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Original article

Tailoring adjuvant chemotherapy regimens for patients with triple negative breast cancer

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ABSTRACT

Cytotoxic chemotherapy remains the systemic therapy of choice for triple-negative breast cancer (TNBC), a poor-prognosis subtype of breast cancer. Growing data focusing on TNBC provides an opportunity to assess if we can tailor adjuvant chemotherapy based on patient and tumor characteristics. The standard of care for moderate-to-high risk TNBC remains a sequential anthracycline-taxane combination, with the potential for shorter and less toxic regimens in stage I disease. Platinums are promising in the neo-adjuvant and metastatic settings but we await long-term outcome data before incorporation into standard regimens in the adjuvant setting. Specific subgroups within TNBC, such as BRCA mutation carriers, require special attention, and the role of platinums in these patients warrants further consideration. There is hope that in the future, further subdividing TNBC by gene expression profile, mutation, immune infiltrate, and others will reveal novel susceptibilities.

Introduction

In March 2015, the International Breast Cancer Study Group and the Austrian Breast and Colorectal Study Group organized the 14th International St. Gallen Breast Cancer Conference on Primary Therapy of Early Breast Cancer. This conference brought together experts from around the world to assess the most up-to-date basic and clinical research and concluded with the St. Gallen consensus on the optimal treatment of early breast cancer. This review focuses on adjuvant chemotherapy regimens for triple-negative breast cancer (TNBC), the subset of breast cancers that are negative for estrogen receptor (ER), progesterone receptor, and HER2.

Triple-negative breast cancer accounts for approximately 10–15% of all breast cancers and is associated with a worse prognosis than hormone receptor- or HER2-positive breast cancers, particularly in the first 5 years after diagnosis [1]. In a study of over 50,000 women with first primary breast cancer, 5-year survival of TNBC was 77% compared with 93% for other breast cancer subtypes [2]. This 5-year survival is driven by uneven patterns of early recurrence: TNBC recurs at a rate of 10–15% per year for the first several years after initial surgery, while hormone receptor-positive breast cancer recurs at a rate of 3–5% per year but can recur decades after diagnosis [3]. Despite the remarkable progress of the past decade with multiple novel agents targeting HER2 or ER, progress in triple-negative breast cancer has been limited with cytotoxic chemotherapy remaining the mainstay of systemic therapy for TNBC [4].

Adjuvant chemotherapy for TNBC

Current standards of care

There is clear evidence that adjuvant chemotherapy provides long-term benefit for many women with TNBC, through the efforts of clinical trials involving thousands of women with breast cancer. A meta-analysis of 46 trials from the 1970s to the 1990s involving over 6000 women with ER-negative breast cancer (prior to routine staining for HER2) evaluated the impact of adding of chemotherapy to local therapy alone. The use of polychemotherapy led to a significant reduction in breast cancer recurrence, breast cancer mortality, and all-cause mortality (odds ratio 0.75, $p = 0.0003$ age < 50 and 0.87, $p = 0.0009$ age 50–69) [5]. Another meta-analysis evaluated 6644 node-positive breast cancer patients and demonstrated that the addition of adjuvant chemotherapy improved overall survival of ER-negative patients by 16.7% compared with only 4.0% for ER-positive patients [1]. A retrospective analysis of the CALGB 9344/INT0148 trial suggested that the addition of paclitaxel after adjuvant doxorubicin and cyclophosphamide improved disease-

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free survival in TNBC as well as ER-negative, HER2-positive disease [6]. As a general principle, the improvements in adjuvant chemotherapy over the past two decades have had a greater impact on the prognosis of triple negative disease than patients with estrogen receptor positive breast cancer.

Among the many potential regimens, a sequential anthracycline-taxane combination is the standard of care for moderate-to-high risk TNBC. The NSABP B-30 study suggested that sequential therapy with doxorubicin/cyclophosphamide followed by docetaxel (AC-T) showed a small but significantly improved disease-free survival compared to concurrent regimens [7]. While there is no large trial comparing epirubicin- versus doxorubicin-based regimens, 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by paclitaxel was superior to FEC alone in lymph-node positive disease and can also be considered an acceptable regimen for patients with moderate to high-risk triple negative disease [8]. Unfortunately, the addition of bevacizumab to adjuvant chemotherapy for TNBC did not improve disease-free survival and is not recommended [9].

The role of platinum salts in adjuvant therapy for TNBC

Early studies of cisplatin in breast cancer suggested a response rate >40% as a first-line agent in metastatic disease [10]. Platinum agents induce DNA crosslinking events and subsequent apoptosis leading to cell death, particularly in cells where DNA damage overwhelms existing DNA repair capacity due to mutated or downregulated DNA repair machinery [11]. Interest in platinum agents re-emerged over the past decade specifically in TNBC given evidence of DNA repair deficiency as well as data supporting their efficacy both pre-clinically and in patients [11,12]. The TNT trial, which prospectively randomized patients with metastatic TNBC to first line carboplatin versus docetaxel, showed similar overall response rates between the two arms supporting the use of platinums as a first-line agent in metastatic disease [13]. The study failed to demonstrate that the platinums were superior to docetaxel except in patients with BRCA alterations (discussed below). A non-randomized phase II trial of single-agent platinum in metastatic TNBC demonstrated a response rate of 25.6% across all patients, likewise demonstrating higher response rates in patients with BRCA mutation [14].

