Concurrent Chemo-radiation As a Means of Achieving Pathologic Complete Response in Triple Negative Breast Cancer

Maryam Nemati Shafaee, 1 Shalini Makawita, 2 Bora Lim, 1 Matthew J Ellis, 1,3 Michelle S Ludwig 4

Abstract

Management of triple negative breast cancer (TNBC) that is resistant to chemotherapy remains a challenge. Many studies have investigated the unconventional approach of concurrent chemotherapy with radiation in management of TNBC that is resistant to neoadjuvant anthracycline and taxane containing chemotherapy. Various chemotherapies have been used as radiosensitizers. In this report we summarize the published literature and highlight clinical trials that pertain to management of TNBC.

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Keywords: Concurrent Chemo-radiation, Triple negative breast cancer, Pathologic complete response, Primary resistant TNBC

Introduction

Pathologic complete response (pCR) post neoadjuvant therapy in breast cancer is associated with improved overall survival (OS), and disease-free survival (DFS).1,3 While varying definitions of pCR exist, three most commonly used definitions across clinical trials are ypT0 ypN0, ypT0/is ypN0, and ypT0/is.4 While pCR is not validated as a surrogate for the endpoints of long-term outcomes, eg DFS and OS, it does provide valuable prognostic information especially in aggressive subtypes of breast cancer.4,9 For patients with triple negative breast cancer (TNBC), presence of residual disease post neoadjuvant chemotherapy is associated with a higher risk of recurrence and death compared to other subtypes.7,9 Achieving pCR is associated with excellent prognosis in this tumor subtype and is therefore a much-desired outcome of neoadjuvant therapy.10

Epidemiologically, TNBCs have an earlier age of onset, a higher rate of local relapse as well as visceral metastases, and disproportionately affect women of African heritage, as well as patients with BRCA1 and BRCA2 germline mutations. Based on genomic profiling of 587 TNBC, Lehmann et al sub-classified TNBC into 6 distinct subtypes; basal like 1 (BL1), basal like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem like (MSL), and luminal androgen receptor (LAR) type, showing that this is a heterogeneous disease with distinct molecular players.11 PAM50, another clinically recognized tool for molecular profiling, divides breast cancer into 5 groups. These include luminal A, luminal B, Her2 overexpression, normal, and basal like.12 Over 86% of TNBCs are identified as basal like based on this classification, which includes all of BL1, BL2 as well as majority of M and MSL TNBCs.13 Basal Like TNBC based on intrinsic PAM50 breast cancer classification is characterized by enrichment of genes involved in proliferation, DNA damage response and cell cycle checkpoint.14 This group shares many features with BRCA1-mutated tumors, including basal-like gene expression profile, frequent p53 mutations, and a high burden of genomic aberrations such as loss of heterozygosity.16 Impairment of BRCA1 pathway through loss of heterozygosity and homologous recombination (HR) failure results in impaired repair of double-strand DNA break (DSB). This deficiency renders tumors susceptible to genomic instability, and consequently, sensitive to DNA crosslinking agents such as platinum salts.17 Predictably, adding carboplatin to neoadjuvant chemotherapy in TNBC is associated with increased likelihood of achieving pCR.18 GeparSixo19 and CALGB 4060320 were two adequately powered studies that demonstrated statistically significant improvement in pCR with the addition of carboplatin to neoadjuvant chemotherapy in stage II or III TNBC, resulting in carboplatin becoming a standard of care choice.21 However, whether the improved pCR with carboplatin translates into meaningful better survival remains controversial.22 Practically the only clinically meaningful distinction within TNBCs are between tumors that are associated with a germline BRCA mutation and those that are not because the indications for a PARP inhibitor are largely restricted to patients...
with inherited cancer syndromes. Results from a recent phase II trial evaluating efficacy of single agent PARP inhibitor talazoparib in neoadjuvant setting among patients with operable breast cancer and germline BRCA ½ mutation reported pCR rate of 53% and manageable toxicity profile.29

Across different tumor types, concurrent chemoradiation is a widely applied method for improving local response but this dual modality therapy has not been widely adopted in management of breast cancer. Ionizing radiation is established to induce DSB as a major mode of action.24 Cells are most radiosensitive during the G2 and M phases of the cell cycle. Rapidly proliferating cancer cells are most susceptible to radiation induced cell death due to inefficient DNA repair. Concurrent chemotherapy with radiation can improve pCR by destroying radio-resistant clones of cancer cells with chemotherapy acting as a radio-sensitizer. Agents that favorably improve pCR rate when added to radiation include platinums, fluoropyrimidines, and taxanes.25 Several studies have investigated the endpoint of pCR post concurrent chemoradiation in breast cancer (Figure 1.) and findings pertinent to TNBC are highlighted in this review.

