administration of adjuvant treatment implies also deciding about the ovarian suppression with or without hormonal therapy, the application of targeted therapy in HER2 positive patients, and side effects and severe toxicity related to administered therapy. The use of ovarian suppression only is an option in patients who want to preserve fertility.

Treatment of breast cancer in very young patients requires a multidisciplinary approach; it includes clinical and pathological risk factors and it is associated with emotional and physical condition of patients.

Breast cancer is a heterogeneous group of diseases that vary in morphology, biology, behavior and response to therapy. Currently, breast cancer patients are managed according to algorithms based on constellation of clinical and histopathological parameters in conjunction with assessment of hormone (estrogen and progesterone) receptor status and HER2 overexpression/gene amplification. In recent years, the term “triple-negative” (TN) breast cancer has emerged to describe those cancers which do not express estrogen receptor (ER), progesterone receptor (PgR) or overexpression human epidermal growth factor receptor 2 (HER2) (1). While effective targeted therapies have been developed for patients with hormone receptor-positive and HER2-positive disease, triple-negative breast cancer is a disease with aggressive clinical behavior which lacks effective tailored therapies, and presently, chemotherapy stays the only standard modality of systemic therapy for patients with triple negative breast cancers. The differences in clinical behavior of breast cancers, such as different prognosis and different response to therapy, are probably mostly due to molecular differences between histologically similar tumors. Transcriptional profiling of breast cancer has identified five distinct molecular subtypes: luminal A, luminal B, normal breast-like, HER2 overexpressing and basal-like (2, 3, 4). Basal-like breast carcinomas were so named because the neoplastic cells of this tumor type consistently express genes usually found in normal basal/myoepithelial cells of the breast including high-molecular-weight “basal” cytokeratins (CK 5/6, 14 and 17), high levels of proliferation-related genes and epidermal growth factor receptor (EGFR, HER1), as well as low expression of ER, PgR and HER2. The majority (71%-91%) of triple-negative cancers possess basal-like gene expression profile, while only 77% of basal-like carcinomas have a TN immunophenotype, stressing that tumors TN and basal-like are not synonyms (5).

Triple-negative breast cancer is an immunohistochemical, IHC-based defined, while basal-type is gene expression-based defined (6). Thus, triple-negative breast cancers (not expressing ER, PgR and HER2 proteins detected by IHC) have value in current clinical practice as surrogate marker for basal-like cancers in clinical decision making and protocol design (7). Although both TN and basal-like tumors share many molecular and morphological features, equating both tumor classes may be misleading because there is a risk that TN breast cancers included in clinical trials are not exactly identical to basal breast carcinomas leading to a falsely negative conclusion of inactivity of the drug in basal cancers. A better understanding of the molecular and histopathological features of TN and basal-like cancers is of great importance, in particular for unrevealing the heterogeneous nature of these tumor subgroups and for the identification of prognostic biomarkers, ideal systemic therapy regimens and novel therapeutic targets for these aggressive tumors (8).

Triple-negative breast cancers account approximately 15% of all breast carcinomas (9). Triple-negative breast tumors have been characterized by several aggressive clinicopathologic features including onset at a younger age, higher mean tumor size, higher-grade tumors, as well as increased mitotic count, central necrosis, pushing borders of invasion and stromal lymphocytic response. The majority of triple-negative breast cancers are ductal in origin; however, several other aggressive phenotypes appear to be overrepresented, including metaplastic, atypical or typical medullary and adenoid cystic (10). Triple-negative breast cancers have many similarities to BRCA1-associated basal breast cancers, as it has been observed that the majority of BRCA1-associated breast cancers are triple-negative and express a high proportion of basal markers such as cytokeratins 5, 14, 17 and EGFR (11). Triple-negative breast cancers are more likely to occur among premenopausal women of African-American descent (12). Several large population-based studies have illustrated that compared to luminal A tumors (ER-positive and/or PgR positive and HER2 negative), basal-like breast tumors were more likely to arise among women with a younger age at menarche, higher parity, younger age at full-term pregnancy, shorter duration of breastfeeding, higher body mass index, oral contraceptive use ≥ 1 year, especially among young patients, as well as in those women who used methods to suppress lactation (13, 14).

