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Breast Cancer: Basic and Clinical Research

Update on Adjuvant Chemotherapy for Early Breast Cancer

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ABSTRACT: Breast cancer is the second most common cancer in women worldwide. Although most women are diagnosed with early breast cancer, a substantial number recur due to persistent micro-metastatic disease. Systemic adjuvant chemotherapy improves outcomes and has advanced from first-generation regimens to modern dose-dense combinations. Although chemotherapy is the cornerstone of adjuvant therapy, new biomarkers are identifying patients who can forego such treatment. Neo-adjuvant therapy is a promising platform for drug development, but investigators should recognize the limitations of surrogate endpoints and clinical trials. Previous decades have focused on discovering, developing, and intensifying adjuvant chemotherapy. Future efforts should focus on customizing therapy and reducing chemotherapy for patients unlikely to benefit. In some cases, it may be possible to replace chemotherapy with treatments directed at specific genetic or molecular breast cancer subtypes. Yet, we anticipate that chemotherapy will remain a critical component of adjuvant therapy for years to come.

KEYWORDS: neoadjuvant, toxicity, pathologic response, metastases

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Introduction

Breast cancer is a common malignancy in women and causes over a half-million deaths each year worldwide.[1] In the United States, 232,670 women will be diagnosed with breast cancer in 2014 and ~40,000 will succumb.[2]

Although 90% of women are diagnosed with early breast cancer, prospective studies have shown breast cancer–specific mortality rates exceeding 50% at 30-year follow-up in women treated with surgery alone.[3] Although local therapies can eradicate disease in the breast and axilla, early systemic dissemination of microscopic disease often precedes local therapy. Hence, the rationale for medical therapies after surgical resection is to eliminate, or perhaps suppress, this microscopic disease.[4] Postoperative medical therapy saves lives by reducing the likelihood of incurable recurrence of breast cancer. However, it is difficult to identify the patients who have no micro-metastatic disease, and so these patients are often exposed to chemotherapy even though they would be cured with surgery alone.

Etymologically, "Adjuvant" is derived from Latin *adiuvare*, to aid. Adjuvant therapy aids surgery in effecting cure of breast cancer. Adjuvant treatments for breast cancer can include chemotherapy, hormonal therapy, human epidermal growth factor receptor (HER2)–directed therapies, and radiation. Of these, radiation can eradicate loco-regional microscopic disease in the breast, chest wall, skin, and nearby lymph node basins, whereas systemic medications can also destroy microscopic disease distant from the breast. Significant improvements in efficacy and tolerability in adjuvant therapy have been achieved in the last 50 years. Here, we discuss these improvements, customization for specific breast cancer

subtypes, address recent controversies, and provide our vision for how chemotherapy will be used in the future.

The Advent of Modern Adjuvant Chemotherapy

Adjuvant chemotherapy was spawned by poor outcomes after maximal surgical and radiotherapy interventions. The idea of using chemotherapy as an adjuvant to surgery was supported by the discovery of hematogenous cancer cells and by encouraging animal studies suggesting that these could be eliminated with chemotherapy. Early trials showed promising outcomes in patients who received chemotherapy. One of the first trials was a randomized study of nitrogen mustard given at the time of mastectomy and at 4, 8, and 12 month intervals with 1–3 years of follow-up. Among the 37 controls, there were 12 recurrences and 7 deaths, whereas there were only 5 recurrences and 1 death in the 37 treated patients. These promising preliminary data supported larger studies.

One early adjuvant chemotherapy trial in breast cancer was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-01 study, wherein a short course of ThioTEPA (N,N′,N″-triethylenephosphoramide) given as adjuvant therapy after a radical mastectomy reduced the risk of recurrence and improved overall survival (OS) in premenopausal women with four or more positive nodes.[5] Similarly, the NSABP B-05 trial demonstrated improved disease-free survival (DFS) with adjuvant melphalan in node-positive early breast cancer.[6] Given the effectiveness of combination chemotherapy for curing lymphomas, there was an intense interest in applying this strategy to breast cancer, leading to the development of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).[7] The Milan group evaluated 12 cycles of adjuvant CMF and discovered that this improves DFS and OS. Subsequently, 6 months of adjuvant CMF was found to be equivalent to 12 months.[8] These studies established 6-month CMF as a standard adjuvant chemotherapy for breast cancer by the 1980s.

