Chapter 4

Neoadjuvant Chemotherapy: Role in Breast Cancer

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1. Introduction

Neoadjuvant chemotherapy (NAC), also referred to as preoperative or primary chemotherapy refers to chemotherapy administered prior to tumor resection. It is a standard of care for management of locally advanced or inoperable breast tumors.

2. Rationale for NAC

The clinical rationale of NAC administration lies in the fact that it significantly downstages the existing tumor, enabling greater breast conservation (BSC). Although preoperative chemotherapy has not been shown to improve disease free (DFS) and overall survival (OS) for breast cancer when compared to post-operative therapy in operable patients, achievement of pathological complete response (pCR) defined as absence of any residual invasive tumor, is an important predictor of superior DFS and OS. In the B-27 trial looking at addition of taxanes to anthracycline based regimen in NAC, after 8 years of follow, patients who achieved pCR had superior DFS (HR: 0.49, $p<0.0001$) and OS (HR: 0.36, $P<0.0001$) rates. [1]- [5] The more recent I-SPY 1 study amongst several other studies [6]- [8], have found pCR to be an important predictor of recurrence free survival. [9], [10]

NSABP B-18 study was one of the earliest trials comparing neoadjuvant to adjuvant chemotherapy. The regimen of choice in this trial was the combination of adriamycin and cyclophosphamide (AC) either pre- or post operatively in 1523 women with operable palpable (T1-3, N0-1, M0) newly diagnosed breast cancer. There was no difference in overall survival between the two groups. However, a significantly greater number of patients underwent BCS in the NAC group (67vs. 60%, p=0.002).

In another trial of 1355 women with operable breast cancer, doxorubicin and paclitaxel followed by CMF in the neoadjuvant setting yielded similar RFS and OS rates when compared to adjuvant chemotherapy. However, patients with neoadjuvant chemotherapy achieved much higher breast conservation rates (63% vs. 34%, p<0.001). Distant relapse free survival was inferior in patients who did not achieve pCR (HR, 0.43; p- 0.025). [11]

3. Prognostic factors

Clinical trials have described various clinical and histological features of breast tumors, which may predict response to neoadjuvant chemotherapy. Higher nuclear grade is a significant predictor of pCR with NAC in several studies. [12]- [17] Proliferation index or Ki-67 [18] is shown to correlate positively to response. In the I SPY 1 trial, pCR rates in patients with high Ki-67 (defined as >20 percent) were 35% vs. 5% in patients with low Ki-67 (defined as <10 percent). [19] [9], [20] Pathologic examination of 82 breast cancer tumors after NAC with paclitaxel followed by 5-fluorouracil, adriyamicin and cyclophosphamide (T ▪ FAC) showed that basal like tumor pathology was a predictor of good response to NAC. [21] In the I SPY 1 trial luminal A histology had lowest pCR rates. [8], [19], [22] Negative estrogen and progesterone receptor status has shown to predict better response to NAC [7], [8], [13], [18], [23] In the I-SPY 1 trial pCR was highest for hormone receptor negative and HER-2 positive cancer (54%) and lowest for HR+/ Her-2 negative cancer (9%). [19], [24] In a study of 388 patients in which 16 percent patients were Her-2 positive, Her-2 positivity and young age were important predictors of achievement of pCR with anthracycline based NAC in univariate analysis. [25]

There is no single genetic marker that predicts complete response to NAC. However, gene expression profiling has been studied to predict response to various chemotherapy regimens with reasonable accuracy. [26] [27], [28] van't Veer et al developed a 70-gene expression model for prognostication using microarray analyses on 117 breast tumors. They found that genes associated with poor prognosis regulated cell cycle, metastasis, invasion and angiogenesis (eg. cyclin E2, MCM6, metalloproteinases MMP 9, MP1, RAB6B, PK428, VEGF receptor FLT1). [29] In the I SPY 1 trial, patients with p-53 null mutations and 17q amplification were also associated with high pCR rates (47% and 45% respectively). [19]