**Platinums with Concurrent Radiation**

Platinums with concurrent radiation are used with curative intent in the treatment of several highly aggressive tumor types, such as oropharyngeal, cervical, and lung cancer.25 Combination cisplatin and 5-fluorouracil with concurrent radiation in non-metastatic inflammatory breast cancer (IBC) has been demonstrated to be safe, and results in improved surgical outcomes and local / systemic control in this particularly aggressive form of breast cancer.26 After entry into cells, platinums forms soluble chloride complexes which form DNA platinum adducts causing denaturation of DNA.27 Combination of cisplatin with radiation is attractive because this platinum agent attaches onto DNA or RNA close to a radiation-induced single-strand break and acts synergistically in making the defect significantly more difficult to repair, inducing apoptosis.

Platinum chemotherapy has shown efficacy in neoadjuvant setting in one trial with BRCA1-positive patients and two clinical trials with non-BRCA1/2-mutated TNBC (Table 1). All three of these studies evaluated pCR as their evaluable end point, and reported on clinical response rate, either complete (CCR) or partial (CPR). In the study by Byrski et al.,28 conducted in Poland, 9 patients with stages I-III TNBC, and one patient with unknown tumor markers, all with BRCA1 mutation received neoadjuvant cisplatin followed by mastectomy and axillary LN dissection. Seven patients received 4 cycles of therapy, and three received 2 doses. Rate of pCR was reported at 90%. One patient that did not achieve pCR had residual disease in 3 of 11 axillary lymph nodes but no residual disease in the breast. Only one patient stopped therapy after 2 doses due to side effect, reported as severe nausea and vomiting.

In 2010, Silver et al.,29 published a neoadjuvant trial of cisplatin in 28 treatment naive patients with stage II or III TNBC (2 patients with BRCA germline mutations; 26 without) where patients received 4 cycles of cisplatin prior to definitive surgery. 6 (22%) of their patients had pCR, which included the two BRCA+ patients. Favorable response to cisplatin was significantly associated with low BRCA1 mRNA expression, young age, BRCA1 promoter methylation, E2F3 gene expression signature activation and p53 nonsense/frameshift mutations (P < .05 in all cases). Overall, fifty percent showed Miller-Payne class 3-5 pathological responses; 36% showed minor responses (Miller-Payne class 1-2) and four (14%) patients progressed.

In a related study, Ryan et al.30 assessed the efficacy of adding Bevacizumab to cisplatin in the treatment of TNBC. 51 patients with confirmed TNBC (median age of 50 and 80% with clinically T2 disease) had been enrolled in a single arm phase II trial with four cycles of neoadjuvant cisplatin and three cycles of bevacizumab prior to definitive surgery. 5 patients were unable to complete neoadjuvant treatment due to adverse effects. Of the remaining 46 patients, at the time of their report, 15% of patients were found to have pCR (Miller-Payne 5) and 22% with Miller-Payne 5 response. Post operatively, these patients received doxorubicin and cytoxan (AC) plus bevacizumab or AC/Taxol plus bevacizumab. CCR was reported in 26% of patients. Evaluation of postoperative complications by the same group showed no significant difference in complications with cisplatin alone or cisplatin/bevacizumab in a single arm study.31