By the 1970s, doxorubicin had also emerged as a promising new drug derived from a mutant soil bacterium.[9] This drug, now familiar to many breast cancer and lymphoma survivors due to its red color, was initially named after the Adriatic Sea, and retains the abbreviation "A" for adriamycin in breast cancer regimens. Again, the Milan group pioneered development and ultimately demonstrated its benefit in metastatic and then adjuvant treatment of breast cancer.[10,11] NSABP B-15 compared CMF against doxorubicin combined with cyclophosphamide (AC), revealing that outcomes were equivalent.[12] However, AC was better tolerated and completed in 3 months rather than 6 months for CMF. These trials established AC as the dominant adjuvant regimen for node-positive early breast cancer in North America. Similarly, other groups developed anthracycline-based regimens such as FAC (doxorubicin, cyclophosphamide, and 5-fluorouracil) and FEC (epirubicin, cyclophosphamide, and 5-fluorouracil).[13–15]

In the early 1990s paclitaxel (Taxol®) was identified as a highly effective therapy for metastatic breast cancer.[16] The NSABP B-28 trial evaluated the addition of paclitaxel sequentially after AC chemotherapy (AC-T) and showed that this improved DFS in node-positive early breast cancer with a trend toward improved OS.[17] Similarly, the National Cancer Institute Intergroup study showed improved DFS and OS with the addition of four cycles of paclitaxel every 3 weeks after the completion of adjuvant AC.[18] Docetaxel also improved DFS and OS in combination with doxorubicin and cyclophosphamide (TAC) in node-positive and node-negative early breast cancer.[19,20] Subsequently, weekly administration of paclitaxel was found to have superior DFS and OS to administration every 3 weeks.[21–23]

One limitation of prior regimens was the rare but serious risk of permanent heart failure from doxorubicin. To obviate this, the US Oncology 9735 trial compared four cycles of adjuvant docetaxel and cyclophosphamide (TC) with standard AC to evaluate efficacy of a safe anthracycline-free adjuvant regimen. This study revealed that four cycles of TC is superior to AC in both DFS and OS.[24] Elderly women (>65 years) constituted 16% of the study population, and ~90% of women had node-negative or one to three node-positive early breast cancer. Based on these data, TC is considered a standard regimen for adjuvant therapy for node-negative or low-risk node-positive breast cancer.[25] For high-risk breast cancer, good evidence suggests that four cycles of TC is inferior to sequential AC-T (even when concurrent anthracycline is added to TC).[26,27] Although AC-T has superior breast cancer–specific outcomes, using anthracyclines incurs risk for cardiac toxicity and rare secondary blood dyscrasias. NSABP-49 is testing if six cycles of TC is as effective as AC-T in reducing breast cancer recurrence without the risks.[28]

Side effects from adjuvant chemotherapy. Although adjuvant chemotherapy reduces the risk of recurrence and improves odds of cure, it does carry risks of side effects, some of which can be severe and persistent. During chemotherapy, two thirds of patients experience severe fatigue.[29] In early studies with adjuvant chemotherapy, a significant number of women (~70%) had nausea and vomiting.[12,14] However, with the advent of effective antiemetic medications, this has greatly reduced. Alopecia is nearly universal with anthracycline-based or TC chemotherapy.[12,14] A reduction in the white cell count occurs after each cycle of chemotherapy, though this persists only for a few days and hospitalization for neutropenic fever is uncommon (<10%).[30] For regimens with rates of neutropenic fever exceeding 20%, granulocyte colony-stimulating factor is available to accelerate recovery from neutropenia and prevent neutropenic fever.[31] Common side effects seen with adjuvant taxanes include neuropathy (15%–20%), myalgia, and arthralgia (10%–15%).[17,21] Immediate hypersensitivity reactions may occur during paclitaxel infusion and occasionally are life threatening; these may present as flushing, urticaria, fever, bronchospasm, and serum sickness.[17] Pretreatment steroids and antihistamines reduce but do not eliminate this risk.

