Predictive Biomarkers of Neoadjuvant Chemotherapy in Breast Cancer

Subjects: Oncology

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Pathological complete response (pCR) after neoadjuvant chemotherapy in patients with early breast cancer is correlated with better survival. Meanwhile, an expanding arsenal of post-neoadjuvant treatment strategies have proven beneficial in the absence of pCR, leading to an increased use of neoadjuvant systemic therapy in patients with early breast cancer and the search for predictive biomarkers of response. The better prediction of response to neoadjuvant chemotherapy could enable the escalation or de-escalation of neoadjuvant treatment strategies, with the ultimate goal of improving the clinical management of early breast cancer.

Keywords: breast cancer ; neoadjuvant chemotherapy ; biomarkers ; predictive factors

1. Introduction

Breast cancer remains one of the most prevalent cancers in women, with 2,261,419 new cases and 684,996 deaths worldwide in 2020, despite major improvements in terms of prevention, diagnosis and treatment [1]. In current clinical practice, breast cancers are classified in five subtypes based on the expression of hormone receptors (estrogen and/or progesterone receptors (ER and/or PgR)), the overexpression of epidermal growth factor receptor 2 (HER2/Neu) and the percentage of tumor cells expressing Ki-67. These subtypes comprise luminal A, luminal B, HR+ HER2-positive, HR- HER2-positive and triple-negative breast cancers (TNBC) [2]. The majority of patients are diagnosed with early-stage disease, while 3–10% of patients are diagnosed with de novo metastatic breast cancer [3]. Although most early breast cancers are curable with the current treatment options, up to 20% of patients will relapse within 10 years. At present, treatment decisions in both the early and the metastatic settings depend on the immunohistopathological classification, with adaptation of the chemotherapy regimen based on the surrogate molecular subtype (e.g., the addition of anti-HER2 monoclonal antibodies in the HER2+ subtype, the addition of carboplatin in the early triple negative subtype, adjuvant hormonotherapy in the HR+ subtypes, etc.) [2][4]. The implementation of neoadjuvant chemotherapy (NAC) as the current standard of care for patients with high-risk early-stage or locally advanced breast cancer is one of the major changes in the evolving breast cancer landscape [2]. The high-risk breast cancers concerned by this change in the treatment paradigm are mainly TNBC and HER2-positive tumors but also include hormone-receptor-positive (HR+) cancers larger than 2 cm and/or with axillary lymph node involvement. While providing the same overall survival (OS) and disease-free survival (DFS) as adjuvant chemotherapy, NAC has several advantages, such as: allowing for more conservative surgeries by reducing the tumor size and down-staging the lymph node status, assessing the sensitivity of the tumor to chemotherapeutic agents and eradicating micro-metastases but also adding the possibility of escalating treatment with adjuvant drugs in case of residual disease, a feature of worse prognosis [5][6][7]. Despite this, NAC also has disadvantages, including: drug-related side effects, the postponement of surgery in some cases (e.g., the postponement of NAC due to side effects resulting in a longer delay before surgery), difficulties in healing after surgery and disease progression that may occur during treatment [8] (**Figure 1**).