Enzymes of cytochrome P450 family play an important role in cancer drug metabolisms and polymorphism CYP2C9*2 polymorphism has been found to be associated with NAC resistance. [30] Tumor stage, lymph node positivity and dose intensity of chemotherapy have not been found to correlate to NAC response. [31] [17], [32]

Apoptotic responses to first dose of NAC measured by serial fine needle aspirations during first 4 days after chemotherapy administration was also found to be an indicator of response. [33]. Persistently elevated levels of CXCR4, a G-protein coupled receptor post chemotherapy has been found to be a negative predictor for response. [34]. A retrospective study of 562 patients concluded that metaplastic, mucinous and apocrine carcinoma responded poorly to NAC. [35]

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4. Chemotherapy regimens

In the pre-taxane era, initial trials of NAC were performed with anthracycline based regimens, such as AC [3]; 5-Fluorouracil, Adriyamicin and Cyclophosphamide (FAC)[36] and 5-Fluorouracil, Epirubicin, Cyclophosphamide (FEC). [37] However, more recent trials have demonstrated that taxanes, when added to anthracycline based regimens, significantly improve survival outcomes [38] and therefore, should be used in combination with anthracycline based regimens. NSABP B-27 trial was designed to observe the impact of addition of 4 cycles of docetaxel to standard AC regimen in the preoperative setting. 2411 patients with T1C-3N0M0 or T1-3N1M0 breast tumors were assigned to ACX4 cycles vs. ACX 4 cycles followed by docetaxel X4 cycles vs. AC X 4 cycles preoperatively and docetaxel X 4 cycles postoperatively. Although the trial did not meet it's primary end point of demonstrating survival benefit, addition of docetaxel did double the pCR rates (from 13% to 26%). pCR rates were also significant predictor of improved DFS (HR: 0.49) and OS (HR: 0.36) after more than eight years of follow-up. Patients who achieved clinical partial response with AC had significantly increased DFS with addition of docetaxel [39]

For patients with the Her-2 positive cancer, trastuzumab has been incorporated in the initial neoadjuvant chemoregimens. Options include sequential trastuzumab and paclitaxel and FEC in combination with trastuzumab (PH- FECH) with pCR rates ranging from 55-65 percent. [40] However, in patients where cardiac morbidity is a concern docetaxel and cyclophosphamide in combination with trastuzumab (TCH) is also an effective choice. [41]

Capecitabine is an effective drug, which has yielded promising results in metastatic breast cancer. Capecitabine in combination of Vinorelbine has been found to be non inferior to Docetaxel, Adriyamicin, Cyclophosphamide (TAC) in terms of sonographic and pathologic complete response and breast conservation rates in the phase 3 Gepar trio trial [42]

5. Dose dense NAC

Dose intensity is achieved by increasing the drug dose delivered per cycle of chemotherapy by either increasing dose or decreasing inter-treatment interval. The PREPARE trial used dose dense (dd) and dose intensified regimens of E+ P followed by CMF and compared it with standard dose EC→T regimen. Patients were treated with E (dd) → T (250mg/m2)(dd) → CMF, each 2 weekly for 3 cycles with or without darbopoeitin versus standard E (90mg/m2) and C followed by P (150mg/m2) for four cycles (EC→T). The pCR rate was higher in the dose-dense, dose-intensified group (18.7% vs. 13.2%; p=0.04). Patients with non-inflammatory breast cancer had significantly improved disease free and overall survival from the dose dense regimens. [43]. A few other trials demonstrate similar increased in pCR rates with dose dense chemotherapy. [44] Currently, the value of dose dense chemotherapy in breast cancer is unclear amongst unselected patients.

