Primary Systemic Therapy for Breast Cancer

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38.1 The Principle of Primary Systemic (Neoadjuvant, Induction) Therapy for Operable Breast Cancer

Breast cancer is a malignancy with a comparably long natural history with mortality basically caused by distant metastases and not by local disease. Therefore, even aggressive local therapy alone may be insufficient to achieve long-term survival in those cases where micrometastases are already present at the time of diagnosis. In 1975, follow-up data revealed that only 25% of patients with lymph node involvement survived beyond 10 years after diagnosis despite ultraradical surgery [1]. This led to the first trials comparing chemotherapy versus no chemotherapy [2] and tamoxifen versus no adjuvant endocrine therapy [3] yielding significant survival benefits in both cases. In a mouse model (using a highly aggressive mouse mammary adenocarcinoma strain), Adriamycin caused a complete remission in over 80% of the mice when given before surgery [4]. In the early 1980s, the first non-randomized studies evaluated the benefit of primary systemic therapy in humans. Although these studies were very heterogeneous, showed varying breast conservation rates (from 24% to 88%) and examined response and rates of pathological complete remission (pCR) as the only endpoints, they were still a «proof of concept» for the neoadjuvant approach in a time when a tumour size of larger than 3 cm was an indication for a mastectomy [5–7].

In 1998, the first dataset comparing preoperative and postoperative chemotherapy was published (NSABP-B18). A total of 1523 patients were randomized to four cycles of AC administered preoperatively versus postoperatively. The survival variables showed no difference, whereas the rate of breast-conserving therapy was significantly higher in the neoadjuvant arm. Achieving a pathologic complete remission was associated with a better overall prognosis [8]. In the subsequent NSABP trial, the NSABP-B27 study, patients were randomized into three arms: four cycles of preoperative AC versus the same schedule with the addition of four cycles of docetaxel versus four cycles of preoperative AC followed by four cycles of docetaxel after surgery. As expected both arms with four cycles of AC preoperatively yielded similar pCR rates (12.9% versus 14.4%), whereas the arm containing AC followed by docetaxel in the preoperative setting was significantly superior with a pCR rate of 26.1%. A significant survival benefit with DFS and OS superior by about 20% was observed for the patients achieving a pCR [9].

In recent years neoadjuvant therapy has become a standard of care not only for inoperable or locally advanced cases but also for smaller operable tumours. It is an option for all patients where systemic therapy is definitely indicated at the time of diagnosis with the goal of improving disease-free and overall survival [10]. The improvement in rates of breast conservation surgery with primary systemic therapy should not be forgotten but has become a secondary goal particularly in the era of oncoplastic surgery. The cytotoxic regimens used in the neoadjuvant setting in routine clinical practice are the same as used for adjuvant therapy. This implies that the indication for primary systemic therapy comprising chemotherapy should be restricted to cases where the need for chemotherapy is certain. The neoadjuvant approach carries the potential for response-guided treatment because of its efficacy at in vivo sensitivity testing, which may increase the rate of breast-conserving surgeries. In addition, especially in triple-negative cases, primary systemic therapy provides time for genetic testing which may have consequences for subsequent surgical management. A choice of arguments for and against primary systemic therapy is presented in Table 38.1.

Table 38.1 Arguments pro and contra primary systemic therapy

Pro	Contra
In vivo sensitivity testing	Fear of patients to leave the tumour in place
Strong prognostic value of pCR	Discrepancy in grading for core biopsy and definite specimen: risk of overtreatment
Higher rate of breast-conserving surgery/higher rate of operability/improved cosmetic outcome	Discrepancy between clinical and pathological nodal status: risk of undertreatment
Therapy monitoring possible	Prognostic value of pCR not demonstrated for all subtypes and regimens
Psychologic effect of tumour shrinking	Lack of guidelines for progressive disease under neoadjuvant therapy
Post-neoadjuvant concepts in case of non-pCR	

