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Chemotherapy in Early Breast Cancer: When, How and Which One?

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Keywords

Breast cancer · Prognosis · Chemotherapy

Summary

The efficacy of chemotherapy depends on the level of risk of the individual patient. Because of this, careful estimation of the risk level is mandatory. In addition to well-established clinicopathological factors, validated gene expression signatures might be useful in selected patients if all other criteria are inconclusive for therapeutic decision-making. If indicated, chemotherapy can be used either after surgery (adjuvant) or before surgery (neoadjuvant). Both approaches lead to comparable long-term survival. The neoadjuvant setting offers the additional opportunity for elaborate translational studies to develop and validate predictive biomarkers and to discover mechanisms of resistance to therapy. If possible, chemotherapy regimens should include both anthracyclines and taxanes. Docetaxel should be used every 3 weeks; better tolerability with equivalent efficacy favors the concurrent over the sequential approach. Paclitaxel, on the other hand, should be administered sequentially, either weekly or every 2 weeks. Especially, intense dose-dense sequential chemotherapy with granulocyte colony-stimulating factor support is very effective in high-risk breast cancer patients. In order to decrease toxicities, anthracycline-free regimens or a shortening of the duration of adjuvant chemotherapy are potential options that should be further explored.

When to Use Chemotherapy in Early Breast Cancer?

It is evident that the magnitude of chemotherapy benefit depends on the level of risk of the individual patient [1]. In order to avoid both over- and undertreatment, it is advisable to select the appropriate treatment strategy on the basis of a careful risk assessment for each individual patient. According to the most recent St. Gallen consensus recommendations, conventional clinicopathological factors arguing for the indication of chemotherapy were histological grade 3 carcinomas, high Ki-67 levels, low hormone receptor status, human epidermal growth factor receptor 2 (HER2) positivity or triple-negative status, and the involvement of more than 3 lymph nodes [2]. In addition to these time-honored clinicopathological factors, a plethora of novel prognostic and predictive factors has emerged over the last decades. To improve the quality of research on biomarkers, a refined system for biomarker study design and evaluation was introduced that incorporates a revised level of evidence (LoE) scale for tumor marker studies, including those using archived specimens (table 1) [3]. Although fully prospective randomized clinical trials to evaluate the medical utility of a prognostic or predictive biomarker are still considered the gold standard, such trials are costly; so, more efficient indirect 'prospective-retrospective' designs using archived specimens might reach LoE I if validated with consistent results.

Since the field of biomarker evaluation for therapy stratification is rapidly evolving, the American Society of Clinical Oncology (ASCO) updated their recommendations for the use of tumor markers in breast cancer [4]. In addition to the estrogen receptor (ER) and HER2, parameters like urokinase plasminogen activator (uPA), plasminogen activator inhibitor 1 (PAI-1), and certain multiparameter gene expression assays like the recurrence score (RS) showed evidence of clinical utility and were recommended for use in practice.

The RS (Oncotype DX™) is a well-known and broadly used assay using formalin-fixed paraffin-embedded (FFPE) tissue. This reverse transcription-polymerase chain reaction (RT-PCR) assay measures the expression of 21 genes in RNA extracted from FFPE samples of tissue from primary breast cancer. This test was developed specifically for patients with ER-positive node-negative breast cancer patients treated with adjuvant tamoxifen [5] and helps to identify patients with little additional benefit from adjuvant chemotherapy [6]. The independent prognostic and predictive significance of the RS was also confirmed in endocrine-responsive node-positive patients receiving anthracycline-based chemotherapy [7]. Again, only patients with high RS derived substantial benefit from chemotherapy.

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More recently, another gene expression assay using FFPE tissue was developed to assess the prognosis of early breast cancer patients treated with endocrine therapy [8]. This multigene EndoPredict™ (EP) risk score provided additional prognostic information on the risk of distant recurrence of breast cancer patients, independent from conventional clinicopathologic parameters. Combination of EP with tumor size and number of involved lymph nodes (EPclin) led to an even better prognostication. Additionally, EP improved the prognostic classification derived from common clinical guidelines like the National Comprehensive Cancer Center Network, German S3, and St. Gallen guidelines in ER-positive, HER2-negative early breast cancer [9].

Using supervised analysis, genes were identified that were differentially expressed in tumors of node-negative and untreated patients who developed a metastasis within 5 years or remained disease free for at least 5 years [10]. The respective classification algorithm outperformed conventional prognostic factors and was confirmed in subsequent retrospective validation studies (MammaPrint™).