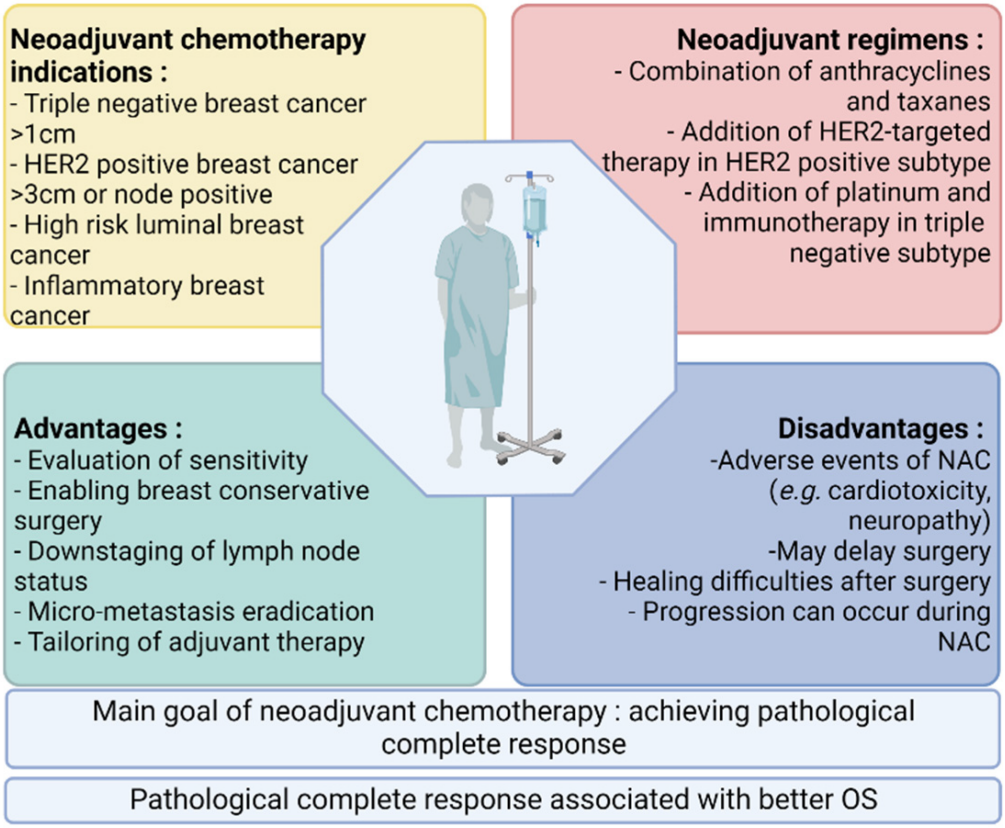

Figure 1. Overview of current indications, regimens, advantages and disadvantages of NAC.

2. Breast Cancer Subtypes and Intratumoral Heterogeneity

2.1. Molecular Classification and Intrinsic Subtypes

Over the past 20 years, several molecular classifications have been determined by genomic and transcriptomic clustering in order to better understand the intratumoral heterogeneity in breast cancer. However, these intrinsic subtypes have not yet supplanted the surrogate molecular subtype (determined by immunohistochemistry) in clinical practice for therapeutic decision making. In 2000, Perou et al. analyzed 65 surgical pieces of breast cancers from 42 individuals and identified 4 intrinsic subtypes by gene expression analysis: luminal-like, basal-like, normal-like and HER2-enriched [9]. Later, the PAM50 classification distinguished the luminal A and luminal B categories within the luminal-like group. Studies have shown that these subgroups differ in both their clinical characteristics and their response to treatment. Prognosis also differs between the intrinsic subtypes, regardless of the immunohistopathological subtype [10][11][12][13][14]. Within the immunohistochemical triple negative subtype, Prat et Perou later highlighted two intrinsic subtypes: the claudin-low and the basal-like subtypes, the claudin-low being associated with poorer prognosis [15][16]. The heterogeneity of the triple negative disease is nevertheless more complex, and in 2011, Lehmann et al. described seven subtypes (TNBCtype): basal-like 1 (BL1), basal-like (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR) and unstable (UNS) [17][18]. In a retrospective study, the response to NAC containing anthracyclines and cyclophosphamide was different among subgroups, with a better pCR rate in the BL1 subgroup (52%) in comparison to the BL2 and LAR subgroups (0% and 10%) [17]. After refining this TNBCtype classification by considering the transcript of normal stroma and immune cells, four subtypes have been largely studied (TNBCtype-4): BL1, BL2, M and LAR [17] (**Figure 2**).