Many patients such as those with, for example, non-inflammatory HR-positive and HER2-negative, low proliferative index breast cancer have no indication for chemotherapy due to a low expected relative and absolute treatment benefit and thus are not candidates for neoadjuvant chemotherapy. In cases of high tumour burden, they may benefit from primary endocrine therapy in order to perform breast-conserving surgery. In contrast, high-risk HR-positive/HER2-negative patients with tumours showing a high proliferation rate, high tumour burden in the breast and/or axilla or further risk factors such as grade 3 or high-risk classification based on a multigene assay may benefit from cytotoxic therapy and are therefore also candidates for neoadjuvant chemotherapy. The use of chemotherapy in HER2-positive and triple-negative breast cancer is common clinical practice. A lack of expression of oestrogen and progesterone receptors with or without overexpression of HER2 in combination with high proliferative activity, high tumour grade, high expression of Ki-67 or high genomic grade index is the main predictors for response to neoadjuvant therapy [11, 12]. Other predictors with a lower impact are age, non-lobular tumour type or early clinical response [13].

The indications for primary systemic therapy (irrespective of whether the recommended therapy is combination chemotherapy, an antibody-containing regimen or endocrine therapy) are easily summarized:

- Inflammatory breast cancer
- Inoperable breast cancer
- To facilitate breast conservation surgery
- **If the same systemic therapy would also be indicated in the adjuvant setting**
- If adjuvant chemotherapy is likely to be advised and complex surgery is planned which may otherwise delay systemic therapy
- If adjuvant chemotherapy is likely to be advised and the results of gene testing are awaited which may affect subsequent treatment decisions

Women must be counselled about the success or failure rate of PST in facilitating BCS if this is the aim, and a pretreatment MRI should be done to ensure unifocality if this is the aim. During and after PST, imaging with MRI to assess response may be useful to monitor response and guide subsequent therapy. In some cases a complete pathological and imaging response may occur, and in women wishing breast conservation therapy, it is important that a marker clip is placed in the tumour to facilitate subsequent tumour localization.

Following completion of primary systemic chemotherapy, surgery should take place between 4 and 6 weeks later to allow leucocyte counts to recover.

38.2 The Prognostic Relevance of Pathological Complete Emission (pCR)

Numerous studies have shown that achieving a histopathological complete remission represents an independent prognostic parameter in the preoperative setting and therefore may serve as a surrogate marker for long-term survival of breast cancer [14, 15]. However, there is variability regarding both the probability and the prognostic validity of achieving a pCR among the distinct intrinsic breast cancer subtypes: while pCR is an important outcome parameter among patients with high-risk breast cancer subtypes (such as triple-negative breast cancer (TNBC) or HER-positive/hormone receptor (HR)-negative breast cancer), other breast cancer subtypes (such as low-risk hormone receptor positive (luminal A)) may have a favourable prognosis even in cases where there is residual tumour at the time of surgery. Nevertheless, achievement of a pCR is considered to be a relevant endpoint for regulatory authorities as the Food and Drug Administration in granting approval for new agents.

Another matter of debate is the optimal definition of pCR: at present there is debate about whether residual DCIS should be included in the definition of pCR [15, 16] and whether nodal response should be considered [17].

Finally, the simple dichotomy of chemotherapy response (i.e. pCR vs. any residual tumour) may not accurately reflect the heterogeneity of response. Consequently, optimized quantification of chemotherapy response has been suggested, for instance, by the use of semi-quantitative scoring systems such as the Residual Cancer Burden (RCB) [18] which combines histopathological tumour diameter, tumour cellularity, the number of axillary lymph node metastases and the diameter of axillary lymph node metastases by the use of a mathematical model to convert these into a single parameter that reflects the extent of chemotherapy response on a scale of 0–3. A value of 0 corresponds to a pCR. These values have been shown to correlate significantly with the prognosis of the patient in a semi-quantitative matter. Although the RCB score is used primarily in the USA, the use of this parameter can also be seen to be extending into Europe; however, this is largely in the context of clinical trials at present.