Perou et al. [11] described breast cancer subtypes identified after 2-dimensional hierarchical clustering, which they called luminal, basal like, normal like, and ERBB2 like. These intrinsic subtypes differed in their clinical outcome, their preferential site of relapse, and their response to chemotherapy. A 50-gene subtype predictor was developed using microarray and quantitative RT-PCR data (PAM50) [12]. PAM50 is also commercially available and works in FFPE tissue (Prosigna™). These signatures show analytical and clinical validation. However, evidence for these tests is 'prospective-retrospective' using archival tissue of completed clinical trials, while prospective evidence is still missing (table 2).

Based on these encouraging findings, the St. Gallen consensus conference recently confirmed a classification based on the recognition of intrinsic biological subtypes within the breast cancer spectrum [2]. Even though the original subtype classification was based on gene expression arrays, immunohistochemical determination of ER, progesterone receptor (PR), HER2, and Ki-67 expression is considered as useful by providing a surrogate subtype classification. This classification simplifies the definition of therapy indications, since the subtypes themselves incorporate many of the risk and predictive factors used in previous consensus recommendations. Essentially, the current recommendations advise chemotherapy for triple-negative and for high-risk luminal A, luminal B and HER2-positive breast cancer patients (table 3). Concerning the latter group of HER2-positive patients, it is mandatory to combine chemotherapy with an anti-HER2 therapy.

Table 1. Revised determination of LoEs using elements of tumor marker studies [3]

LoE	Category	Validation studies available
I	A	none required
I	B	1 or more with consistent results
II	B	none or inconsistent results
II	C	2 or more with consistent results
III	C	none or 1 with consistent results or inconsistent results

Table 2. Commercially available molecular tests

	Mammaprint™	Oncotype DX™	EndoPredict™	Prosigna™
Provider	Agendia	Genomic Health	Sividon	NanoString
Type of assay	70-gene assay	21-gene RS	11-gene assay	50-gene assay
Type of tissue	fresh frozen	FFPE	FFPE	FFPE
Technique	DNA microarrays	qRT-PCR	qRT-PCR	qRT-PCR
Central laboratory	yes	yes	no	no
Indication and population studied	prognostic, N0–1	prognostic, N0–1 ER+	prognostic, N0–1 ER+/HER2–	prognostic, N0–1
Analytical validation	yes	yes	yes	yes
Clinical validation	yes	yes	yes	yes
Prospective-retrospective evidence (% of recruited patients)	observational feasibility study (RASTER) (73%)	NSABP B-14 (14%), NSABP B-20 (28%), SWOG 8814 (40%), ATAC (30%)	ABCSG 6 (19%), ABCSG 8 (36%), GEICAM/9906 (64%)	MA.12 (49%), MA.5 (66%), ABCSG 8 (40%), ATAC (16%), GEICAM/9906 (66%)
Prospective evidence (pending)	MINDACT	$TAILOR_X$, RxPONDER, ADAPT		
CTS	C	B	B	B
LoE_{2009}	II	I	I	I
AGO recommendation	+/–	+[a]	+[a]	+/–

AGO = Arbeitsgemeinschaft für Gynäkologische Onkologie, CTS = category of tumor marker studies, ER = estrogen receptor, FFPE = formalin-fixed paraffin-embedded, HER2 = human epidermal growth factor receptor 2, LoE = level of evidence, qRT-PCR = quantitative reverse transcription-polymerase chain reaction, RS = recurrence score.

[a]Should only be used in selected node-negative patients if all other criteria are inconclusive for therapeutic decision-making.

Table 3. Systemic treatment recommendations according to subtypes [2]

Subtype	Type of therapy
Luminal A like	endocrine therapy is the most critical intervention and is often used alone
Luminal B like (HER2 negative)	endocrine therapy for all patients, cytotoxic therapy for most
Luminal B like (HER2 positive)	cytotoxics + anti-HER2 + endocrine therapy
HER2 positive (non-luminal)	cytotoxics + anti-HER2
Triple-negative	cytotoxics

Meanwhile, it is becoming increasingly popular to base chemotherapy decisions for patients with luminal disease on genomic results rather than on the surrogate subtype definitions [2]. As outlined above, several multigene molecular assays were recognized as providing accurate and reproducible prognostic information and, in some cases, as providing prediction of response to chemotherapy.

How to Use Chemotherapy in Early Breast Cancer?