In a phase 3 trial (SWOG 0012), standard 3 weekly AC regimen was compared to weekly doxorubicin and daily oral cyclophosphamide with GCSF support in the neoadjuvant

setting for inflammatory and locally advanced breast cancer. pCR rates with the dose dense regimen were superior only in stage IIIB breast cancer and IBC. There was no difference in DFS and OS. [44]

6. Assessment of response after NAC: Definition of pCR

In most studies, pCR has been defined as absence of any residual invasive tumor in the pathologically examined tissue. Prior studies have indicated that there is no survival difference in patients with no residual tumor (in-situ or invasive) versus patients with residual in-situ (non- invasive tumor) cancer. [45] In a study performed at MD Anderson, 2302 patients treated with NAC showed similar disease free, overall and local recurrence free survival for patients who had in-situ cancer at the end of treatment when compared to patients who had no residual cancer. [46] However a recently published pooled analysis of 6,377 patients trials shows that DFS is better in patients with no residual tumor when compared to patients with residual in-situ tumor (HR:1.74, 95% CI 1.28-2.36, $p<0.001$). This study concluded that definition pCR should strictly be limited to absence of residual invasive or in-situ tumor either in the breast or lymph nodes [47].

7. Estrogen or progesterone receptor positive cancer

Although the use of endocrine therapy in the adjuvant setting is very common, it's use in the neoadjuvant setting is relatively recent. Neoadjuvant endocrine therapy has shown to cause tumor shrinkage [48] and reduce tumor proliferation as evidenced by decrease in Ki-67 and other markers of proliferation. [49] pCR is less commonly observed, therefore, response assessment in most of the trials involving endocine therapies is clinical (palpation and radiological techniques) as well as pathological assessment of proliferation markers. [50]

Comparisons have also been made between the 3 aromatase inhibitors exemestane, letrozole or anastrozole, in the neoadjuvant setting. 377 postmenopausal women with stage II/III ER positive breast cancer were treated with neoadjuvant exemestane (25mg/d), letrozole 2.5mg/d and anastrozole 1mg/d for 16-18 weeks. Clinical response rate, which was the primary end point of the trial, was 62.9%, 74.8% and 69.1% respectively. Breast conservation rates were comparable amongst the three groups. No difference was observed in terms of Ki-67 levels or changes in KI-67 expression among all the groups suggesting that they have biological equivalent effects. Overall, Luminal A tumors were likely to have a preoperative endocrine operative index (PEPI) score of zero before surgery when compared to luminal B tumors. [51]

Combination of neoadjuvant hormone and chemotherapy is also being investigated. In a phase 3 trial of 101 post menopausal women with locally advanced hormone receptor positive breast (stage T3, T4 and/ or N2 N3) cancer, neoadjuvant chemotherapy with FAC combined with letrozole 2.5mg daily produced superior pCR (25.5% VS. 10.2%, p=0.049) and clinical complete response rates (27.6% VS. 10.2%, P=0.037) when compared to FAC alone. [52]

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It has been postulated that phosphotidyl kinase 3/ AKT/ mTOR pathway may be involved in endocrine resistance. For this reason, mTOR inhibitor like everolimus have been combined with hormone therapy in clinical trials. In a phase 2 trial comprising of 270 untreated patients with ER positive breast cancer, the control group was treated with letrozole (2.5mg/day) + placebo while the experimental treatment group was treated with letrozole plus everolimus (10mg/day). Patients treated with letrozole plus mTOR (mammalian target of Rapamycin) inhibitor had significantly improved clinical response rates, as well as response rates as assessed by ultrasound and mammography. Decrease in the proliferation index Ki-67 was significantly more marked with the combination treatment. Toxicities with the combination group were higher with 52.9% patients in the combination group having treatment stopped or delayed as a result of toxicities (only 7.6% in the placebo group). It was inferred that mTOR inhibitor can significantly increase the efficacy of hormone therapy. [53]

8. HER-2 receptor positive cancer

Trastuzumab or herceptin (H), a monoclonal antibody against HER-2 neu receptor, is an integral part of neoadjuvant chemotherapy in HER-2 positive tumors. In a phase 3 trial, FEC + Trastuzumab followed by P + trastuzumab has shown significantly higher pCR rates when compared to FEC→ P alone (66.7% vs. 25%). [54]

In the NeOAdjuvant herceptin (NOAH) trial, patients with HER-2 positive inflammatory or locally advanced breast cancer were treated with neoadjuvant chemotherapy alone (A+P → P→ CMF) or neoadjuvant chemotherapy combined with neoadjuvant H (added to the CMF part of neoadjuvant chemotherapy). Addition of H not only improved the rates of pathological response, (50% vs. 26%; p=0.002) but also the rates of event free survival, which was the primary end point of the study. More patients were able to undergo breast conservation surgery with the addition of H (35 vs. 13% p=0.07). [55]