38.3 Regimens in Neoadjuvant Therapy

38.3.1 Neoadjuvant Endocrine Approaches

Although some physicians feel that primary endocrine therapy is mainly used in older postmenopausal women with comorbidities in order to achieve operability in large tumours or to avoid surgery at all in cases of severe risks for operative complications, basically all patients with endocrine responsive tumours and favourable risk factors such as ER/PR sensitivity, low nuclear grade or low Ki-67 [19] are candidates for a primary endocrine approach due to the low expected response rates to neoadjuvant chemotherapy [20]. In clinical practice this approach is rarely chosen for fit patients with good operability that are usually treated with endocrine therapy after surgery.

In general the endocrine regimen should be chosen according to the adjuvant data on endocrine therapy, but it is also helpful to look at the literature specifically looking at primary endocrine therapy.

In analogy to adjuvant studies, comparisons in the neoadjuvant setting have demonstrated the superiority of aromatase inhibitors over tamoxifen [21, 22]. Direct comparisons of letrozole, anastrozole and exemestane have shown similar efficacy for all three drugs [23].

The optimal duration of neoadjuvant endocrine therapy is unclear. Many patients are treated preoperatively for 4–6 months in clinical practice although 37% of patients may achieve maximal response only after 6–12 months [24].

For the reasons discussed above regarding which patients are candidates for neoadjuvant endocrine therapy, direct comparisons with neoadjuvant chemotherapy are rare. The few data indicating that in selected cases neoadjuvant endocrine therapy and neoadjuvant chemotherapy have the same response rates [25] reflect the fact that most patients in the chemotherapy arms should not have received neoadjuvant chemotherapy because of the favourable characteristics of their tumours: simply put, the biology of disease likely to respond to endocrine therapy is less likely to respond to chemotherapy and vice versa.

Table 38.2 Clinical trials investigating neoadjuvant endocrine therapy combined with agents targeting endocrine resistance

Trial number and planned recruitment	Phase	Arms	Duration	Primary endpoints
PI3K inhibitor				
NCT02273973*N* = 330	Phase II	Arm A: taselisib + letrozole Arm B: placebo + letrozole	16 weeks	pCR
NCT01923168*N* = 360	Phase II	Arm A: BYL719 + letrozole Arm B: buparlisib + letrozole Arm C: placebo + letrozole	24 weeks	pCR
AKT inhibitor				
NCT01776008*N* = 87	Phase II	MK-2206 + anastrozole; goserelin acetate if premenopausal	Maximum four cycles of 28 days each	pCR based on Ki-67 values
CDK4/6 inhibitor				
NCT01723774*N* = 29	Phase II	PD0332991 + anastrozole + goserelin acetate if premenopausal	Maximum four cycles of 28 days each	Complete cell cycle arrest (CCCA) based on Ki-67 values
NCT0229801*N* = 306	Phase II	Arm A: letrozole Arm B: letrozole (2 weeks) and then letrozole + palbociclib (12 weeks) Arm C: palbociclib (2 weeks) and then letrozole + palbociclib (12 weeks) Arm D: letrozole + palbociclib	14 weeks	Change in Ki-67 values, cCR
NCT02400567*N* = 132	Phase II	Arm A: chemotherapy (FEC-Doc) Arm B: letrozole + palbociclib (12 weeks)	18 weeks	Residual cancer burden