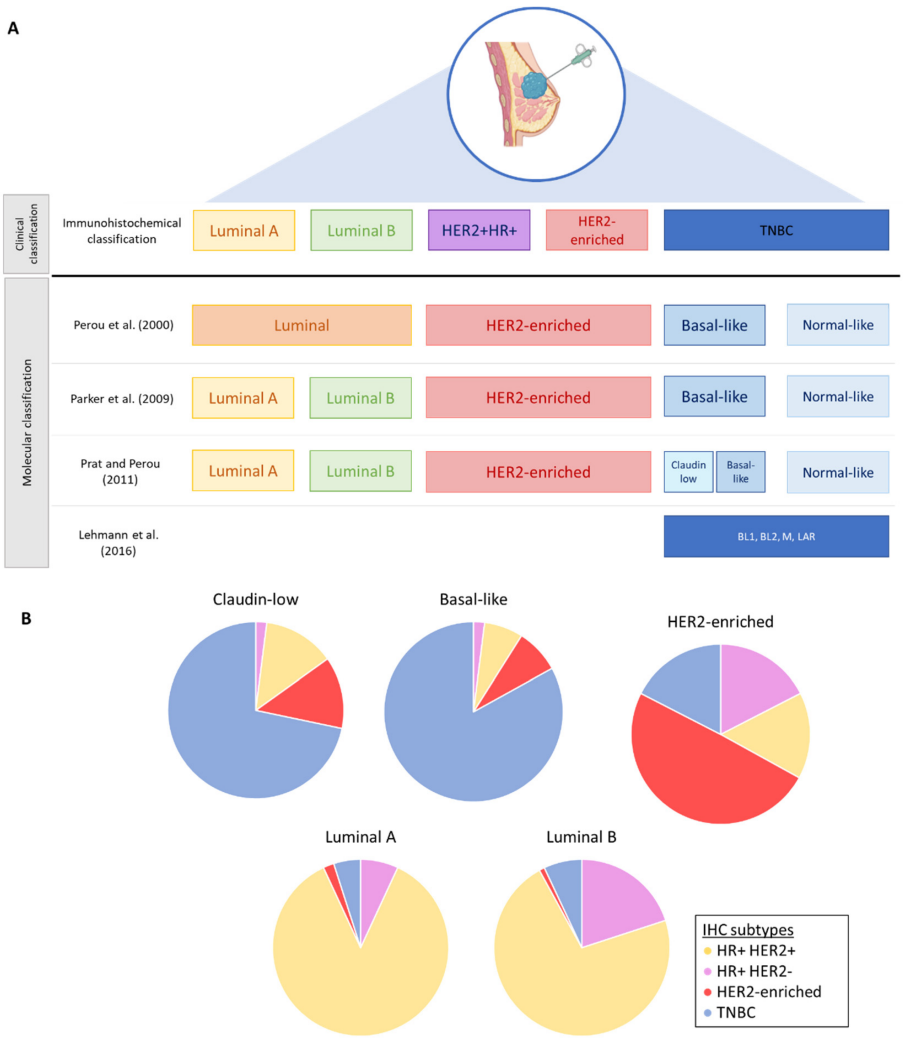

Figure 2. Breast cancer subtypes and intrinsic classification. (**A**) Comparison between immunohistochemical classification and molecular classification [9][10][16][17]. (**B**) Distribution of immunohistochemical subtypes in the molecular classification, as defined by Prat and Perou [16]. HR+: hormone receptor-positive; TNBC: triple negative breast cancer; BL1: basal-like 1; BL2: basal-like 2; M: mesenchymal; LAR: luminal androgen receptor.

2.2. Intratumoral Heterogeneity in Breast Cancers

Intratumoral heterogeneity (ITH) in breast cancer refers to the diversity found within tumors, existing at several levels [19][20]. ITH includes multiple concepts and principles such as clonal heterogeneity and cell state heterogeneity [19][21][22]. Clonal heterogeneity concerns the phenotypic variability between cells within a tumor depending on spatial and temporal factors, leading to different clones of cells with different sensitivities to treatment. Many spatial factors can influence the clones of cells: hypoxia variance from the center of the tumor to the periphery, angiogenesis, pH variation inside the tumor and interactions with cells from the tumor microenvironment (TME). Depending on their exposure to hypoxia, or other factors, cells will acquire different metabolisms and different sensitivities to treatment. Temporal factors are more related to the sequential exposure of the tumor to different lines of treatment that could lead to a selection of resistant clones within the tumors [19][21]. Cell state heterogeneity is the fact that people can observe cells at different states in a single tumor, with some cells exhibiting stem cell properties (CSC) and others with differentiated properties or progenitor's properties, altogether forming tumors with different levels of mechanisms of resistance to treatment [19][22]. The heterogeneity found inside each breast cancer has been described as a strong mechanism of resistance to chemotherapy, with the evolution of cell-to-cell interactions but also genetic modifications under treatment pressure [23]. In breast cancer, several molecular subtypes can also be found within a single tumor. Indeed, molecular subtypes are not a static state, and interconversion between subtypes can occur and lead to tumor progression, metastasis or resistance to chemotherapy [22][24].

3. Resistance to Neoadjuvant Chemotherapy

3.1. Drug-Associated Resistance

It is well known that the metabolism of most chemotherapy drugs involves cytochrome P450 enzymes (CYP) [25]. Polymorphisms in the *CYP1B1* gene appear to correlate with resistance to taxanes, while CYP2B6 is involved in the metabolism of cyclophosphamide and doxorubicin [26][27]. In one study, CYP2C9*2 heterozygote breast cancer patients had a decrease in the efficacy in neoadjuvant chemotherapy compared to patients with wild-type alleles [28]. Many other CYP enzymes were reported to be associated with the efficacy of neoadjuvant chemotherapy in breast cancer, and this could explain the clinical resistance to certain drugs [25].