Basically, there are 2 options of how to use chemotherapy: either after surgery (adjuvant) or before surgery (neoadjuvant). It is well accepted that both approaches lead to comparable long-term survival. Beyond local downstaging of large tumors, several advantages speak in favor of investigating new therapies in the neoadjuvant setting. Besides requiring a smaller sample size than adjuvant studies and delivering the efficacy results of a new treatment much earlier, the neoadjuvant setting offers the opportunity for elaborate translational studies to develop and validate predictive biomarkers and discover mechanisms of resistance to therapy. Additionally, interest was raised in whether pathological complete response (pCR) might be a good surrogate for survival. A recent meta-analysis including 11,955 patients from 12 international neoadjuvant trials indeed confirmed that pCR was associated with event-free survival (EFS) and overall survival (OS) [13]. The prognostic value was most pronounced in aggressive tumor subtypes like triple-negative breast cancer (TNBC), HER2-positive or ER-positive poorly differentiated breast cancer. However, at the trial level, there was little association between increases in frequency of pCR and the effect of treatment on EFS or OS. The authors thus concluded that these findings did not support the use of pCR as a valid surrogate endpoint for improved survival in early breast cancer.

In clinical routine, neoadjuvant chemotherapy could be considered for patients who would otherwise meet the criteria for adjuvant therapy [14]. The largest benefit is expected in those patients with a high likelihood for pCR (age < 40 years, tumor size < 2 cm, invasive-ductal histology, poor grade of differentiation, high Ki-67 level, low-level or absent ER, intrinsic subtype basal like or HER2 enriched. In contrast, neoadjuvant treatment should not be recommended routinely when there is uncertainty regarding the indication of chemotherapy. During neoadjuvant treatment, careful monitoring of response is mandatory. Monitoring during treatment must include at least clinical breast examination before each cycle. The frequency of imaging assessment during chemotherapy is a matter of debate. Very recently, a large phase III trial showed that response-guided therapy after only 2 cycles of therapy improved survival especially in ER-positive but not in ER-negative patients [15]. 2,072 patients were treated with 2 cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) in the neoadjuvant setting. Early responders were randomized to 4 or 6 additional TAC cycles, and early nonresponders to 4 cycles of TAC or vinorelbine and capecitabine (NX) before surgery. Disease-free survival (DFS) was longer in early responders receiving TAC × 8 (hazard ratio (HR) 0.78; 95% confidence interval (CI), 0.62–0.97; p = 0.026) and in early nonresponders receiving TAC-NX than in those receiving TAC × 6 (HR 0.59; 95% CI, 0.49–0.82; p = 0.001). DFS was longer after response-guided chemotherapy in all hormone receptor-positive tumors (luminal A HR = 0.55, luminal B (HER2 negative) HR = 0.40, and luminal B (HER2 positive) HR = 0.56), but not in hormone receptor-negative tumors (HER2 positive (non-luminal) HR = 1.01 and triple-negative HR = 0.87). This novel response-guided approach could ultimately provide a clinically meaningful advantage for neoadjuvant over adjuvant treatment in early breast cancer [15].

More recently, von Minckwitz et al. [16] examined the efficacy of the addition of carboplatin to neoadjuvant therapy for TNBC and HER2-positive breast cancer. They could show in a randomized phase II study that the addition of neoadjuvant carboplatin to an anthracycline- and taxane-containing regimen significantly increased the proportion of patients achieving a pCR. This improved efficacy was most pronounced in TNBC (odds ratio 1.94; 95% CI, 1.24–3.04). 53.2% of TNBC patients allocated to carboplatin showed a pCR as compared to 36.9% without carboplatin. These results support preclinical data suggesting that TNBC is sensitive to interstrand crosslinking agents. Conversely, the addition of carboplatin to an anthracyclin- and taxane-containing regimen failed to show a higher pCR in HER2-positive breast cancer (32.8% vs. 36.8%). Notably, the addition of carboplatin significantly increased both hematological and non-hematological toxicity. However, these results await confirmation in independent studies.

Considering the choice of chemotherapy, the same regimens should be used for neoadjuvant therapy as in the adjuvant setting. Based on the background outlined above, neoadjuvant chemotherapy is an interesting option that could be

offered to a substantial proportion of breast cancer patients for whom chemotherapy is indicated.

Which Chemotherapy to Use in Early Breast Cancer?

The successful history of adjuvant chemotherapy in early breast cancer started almost 4 decades ago when Bonadonna et al. [17] in 1976 published the first report on the efficacy of cyclophosphamide, methotrexate, and fluorouracil (CMF) as adjuvant treatment for node-positive breast cancer.