Ki-67 may represent a potential biomarker for use among patients undergoing primary endocrine therapy. In the IMPACT trial, Ki-67 measurements after 2 weeks of endocrine therapy were able to predict recurrence free survival [26]. The POETIC trial, which recruited 4000 patients until April 2014, was designed to test the significance of 2-week Ki-67 measurements during endocrine therapy as a prognostic marker for survival variables. However, results from this trial are not available yet [27]. Similarly, a 3-week approach regarding Ki-67 re-biopsy is investigated by the ADAPT trial. Pre- and postmenopausal patients with less than four positive lymph nodes are receiving 3 weeks of endocrine induction therapy according to guidelines. Risk of recurrence is furthermore assessed using the recurrence score: patients with a recurrence score of 11 or lower are treated with postoperative endocrine therapy alone; patients with a recurrence score of 26 or higher will receive neoadjuvant chemotherapy. In the group of patients considered to carry an intermediate risk of recurrence (i.e. recurrence scores 12–25), further therapy is decided based upon Ki-67 measurements following 3 weeks of endocrine therapy: patients with a Ki-67 higher than 10% after 3 weeks of endocrine induction therapy are classified as nonresponders and will receive neoadjuvant chemotherapy, whereas in cases of a drop of Ki-67 below 10%, patients are operated on and will stay on endocrine therapy according to guidelines [28]. This trial is also still recruiting patients.

Studies are evaluating combinations of endocrine therapy with agents targeting endocrine resistance such as PI3K inhibitors, AKT inhibitors and CDK4/CDK6 inhibitors in the neoadjuvant setting. Several trials investigating this approach are currently recruiting (Table 38.2) [29].

38.3.2 General Considerations Regarding Primary Systemic Chemotherapy Regimens

Usually, neoadjuvant treatment regimens consist of combination chemotherapy regimens containing both taxanes and anthracyclines sequentially or simultaneously. However, anthracycline-free chemotherapy regimens may be considered a valuable alternative. It is suggested to use those chemotherapy regimens that would have been applied in the adjuvant setting rather than primary systemic setting. Response control during PST is important and is usually carried out by ultrasound evaluation every 6 weeks. However, data regarding an adjustment of the treatment regimen during the course of therapy in case of lack of sufficient response is insufficient despite the fact that there is data suggesting that patients with hormone receptor-positive breast cancer might benefit from switching to a non-cross-resistant regimen [30]. It is a common practice that patients not responding to PST and demonstrating tumour progression should stop treatment and immediately undergo adequate local therapy.

38.3.3 Choice of Therapy Regimens in HER2-Positive Breast Cancer

Choice of neoadjuvant therapy is largely decided upon based on established combinations of chemotherapy with trastuzumab or dual HER2 blockade. There is a large body of evidence suggesting that the poor prognosis associated with HER2 overexpression/amplification is counterbalanced by the high probability of benefit from HER2-directed therapies: in the neoadjuvant setting, the addition of the anti-HER2-directed antibody trastuzumab to chemotherapy is associated with a significant increase of pCR in several large-scale clinical trials leading to its approval as part of primary systemic therapy among patients with HER2-positive breast cancer (see Table 38.3).

Since the development of trastuzumab, several novel agents have been evaluated for the use among patients with HER2-positive breast cancer mainly in the primary systemic therapy setting. There is a large body of evidence suggesting that the small molecule lapatinib is inferior to trastuzumab with regard to rates of pCR as part of a combination regimen [31], but may increase pCR rates significantly if added to trastuzumab [32]. The increase in pCR, however, did not translate into a significant improvement of disease-free survival in a clinical trial using lapatinib and trastuzumab as part of an adjuvant treatment regimen (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) Trial [33]). Therefore, lapatinib is not acknowledged as an optimal combination partner for trastuzumab in the potentially curative setting.

In contrast, data regarding the HER2 dimerization inhibitor pertuzumab seem to be more promising as findings from the neoadjuvant NeoSphere trial suggest [34]: Gianni and colleagues reported results obtained from 417 patients with HER2-positive breast cancer with a tumour size larger than 2 cm who were randomized to four 12-week treatment arms: trastuzumab/docetaxel, pertuzumab/trastuzumab/docetaxel, pertuzumab/trastuzumab and pertuzumab/docetaxel. The authors observed a significant increase in the rate of pCR by the addition of pertuzumab to trastuzumab and docetaxel (45.8% versus 29.0%). In the subgroup of patients with HER2-positive/HR-negative breast cancers, the pCR rate achieved by the use of dual HER2 blockade in combination