One of the principal concerns with anthracycline-based adjuvant chemotherapy is the risk of cardiotoxicity. In the adjuvant setting, where the total dose of doxorubicin is typically limited to less than 300 mg/m^2, the incidence of clinically significant cardiomyopathy is less than 1%.[29] However, the incidence rises with escalating cumulative dose and presence of other cardiac risk factors.[32] Another concern attributed, in part, to anthracyclines is the potential risk of secondary myelodysplastic syndromes and acute myelogenous leukemia (AML). A combined analysis of six adjuvant studies conducted by the NSABP using AC chemotherapy reported a 5-year incidence of AML ranging from 0.3% to 1.2%.[33] Unlike the leukemia associated with alkylating agents, that associated with anthracyclines is more likely to be monocytic, to involve a specific cytogenetic abnormality (11q23), and to develop within a few years after treatment.[34]

The risks of chemotherapy are serious, but can be managed by physicians with expertise in these medications. Prior to initiating adjuvant chemotherapy, the physician must determine that the risks outweigh the benefits of chemotherapy. Given the risk of permanent toxicity or death due to chemotherapy in a small fraction of patients, it is typically deemed worthwhile if there is at least a 5% decrease in risk in cancer recurrence or death, as demonstrated by strong clinical evidence.

Dose intensity and dose density. While early efforts focused on adding chemotherapy agents to improve patient outcomes, recent efforts have focused on the intensification of effective agents. Dose intensity is a measure of chemotherapy drug delivered per unit time.[35] However, escalation of drug dosage proved unsuccessful at improving cancer outcomes.[36,37] Additionally, increasing the number of chemotherapy cycles of AC or paclitaxel failed to improve clinical outcomes.[38]

In contrast to the failure of dose intensification, "dose density" refers to more frequent administration of cytotoxic chemotherapy. This approach is based on the observation that human cancers grow by nonexponential Gompertzian kinetics with the regrowth of cancer cells between cycles of chemotherapy being more rapid than in exponential models. The CALGB 9741 study evaluated this concept comparing dose-dense (every 2 weeks) versus conventional (every 3 weeks) as well as sequential versus concurrent combination chemotherapy. Dose-dense treatment significantly improved DFS and OS, and there was no difference between the sequential and concurrent approaches.[39] Subsequent meta-analysis has confirmed the benefit of increasing dose density.[40]

The dose-dense approach has also been used with taxane-based therapy. Our group recently demonstrated that docetaxel and cyclophosphamide (TC) on a dose-dense schedule is safe. In this study, patients received adjuvant dose-dense TC every 2 weeks with pegfilgrastim support for four cycles; 90% completed therapy within 10 weeks with 83% completing in 8 weeks without dose modification. The rate of neutropenic fever was low (2.5%), neuropathy was similar to previous reports, and rash and palmar-plantar erythrodythesia were common. Thus, our study showed that dose-dense TC has tolerability profiles similar to standard TC, has low risk of neutropenic fever, and is expected to be equally effective to or more effective than standard TC.[41] Among the standard chemotherapy regimens, dose-dense TC is completed in 8 weeks, making it the most expeditious standard regimen available today (Fig. 1).

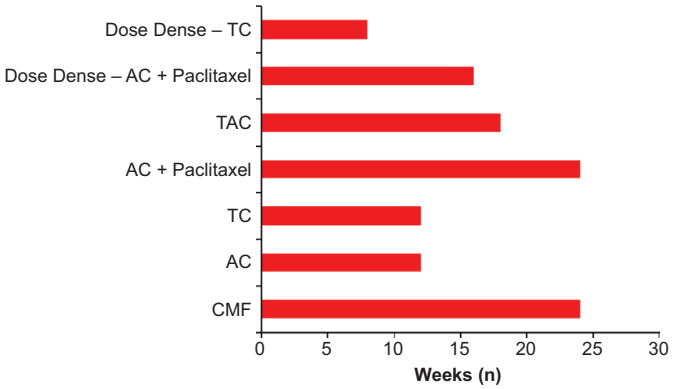

Figure 1. Duration of different adjuvant chemotherapeutic regimens.

Who Needs Adjuvant Chemotherapy?

The value of adjuvant chemotherapy depends on a balance of absolute benefit and risk. Physicians estimate the likelihood of distant dissemination based on the stage and subtype of breast cancer and then estimate the probability that chemotherapy will prevent recurrence.