In the neoadjuvant setting, two prospective trials demonstrated improved rates of pathologic complete response (pCR) with the addition of a platinum agent to an anthracyline and a taxane. The GeparSixto trial by the German Breast Group evaluated neoadjuvant paclitaxel and liposomal doxorubicin with or without carboplatin [15]. The addition of carboplatin significantly increased the rate of pCR in patients with TNBC (53.2% vs. 36.9%, $p = 0.005$) [15]. A second study, CALGB/Alliance 40603, evaluated neoadjuvant paclitaxel followed by doxorubicin and cyclophosphamide with or without carboplatin [16]. As in GeparSixto, addition of carboplatin significantly increased the rate of pCR in the breast (60% vs 44%; $p = 0.0018$) [16]. The long-term outcomes from these recent studies are still pending.

While there are promising data regarding platinum agents in the neoadjuvant and to a lesser degree in the metastatic setting, it remains unclear how to incorporate platinum salts in the neoadjuvant or adjuvant setting outside of a clinical trial. There is no definitive study showing improvement in disease-free and/or overall survival using a platinum in either the neoadjuvant or adjuvant settings. If platinum is ultimately used, it is unclear if it should be added to standard therapy or substituted for one or more drugs. In addition, it is unclear whether all patients equally benefit or if a subset derives particular benefit. In CALGB 40603, the overall pCR breast rate based on microarray subtype did not differ between basal-like (170/314; 54%) and non-basal-like (24/46; 52%) cancers, although the numbers of non-basal-like were small [17]. Predictive biomarkers to identify TNBC with increased susceptibility to platinums, primarily by evaluating activity or deficiency of homologous recombination repair, are currently under investigation [18,19]. With these important remaining outstanding issues, platinums are not ready for routine use in the adjuvant setting.

Adjuvant therapy for specific TNBC subgroups

Early-stage triple-negative breast cancers

Overall, patients with small, node-negative TNBC do well. Two retrospective series demonstrated distant relapse-free survival (DRFS) rates of 90–93.7% at 5 years for untreated T1a/b, node-negative tumors [20,21]. In the setting of chemotherapy administration, the DRFS was 96–100%, however there are no randomized trials in patients with small tumors [21]. In these patients, as well as women who have T1cN0 tumors, four cycles of AC, four cycles of TC, or 6 cycles of traditional CMF are all reasonable regimens and are generally easier to tolerate that a sequential anthracycline-taxane approach. The US Oncology study suggested that docetaxel and cyclophosphamide (TC) may actually be superior to AC and has been widely adopted in the United States [22]. The result has not been confirmed by another trial and whether it is truly superior to AC is uncertain, but it is regimen that should be at least as effective as AC for the majority of patients [22]. CMF has been shown to be active in the triple negative setting, and although it is relatively lengthy (in terms of weeks), it is associated with lower degrees of short and long-term toxicity than the other regimens [23,24].

BRCA-mutant breast cancers

In individuals with an underlying germline BRCA1 mutation, approximately 70% of breast cancers that develop are triple negative and these tumors tend to be basal-like on expression profiling [25,26]. Because of underlying defects in DNA damage repair, BRCA-associated cancers tend to demonstrate genomic instability and appear to be susceptible to DNA-damaging agents, particularly those that induce DNA crosslinks [25]. In patients with metastatic BRCA-associated breast cancer, there are promising data on the activity of the PARP inhibitors [26–28]. In both the metastatic and the neoaduvant settings, there is developing data regarding activity of the platinum salts.

In the neoadjuvant setting, both retrospective and randomized studies suggest benefit with platinums in patients with underlying BRCA mutation. In a large series of women with BRCA-associated breast cancer receiving neoadjuvant chemotherapy, 61% of women with a BRCA1 mutation achieved pathologic complete response with 4 cycles of cisplatin alone [27]. Germline BRCA mutation, low BRCA1 mRNA espresson, and BRCA1 promoter methylation were all associated with a favorable response to four cycles of cisplatin [25]. In the Geparsixto trial, a neoadjuvant trial that randomized patients with triple negative disease to an anthracline and taxane or the same regimen plus carboplatin, the presence of a germline BRCA mutation (odds ratio 2.75) or a strong family history (OR 2.29) were both predictive of a greater benefit from carboplatin [28]. It is possible, however, that BRCA-associated disease is simply more sensitive to chemotherapy in general or, in particular, DNA-damaging chemotherapy. Investigators at MD Anderson reported a pathologic complete response rate of 47% in a group of patients with BRCA mutations who received anthracycline-based chemotherapy [29].

Results in the metastatic settings also suggest a role for the platinum salts in the management of BRCA-associated triple