Table 38.3 pCR rates of combined HER2-directed therapies in the neoadjuvant setting

NeoSphere (n = 417)	*pCR (ypT0)*	
Trastuzumab + docetaxel	29.0%	
Pertuzumab + trastuzumab + docetaxel	45.8%	
Pertuzumab + trastuzumab	16.8%	
Pertuzumab + docetaxel	24.0%	
Neo-ALTTO (n = 455)	pCR (ypT0/is ypN0)	
Trastuzumab → trastuzumab + paclitaxel	29.5%	
Lapatinib → lapatinib + paclitaxel	24.7%	
Trastuzumab/lapatinib → trastuzumab/lapatinib + paclitaxel	51.3%	
TRYPHaena (n = 225)	*pCR (ypT0/is)*	*pCR (ypT0 and ypN0)*
FEC + pertuzumab + trastuzumab × 3 → pertuzumab + trastuzumab + docetaxel × 3	61.6%	50.7%
FEC × 3 → pertuzumab + trastuzumab + docetaxel × 3	57.3%	45.3%
Docetaxel/Carboplatin + trastuzumab + pertuzumab × 6	66.2%	51.9%
GeparQuinto (n = 620)	*pCR (ypT0 and ypN0)*	
Epirubicin + cyclophosphamide + trastuzumab → docetaxel + trastuzumab	30.3%	
Epirubicin + cyclophosphamide + lapatinib → docetaxel + lapatinib	22.7%	
GeparSixto (n = 137)	*pCR (ypT0 and ypN0)*	
Weekly paclitaxel + non-pegylated liposomal doxorubicin + trastuzumab + lapatinib × 18	36.8%	
Weekly paclitaxel + non-pegylated liposomal doxorubicin + trastuzumab + lapatinib × 18 + carboplatin	32.8%	
GeparSepto (n = 1.200)	*pCR (ypT0 and ypN0)*	
Weekly nab-paclitaxel × 12 → 4 × EC + trastuzumab + pertuzumab	74.6%	
Weekly paclitaxel × 12 → 4 × EC + trastuzumab + pertuzumab	66.7%	

with docetaxel was as high as 63.2%. Of note, among patients in the chemotherapy-free arm, dual HER2 blockade alone resulted in an impressive pCR rate of 16.8%.

Consequently, pertuzumab has received a label extension for the primary systemic setting in combination with trastuzumab and is registered in many countries as part of a standard neoadjuvant chemotherapy regimen. There is still, however, an ongoing debate as to whether this improvement in pCR will also translate into an improvement of prognosis. Survival analyses from the NeoSphere trials suggest a significant benefit regarding 3-year DFS (85 vs. 92%, HR 0.60 (95% CI 0.28–1.27)) [35]; however, data from the corresponding adjuvant Aphinity trials have not been reported yet.

38.3.4 Choice of Therapy Regimens in Patients with HER2-Negative Breast Cancer

Choice of chemotherapy regimen among patients with HER2-negative breast cancer is largely independent of hormone receptor expression status. Sequential or simultaneous combination chemotherapy containing both anthracyclines and taxanes has long been regarded as the standard primary systemic chemotherapy approach. Adjuvant studies have suggested benefit from the application of dose-dense chemotherapy if metastatic disease is diagnosed in more than three axillary lymph nodes [36] as well as in patients with TNBC [37].

Despite these data being limited largely to the adjuvant setting, dose-dense chemotherapy is increasingly applied in the primary systemic therapy setting as well in case of high axillary tumour burden and other high-risk features.

Despite patients with TNBC carrying an overall unfavourable prognosis, they are also characterized by an increased chance of response to neoadjuvant chemotherapy, which is reflected by increased rates of pCR [12]. This phenomenon is often referred to as the «triple-negative paradox» in the literature [38].