Chemotherapy drug concentration is also regulated by the efflux of drugs out of the cells via transmembrane proteins. These proteins include the ATP-binding cassette (ABC) transporter family, in which the P-glycoprotein (P-gp) has already been associated with drug resistance in breast cancer [29]. In TNBC, several related genes are more expressed, such as *ABCC1*, *ABCC11* or *ABCG2*, and those could be involved in chemoresistance to commonly used drugs [30].

3.2. Cancer Cell-Associated Resistance

CSCs are a population of cells with self-renewal properties present in breast cancer tumors, and they have been found in residual tumors after NAC, indicating that these cells are resistant to conventional treatment [31][32]. Moreover, CSCs are found more often in TNBC than in other subtypes and could be involved in the poor survival of this subtype [33][34]. Changes in the genes involved in the DDR system have also been pointed out as a cause of resistance to chemotherapy. Among the incriminated genes, *HORMAD1* could play a role in chemoresistance in TNBC [35]. EMT plays an important role in breast cancer, which could lead to chemotherapy resistance and metastasis [36]. Cells that undergo EMT have common characteristics with CSCs, explaining part of their resistance to chemotherapy. The evasion of apoptosis is another mechanism leading to the resistance to several drugs such as doxorubicin, cyclophosphamide and paclitaxel. The overexpression of factors such as Bcl2, MCL1 or NF-KB has been shown to decrease the sensitivity to chemotherapy [37][38][39].

4. Current Biomarkers Used for the Clinical Decision Making of Breast Cancer Patients

4.1. Ki-67 before NAC

Ki-67 is a marker of cell proliferation used in clinical practice to assess the aggressiveness of the tumor at the time of diagnosis [40]. Ki-67 is expressed in all the cell cycle phases, with the exception of the G0 phase, and high Ki-67 expression is related to high tumor proliferation and thus a large number of dividing cells [41]. Ki-67 has been evaluated in several studies for its predictive potential, but its use in that indication is still controversial [42]. Nevertheless, in a meta-analysis, Chen et al. [43] analyzed 44 studies and concluded that high Ki-67 expression at diagnosis was associated with increased pCR rates in breast cancer patients treated with anthracycline- and/or taxane-containing NACs. This finding concerned all subtypes of breast cancer and remained significant using different thresholds of Ki-67 (e.g., >15%, >20%, >50%). Even though Ki-67 has not been validated as a predictive marker of pCR, its prognostic value has been largely studied at the moment of diagnosis but also in residual tumors after NAC [40].

4.2. Tumor Size

Tumor size plays a key role in the response to chemotherapy. Livingston-Rosanoff et al. included 38,864 patients between 2010 to 2013 in a retrospective study. These patients underwent NAC and surgery for unifocal lesions ranging in size from cT1 to cT3. Tumors with a size > 5 cm have a lower chance to achieve pCR, regardless of their immunohistological subtype [44]. This could be explained by the fact that larger tumors have a higher probability of displaying increased heterogeneity, with different populations of cells susceptible to having a variable sensitivity to treatment. Tumor size is therefore a relevant predictive factor of non-response to NAC, but it is not sufficient to predict whether patients will achieve a pCR or not.

4.3. Surrogate Molecular Subtypes as Determined by Immunohistochemistry

Tumor subtype is defined by hormone receptor and HER2 status, as well as by Ki-67 immunoreactivity, and has extensively been described as a feature that could influence response to NAC [7][45][46][47][48][49].

The CTNeoBC study pooled data from 12 international trials that included 11,955 early BC patients treated with NAC. The more aggressive subtypes were associated with pCR and better long-term outcomes. Those aggressive subtypes were TNBC, HER2-enriched and high-grade HR-positive tumors. These results are similar to the ones obtained by the pooled analysis of the German neo-adjuvant chemotherapy trials conducted by von Minckwitz et al. [49].

4.4. Tumor-Infiltrating Lymphocytes (TILs)

TILs are evaluated on hematoxylin and eosin slides and can be assessed in the stroma and in the intratumoral area. Stromal TILs are present in the tumor microenvironment without contact with the tumor cells, whereas intratumoral TILs are defined as TILs found in the tumor zone or in the peritumoral area in contact with tumor cells. In breast cancer, stromal TILs evaluation is considered the most reproducible parameter since stromal TILS are more abundant than intratumoral TILs [50][51][52].