In the study by Isakov et al.,32 the authors report an overall response rate of 25.6% to platinum therapy with cisplatin or carboplatin in locally advanced or metastatic TNBC patients who had previously been treated with an anthracycline or taxane. The best responders were noted to be those with germline BRCA1/2 mutations. In patients lacking BRCA germline mutations, the
The authors found tumor specific genomic instability patterns characteristic of BRCA1/2 deficiency to be associated with responders to platinum-based therapy. Unlike single agent platinum trials, the data on concurrent radiation with a platinum is very limited. For example, a retrospective analysis of 30 patients based on a single institution experience has recently been published. These patients had disease resistant to neoadjuvant anthracycline and/or taxane and underwent a number of salvage therapies; 2 received additional chemotherapy, 3 received radiation, 13 had upfront surgery, and 12 underwent concurrent weekly cisplatin and radiation for 5 weeks. 24 patients underwent surgery and one patient was found to have pCR. The investigators do not comment on the salvage therapy that was used on the patient with pCR, however, they do report strong correlation between improved disease-free survival (DFS) at 3 years in TNBC in patients who received salvage therapy with concurrent cisplatin radiation. It is important to note that numbers are too small to support any definitive recommendations for concurrent cisplatin radiation for treatment of locally advanced TNBC post failure of neoadjuvant chemotherapy based on this study, given that only 12 patients were treated with this regimen, with only 6 or 7 with TNBC.

**Fluoropyrimidines with Concurrent Radiation**

Fluoropyrimidines such as 5-fluorouracil (5-FU) and capecitabine exert their antineoplastic effects through several mechanisms including inhibition of thymidylate synthase and incorporation into DNA with resultant DNA with resultant DNA damage and cell death. These drugs need to be converted to their active metabolite by thymidine phosphorylase (TP) which is preferentially expressed in tumor cells. Ionizing radiation upregulates TP which synergistically improves the therapeutic index of these agents.

Kosma et al. evaluated radiation with bolus 5-FU in woman with locally advanced or metastatic breast cancer who had progressed on prior chemotherapy and hormonal therapy. The study reported 29% rate of CCR. In the 5 patients with CCR, 3 underwent surgery which was significant for pCR in the breast and axilla. The study does not report on the hormonal status of the tumors, however given that all patient had previously received hormone therapy, it is fair to assume that all participants had hormone receptor positive disease.

Bollet et al. evaluated the safety and efficacy of 5-FU (bolus plus continuous infusion) and vinorelbine every 3 weeks for 4 cycles with concurrent radiation as pre-operative therapy in locally advanced breast cancers (LABC) on a phase II design. Triple negative status was not evaluated. The rate of dose limiting toxicity was 7%, grade 4 neutropenia reported in 20% of patients, while 53 (90%) of patients completed the scheduled therapy. 12 patients (20%) had CCR and sixteen patients (27%) had pCR.

In a Brazil-based Phase II study, Gauj et al. studied the efficacy of neoadjuvant chemotherapy with capecitabine 850mg/m^2^ 2 times a day for 14 days in a three-week cycle in combination with radiation therapy (50 cGy) for patients who fail neoadjuvant anthracycline-based chemotherapy. Of 28 patients in the study, five patients were not amenable to surgery due to disease progression and 23 (82%) underwent surgery. In this subset, one patient achieved complete pathologic response and 3 (13%) had only residual microscopic disease (<1cm). 19 (82%) of patients had residual tumor >1cm in resected specimen. The authors concluded capecitabine in combination with radiation to be a safe and viable option as a secondary neoadjuvant therapy in LABC; however, sample size is lacking.

Woodward et al. evaluated concurrent preoperative radiotherapy and capecitabine 825 mg/m^2^ twice daily 5 days a week on radiation treatment days in patients with residual nodal disease, unresectable chest wall disease, nodal recurrence after prior mastectomy, or oligometastatic disease. In this MD Anderson phase II trial, 10 of the 26 patients who were enrolled and completed trial had TNBC. 19 patients (73%) had a partial or complete response however, the trial was stopped due to slow accrual which prompted an unplanned interim analysis and was subsequently closed due to futility. In 9 out of the 10 patients with TNBC, metastatic disease was diagnosed immediately post-op.
Table 2  Neoadjuvant Concurrent Chemo-XRT in Breast Cancer