Given the importance of pCR as a prognostic parameter among patients with TNBC, there is an urgent need to optimize the efficacy of primary systemic chemotherapy and thereby improve prognosis among patients with TNBC. This may be achieved by the following considerations:

- Optimization of chemotherapy scheduling (i.e. through dose-dense/dose-intensified regimens) [39]
- Use of additional agents in combination with standard combination chemotherapy regimens
- Development of novel targeted agents for patients with TNBC
- Identification of biomarkers for response to neoadjuvant chemotherapy in TNBC to allow for treatment individualization

Several studies have aimed at increasing chemotherapy efficacy through addition of novel agents such as capecitabine [40, 41] or eribulin [42]. However, solid data and validation studies are lacking despite the fact that subgroup analyses showed a significant benefit in TN breast cancer subgroups by these approaches. In contrast, there is an accumulating body of evidence suggesting that platinum salts should be added to anthracycline/taxane chemotherapy in case of triple-negative breast cancer.

While historical data has suggested for several years that platinum-containing chemotherapy may be particularly beneficial to patients with TNBC [43, 44], prospective evidence was lacking until the publication of two important neoadjuvant clinical trials:

The first study (GeparSixto (NCT01426880) by the *German Breast Group (GBG)* [45]) showed an increase regarding the primary study endpoint (i.e. pCR defined as ypT0 ypN0) from 36.9% (58 of 157 patients, 95% CI 29.4–44.5) to 53.2% (84 of 158 patients, 95% CI 54.4–60.9) (p = 0.005) through the addition of carboplatin to an anthracycline/taxane chemotherapy regimen. In addition to this, the addition of carboplatin not only led to an increase in pCR but resulted in an improved prognosis among patients with TNBC: after a median follow-up of 3 years, disease-free survival for patients assigned to carboplatin was 85.5% compared with 76.1% for patients assigned no carboplatin [46].

The second study (CALGB/ALLIANCE-40603 (NCT00861705) by the *Cancer and Leukemia Group B (CALGB)* [47]) analysed the use of carboplatin (and bevacizumab) among patients with TNBC in addition to a sequential anthracycline/taxane chemotherapy regimen and demonstrated an increase in the pCR rate from 41% to 54% (p = 0.0018). Given that hematologic toxicity and particularly serious adverse events were less common in association with the sequential regimen, it is regarded by many as representing a more feasible regimen in daily clinical management of patients with TNBC. In contrast to the survival analyses derived from GeparSixto trial, survival analysis of CALGB-40603 regarding the secondary endpoints of event-free (EFS) and overall survival (OS) suggested an insignificant effect with hazard ratios of 0.84 (95% CI 0.58–1.22, P = 0.36) and 1.15 (95% CI 0.74–1.79, P = 0.53), respectively [48].

Overall, two distinct scenarios regarding the future use of carboplatin among patients with TNBC seem imaginable:

- Use of platinum salts to increase efficacy at the cost of increased toxicity (i.e. therapy intensification)
- Use of platinum salts to improve the therapeutic index through improvement of treatment tolerability (i.e. therapy de-escalation by replacing taxanes or more importantly anthracyclines) (See Fig. 38.1.)

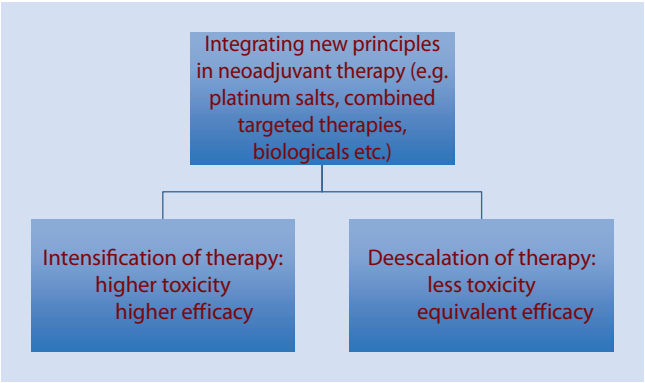

Fig. 38.1 Different modern approaches in primary systemic therapy for breast cancer