Trastuzumab has been compared to lapatinib (L), a tyrosine kinase inhibitor which is a dual inhibitor of EGFR and Her-2 receptors, in the neoadjuvant setting. In the Gepar Quinto trial, patients were treated with standard chemotherapy with four cycles of Epirubicin and cyclophosphamide followed by four cycles of docetaxel along with either H (6mg/kg every 3 weeks) or L (1250mg daily) starting on the day 1 of the first EC cycle till the day 21 of the fourth cycle of docetaxel. pCR rates with H were significantly higher (30%) when compared to L (30% vs. 22%; p=0.04). Overall difference in the clinical response and the number of breast conservation surgeries between the two groups was not significant. Edema and dyspnea were more common with trastuzumab while rash and diarrhea were more common with lapatinib. [56]

Neo-Altto trial was a randomized phase 3 trial comparing dual (trastuzumab/lapatinib combination) versus single Her-2 receptor blockade (trastuzumab or lapatinib alone) for HER-2 positive breast cancer, >2cm in diameter along with a taxane in the neoadjuvant setting. 154 patients received 1500mg of PO lapatinib, 149 received 4mg IV trastuzumab (2mg/kg subsequent doses) and 152 received the combination of trastuzumab with 1000mg PO lapatinib. pCR rates were significantly higher with dual blockade (51.3 percent; 95% C.I.

43.1-59.5%) when compared to single blockade with trastuzumab alone (29.5%; 95% C.I. 22.4-37.5). No significant difference in the pCR rates between trastuzumab and lapatinib groups was observed (p=0.34). Grade 3 diarrhea and elevation of liver enzymes were more common side effects in the lapatinib (23.4%) and lapatinib plus trastuzumab group (21.1%) when compared to trastuzumab only group (2%). The rate of breast conservation surgery in all the three groups was similar. pCR rate was higher in the ER negative tumors. [57]

In the preliminary results of the NSABP B-41 trial presented in American Society of Clinical Oncology's (ASCO) annual meeting in 2012, when H is substituted with L, the responses pCR rates are found to be comparable. This trial comparing AC→ weekly paclitaxel (WP)+ H vs. AC→ WP + L vs. AC→ WP+ H+L; showed that pCR rates with H and L were comparable (52.5% for T vs. 53.2% for L). pCR rates with the combination of both T and L with NAC was slightly higher but the results were not statistically significant (62% p= 0.075). [58]

Trastuzumab has been combined with another humanized monoclonal antibody against HER-2, Pertuzumab, which binds the dimerization site of HER-2 receptor and inhibits ligand dependent signaling. The phase 2 multicenter Neosphere trial compared combinations of H+ T (group A), H+ Pertuzumab +T (group B), Pertuzumab +H (group C) and pertuzumab + T (group D) as neoadjuvant treatment of Her-2 positive breast cancer. The pCR rates in group B was significantly higher (45.8%, p=0.0141) when compared to groups A, C or D (29%, 16.8% and 24 % respectively). Clinical responses to NAC were also highest in group B. The rate of febrile neutropenia was similar in the trastuzumab+ pertuzumab + chemotherapy group to the H+ T group and was 7-8%. [59]

Trastuzumab combined with bevacizumab and chemotherapy was found to be very effective in Her-2 positive inflammatory breast cancer in the phase 2 BEVERLY-2 trial. In this study, 52 patients were treated with FEC + Bevacizumab (cycles 1-4) and docetaxel +bevacizumab and trastuzumab (cycles 5-8). pCR was seen in 33 patients (63.5%). The frequency of grade ¾ neutropenia was 48%. [60]