Later trials showed that substitution of methotrexate with epirubicin (CEF) was even more efficacious both in terms of DFS and OS in premenopausal women with axillary node-positive breast cancer [18]. The advantage of anthracycline-containing 3-drug combinations over CMF was unequivocally confirmed in an individual-patient data meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [1]. Altogether, 100,000 patients in 123 randomized trials were included. Anthracycline-based regimens with substantially higher cumulative dosage than standard 4 × AC (adriamycin and cyclophosphamide) (e.g. CAF (cyclophosphamide, adriamycin, and fluorouracil) or CEF) were superior to standard CMF (response rate (RR) 0.78; p = 0.0004).

Taxanes

Taxanes received increasing attention since Henderson et al. [19] published a clinical trial in node-positive breast cancer showing that the addition of 4 cycles paclitaxel 175 mg/m^2 improved DFS (HR 0.83) and OS (HR 0.82). This resulted in an absolute improvement of DFS and OS at 5 years of 5% and 3%, respectively. However, the design of this trial raised some criticism. On the one hand, the duration of the 2 regimens was strikingly different: 12 weeks for the standard AC compared to 24 weeks for AC followed by paclitaxel. On the other hand, many argued that 4 × AC was not an optimal standard arm. To circumvent these limitations, the PACS01 trial investigated taxane-containing chemotherapy in early breast cancer which used an adequate anthracycline-containing standard therapy with an identical duration of treatment for comparison [20]. 1,999 node-positive breast cancer patients were randomized to either 6 cycles of FEC (fluorouracil, epirubicin, and cyclophosphamide) every 3 weeks or 3 cycles of FEC followed by 3 cycles of docetaxel every 3 weeks. After a median follow-up of 60 months, the 5-year DFS and OS rates were 73.2% and 86.7% with FEC and 78.4% and 90.7% with FEC-docetaxel, respectively.

Unlike these trials which used a sequential design, Martín et al. [21] compared a concurrent therapy with TAC (docetaxel 75 mg/m^2, doxorubicin (= adriamycin) 50 mg/m^2, and cyclophosphamide 600 mg/m^2) with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) as adjuvant chemotherapy for node-positive breast cancer. Long-term follow-up confirmed that the initial therapeutic outcomes seen at the 5-year follow-up with a docetaxel-containing adjuvant regimen were maintained at 10 years [22]. At a median follow-up of 124 months, DFS was 62% among the 745 patients randomly assigned to receive TAC and 55% among the 746 patients randomly assigned to receive FAC. The estimated rates of OS at 5 years were 76% and 69%, respectively. TAC improved DFS relative to FAC irrespective of nodal, hormone receptor, and HER2 status. However, this increased efficacy came with an increased price in the form of toxicities. Short-term toxicities like febrile neutropenia were markedly increased in patients receiving TAC, which resulted in rates of febrile neutropenia of 24.7% compared with 2.5% in patients receiving FAC. The initially high rate of febrile neutropenia after TAC was considerably reduced to 6.5% when the patients received primary granulocyte colony-stimulating factor (G-CSF) prophylaxis after a protocol amendment [21]. Grade 3–4 heart failure occurred in 26 (3%) patients in the TAC group and 17 (2%) patients in the FAC group, and caused death in 2 patients in the TAC group and 4 patients in the FAC group. A substantial decrease in left ventricular ejection fraction was seen in 58 (17%) patients who received TAC and 41 (15%) patients who received FAC. 6 patients who received TAC developed leukemia or myelodysplasia, as did 3 patients who received FAC [22].

This first generation of taxane-containing trials was conducted almost exclusively in node-positive breast cancer. However, it is evident that node-negative breast cancer patients with adverse prognostic features like poor histological grade, negative ER status, or lymphovascular involvement are also under increased risk of relapse [23]. Accordingly, 1,060 node-negative breast cancer patients with at least 1 additional risk factor were randomized to 6 cycles of FAC or TAC, respectively [24]. At a median follow-up of 77 months, TAC was significantly associated with improved DFS (HR 0.6; 95% CI, 0.49–0.93; p = 0.01). This benefit was independent of hormone receptor or menopausal status. Grade 3 or 4 adverse events were significantly more common with TAC (28.2%) compared with FAC (17.0%). A comparison of both adjuvant TAC trials clearly shows that the efficacy of TAC is similar in node-positive and node-negative breast cancer patients.