38.4 Predictive Markers for the Benefit of Primary Systemic Therapy

There are a large number of biomarkers that have been suggested to predict an improved chance of benefit from primary systemic chemotherapy (i.e. associated with an increased chance of pCR). Currently, there are four parameters that are of particular interest:

- The presence of tumour-infiltrating lymphocytes
- Individual biomarkers
- Parameters reflecting tumour cell proliferation
- BRCA mutation status

38.4.1 Tumour-Infiltrating Lymphocytes (TILs)

There is a high level of evidence suggesting that the presence of tumour-infiltrating lymphocytes (TILs) is able to reliably predict treatment response. This parameter seems to be particularly relevant among high-risk breast cancer subtypes such as TNBC and HER2-positive disease. However, there is uncertainty as to whether TILs may predict a subtype-specific effect or are rather associated with overall chemotherapy-sensitivity. Furthermore, before this biomarker justifies introduction into daily clinical routine, hurdles such as lack of standardization in analysis of TILs have to be overcome [49].

38.4.2 Individual Molecular Biomarkers of Resistance

The phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) is a class I PI 3-kinase catalytic subunit. It has repeatedly suggested mediating both endocrine resistance and resistance against endocrine therapy. Recently, results of a pooled analysis of four different clinical trials (GeparQuattro/GeparQuinto, GeparSixto, NeoALTTO, CHERLOB) were presented analysing the association between PIK3CA mutation status and neoadjuvant therapy response (i.e. pCR rates) among patients with HER2-positive breast cancer undergoing HER2-targeted agents. Results of this analysis suggest that in fact the presence of PIK3CA mutations in HER2+ breast cancer predicts for a significantly lower rate of pCR: within the subgroup of patients with hormone receptor-positive breast cancer, patients with PIK3CA mutations had a pCR rate of only 7.6% compared to 24.2% among patients with PIK3CA wild-type status ($p < 0.001$). In contrast, no difference in pCR (27.2% vs. 36.4%) according to PIK3CAmutation status was observed among patients with HER2-positive/HR-negative breast cancer ($p = 0.125$).

38.4.3 Tumour Cell Proliferation

The significance of expression of the proliferation marker Ki-67 in particular in the differentiation of luminal breast cancer subtypes (luminal A vs. luminal B) is a matter of intense discussion. It is an acknowledged fact that hormone receptor-positive breast cancer with an increased expression of Ki-67 (luminal B subtype) shows a poorer prognosis but a higher probability of responding to neoadjuvant chemotherapy.

Denkert and colleagues examined the association between the expression of the proliferation marker Ki-67 and the response to neoadjuvant chemotherapy as well as disease prognosis in individual breast cancer subtypes [50]. Patients were stratified based on Ki-67 expression in three groups with cutoff values of lower than 15%, 15–35% and higher than 35%, respectively. Ki-67 was found to be of different prognostic and predictive values among different breast cancer subtypes.

For patients with TNBC, a significant correlation between expression of Ki-67 and the pCR rate could be demonstrated. The pCR rates for Ki-67 expression of ≤15%, 15–35% and ≥35% were 15%, 22% and 38% ($p = 0.003$). However, no significant differences regarding overall survival probabilities were observed. KI-67 was similarly associated with pCR among patients with HR-positive/HER2-negative breast cancer ($p < 0.0005$); no significant association with pCR was observed among patients with hormone receptor-positive/HER2-positive breast cancer and patients with hormone receptor-negative/HER2-positive breast cancer. The only breast cancer subtype in which Ki-67 expression was associated with OS was hormone receptor-positive/HER2-negative breast cancer.

38.4.4 BRCA Status

Both in vitro and preclinical analyses suggest a particular sensitivity of BRCA1-associated breast cancers against platinum salts [51]. Between 10 and 20% of patients with TNBC carry a BRCA1 mutation. Furthermore, TNBC carries many histological and molecular features that are commonly found among hereditary breast cancers. This has triggered an intense (and yet ongoing) debate as to whether either diagnosis of TNBC or rather diagnosis of hereditary breast cancer (regardless of molecular subtype) seem to represent the optimal predictive factor for use of platinum salts as part of a neoadjuvant treatment regimen.