9. Role of bevacizumab

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF), which has been found to be very effective when added to anthracycline- taxane based neoadjuvant therapy. In the phase 3 NSABP- 40 trial, [61] patients with T1c-T3/ N0-N2 were treated with the following regimens: Docetaxel (T) alone followed by EC vs. T + Gemcitabine followed by EC vs. T + G + Bevacizumab followed by EC vs. T + Capecitabine (X) followed by EC vs. T + X + Bevacizumab followed by EC. Addition of bevacizumab significantly increased the pCR rates in the breast, which was the primary end point of this study (28.2% to 34.5%, p=0.02). pCR rate in breast and nodes (secondary end point) was also increased but the result was not significant. Rate of clinical complete responses was significantly increased with addition of bevacizumab. Effect of bevacizumab was more pronounced in hormone receptor positive tumor and higher tumor grade. Side effects observed with bevacizumab included

significantly higher rates of hypertension, left ventricular systolic dysfunction, mucositis and hand-foot syndrome.

Another phase 3 trial (GEPAR QUITNO) consisting if 1948 HER-2 negative patients concluded that rates of pCR were significantly improved when bevacizumab was added to EC→ T regimen (14.9% with EC→T alone and 18.4% with EC→ T+ Bevacizumab). In this study, improvement in pCR was limited to patients with hormone receptor negative tumor (39 with bevicizumab VS. 28% without bevacizumab). Side effect profile of bevacizumab was similar to the abovementioned study. [62]

Findings of the above two studies have led to conflicting results. While former has shown benefit of bevacizumab in hormone receptor positive patients, the latter has shown benefit in hormone negative cancer. A phase 3 ARTemis trial is currently underway which compares addition of bevacizumab to standard chemotherapy to chemotherapy alone. The study is to finish recruitment in December 2012 and primary outcome analysis due by December 2013. [63]

However, in some other trials, addition of bevacizumab to chemotherapy has shown less efficacy with additional toxicity. In one study, 45 women with Her2 negative locally advanced breast cancer were treated with neoadjuvant AC + bevacizumab X4 cycles followed by TX+ bevacizumab X4 cycles, with pCR rates of only 9 percent with substantial added toxicity such as fatigue, mucositis and headache. [64]

Trials looking at pathological markers predicting response to bevacizumab have shown positive responses associated with negative hormone receptor status, high Ki67 index and changes in phosphorilation status of VEGF receptor 2 (
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10. NAC in triple negative breast cancer

Triple negative breast cancer is a more aggressive form of breast cancer that has poor prognosis despite response to chemotherapy. TNBC has been found to be sensitive to platinum based treatment in the metastatic setting due to inherent genomic instability. Encouraged by success in the metastatic setting, trials have been conducted with platinum agents in the primary setting. Silver et al. treated 28 patients with stage II/III TNBC with four three weekly cycles of cisplatin. pCR was seen in 22% patients; good pathological response (Miller Payne score of 3,4 or 5) in 50% and progression in 14% patients. Positive response to cisplatin in this study was associated with young age, low BRCA expression, BRCA-1 prominent methylation, p-53 frameshift or nonsense mutation and gene expression significant of E2F3 activation. [65] More pCR rates have been demonstrated in BRCA-1 mutated breast cancers with cisplatin than with conventional regimens such as AC or CMF. [66] In another study, 17 patients with triple negative breast cancers >2cm in size, were treated with weekly doxorubicin plus daily oral cyclphosphamide followed by weekly paclitaxel and carboplatin, 14 out of 15 assessable patients showed clinical response. pCR rate was 46.6%. Seven patients had grade ¾ hematological toxicity with this combination. [67] Similar high pCR rates have been reported with

neoadjuvant bevacizumab, docetaxel and Carboplatin combination. [68] However, in a multicenter phase 2 study, addition of carboplatin to standard EC→T regimen for basal like breast cancer (defined as ER-/PR-/Her2-/Cytokeratin 5/6+ and /or EGFR+) did not enhance efficacy of standard chemotherapy (pCR rates: 35% vs. 30% in Carboplatin vs. no Carboplatin group, p=0.6064). [69]

The phase 3 GeparQuinto study demonstrated that addition of Bevacizumab to conventional chemotherapy (EC→ T) can further improve pathological CR (pCR) rates in triple negative breast cancer. [62]. However, as mentioned above, these findings contradict with the NSABP B40 study where major benefit was obtained in hormone positive cancer. [70] Carboplatin in combination with weekly nab paclitaxel and bevacizumab is also currently being evaluated in a clinical study. [71]