Several tools are available to assist with risk stratification and assessing magnitude of benefit of adjuvant chemotherapy. Adjuvant Online is an open-access prediction program which takes into account tumor size, lymph nodes, grade, estrogen receptor (ER) status, and patient factors including age and co-morbidities.[42] The drawback of this model is that it does not take into account HER2 status.[43] Also, predictions can be strongly affected by tumor grade, which has high interobserver variability.[44,45] A similar model used for risk assessment and decision making is the PREDICT model which accounts for HER2 status and Ki-67 proliferation markers.[46] These tools can assist with shared informed decision making about the risks and benefits of chemotherapy customized to each patient.

Current treatment strategies.

Triple-negative breast cancer. Chemotherapy is the mainstay of adjuvant treatment for patients with triple-negative disease. We consider adjuvant chemotherapy for tumors >0.5 cm or axillary lymph node involvement. For node-positive disease, typically, we would recommend dose-dense AC-T.[39] However, TC is a reasonable adjuvant therapy choice for node-negative or low-risk node-positive breast cancer.

Platinum agents, such as cisplatin and carboplatin, are DNA-damaging agents with activity in breast cancer,

particularly in the triple-negative subgroup. The majority of BRCA1-associated breast cancers are basal-like and are sensitive to DNA-damaging agents because of impaired repair by homologous recombination of double-strand breaks (DSB) induced by platinums.[47,48] Platinum-based agents have shown efficacy and are a preferred regimen in the metastatic setting with triple-negative breast cancer.[49–51]

The GeparSixto trial assessed the benefit of adding carboplatin to neo-adjuvant chemotherapy in triple-negative and HER2+ early breast cancer and found a significant improvement in pathological complete response (pCR).[52] However, a major criticism is that the anthracycline backbone was nonstandard with weekly doxorubicin and paclitaxel combined with bevacizumab. It is possible that carboplatin is superfluous when compared with conventionally dosed anthracycline-based therapy. Similar data supporting the use of platinums were reported from CALGB 40603, a randomized phase II trial. This showed significantly improved pCR rates by the addition of carboplatin to neo-adjuvant chemotherapy in early triple-negative breast cancer.[53] Side effects with neutropenia and thrombocytopenia were significantly increased with carboplatin. Interestingly, similar effects were seen with bevacizumab, even though it is not found to be effective in the adjuvant setting. Although these data are promising, we believe more conclusive data will be required before routine use of platinum agents to adjuvant therapy for triple-negative breast cancer. Moreover, it will be important to learn whether any benefit of platinum therapy is restricted to patients with impaired DSB, as occurs, eg, by loss of BRCA1/2 function. If so, this escalation of therapy could be targeted specifically to individuals likely to benefit.

HER2+ breast cancer. Trastuzumab is a recombinant monoclonal antibody to HER2 and was the first agent developed for HER2+ early breast cancer. Several large clinical trials showed a significant improvement in DFS and OS with the addition of 1 year of trastuzumab (H) to adjuvant anthracycline-based chemotherapy.[54–57] Subsequently, the Breast Cancer International Research Group identified a non-anthracycline regimen with docetaxel and carboplatin combined with trastuzumab (TCH), which had similar efficacy but lower risk of cardiotoxicity.[58] Although the TCH regimen appeared to have a lower risk of long-term side effects, this regimen is associated with high rates of acute toxicities, particularly myelosuppression.[59] It is important to note that the comparator anthracycline arm in this trial differed from preferred anthracycline-based regimens with substitution of docetaxel for paclitaxel. Based on these studies, TCH, AC-TH, and sequential anthracycline–trastuzumab are standard adjuvant therapy options in this population.

Adjuvant chemotherapy is recommended even for small node-negative HER2-breast cancer, but the threshold for treatment is disputed. For node-positive disease and node-negative cancers >1 cm, chemotherapy and trastuzumab is generally recommended. In node-negative disease, for tumors ≤0.5 cm in size, we and many others do not routinely recommend adjuvant chemotherapy or trastuzumab. The reason is that, although patients with small tumors were included in early adjuvant trastuzumab studies, more recent cohort studies have shown excellent outcomes in this population with a 5-year DFS of >95% without any adjuvant therapies.[60] For node-negative tumors 0.6–1.0 cm, adjuvant chemotherapy with HER2-targeted therapies can be considered based on age and co-morbidities. Oncologists today vary in their practice for treating small HER2+ breast cancer.[59] Paclitaxel with trastuzumab is well tolerated and may become a future standard for small HER2-positive cancers.[61]

ER+ breast cancer. The threshold for recommending chemotherapy in hormone receptor–positive, HER2-negative early breast cancer is difficult to define because low- and high-risk patients have distinct benefits from receiving chemotherapy.[62] For node-positive disease, we recommend standard chemotherapy. Typically, we would recommend dose-dense AC-T.[39] However, TC or dose-dense TC is also a reasonable adjuvant therapy choice for low-risk node-positive breast cancer. The South West Oncology Group (SWOG) RxPONDER trial (S1007) will determine whether chemotherapy can be safely omitted for certain women with one to three positive axillary lymph nodes.