<table>
<thead>
<tr>
<th>Author, Y</th>
<th>Pt n</th>
<th>Tumor Markers</th>
<th>Stage</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kosma et al. 1997</td>
<td>17</td>
<td>No indicated – but all patients were previously treated with hormone therapy</td>
<td>Locally advanced or Stage IV</td>
<td>5-FU 500 mg/m² BIW + 75-90 Gy</td>
<td>5/15 pCR</td>
</tr>
<tr>
<td>Skinner et al. 2000</td>
<td>28</td>
<td>Not indicated</td>
<td>IIB, IIIA and IIB</td>
<td>Paclitaxel 30 mg/m² BIW x 8 w + 45 Gy</td>
<td>7 (26%) pCR</td>
</tr>
<tr>
<td>Formenti et al. 2003</td>
<td>44</td>
<td>Not indicated</td>
<td>IIB, IIIA and IIB</td>
<td>Paclitaxel 30 mg/m² Bi weekly x 8 - 10 W + 45 Gy at 1.8 Gy/fraction to breast and nodal basin</td>
<td>Clinical Response 91%, 7/44 pCR, 8/44 Partial path response, 28/44 no response</td>
</tr>
<tr>
<td>Kao, et al. 2005</td>
<td>33</td>
<td>30% ER+, 6% PR+, 55% ER-/PR-, 9% unknown</td>
<td>IIIB, IIIC, IV</td>
<td>Bolus vinorelbine 20 mg/m² + CI 20-30 mg/m² CI x 4 days + 60 Gy</td>
<td>pCR 7/15</td>
</tr>
<tr>
<td>Boillet, et al. 2006</td>
<td>60</td>
<td>Her2+ 14%, ER+ and/or PR+ 70%, ER/PR- 27%</td>
<td>IIA, IIB and IIIA</td>
<td>5-FU CI 500 mg/m²²/d (d1–d5) + vinorelbine 25 mg/m²² (d1; d6), w C62 50 Gy primary + 46 Gy to IM, supra/infra-clavicular LN</td>
<td>12/60 CCR, 20/60 (34%) CPR 17/16 (29%) SD 2/60 POD, 16/60 pCR 27%, surg 69%</td>
</tr>
<tr>
<td>Chakravarthy et al. 2006</td>
<td>38</td>
<td>42% ER+, 34% PR+, 34% HER2+</td>
<td>IIA, IIB, IIIA, IIB</td>
<td>Paclitaxel 30 mg/m² BIW + 45 Gy + 14 Gy</td>
<td>pCR in 13/38 (34%)</td>
</tr>
<tr>
<td>Gau, et al. 2007</td>
<td>28</td>
<td>25% ER+/PR+, 14% ER+ only; 18% PR+ only; 43% ER-/PR-</td>
<td>IIB, IIIA, IIID</td>
<td>Capecitabine 850 mg/m² bid x14 d + 50 Gy</td>
<td>pCR in 1/28; 82% became operable</td>
</tr>
<tr>
<td>Alvarado-Miranda, 2009</td>
<td>112</td>
<td>43% ER+, 2% Her2 Positive</td>
<td>IIB, IIIA and IIIB</td>
<td>FAC or AC Q 3w x 4 w + 60 Gy + EITHER mitotycin 5 mg/m² + 5-FU 500 mg/m² + Dex 16 mg, OR cisplatin 30 mg/m² + gemcitabine 100 mg/m² + dex 16 mg weekly → Taxane or Anthraclyline adjuvant chemotherapy</td>
<td>pCR in both breast and Axilla: 30% 1/121 recurrent dz 5 y OS: 84.2%</td>
</tr>
<tr>
<td>Adams et al. 2010</td>
<td>105</td>
<td>52% ER+, 39% PR+, 32% HER2+</td>
<td>II, III. One pt missing staging info.</td>
<td>Paclitaxel 30 mg/m² BIW + 45 G + 14 Gy</td>
<td>pCR in 34%</td>
</tr>
<tr>
<td>Shaughnessy, et al. 2015</td>
<td>20</td>
<td>60% ER+, 30% PR+, 20% HER2+ , 23% TNBC.</td>
<td>≥ IIIA (9 patients nonmetastatic; 11 metastatic)</td>
<td>12 Capecitabine, 6 paclitaxel, 2 cisplatin/etoposide + 45Gy</td>
<td>½ pCR (no surgery for the remaining 16)</td>
</tr>
<tr>
<td>Raphael et al. 2017</td>
<td>12</td>
<td>57% TNBC, 23% ER+, 20% ER/PR+</td>
<td>III and III</td>
<td>cisplatin 25 mg/m² weekly + daily radiation x 5 w</td>
<td>Improved 3 y DFS in TNBC</td>
</tr>
<tr>
<td>Woodward et al. 2017</td>
<td>32</td>
<td>38% TNBC, 61% other</td>
<td>50% with residual nodal disease, 15% unresectable chest wall or nodal recurrence, 15% pre-op, 19% stage IV</td>
<td>Capecitabine 825 mg/m² bid for 5 days per week with radiation, total 50–57 Gy</td>
<td>26 patients evaluable, CR 8%, PR 65% 9 of 10 patients with TNBC had M1 disease immediately post-op, versus 6 of 16 other</td>
</tr>
<tr>
<td>Brackstone et al. 2017</td>
<td>32</td>
<td>33% luminal A, 37% luminal B, 11% Her2+, 19% Basal</td>
<td>Any T3 or T4 or any N2 or N3</td>
<td>5-FU 500 mg/m², epirubicin 100 mg/m², and cyclophosphamide 500 mg/m² every-3-weekly x 3 cycles, then docetaxel 35 mg/m² IV weekly x 9 cycles, then weekly docetaxel 35 mg/m² with 45 Gy/25 fractions ± 5.4 Gy/3 fractions or 9 Gy/5 fractions boost for gross residual disease</td>
<td>pCR 22.6% vs 14.9% in the control cohort 30 patients completed surgery</td>
</tr>
</tbody>
</table>
**Taxanes with Concurrent Radiation**