The optimal schedule of (neo)adjuvant chemotherapy (either concurrent or sequential) is still a matter of discussion. Recently, a large study including 3,298 node-positive and HER2-negative breast cancer patients shed some light on this debate. Patients were randomized to either 6 cycles of concurrent TAC every 3 weeks or a sequential schedule of 4 cycles of AC followed by 4 cycles of docetaxel without primary G-CSF prophylaxis [25]. However, despite comparable efficacy across all subgroups, the 2 regimens differed in terms of toxicity. TAC was associated with more febrile neutropenia and thrombocytopenia. Patients randomized to AC followed by docetaxel had more sensory neuropathy (42.8% vs. 27.5%), myalgia (50.9% vs. 35.8%), and nail changes (44.5% vs. 22.1%) as compared to TAC. This differing toxicity profile

led to a higher rate of discontinuation of therapy in the sequential arm (97 vs. 61 patients). When balancing the comparable efficacy with the differing toxicity profile and duration of treatment of these 2 regimens, the authors concluded that TAC remains an appropriate standard adjuvant chemotherapy regimen for women with early-stage HER2-negative breast cancer.

The aforementioned meta-analysis also included for the first time taxane-based versus non-taxane chemotherapy (n = 44,000) [1]. Subgroup analyses of breast cancer mortality showed that taxane-containing therapy slightly but significantly improved the outcome in comparison with an anthracycline-based control regimen (HR 0.872; $p < 0.00001$). Proportional risk reductions were little affected by age (up to at least 70 years), nodal status, tumor size, grade of differentiation, ER status, or use of endocrine therapy. Taxane- and anthracycline-based regimens reduced the breast cancer mortality by about one-third. However, the authors clearly stated that this proportional reduction of mortality depended on the level of risk of an individual patient: 'Low absolute risk implies low absolute benefit.'

Dose-Dense Chemotherapy

In an attempt to increase the efficacy of anthracycline- and taxane-containing regimens in the adjuvant treatment of primary breast cancer, the concept of dose-dense (DD) and sequential chemotherapy received increasing attention. Based on this concept, 2,005 node-positive breast cancer patients were randomly assigned in a 2 × 2 factorial design [26]. At a median follow-up of 36 months, DD treatment with G-CSF support improved DFS (HR 0.74; $p = 0.010$) as well as OS (HR 0.69; $p = 0.013$).

Utilizing an intense DD (IDD) and sequential adjuvant chemotherapy, Moebus et al. [27] conducted a clinical trial in 1,284 high-risk breast cancer patients with 4 or more involved axillary lymph nodes. Patients were randomly assigned to receive IDD sequential epirubicin (150 mg/m^2), paclitaxel (225 mg/m^2), and cyclophosphamide (2,500 mg/m^2) (IDD-ETC) every 2 weeks or conventionally dosed and scheduled epirubicin and cyclophoshamide (EC) followed by paclitaxel every 3 weeks. At a median follow-up of 62 months, IDD-ETC significantly increased the EFS from 62% to 70% and OS from 77% to 82%, respectively. This efficacy was independent of menopausal, hormone receptor, or HER2 status. However, when interpreting these encouraging results, one has to consider that paclitaxel every 3 weeks might not be regarded as an adequate standard anymore.

These 2 trials were included in a meta-analysis investigating DD chemotherapy every 2 weeks with G-CSF support as compared to standard schedules. Altogether 10 studies with 11,989 patients were included in this meta-analysis [28]. In the group with similar dosage and agents in both arms (3 trials; 3,337 patients) as well as in the larger group which used different agents and/or dosages in the treatment arms (7 trials; 8,652 patients), DD chemotherapy resulted in significantly better OS (HR 0.84 and 0.85, respectively) and DFS (HR 0.83 and 0.81, respectively). The rate of non-hematological adverse events was higher in the DD chemotherapy arms than in the conventional chemotherapy arms.