In node-negative disease, our chemotherapy recommendations are primarily guided by tumor size, patient age, and co-morbidities. Typically, adjuvant chemotherapy is not recommended for tumors ≤1 cm. Population-based prospective cohort studies have shown an excellent outcome for these patients with 5-year DFS between 93% and 98% without chemotherapy.[63] For tumors >1 cm, multigene tumor assays can provide both prognostic and predictive information. Although assays of the primary tumor cannot directly determine whether cancer cells have or have not disseminated, they can identify tumors with higher or lower propensity for such dissemination. One widely used assay is the 21-gene recurrence score (Oncotype DX®), which predicts chemotherapy benefit in ER+ node-negative breast cancer with high and low recurrence scores.[64,65] Further information on managing patients with intermediate scores based on the Trial Assigning Individualized Options for treatment study is anticipated.[66] Until then, we recommend TC for high scores and discuss risks/benefits of chemotherapy for intermediate scores. Additionally, preliminary evidence using Oncotype DX in node-positive breast cancer is promising.[67] Other assays include the 70-gene MammaPrint® profile, and 50-gene PAM50®, assay which classifies tumors into luminal A, luminal B, HER2-enriched, and basal-like subtypes.[68,69] These assays may aid in decision making for other patient populations including those with hormone receptor–negative disease.

New promising targeted therapies.

Cyclin-dependent kinases 4 and 6 inhibitors. The cyclin D-cyclin-dependent kinases 4 and 6 (CDK4/6)-retinoblastoma pathway governs the cell cycle restriction point. This pathway is

frequently altered in breast cancer and is a potentially relevant target for anticancer therapy.[70,71] Palbociclib (PD 0332991) is a potent and selective inhibitor of CDK4 and CDK6 and the most widely studied agent in this field.[72] In the recently reported PALOMA-1 study, combination of palbociclib plus letrozole doubled progression-free survival (PFS) in patients with metastatic ER-positive, HER2-negative breast cancer.[73] Trials assessing the benefit of adding adjuvant palbociclib to endocrine therapy for hormone receptor–positive breast cancer are ongoing.

Mammalian target of rapamycin inhibitors. The mammalian target of rapamycin (mTOR) pathway is often activated in breast cancer and may be an important mechanism of resistance to hormonal therapies. mTOR can be inactivated with inhibitors like everolimus. The BOLERO-2 study showed a significant improvement in PFS with the addition of everolimus to exemestane in advanced postmenopausal hormone receptor–positive breast cancer lending credence to the importance and feasibility of targeting this pathway.[74] Currently, the SWOG S-1207 study is enrolling to assess the efficacy of 1 year of adjuvant everolimus in high-risk, hormone receptor–positive and HER2-negative early breast cancer. In the neo-adjuvant setting, the combination of everolimus with letrozole in early hormone receptor–positive breast cancer showed a significant improvement in clinical response by palpation and ultrasound in small clinical studies.[75] Although, this may be a useful adjunct to standard hormonal therapy, the CDK4/6 inhibitors appear to have stronger effects in metastatic disease. Thus, we anticipate that mTOR inhibitors will ultimately be superseded by CDK4/6 inhibitors.

Poly ADP-ribose polymerase inhibitors. Poly ADP-ribose polymerase (PARP) enzymes, especially PARP1, are critical for appropriate recognition and repair of DNA breaks in cells lacking functional BRCA1 or BRCA2.[76] In tumors with BRCA1 or BRCA2 mutations, inhibition of PARP1 further compromises DNA repair leading to cell death, thus making PARP inhibitors an attractive therapeutic for triple-negative and BRCA-mutated breast tumors.[77] In the iSPY2 study, a master protocol toward evaluating a variety of targeted agents in the neo-adjuvant setting, addition of a PARP inhibitor veliparib and carboplatin to standard neo-adjuvant chemotherapy produced an impressive pCR rate of 52% in the triple-negative signature.[78] This combination of a platinum and a PARP inhibitor has now been graduated to the phase III setting. However, the strongest preclinical and clinical evidence supports the use of PARP inhibitors in the setting of BRCA1/2 mutations. Therefore, we anticipate that these agents will be most useful in this subset of patients.