Triple-negative breast cancers have a more aggressive clinical course than other forms of breast cancer (1, 10, 11 and 15). The inferior prognosis associated with triple-negative breast cancer was originally recognized in the initial studies examining outcome by intrinsic subtype, uniformly demonstrating a poorer prognosis among patients with breast cancer classified as basal-like, particularly compared to those in good-prognostic subclasses (i.e., luminal A) via gene expression profiling (3,4). Population-based studies have also demonstrated reduced breast cancer-specific survival among patients with triple-negative disease. In Canadian study, patients with triple-negative breast cancer had an increased likelihood of distant recurrence (HR 2.6, p<0.0001) and death (HR 3.2, p<0.0001) compared with women with non-triple-negative breast cancer. The pattern of recurrence over a 5-year follow-up period was substantially different among groups: patients with triple-negative breast cancer were much more likely to develop a recurrence during the first 3 years following therapy with rapid declines thereafter (15). In addition to a distinct pattern of timing of recurrence, unique patterns of relapse sites are recognized among triple-negative breast cancer patients: basal-like breast cancers have a tendency toward more aggressive visceral (versus bone) metastasis (16), with lung and brain metastases more frequently observed among triple-negative breast cancer patients (10, 15).
Although triple-negative breast cancer is associated with a generally poor breast cancer-specific outcome, it is not resistant to chemotherapy (9, 10, 16 and 17). In the adjuvant setting, retrospective review of a subset of patients treated on Cancer and Leukemia Group B (CALGB) 9344 suggested that the benefit of a taxane added to an anthracycline was primarily among patients with triple-negative or HER2-positive disease. Furthermore, two neoadjuvant studies revealed proportionally higher sensitivity to anthracycline- or anthracycline-taxane based chemotherapy for basal-like/ER-negative breast cancers compared to luminal/ER positive subtypes (16). Preclinical and clinical studies indicate that tumors with BRCA1 dysfunction harboring deficient double-stranded DNA break repair mechanisms are sensitive to agents that cause DNA damage, such as platinum agents (cisplatin and carboplatin). The association between triple-negative breast cancer and BRCA1 mutation status has led to several (neo) adjuvant and metastatic studies illustrating activity of platinum-based regimens in the treatment of triple-negative breast cancer (18). Several targeted strategies are being tested for the treatment of patients with triple-negative breast cancer. These include inhibition of poly(ADP-ribose) polymerase (PARP), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) receptor, microtubules, Src kinase, mammalian target of rapamycin (mTOR), checkpoint kinase 1 and other (9,10,17).

In summary, triple-negative breast cancer is a subtype of breast tumors with unique molecular and clinical characteristics, distinctive risk factors and patterns of recurrence, association with BRCA1 mutation status, inferior prognosis and expanding therapeutic options. Current research strategies are mostly aimed at better understanding the biology underlying triple-negative breast cancer, with the goal of improving treatment strategies for this challenging subtype of breast cancer (10).

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Targeted therapy for early breast cancer – a new chance for cure

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Treatment of early stage breast cancer (BC) requires a multimodality approach in order to eradicate residual cancer and prevent recurrent disease. Targeting the pathways that promote or sustain cancer cell growth and invasion is critical for the effective treatment of BC. This kind of treatment aims to improve and maintain and prolong the life of patients. The prognosis and probability of response to different therapies is related to a patient (age, PS, comorbidities and menopausal status) and the tumor characteristics such as histological type, grade, size, lymphnode involvement, ER/PR status, HER2 status and gene profile (5).

Amongst BC cells, the first critical target to be identified was the ER. Tamoxifen is a selective modulator of ER, used in ER pos. BC and in clinical use since 1970s. Responses of greater than 80% have been observed (major improvement in cure rates, quality of life and disease prevention during the past 25 years).