Taxanes are known radiosensitizers. Taxanes are microtubule-stabilizing agents, prolonging the G2/M phase of the cell cycle, hence arresting cells in a radiosensitive state. 40

Formenti et al. 41 evaluated the role of concurrent paclitaxel radiation in LABC. Treatment naïve patients with LABC received biweekly paclitaxel at 30 mg/m2 for total of 8 weeks with concurrent radiation to the breast and nodal basin. Forty (90%) of patients completed this therapy and no grade 4 toxicities were reported. Seven (14%) had pCR and 8 patients (18%) had partial pathologic response, defined as < 10 microscopic foci of invasive disease. Although in this paper the investigators do not discuss tumor biomarker status with regards to pCR rate, in a separate report of the same patients’ specimens, they correlate higher pCR rates with ER negativity and low Her-2 expression. 42

In a study by Kao et al. 43 the use of chemotherapy with paclitaxel +/- vinorelbine in combination with radiation therapy (60-70Gy) in a week on/week off fashion was assessed in two consecutive Phase I/II trials in stage IIIB-C and IV disease. Patients with prior nitrosourea, mitomycin, high dose chemotherapy or prior chest wall or ipsilateral radiation therapy were excluded from the trial. Sixteen patients were noted to have stage IIIB-C disease and six out of thirteen of those patients who had undergone surgical resection had shown a complete pathological response. One additional patient had a complete response with a shorter course of chemo-radiation (treatment interrupted due to emergent cardiac procedure). Disease free survival (DFS) was noted in 40% (SE, +/- 12.7%) and 33% (SE, +/- 12.2%) at 2 and 4 years, respectively. The most commonly associated toxicities were moist desquamation (50%) and grade 3-4 neutropenia (19%).

Skinner et al. 44 published report evaluates 28 patients who were chemotherapy naïve and had LABC. Patients were treated with biweekly paclitaxel and concurrent radiation for total of 8 weeks and reported 26% pCR. Treatment was generally well tolerated however, postsurgical complications such as flap necrosis and noninfectious mastitis likely due to radiation recall were reported. Tumor biomarker status of these patients were not included in this report.