The correlation between the levels of TILs and pCR in the neoadjuvant setting has been evaluated in several studies and in all immunohistological subtypes (**Table 2**). Luminal breast cancer presents fewer TILs than the HER2-enriched and TNBC subtypes.

4.5. PD-L1 Expression

Breast cancer is considered less immunogenic than other cancer types. Nevertheless, TNBC has been highlighted as the subtype with the highest expression of PD-L1 due to the genomic instability found in this particular subtype [53]. Several studies have evaluated PD-L1 expression in breast cancer, especially in TNBC, with conflicting results concerning the correlation between PD-L1 expression and its predictive value in the neoadjuvant setting [54][55]. These reported conflicting results could be explained by several factors: the heterogeneity of breast cancer itself, the biopsy type (surgical piece vs. needle), the use of different FDA-approved PD-L1 antibodies, and the different methodologies used across studies to evaluate PD-L1 (the consideration of the tumor cells and/or immune cells, the calculation of the combined positive score (CPS) or tumor proportion score (TPS), the use of different cut-offs) [54][56].

5. Predictive Biomarkers under Investigation

5.1. Imaging and Radiomics Biomarkers

5.1.1. MRI

Chamming and colleagues analyzed texture features on MRI data before NAC and found that some of them were associated with pCR in TNBC [57]. Another study suggested that, with the parameters from intratumoral and peri-tumoral texture, molecular subtypes could be identified by radiomics [58]. Liu et al. developed a radiomics signature with a combination of images from T2-weighted imaging, diffusion-weighted imaging and contrast-enhanced T1-weighted imaging. The signature itself had an accuracy of predicting pCR of 0.79, while the addition of clinical information (e.g., age, molecular classification, Ki-67 status, stage) to this signature improved the accuracy to an AUC of 0.86. They furthermore validated their models on an external dataset [59].

5.1.2. Quantitative Ultrasound

Compared to MRI, ultrasound imaging has several advantages such as its lower cost, the absence of the injection of exogenous contrast agents and the fact that it is transportable. It is therefore more accessible for the screening and evaluation of all patients. QUS is a technique that extracts characteristics of the physical properties of tissues (e.g., elastography) both in intratumoral and marginal regions. Different studies have evaluated the evolution in the structure of the tumor tissue after treatment by QUS. This technique can detect tumor cell death in response to chemotherapy and, in addition, could predict response to NAC after one-to-four weeks of chemotherapy [60][61][62][63][64][65].

5.1.3. ^{18}F-FDG PET/CT

^{18}F-FDG PET/CT is a molecular imaging technique used in clinical practice in oncology [66]. In breast cancer, PET/CT is essentially used to screen for distant metastases, but numerous studies from the past decade have described a potential role of PET/CT as an instrument for predicting response to NAC [4][67][68][69][70]. Higher glycolytic activities at diagnosis and significant reductions in the standardized uptake value (SUVmax) of the tracer during NAC have been described as predictive factors of response to NAC, but they are still controversial [66].

5.2. Plasmatic Biomarkers

5.2.1. Peripheral Blood Cells and Ratios

Systemic inflammation at the time of cancer diagnosis is of interest, as it may reflect tumor-associated inflammation. Moreover, neutrophil and lymphocyte counts have been described as predictors of survival and response to therapy in multiple cancer types [71][72]. The neutrophil-to-lymphocyte ratio (NLR), which is the ratio between the absolute numbers of neutrophils and lymphocytes, has been evaluated in several studies in breast cancer, but its use in clinical practice has not yet been implemented because of contradictory findings [71][72][73][74][75][76]. In 2021, Zhu et al. performed a retrospective study of NLR in 346 patients with BC and concluded that NLR could be an independent predictor of pCR after NAC [77]. A higher NLR was indeed associated with lower pCR. Patients were rigorously selected, and patients with a recent surgery or biopsy or with an autoimmune disease or recent infection were excluded. All selected patients received the same NAC regimen, which was not always the case in previous studies. The threshold value was 1.695 and was determined by ROC curve analyses, which is consistent with previous studies using cut-off values ranging from 1.7–4 [72].

5.2.2. Liquid Biopsies

Liquid biopsies offer a minimally invasive technique for diagnosis, disease monitoring and the evaluation of the response to treatment. Several components of the tumor can be analyzed with liquid biopsy samples, such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs) and tumor-educated platelets (TEPs) and exosomes. While TEPs and exosomes are currently studied primarily as diagnostic tools, ctDNA and CTCs show promising results in assessing response to treatment and predicting resistance in early breast cancer [78][79][80][81][82][83].