The issue of dose density of paclitaxel or docetaxel was further investigated by the Eastern Cooperative Oncology Group (ECOG) [29]. 4,950 women with axillary lymph node-positive or high-risk, lymph node-negative breast cancer were enrolled in this trial. After 4 cycles of AC every 3 weeks, patients were randomized to receive either paclitaxel or docetaxel given at 3-week intervals for 4 cycles or at 1-week intervals for 12 cycles. As compared to the control arm (paclitaxel every 3 weeks), the HR for DFS after a median follow-up of 63.8 months was 1.27 among those receiving weekly paclitaxel (80 mg/m^2) ($p = 0.006$), 1.23 among those receiving docetaxel every 3 weeks ($p = 0.02$), and 1.09 among those receiving weekly docetaxel ($p = 0.29$). Weekly paclitaxel was also associated with improved OS (HR 1.32; $p = 0.01$). The regimens differed in terms of toxicity. There were less grade 3 or 4 adverse events with weekly paclitaxel (28%) as compared with 71% of those receiving docetaxel every 3 weeks ($p < 0.001$). However, grade 2, 3, or 4 peripheral neuropathy was more pronounced after weekly paclitaxel (27%).

In an attempt to compare both incorporation of gemcitabine (G) and DD chemotherapy with TAC, Swain et al. [30] randomly assigned 4,894 women with node-positive early-stage breast cancer to 6 cycles of TAC, 4 cycles of DD AC→P (P = paclitaxel), or DD AC→P with 4 cycles of G added to the DD paclitaxel (DD AC→PG). After 5 years of follow-up there were no significant differences in DFS and OS between these 3 arms.

Conversely, Shulman et al. [31] recently examined in a phase III factorial design the issue of reducing toxicity of DD chemotherapy. They tried to elucidate whether 6 cycles of a chemotherapy regimen were superior to 4 cycles in patients with 0–3 involved lymph nodes. A total of 3,171 patients were randomly assigned to either 4 or 6 cycles of either AC or paclitaxel. After 2003, all treatment was administered in DD fashion with G-CSF support. The 4-year relapse-free survival (RFS) was 90.9% and 91.8% for 6 and 4 cycles, respectively. The HR of 6–4 cycles regarding RFS was 1.03 ($p = 0.77$). The 4-year OS was 95.3% and 96.3% for 6 and 4 cycles, respectively, with an HR of 1.12 ($p = 0.44$). As expected, toxicity was more severe in the 6-cycle arms. Based on these results, the authors concluded that extending chemotherapy regimens of DD AC or single-agent paclitaxel from 4 to 6 cycles did not improve the clinical outcome but led to increased toxicity. However, shortening adjuvant chemotherapy might be at odds with current guidelines which recommend at least 6 cycles of adjuvant chemotherapy. It might be a reasonable approach to deliver 4 cycles to patients with luminal A breast cancer and large tumor volume or to follow the patient's preference as suggested by Goldhirsch et al. [2].

Another way to reduce therapy-induced toxicity is the abandonment of anthracyclines. Jones et al. [32] randomized 1,016 patients with node-positive or high-risk node-negative breast cancer to 4 cycles of either standard-dose AC or docetaxel and cyclophosphamide (TC), administered every 3 weeks. At a median follow-up of 7 years, the difference in DFS between TC and AC was significant (81% TC vs. 75% AC; HR 0.74; p = 0.033) as in OS (87% TC vs. 82% AC; HR 0.69; p = 0.032). Despite the obvious limitations of a single and rather small clinical trial, the use of anthracyclines in the USA has substantially declined and been replaced by taxane-based regimens [33].

Conclusions

The efficacy of chemotherapy depends on the level of risk of the individual patient. In addition to well-established clinicopathological factors, validated gene expression signatures might be useful in selected patients if all other criteria are inconclusive for therapeutic decision-making. Besides reducing large tumors in size, neoadjuvant chemotherapy offers an opportunity for 'in vivo' chemosensitivity testing. If not otherwise contraindicated, chemotherapy regimens should include both anthracyclines and taxanes (e.g. TAC or 4 × AC followed by 12 × paclitaxel weekly). Especially, IDD sequential chemotherapy with G-CSF support is very effective in high-risk breast cancer patients. Since these well-established regimens have slightly differing toxicity profiles, it is mandatory to discuss not only efficacy but also side effects and duration of chemotherapy with the patients.

Disclosure Statement

M.S. is named inventor on patent applications regarding prediction of chemotherapeutic response in breast cancer and molecular markers for breast cancer prognosis. He has acted as consultant for Roche, Eisai, Celgene, Pierre-Fabre, and Sividon and has received honoraria from AstraZeneca, Novartis, Pfizer, Essex, Celgene, Pierre-Fabre, GlaxoSmith-Kline, Lilly, Sanofi-Aventis, Roche, Sividon, Genomic Health, and Amgen. He has received previous funding from Siemens Healthcare Diagnostics Products GmbH, Sanofi-Aventis, and the Bundesministerium für Bildung und Forschung (BMBF).

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