Pertuzumab and trastuzumab emtansine. Several ongoing studies are assessing the efficacy of new HER2-targeted agents in adjuvant therapy. Pertuzumab is a second HER2-targeted monoclonal antibody directed at the dimerization domain. Pertuzumab improves PFS markedly when added to trastuzumab plus docetaxel in the first-line treatment of HER2+ metastatic breast cancer.[79] In the neo-adjuvant setting, the addition of pertuzumab to trastuzumab and taxane significantly improved pCR rates, and this led to the approval of pertuzumab as a new standard for neo-adjuvant chemotherapy.[80,81] Although neoadjuvant pertuzumab was tested in combination with FEC and TCH,[81] we often use AC-TH and add pertuzumab every 3 weeks concurrent with weekly paclitaxel and trastuzumab.

One ongoing controversy concerns whether pertuzumab should also be used in postoperative adjuvant therapy of breast cancer. The US Food and Drug Administration (FDA) approved pertuzumab for neo-adjuvant, but not adjuvant, therapy of HER2+ breast cancer based on the endpoint of pCR. Yet, if pCR is a valid surrogate for survival, then pertuzumab should also be used in the postoperative adjuvant setting since pCR predicts that this drug helps eliminate distant micro-metastases. For this reason, we often use four doses of pertuzumab every 3 weeks concurrent with paclitaxel–trastuzumab in both the neo-adjuvant and adjuvant settings.

Another newer HER2-targeted agent is trastuzumab emtansine (T-DM1), an antibody–drug conjugate incorporating trastuzumab with cytotoxic activity of the microtubule-inhibitory agent DM1, and this has shown excellent activity with significant improvement in PFS and OS in metastatic breast cancer.[82]

Given the new HER2-targeted therapies, it is time to consider eliminating some of the multiple cytotoxic agents for treatment of HER2+ breast cancer. The future paradigm of chemotherapy regimens should focus on de-escalating chemotherapy and minimizing side effects without sacrificing efficacy. This is reinforced by the results of dual HER2 blockade by trastuzumab and pertuzumab showing ~16% of patients have pCR from neo-adjuvant HER2-directed therapy alone without chemotherapy.[80] Future trials for this type of cancer should strongly consider using these HER2-targeted therapies either as monotherapy or using a taxane-only chemotherapy backbone on which to further develop targeted agents (Fig. 2).

Can we Reduce or Eliminate Chemotherapy?

Chemotherapy has been a mainstay of adjuvant therapy of breast cancer for over four decades. However, with the advent of improved targeted therapies, it is appealing to imagine a future where chemotherapy is eliminated entirely. However, it may be difficult to realize this vision with targeted agents. Targeted drugs are often cytostatic rather than cytotoxic, suggesting they will forestall tumor growth rather than eliminate micrometastases. Even so, there is hope for significant advancement in reducing needless exposure to adjuvant therapy:

(1) Ongoing tumor genotyping may improve cancer prognosis beyond the current state of the art. If so, it may be possible to identify more patients who will do well without adjuvant therapy.