Ixabepilone is a new class of semisynthetic microtubule inhibiting drugs which is derived from natural epithilones. It has shown promising results in metastatic and multidrug resistant (anthracyclines, capecitabine, taxanes) breast cancer. [72]- [76] In a phase 2 study designed to assess benefit of ixabepilone in the neoadjuvant setting, 161 patients were treated with four cycles of ixabepilone. pCR was observed in 18% in all patients, but in 29% of ER negative patients, ER gene expression was inversely related to response in this study. [77] A pooled analysis of data from five phase 2 and two phase 3 trials, pCR rates with ixabepilone in the neoadjuvant setting were 26% in TNBC vs. 15% in non TNBC. [77], [78] Newer non-taxane microtubule inhibiting agents such as eribulin are being evaluated as NAC for TNBC in clinical trials.

Poly ADP ribose polymerase (PARP) inhibitors inhibit the PARP-1 enzyme which is a DNA base excision repair enzyme and along with BRCA, is involved in cell's DNA repair. [79], [80] It's role in tumorigenesis in evidenced by it's upregulation seen in tumor cells, thus protecting cancer cell DNA from damage and cell death. [81] PARP inhibition leads to cell death by two mechanisms. First, it causes accumulation of single and double stranded DNA breaks causing subsequent cell death. Secondly, it causes sensitization to therapeutic DNA damage. [82] Two trials utilizing PARP inhibitor Iniparib in combination of preoperative setting are underway and results are expected soon.

11. Role of neoadjuvant chemoradiation

In a multi-institutional study, 105 patients with locally advanced breast cancer were treated with twice weekly paclitaxel 30mg/m2 for 10-12 weeks and radiation therapy (total 45gy) over weeks 2-7. Trastuzumab was added to this regimen in patients found to be Her-2 positive. Pathological response (complete and partial) was achieved in 34% patients and was found to be significantly higher in hormone receptor negative patients (54%, 95% C.I. 36%-69%) and triple negative tumors (54%). As expected, patients who achieved pathological response had higher disease free survival (57 months vs. not reached, HR: 2.85, $p<0.001$) and overall survival (84 months vs. not reached, HR: 4.27). [83]

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12. Monitoring response to NAC

Assessment of radiological response especially when using MRI or PET scan is very useful since it may help in early differentiation of responders to NAC from non-responders.

Studies have shown that decrease in tumor volume and enhancement on contrast enhanced MRI is associated with major histopathological response. [84], [85] Loo et al showed that MRI was able to monitor response to NAC more accurately in TNBC and Her-2 positive subsets but not in ER+, Her-2 negative subsets. [86] The I-SPY-1 study found that decrease in tumor volume as assessed by MRI early during treatment with NAC was a better predictor of pathologic response than measurement of tumor diameter by physical examination alone.

PET CT is another valuable imaging modality for accurately predicting response to NAC early in the course if therapy. [87], [88] In a study of 33 patients treated with carboplatin based NAC, there was significant correlation between FDG PET metabolic response after first and third cycles and overall survival. [89]

Studies have compared MRI and PET scan as predictors of response to NAC. Choi et al found that compared to PET CT, MRI was highly predictive of pCR ($P<0.005$) and better than PET CT for monitoring response to NAC. [90] However, Rousseau et al found that using 60% cut off value for SUV, the sensitivity, specificity and negative predictive value of PET scan were 89%, 955 and 85% respectively after two cycles of NAC. Values were much lower for US and mammography. Tateishi et al also found PET CT to be superior to DCE MRI for pCR prediction after 2 cycles of NAC. [91]

13. Conclusion

NAC is the standard of care in management of locally advanced and inoperable breast cancer. It significantly downstages the tumor, thereby permitting breast conservation surgery. Anthracycline and taxanes based regimens are most commonly used NAC regimens. For Her-2 positive tumors, trastuzumab should be included in the NAC regimen. Role of other targeted therapies in NAC is being investigated.

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