Analyses derived from patients in the metastatic setting suggest a particular sensitivity to carboplatin in first-line monochemotherapy among patients with metastatic TNBC (response rates 68% vs. 33%, $p = 0.03$) [52]. In contrast, in the curative setting, results obtained in translational analyses of the GeparSixto study did not confirm a predictive association between BRCA1 mutations and carboplatin efficacy among patients with TNBC [53]. Therefore, use of platinum salts may be considered in patients with TNBC irrespective of BRCA1 mutation status.

38.5 Future Concepts in Primary Systemic Therapy for Breast Cancer

Primary systemic therapy clinical trials are of (increasing) interest given the utility of pCR as an early response parameter and strictly defined endpoint. In fact, a significant (and clinically relevant) increase in pCR (i.e. through the addition of a novel therapeutic substance) is an accepted parameter for (provisional) licencing of these agents in the curative setting.

38.5.1 Tailoring Therapy Based on Neoadjuvant Therapy Response

In contrast, patients that do not derive substantial benefit from primary systemic therapy multi-agent approaches and are left with residual cancer at the time of surgery represent a particular challenge to the treating physician. For these patients, additional/alternative treatment approaches are urgently warranted. Post-neoadjuvant treatment options might represent an issue for these patients that are commonly left with a particularly unfavourable prognosis (particularly in case of extensive residual disease or even disease progression on therapy). Options are somewhat limited for these patients. Recent analyses (Japan) suggest that post-neoadjuvant use of capecitabine might become an option for patients with TNBC and residual tumour following preoperative chemotherapy [54]. Current clinical trial concepts focus on the introduction of new substances, such as selective inhibitors of cyclin-dependent kinases (CDK) 4 and 6 in hormone receptor-negative cancers (i.e. Penelope B, NCT01864746) or trastuzumab-DM1 (TDM1) among patients with HER2-positive disease (Katherine, NCT01772472) and olaparib in BRCA1−/BRCA2-positive patients (OLYMPIA study, neoadjuvant cohort).

On the other hand, achievement of a pCR mirroring highly responsive disease might also justify reduction of treatment intensity such as cessation of trastuzumab therapy in the post-neoadjuvant setting. Unfortunately, at present there are insufficient data available to justify this. Studies that will investigate such treatment concepts are still recruiting or in preparation.

38.5.2 Window of Opportunity Trials

Other studies use the primary systemic therapy time window to assess the biological response of tumour cells to a few week period of therapy in an aim to enable modification of the treatment regime by determining tumour cell proliferation before and after the intervention. The Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial (ADAPT, *optimizing risk assessment and therapy response prediction in early breast cancer*) of the West German Study Group (WSG) investigates whether patients with hormone receptor-positive breast cancer and a significant decrease in Ki-67 expression during a 3-week endocrine therapy schedule may be safely spared adjuvant chemotherapy (► http://www.wsg-online.com). Comparable study concepts for patients with other breast cancer subtypes (such as HER2-positive or triple-negative tumours) are ongoing.

38.6 Conclusion

Primary systemic therapy is an exciting area of clinical practice and active research. It has many potential values in treatment personalization, enhanced surgical and oncological outcomes and given us a greater understanding of disease biology and response rates. It also has a role in prediction of prognosis. Understanding of these issues is vital in modern multidisciplinary cancer care.

Key Messages

- Patients whose indication for adjuvant chemotherapy is obvious at the time of diagnosis are candidates for neoadjuvant chemotherapy.
- Chemotherapy regimens commonly equal those used in the adjuvant setting.
- For patients with triple-negative breast cancer, the addition of carboplatin to anthracycline taxane chemotherapy increases response rates and potentially survival.

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