Chakravarty et al. 45 studied the safety of neoadjuvant paclitaxel followed by concurrent paclitaxel and radiation. Of 38 patients enrolled, 30 patients began concurrent chemo-radiation and 28 completed it. 13 patients (of the total 38; 34%) achieved a complete pathological response. Median survival was noted to be 22.5 months from time of diagnosis. The authors also evaluated several biological markers (HER2, ER, PR, Ki-67, TUNEL and mitotic index) for their potential as markers to predict response to the above treatment regime. While no significant differences were noted in immunohistochemical markers, a higher baseline mitotic index as well as higher mitotic index post paclitaxel therapy was associated with pCR.

Adams et al. 46 studied DFS and overall survival (OS) within the context of pathologic response in 105 LABC patients who were treated with paclitaxel (30mg/m2 twice weekly; total 10-12weeks) in combination with daily radiation treatment during weeks 2-7 of paclitaxel (total 45Gy; boost of 14Gy) to breast, axilla and supraclavicular lymphadenopathy. 36 patients (34%) achieved pCR or pathologic partial response (<10 microscopic foci of invasive cancer).

This included 10 of 57 (18% hormone receptor positive patients) and 26 of 48 (54% hormone receptor negative patients). Of 24 TNBC patients included in the study, 13 (54%) achieved pCR. Overall, those with pathological response (complete or partial) had a decreased risk of recurrence or death (HR = 0.35, P =.01) and a longer OS (HR = 4.27, P = .01).

Alvarado-Miranda et al. 47 evaluated the role of concurrent radiation with either mitomycin and 5-fluorouracil or cisplatin and gemcitabine on pCR with both arms containing dexamethasone. Patients in this trial had infiltrating ductal carcinoma (IDC) stages IIIB, IIIA or IIB at diagnosis. They all received neoadjuvant anthracycline containing regimen before proceeding to concurrent radiation chemotherapy. Tumor biomarker status of these patients is not completely clear, but the study reports that 43% had ER positive disease. Triple negative status was not clarified; however a 2% rate of HER2 positivity was noted. Given the incidence of ER negative/PR positive breast cancer is <2%, 48 one can assume that >50% of patients had TNBC. They report a 30% pCR in both breast and axilla with this approach. However, neither clinical response to neoadjuvant therapy nor comparison of pCR between the two cohorts of chemotherapy radiation arms is included in this paper which questions the applicability and interpretation of their findings.

Shaughnessy et al. 49 studied the efficacy and safety of concurrent chemo-radiation in locally recurrent or advanced inoperable breast cancer through a review of prospectively collected data between 2009-2013. 20 patients (9 with primary disease and 11 with recurrent disease; 11 with metastatic disease) were reviewed in total who received either capecitabine, paclitaxel or cisplatin/etoposide chemotherapy with concurrent external beam radiotherapy to primary breast tumor and/or regional lymph nodes. CCR was noted in 65% of patients and CPR in 35%. 2-year OS was 80% and local DFS was 73%. Local control was noted to be better in those without prior infeld radiation and treatment naive.

Brackstone et al. 50 conducted a phase II trial whereby 32 patients with noninflammatory LABC were enrolled to receive 3 cycles of neoadjuvant FEC chemotherapy (5-FU, epirubicin and cyclophosphamide every 3 weeks), followed by docetaxel 35 mg/m2 weekly concurrent with radiation for 6 cycles, then 3 additional cycles of docetaxel weekly. 5 weeks after treatment completion patients underwent modified radical mastectomy. 5 patients had basal subtype. For statistical analysis the investigators matched 27 of the participants with 81 controls and reported improved pCR rate in the concurrent chemoradiation 22.6% vs. 14.9% (P=.19) in the controls. The result does not include the pCR rate among the 5 basal subtypes. Additionally, the controls did not receive exactly the same chemotherapy as the study participants.