5.3. Gene Signatures

Some of them have already been validated in clinical practice, essentially in HR-positive and HER2-negative tumors: EndoPredict, Oncotype DX, MammaPrint and PAM50. Their utility in daily routines consists in providing an individual risk assessment of disease recurrence and prognostic information in order to better guide adjuvant therapy selection in early disease. The potential value of these well-known multigene profiles as predictive biomarkers of response to NAC has also been evaluated, with interesting results. Nevertheless, their indication in this setting has not yet been validated in clinical practice.

5.3.1. EndoPredict—Molecular Score (MS)

EndoPredict is a 12-gene signature measuring the expression of 8 cancer-related genes, 3 reference genes and 1 control gene. The prognostic value of this signature has been validated, stratifying patients treated with adjuvant endocrine treatment (tamoxifen) into a low or a high risk of recurrence at 10 years [84]. Moreover, the addition of clinical features such as nodal status and tumor size to the EndoPredict score is also a good indicator of late recurrence (EPclin) and can help clinicians to decide if additional treatments are needed in case of high-risk scores. In a comparative, non-randomized analysis of two prospective studies of HR-positive and HER2-negative early breast cancer, this multigene score could predict the chemotherapy benefit [85]. Regarding the NAC setting, only a few studies have shown the feasibility of using the MS score in this indication [86][87][88][89].

5.3.2. Oncotype DX—Recurrence Score (RS)

The Oncotype DX recurrence score is the result of the relative expression quantification of 21 genes (16 cancer-related genes and 5 reference genes). This score allows for the classification of patients into three categories: low risk, intermediate risk and high risk. The prognostic value of RS was validated in the prospective TAILORx and RxPONDER studies, demonstrating that patients with intermediate risk could be spared adjuvant chemotherapy in addition to endocrine therapy [90][91]. Later, the potential predictive value of the RS was evaluated in several retrospective and prospective studies.

5.3.3. Mammaprint

The Mammaprint assay is a 70-gene signature used in post-menopausal early breast cancer patients. This signature classifies tumors in two groups that are associated with good or poor prognosis based on the recurrence risk at 5 and 10 years. In the prospective MINDACT study, patients with ER-positive and HER2-negative early breast cancer and a low Mammaprint score who received endocrine therapy could safely be spared adjuvant chemotherapy [92]. The use of Mammaprint as a predictive marker of response to NAC has only been evaluated in small exploratory studies.

5.3.4. PAM50—Prosigna Assay

PAM50 is a 50-gene signature used and validated to identify intrinsic molecular subtypes of breast cancer (luminal A, luminal B, HER2-enriched, basal-like) but also to estimate a Risk of Recurrence (ROR) score capable of classifying tumors into low, intermediate or high risk of distant recurrence [93]. This gene signature was developed in order to evaluate the risk of relapse in patients with HR+ and HER2-negative breast cancer and to evaluate the indication of adjuvant

chemotherapy in high-risk cases. In the neoadjuvant setting, Prat et al. studied this assay in core needle biopsy samples to evaluate if it was suitable for core biopsies [94]. They found that the Prosigna assay performed on core needle biopsies was reliable in terms of ROR score and intrinsic subtypes classification.

6. Conclusions

Predicting the response to NAC in early breast cancer still needs dedicated investigations, since most of the studies performed until now only considered one parameter, limiting their performances. This field remains an area of unmet clinical need, as exemplified by triple negative early breast cancer, where neoadjuvant escalation strategies have recently changed the treatment landscape. In the recently published Keynote-522 trial, the NAC backbone contained carboplatin in both treatment arms, and the addition of pembrolizumab led to a significantly higher pCR rate (64.8 vs. 51.2%) compared to placebo. Nevertheless, in the patients achieving pCR, recurrence rates were not significantly different between the treatment groups [95]. Thus, 50% of the patients do not require the addition of immunotherapy to chemotherapy. As treatment side effects were more pronounced in the more heavily treated patient population, finding a biomarker predictive of response to chemotherapy would be clinically and economically useful. At the same time, a better selection of patients for NAC would avoid directly ruling out promising new agents but also avoid the emergence of resistant clones due to prolonged drug exposure [8]. For a better selection of patients, for developing new drugs and avoiding the residual disease, it is therefore essential to explore and develop new predictive biomarkers with high sensitivity and specificity.

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