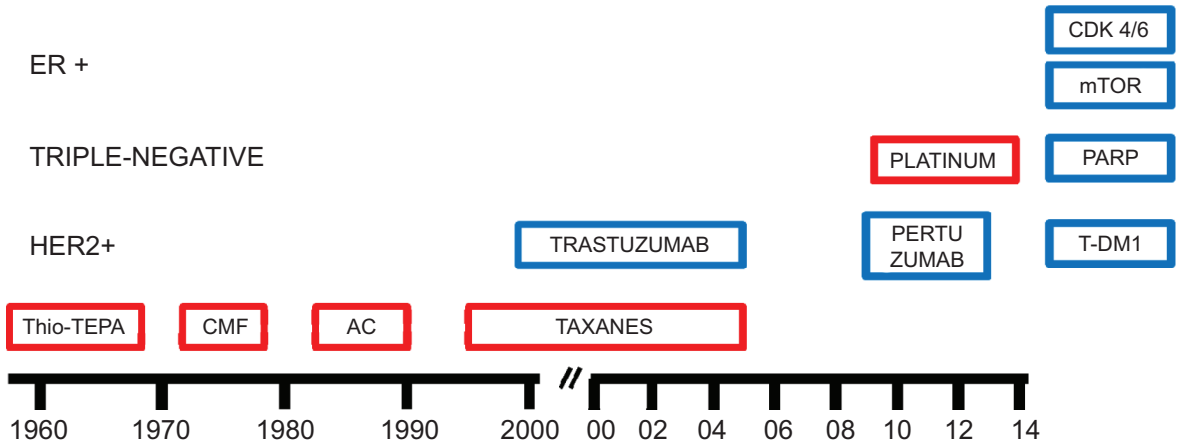

Figure 2. Time-line of development of adjuvant therapies in early breast cancer: promising agents in the near future. Red: chemotherapeutic agents; blue: targeted agents.

(2) It is, in principle, possible to identify micro-metastatic disease. Future advances in imaging or biomarker technology could improve staging to identify the patients who are most in need of adjuvant therapy.
(3) Biomarkers of chemotherapy can be developed to better predict whether specific chemotherapies work for a specific cancer type.

Chemotherapies were largely developed prior to the discovery of molecular-targeted therapies. Although it is recognized that some tumors do/do not respond to specific drugs and that some reasons have been proposed, it is not yet predictable. Discovery of biomarkers for cancer therapy might have a profound effect on customizing tailored chemotherapy regimens to each patient. For example, we and others have identified mechanisms for how paclitaxel elicits its anticancer effects.[83–85] Additionally, some drugs such as methotrexate can have profoundly different effects on cancer cells with distinct genetic backgrounds, suggesting that a biomarker for drug sensitivity can be discovered.[86]

There are significant practical difficulties with eliminating or reducing chemotherapy. In principle, oncologists would demand evidence of noninferiority for de-escalating standard therapy. Such trials would be large and would not offer patients better treatments or better cancer-specific outcomes. When so many promising new therapies are available, such studies may not be a good use of limited resources for clinical trials. Instead, we would support developing innovative adjuvant studies that would directly replace some components of chemotherapy with new agents. This would move the field forward and obviate the requirement for exhaustive and large noninferiority studies that would sap limited patient and financial resources for clinical trials.

Neo-Adjuvant Chemotherapy

For inoperable or inflammatory locally advanced cancers, chemotherapy prior to surgery (neo-adjuvant) is the standard of care. Is there an advantage of neo-adjuvant therapy in tumors that are operable at diagnosis? This question was addressed by the NSABP B-18 and B-27 clinical trials in which preoperative, ie neo-adjuvant, chemotherapy was compared with adjuvant chemotherapy.[87] In NSABP B-18, there was no survival benefit of receiving AC in the neo-adjuvant setting, although a subset analysis did suggest improved outcomes with neo-adjuvant chemotherapy for women younger than 50 years.[87] NSABP B-27 compared three regimens: (1) preoperative AC, (2) preoperative AC followed by preoperative docetaxel, and (3) preoperative AC followed by postoperative docetaxel. There was a significant increase in pCR noted with the addition of preoperative docetaxel, but there was no significant difference in DFS or OS.[87] Thus, neo-adjuvant and adjuvant chemotherapy are considered equivalent in terms of survival benefit for operable tumors.

However, neo-adjuvant therapy offers several other advantages over standard postoperative adjuvant treatment in breast cancer. Principally, neo-adjuvant therapy provides an opportunity for down-staging bulky disease to make breast-conserving surgery more likely. For research and prognosis, the neo-adjuvant approach also offers response assessment to treatment. Several studies have shown a correspondence between DFS and OS with both clinical and pathologic tumor response to neo-adjuvant therapies in triple-negative and HER2+ disease.[88] On the other hand, pCR seems to be a poor marker of survival in hormone receptor–positive breast cancer. Thus, pCR is proposed as a surrogate marker for long-term disease outcomes in triple-negative and HER2+ breast cancer. The benefit of this marker is more rapid development of effective therapies, since pCR can be assessed immediately after chemotherapy and surgery are complete.

