The Breast xxx (2017) 1–4

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

De-escalating and escalating systemic therapy in triple negative breast cancer

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ARTICLE INFO

Article history:
Available online xxx

ABSTRACT

Triple negative breast cancer has the highest relapse risk of all the clinical subsets, although the escalation of chemotherapy has benefited this subset substantially over recent years. Systemic options are limited to chemotherapy, which makes meaningful de-escalation or escalation of therapy more challenging but possible. Observational cohorts suggest a less than 10% risk of relapse and minimal if any benefit of chemotherapy in very small (<1 cm), node-negative triple negative disease. In higher risk, particularly node-positive disease, anthracycline/taxane-based regimens remain standard. Neoadjuvant chemotherapy clearly de-escalates surgery, although there are insufficient data to give less than standard chemotherapy on the basis of response to neoadjuvant therapy. Efforts to meaningfully escalate therapy in high-risk disease have included incorporating platinums into Neoadjuvant therapy, with clear benefit in pCR but uncertain impact on relapse and survival at this time. Residual disease after neoadjuvant chemotherapy carries a particularly poor prognosis; a recent randomized trial of 6 months' capecitabine in this setting suggested a survival advantage to this approach in higher risk residual disease. While not validated at this time, future directions are likely to include biologic prognostication with tumor and immune variables, as well as targeted non-cytotoxic approaches leveraging the molecular heterogeneity of triple negative disease.

1. Introduction

Triple negative breast cancer is an important clinical entity, but it should be noted that it is a histologically, molecularly, and immunologically complex and heterogeneous entity [1]. Unlike hormone receptor-positive and HER2-positive breast cancer, evidence-based approaches to escalating and de-escalating therapy in early triple negative breast cancer are complicated by the paucity of treatment options outside of cytotoxic chemotherapy and the absence of predictive or prognostic biomarkers to tailor treatment. It is also true that decades of improvements in treatment of early breast cancer have resulted in substantial reductions in relapse risk in triple negative breast cancer. Among over 7000 women in a Canadian registry in which women with stage I-III breast cancer diagnosed between 1986 and 1992 were compared with an age-, stage-, grade-, and receptor-matched cohort diagnosed between 2004 and 2008, the hazard rate of relapse was approximately halved, with a marked impact on risk of early relapse in triple negative disease [2]. Within this backdrop of improved outcomes in triple negative disease, augmented understanding of the biology and heterogeneity within this clinical entity, and emerging approaches to tailoring therapy, it is worth examining the evidence supporting either minimizing (de-escalating) or augmenting (escalating) standards of systemic therapy.

2. De-escalating systemic therapy

Several approaches to de-escalating therapy have been tried, with variable results, including efforts to: a) identify triple negative subsets at sufficiently low clinical or molecular risk to make omission of adjuvant chemotherapy possible, b) employ the neoadjuvant paradigm to tailor treatment, and c) examine less toxic or aggressive (neo)adjuvant regimens.

2.1. Can chemotherapy be omitted in low risk triple negative subsets

Triple negative disease carries a poor prognosis with a relatively high risk of relapse, particularly within the first 5 years after

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http://dx.doi.org/10.1016/j.breast.2017.06.041
0960-9776/

diagnosis [2]. However clinical variables remain important in determining this risk. There are no randomized trials of chemotherapy versus no chemotherapy in low risk triple negative disease, however among over 300 patients with T1a-bN0 systemically untreated triple negative cancer, the 5-year risk of distant relapse was less than 10%, a commonly used cutpoint for adjuvant chemotherapy, similar to outcomes in women with similar stage triple negative disease who received chemotherapy [3–5]. The largest study derived from the National Comprehensive Cancer Network database. Among T1aN0 patients with triple negative disease, the untreated cohort of 74 patients had distant relapse-free survival (DRFS) of 93% (84–97%), the chemotherapy-treated cohort of 170 treated patients had DRFS 100%, whereas similar estimates among T1bN0 tumors included 94 untreated patients with DRFS 90% (81–95%) and 25 chemotherapy-treated patients with DRFS 96% (90–98%) [5]. These studies suggest that triple negative tumors no greater than 1 cm in size and node-negative have a good prognosis, and omission of chemotherapy may be considered, although a small benefit of chemotherapy cannot be excluded.