Since 1990 the recommendation is the routine ER testing to facilitate tailored adjuvant treatment – first targeted treatment (TT). In 1998, trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of the HER2 receptor was developed. In the year 1998 trastuzumab was approved in combination with paclitaxel, as first line treatment for HER2-positive MBC. These include monoclonal antibodies and small molecule inhibitors have significantly changed the treatment of BC over the past 10 years. The mechanisms of action and toxicities of TT differ from those of traditional cytotoxic chemotherapy, by blocking the proliferation of cancer cells by interfering with specific molecules required for tumor development and growth (5, 6, 8, 9). Monoclonal antibodies are usually water soluble and large, target extra-cellular components of these pathways, such as ligands and receptor – binding domains. Small molecule inhibitors can enter the cell, thereby blocking receptor signaling and interfering with downstream intracellular molecules. TTs are generally better tolerated than chemotherapy but they are associated with several adverse effects, such as acneiform rash, cardiac dysfunction, thrombosis, hypertension and proteinuria. Small molecules are metabolized by cytochrome 450 enzymes and are subject to multiple drug interaction. TT has raised new questions about the tailoring of cancer treatment to an individual patient’s tumor, the assessment of drug effectiveness and toxicity (7). BC diagnosed patients with amplified (20-30% of all BC patients) or overexpressed HER2 are likely to be more numerous, have poorly differentiated tumors with a high proliferative rate, poor axillary lymph nodes and decreased expression of ER and PR receptors. These characteristics are associated with a short DFS, an increased risk of disease recurrence and death (2,4,5).

Since 2005, it has been approved (in combination with chemotherapy) also for the adjuvant therapy in HER2-positive BC after obtaining interim analyses of the 5 adjuvant trials. The largest adjuvant trial (HERA) which includes over 5000 women after median follow-up (FU) of 23.5 months resulted in significant reduction in risk of recurrence HR: 0.64 and risk of death was significantly reduced HR 0.66. After 4 years, nearly 90% of patients were still alive (1). The joint analysis (N9813B2) of which included about 4000 women, at the median FU of 2.9 years (3) produced significant reductions in the risk of both recurrence (HR: 0.59) and death (HR: 0.59). A small FinHer study which included ~1000 women, but only 232 with HER2 – positive tumors received 9 cycles of trastuzumab weekly. At median FU of 3 years, risk of recurrence was HR: 0.42. The meta analysis (11) of these five trials (published in June 2008), reported the outcome in 13493 women. The analysis showed DFS to be superior for trastuzumab-treated patients for 38% (RR: 0.62), 34% difference in OS (mortality RR: 0.66), locoregional recurrence (RR: 0.58) and distant recurrence (RR: 0.59). Those patients had a higher risk for congestive heart failure (RR: 7.60) and LVEF decline (RR: 2.09). Trastuzumab-mediated cardiac toxicity occurred rarely (< 4%) and is reported to be reversible in the majority of cases. A higher risk for central nervous system metastases as the first recurrence event (RR: 1.60) was also observed in the trastuzumab receiving patients. Presented data indicate that there is a level 1 evidence to support the routine use of one year of adjuvant trastuzumab in conjunction with chemotherapy in women who have an early-stage, HER2-positive BC (10).

The initial peak in recurrences that is generally expected during the first two to three years has been abrogated by trastuzumab. This observation suggests a dramatic and perhaps permanent perturbation of the natural history of the disease, maybe even a cure. All these results have shown that a dramatic progress in the treatment of HER2 positive BC patients occurred (11).

Despite these very promising and cure oriented results, many questions remain open: controversies relating to the use of trastuzumab (such as timing, durations, use with taxanes, radiotherapy, its role in small tumors who are node-negative and resistant to trastuzumab).

There is a tremendous interest in building regimens around multiple targeted therapies, in particular, combining anti-HER2 and anti-angiogenic approaches. The future of adjuvant therapy will be dependent on our understanding of tumor biology. Simply knowing that the target exists is not sufficient to tailor adjuvant therapy, and newer technologies are also aimed at identifying breast cancer subgroups that are most likely to respond to the TT. This newer technologies include gene expression profiling and micro-metastases tracking. From the initial breakthrough with molecular subtypes and prognostic gene
expression signatures, gene expression profiling has also undergone a significant evolution towards predicting treatment response, similar to that of the ER experience (10). There are many adjuvant early BC trials with TT running, results of which are expected in the next future, which would change the today’s practice in the treatment of HER2 -positive BC patients, and probably give us the chance to cure the patient.

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