Yet, pCR has limitations as a surrogate. Even when pathologic complete response is achieved, some patients ultimately have disease progression. In the neo-adjuvant NSABP B-18 and B-27 trials, 25% and 18% developed recurrence despite

pCR.[89,90] This could reflect limitations on assessing complete response by pathologic sampling and analysis, eg, some complete responses may have had undetected residual disease. It is also possible that the primary tumor does not respond the same way as distant micro-metastases. Indeed, some scientists have proposed that disseminated tumor-initiating cells have unique properties that behave different from the bulk primary tumor.[91]

Historically, new drugs in breast cancer have been approved first in the metastatic setting followed by large and long adjuvant clinical trials and subsequent approval in the adjuvant setting coming several years later. The time from initiation of a phase III trial of a drug in metastatic breast cancer to approval for its use in an adjuvant population often exceeds a decade.[92]

Over the last few years, neo-adjuvant approaches have been proposed as a platform for rapid drug development. Yet, there is considerable debate in the breast cancer scientific community regarding the appropriateness of using pCR as an accelerated pathway for drug approval. A large meta-analysis performed and funded by the FDA included 12 large international neo-adjuvant trials comprising 11,955 patients. The results show that pCR is associated with DFS and OS and that the best association is achieved when complete response is defined as eradication of tumor from both breast and lymph nodes. The association between pCR and long-term outcomes was strongest in patients with triple-negative breast cancer and in those with HER2+, hormone receptor–negative tumors who received trastuzumab. However, in the trial-level analysis, improvement in pCR corresponded poorly with improved DFS ($r^2 = 0.03$) and OS ($r^2 = 0.24$).[88]

Recent discrepancies between neo-adjuvant and adjuvant studies have further challenged the utility of pCR as a surrogate endpoint. For example, lapatinib improved pCR in the neo-adjuvant NeoALLTO trial, yet showed no improvement in DFS when added to adjuvant therapy in ALLTO.[93] In our view, such discordant findings are not surprising:

(1) Most clinical trials are powered to detect a difference at with $\alpha = 0.05$ and $\beta = 0.2$. Thus, the NeoALLTO trial has a 5% false-positive rate, and ALLTO has a 20% false-negative rate for detecting a clinically significant effect. In particular, lack of a statistical difference in the ALTTO trial cannot be construed as strong evidence of no difference.
(2) pCR is an imperfect surrogate. Neo-adjuvant trials have demonstrated evidence of disease recurrence in 18%–25% of patients after pCR compared with 35%–42% in those without pCR.[88,90] This would suggest that pCR is only partly predictive of long-term outcomes.

Ultimately, the limitations of pCR and clinical trial designs should be acknowledged. In our view, pCR is a valid but imperfect surrogate endpoint. We believe that it is appropriate to provisionally modify established (neo)-adjuvant therapy based on this surrogate endpoint when effect size is clinically significant (eg, >10% increase in pCR). However, this provisional alteration should be validated by a clinical trial in the adjuvant setting.

Conclusions

Over the past half century, adjuvant chemotherapy has been established as standard for breast cancer treatment and has saved many lives. The current standard of care is sequential anthracycline plus taxane for high-risk breast cancers and four cycles of TC or no chemotherapy for lower risk breast cancers. In the future, we will increasingly customize regimens using genetic profiling and targeted therapies to personalize care. For low-risk patients, this will include defining the subset of patients who can avoid chemotherapy, particularly for ER+ and HER2+ disease. For high-risk patients, novel and more effective targeted therapies will be added. As investigators move with excitement toward developing new agents, there remains a pressing need for better biomarkers to predict benefit of chemotherapy. Although neo-adjuvant clinical trials are promising as a rapid platform for clinical investigation, researchers and oncologists need a renewed appreciation of the limitations of surrogate endpoints and fully appreciate the influences of chance and bias in small neo-adjuvant studies. Moreover, it is possible that response in metastatic disease will be a superior surrogate to neo-adjuvant pCR. We anticipate a future in which chemotherapy is customized to the needs and risks of each patient with continued improvements in morbidity and mortality from breast cancer.

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Author Contributions

Review of literature: MR, GR, MEB. Wrote the first draft of the manuscript: MR. Contributed to the writing of the manuscript: GR, MEB. Made critical revisions: MR, GR, MEB. All authors reviewed and approved of the final manuscript.

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