**Discussion**

While there are anecdotal reports on use of concurrent chemoradiation in breast cancer as a means of achieving pCR, rigorous studies remain scant. Majority of studies have recruited small number of patients, the biomarker status of tumors is not consistently reported, the definition of pCR is not uniform across different studies, neither are the chemotherapy and radiation regimens. All this makes it difficult to draw conclusive statements in support...
Concurrent Chemo-radiation As a Means of Achieving

of this modality. Logically if this approach is used in the setting of chemotherapy resistant disease, the tumors that are most likely to respond, ie, those with homologous recombination deficiency (HRD), have been selected against. A major weakness in the field is our lack of understanding of the nature of chemotherapy resistance. The pivotal CREATE-x trial reported improved DFS and OS with adjuvant capecitabine for patients with TNBC and residual disease post neoadjuvant chemotherapy. In the TNBC cohort, a DFS of 69.8% vs 56.1% in the adjuvant capecitabine vs no adjuvant therapy arms and OS of 78.8% vs 70.3% (HR death 0.52; 95% CI 0.30-0.90) respectively were noted at 5 years of follow up. While adjuvant capecitabine provides a therapy option, the number needed to treat is 11.8, and the prognosis of patients with significant residual disease post neoadjuvant chemotherapy remains poor. On July 26, 2021, the Food and Drug Administration (FDA) approved pembrolizumab in node positive or tumor size ≥2 cm TNBC regardless of the PDL-1 expression. Neoadjuvant immunotherapy with pembrolizumab resulted in at least 7% absolute improvement in pCR rate in the intention to treat arm. While these results are encouraging, moderate and extensive residual cancer burden (RCB II-III) are poor prognostic indicators necessitating individualized precision-driven therapies. There are several studies evaluating preoperative radiation therapy as outlined elsewhere. The review by Pesch et al includes ongoing trials of concurrent radiation and radiation response modulators including PAPR inhibitors and immunotherapy that are not the subject of our manuscript. Recent phase II trials evaluating preoperative dual modality chemoradiation therapy for patients with TNBC are included in Table 3. PANDoRa trial (Clinical Trials Identifier: NCT03872505) was recently withdrawn due to lack of funding, NeoAPBI 01 is the only active trials recruiting patients with early stage TNBC with the endpoint of pCR (NCT02806258). This is a phase II randomized trial designed to evaluate 6-8 cycles of primary systemic therapy with anthracycline and/or taxane-based regimen versus primary systemic therapy followed by sequential partial breast 3D-conformal RT with 25 Gy in 10 fractions twice daily over 5 days or 25 Gr in 8 fractions daily in patients with intermediate/high risk luminal and TNBC. The study results are not reported yet. Concurrent cisplatin radiation in locally recurrent or metastatic TNBC is evaluated in an actively enrolling trial, NCT02422498, open at several Memorial Sloan Kettering centers in New York and New Jersey. The endpoint in this trial is objective response rate based on RECISTs 1.1 criteria.

It is unclear whether the pCR achieved with concurrent chemoradiation carries the same prognostic value as the pCR achieved with neoadjuvant chemotherapy alone. In the study by Brackstone et al. while the pCR rate was statistically improved in the concurrent docetaxel radiation cohort, their disease-free survival and overall survival were not significantly different from the control. In the MD Anderson phase II trial by Woodward et al, 9 of the 10 patients with TNBC were diagnosed with metastatic disease in the immediate post op period. In these patients, while concurrent chemoradiation resulted in reduction in local tumor burden, rendering surgical resection feasible, metastatic disease developed rapidly, suggesting that local control achieved by concurrent chemoradiation in TNBC is not a reliable predictor of systemic control. Additionally early identification of patients with resistant disease who may derive benefit from concurrent chemo-radiation remains a challenge. Several genomic biomarkers have been developed with the intention of guiding personalized radiation dosing and intensification that may have future implications in management of resistant TNBC. Adjuvant Radiotherapy Intensification Classifier (ARTIC) which combines patients age and expression of 27 genes is both prognostic of local recurrence, and predictive of benefit from radiation. ARTIC validation cohort however, included patients with stages I-IIA breast cancer and 81% with ER+ disease. Genomic-adjusted radiation dose (GARD) is a radiation sensitivity metric which uses gene-expression-based radiation-sensitivity index and the linear quadratic model to produce GARD values, which could allow for radiation dose personalization. GARD is found to be predictive of clinical outcomes in breast cancer, and specifically of local control in two cohorts of TNBC. GARD’s prognostic potential, however, remains unclear. Genomically-guided radiation-based clinical trials are needed to establish the best use of these metrics.