It would be helpful if molecular or biologic features of the tumor could be used to further identify those with higher clinical risk but low genomic risk also appropriate for omission of chemotherapy. Genomic prognostic signatures have primarily been studied in early hormone receptor-positive, HER2-negative breast cancer. Triple negative breast cancer was included in the MINDACT trial, which included tumors of any receptor phenotype and demonstrated excellent distant metastasis-free survival among clinical high risk but genomically low risk tumors. However that cohort was largely hormone receptor-positive, with only 1% triple negative disease, and the other discordant cohort of low clinical risk and high genomic risk, who also had excellent outcomes, had only 9% triple negative tumors [6]. For this reason, the level 1 evidence supporting use of the 70-gene signature in treatment decisions cannot be generalized to triple negative disease. Another promising biomarker avenue comes from data suggesting that immune activated and lymphocytically infiltrated subsets of triple negative breast cancer have better outcomes [7,8]. Most of the data examining tumor infiltrating lymphocytes (TILs) have been in treated cohorts, making it impossible to ascertain if the improved outcome reflects natural history (prognosis) or augmented sensitivity to chemotherapy (prediction). However TILs have been examined in two French randomized phase III trials testing anthracycline-based chemotherapy versus no chemotherapy, which found that TILs were prognostic but not predictive of chemotherapy benefit [9]. If validated, this may provide a mechanism to identify a biologically low risk subset in whom chemotherapy may be entirely omitted.

2.2. Neoadjuvant chemotherapy

Administering chemotherapy to early breast cancer preoperatively has many advantages and a few disadvantages. The advantages include the impact of cytoreduction on minimized surgery on both the breast and in the axilla. The disadvantages include reliance upon clinical staging, which means that it may not be optimal for very small, node-negative breast cancers of any subtype, since, as described above, it is possible that these patients may have low enough risk to omit chemotherapy altogether. This would require clearly defined pathologic staging; since it is unlikely that a stage I tumor would benefit in terms of minimized surgery, treating these tumors postoperatively may be optimal.

In addition to minimizing surgery in stage II and larger tumors, neoadjuvant chemotherapy has the advantage of providing a valuable intermediate biomarker of prognosis. Pathologic complete response (pCR) to neoadjuvant chemotherapy is clearly and consistently associated with improved event-free and overall survival [10], a relationship that is the reason that the Federal Drug Administration (FDA) endorsed pCR as an endpoint in registrational drug trials in triple negative and HER2-positive breast cancer [11]. While pCR is an excellent endpoint in clinical trials examining novel drugs or regimens, it is unproven in minimizing or de-escalating standard therapy. This is because while pCR is strongly associated with decreased risk of relapse and death from breast cancer, on the individual level the association is inadequate to make therapeutic decisions. In the triple negative trial participants examined in the CTNeoBC pooled analysis performed by the FDA and participating investigators, those with pCR had 66% lower likelihood of relapse or death than those with residual disease [10]. However, within those with pCR, by 5 years 15–20% had suffered an event, while approximately 50% of those with residual disease had not. No data currently exist suggesting that one may safely treat to pCR then omit the remainder of standard therapy.

2.3. Anthracyclines

A key target of anthracyclines is topoisomerase II alpha, which is part of the HER2 amplicon. Retrospective analyses of anthracycline- versus older non anthracycline-based adjuvant regimens suggested that the benefit of anthracyclines was driven by the HER2-positive subset [12,13]. If so, then one opportunity for de-escalating therapy in triple negative disease would be to omit anthracyclines. The hypothesis that triple negative breast cancer does not benefit from anthracyclines was tested in part in the prospective ABC trials, a joint analysis of three trials with similar objectives, namely to test six cycles of docetaxel plus cyclophosphamide against various anthracycline- and taxane-based regimens (TaxAC) in patients with early HER2-negative disease [14]. Designed as a noninferiority trial, the primary result was in favor of the anthracycline arm, and subset analysis suggested that the triple negative cohort, which comprised 1301 of the approximately 4000 trial participants, benefited from the TaxAC regimens with a HR for invasive DFS of 1.42. In exploratory analyses, the benefit was particularly notable among node-positive triple negative breast cancer patients.

Another recent trial, the Danish Breast Cancer Group 07-READ Trial, presented at the San Antonio Breast Cancer Symposium, ostensibly compared an anthracycline- and taxane-based regimen to DC, however the trial was far smaller, with subsets categorized by ER-negative or borderline versus more strongly positive, and randomization limited to topoisomerase II-negative tumors [15], so contributes minimally to the question posed here. Based on the more directly relevant ABC trials, it is premature to omit anthracyclines from triple negative breast cancer, although a non-anthracycline regimen may be considered for lower risk node-negative disease.

3. Escalating systemic therapy

Triple negative breast cancer has benefited at least as any clinical breast cancer subset from the improvements in adjuvant chemotherapy regimens over the past two decades, however it remains the poorest prognosis group. Efforts to improve outcomes further have come in several arenas: a) the incorporation of platinum agents into (neo)adjuvant therapy, and b) additional cytotoxic therapy after completion of standard treatments, particularly in residual disease after neoadjuvant chemotherapy.

3.1. Platinum agents in early breast cancer regimens

Consideration of the role of platinating agents in triple negative breast cancer treatment is based on the similarities between basal-like breast cancer, which makes up the majority of triple negative

Please cite this article in press as: Carey LA, De-escalating and escalating systemic therapy in triple negative breast cancer, The Breast (2017), http://dx.doi.org/10.1016/j.breast.2017.06.041