Various pre- and post-treatment predictors of relapse are suggested, including proliferative marker ki67, nodal status and circulating tumor cells (CTCs). Intact tumor cells in the circulation can serve as liquid biomarkers. Recent studies have shown its use as a prognostic biomarker in the neoadjuvant and adjuvant settings. CTCs have been detected in approximately 20-25% of women with non-metastatic breast cancer and have been associated with higher histological grade, larger tumor size, HER2 amplification and involvement of lymph nodes. A meta-analysis of 21 studies assessed the utility of CTCs as a prognostic marker in patients with early-stage breast cancer treated with neoadjuvant chemotherapy. Samples from 1574 (n = 405, TNBC) patients prior to neoadjuvant chemotherapy and 1200 (n = 296, TNBC) patients prior to surgery had been analyzed. Approximately 25% of patients had detectable (≥ 1) CTCs prior to neoadjuvant chemotherapy which was significantly associated with tumor size (P < .001). The authors found that the number of CTCs was associated with worse OS, distant DFS and local relapse. A significant difference was noted in pCR rates between those without CTCs detected compared to those with; however no significant association was noted between increasing number of CTCs and pCR rate, or with pCR rate and detection of CTCs prior to neoadjuvant therapy or preoperatively. No statistical difference was noted between receptor status and detection of CTCs; however, the addition of baseline CTC counts to models with clinicopathological data increased prognostic value for post-neoadjuvant survival. The prognostic relevance of CTCs in early-stage breast cancer is supported by similar patterns of results from several other studies as well as its utility in adjuvant therapy and predicting benefit for comprehensive nodal irradiation. In this context, the value of CTCs as a biomarker for treatment intensification may be worth exploring.

Toxicity of concurrent chemoradiation, which varies with the choice of the radiosensitizer, is an additional concern. In the study by Brackstone et al. one death was reported in the trial cohort as a result of pneumonitis and acute respiratory distress syndrome.
Table 3  Pre-Operative Chemo-Radiation Trials in TNBC

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Phase</th>
<th>Patient Group</th>
<th>Name of Agent</th>
<th>Radiation Regimen</th>
<th>Patient Number</th>
<th>Trial Status</th>
<th>Primary Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03872505</td>
<td>A randomized phase II study evaluating pathologic response rates</td>
<td>Phase II</td>
<td>Stage II-III TNBC</td>
<td>Durvalumab with carboplatin and paclitaxel</td>
<td>The second dose of durvalumab will be given in conjunction with an RT boost, consisting of 8 Gy in 3 fractions for a total of 24 Gy</td>
<td>140</td>
<td>Withdrawn due to lack of funding</td>
<td>pCR rate</td>
</tr>
<tr>
<td>NCT02806258</td>
<td>Comparing Sequential Neoadjuvant Treatment Including Chemo and Radiation</td>
<td>Phase I&amp;II</td>
<td>Stage II-III Intermediate and High-risk Luminal or TNBC</td>
<td>minimum of six cycles of anthracycline and/or taxane based regimens</td>
<td>Accelerated partial breast irradiation will be planned sequentially between the primary systemic therapy cycles, 2 weeks after the 3rd/6 or the 4th/8 cycle of primary systemic therapy</td>
<td>362</td>
<td>Recruiting</td>
<td>pCR rate</td>
</tr>
<tr>
<td>NCT02422498</td>
<td>Homologous Recombination Repair Status as a Biomarker of Response in Locally Recurrent/Metastatic Triple Negative Breast Cancer Patients Treated With Concurrent Cisplatin and Radiation Therapy</td>
<td>Phase II</td>
<td>Locally recurrent or Metastatic TNBC</td>
<td>Cisplatin</td>
<td>External-beam whole-breast RT. 37.5 Gy (15 fractions) for metastatic cases or 50 Gy in 25 fractions (optional 10-14 Gy boost) in locoregionally recurrent cases</td>
<td>54</td>
<td>Recruiting</td>
<td>Response per RECIST 1.1</td>
</tr>
</tbody>
</table>

Conclusion

Options for treatment of anthracycline and taxane resistant TNBC are limited. Further studies are needed to clarify the role of concurrent chemo-radiation in the management of primary resistant TNBC.

References

26. Genet D et al. Concomitant intensive chemoradiotherapy induction in...