Review Article

The role of Neo adjuvant Chemotherapy in the treatment of Breast Cancer

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Abstract:

Neoadjuvant chemotherapy (NACT) in breast cancer is giving chemotherapy before surgery, it's an effective initial treatment for large tumors, locally advanced cancer and inflammatory breast cancer. It downstage the disease, allow lesser extensive surgery e.g. breast conservative surgery, the benefit is greater for those who attain pathological complete response (PCR), who get a significantly better overall survival (OS), and progression free survival (PFS), compared with those who don't. This approach is very important in Sudan where the majority, almost 65 % of patients present with locally advanced disease, most of them are denied this treatment.

Introduction:

Neoadjuvant chemotherapy NACT, in breast cancer is giving chemotherapy before surgery it's used in locally advanced TNM stage II and III, inflammatory breast cancer, and sometimes in earlier operable breast cancer. The advantages of this approach are to lower tumor stage and convert inoperable disease to operable disease, and to allow more breast conservative surgery.[1–3]

This approach is particularly important in Sudan as almost 45- 60% of our patients present with locally advanced breast cancer, where initial surgery is commonly performed and patients are often denied this treatment, hence the importance of initially seeing new patients at multidisciplinary consultation clinics, (General Surgeons, Plastic Surgeons, Clinical Oncologists, Radiologists and Pathologists), to plan lines of treatment. Overall patients with breast cancer who experience complete pathological response PCR following NACT had significant improvement in disease free survival DFS (HR=0.48 – 0.69: CI= 0.34- 0.63), and overall survival OS (HR=0.48: CI=0.33-0.69). The prognosis of patients with PCR is excellent; <10% develop distant metastases at 5 years, but patients with triple negative breast cancer TNBC (ER,PR and HER2 negative) who don't experience PCR after NACT have a poorer prognosis.[4–8]

Work up:

In the work up a core biopsy is preferable rather than Fine Needle Aspiration FNA, as its more accurate, and allows hormone receptors testing (ER,PR and Her2),[7] the degree of axillary node involvement is the strongest predictor of subsequent relapse,[8] so axillary assessment by clinical examination, imaging US, MRI, is essential. A recent meta-analysis has shown that sentinel node biopsy before or after NACT is feasible and acurate in patients whose lymph nodes were not clinically palpable after completion of NACT, however this is still controversial.[9,10]

In NACT mostly an Anthracycline (Adriamycin or Epirubicin) with Cyclophosphamide with without 5Florouracil, (5FU), is used, patients response should be assessed after each cycle, if the response is not good chemotherapy is switched to a Taxane regimen e.g. Docetaxel.[11]

Response Assessment:

Is carried out by clinical examination, US and or MRI. MRI in the best available test to assess the

response and suitability for breast conservative surgery BCS.[12,13]

Pathological Response Assessment:

Complete Pathological Response (PCR), after NACT is defined as absence of residual and in situ disease in the breast and the axillary nodes. This is the most important prognostic factor in patients treated with NACT. Patients who don't achieve PCR, are 6 times more likely to develop recurrence, patients who had PCR have significantly better overall survival OR, and DFS.[12]

The Residual Cancer burden, (RCB), formula, is used which combines the diameter of the residual primary, the cellularity fraction of the invasive cancer with the diameter of the largest regional lymph node, this identifies Pathological Complete Response (PCR), and subgroups of residual disease. [12,13]

The National Surgical Adjuvant Breast and Bowel project NSABP B-18 study of 1523 women with operable breast cancer, a median tumor size of 3.5cm, independent of hormone receptors, were randomized to 4 cycles of Cyclophosphamide and Adriamycin (AC), given preoperatively NACT, or postoperatively adjuvant. In the NACT arm, after 9 years follow up the DFS for patients achieving PCR was (75% vs. 58%) in patients with residual disease following NACT (P= 0.00005) OS was (85%vs 75%) (P= 0.008). [14]

The optimal duration and number of cycles of NACT is still an unresolved issue as some patients may achieve Complete response (CR), after 1-3 cycles, others require 6 –8 cycles, however some studies suggested that responders and non-responders of an initial Anthracycline based chemotherapy benefit from adding a Taxane drug, Docetaxel or Paclitaxel. [14–18]

Neoadjuvant Chemotherapy in Triple Negative Breast Cancer (TNBC):

TNBC is defined as negative (ER, PR and Her 2), it forms about 15–20 % of all breast cancers. They have aggressive behavior and poor prognosis in general, anthracyclines regimen followed by taxanes are used as NACT in TNBC. This produced PCR rate of 30 – 40 % in (T2 N0 M0), (18,19) which is consistent with findings of a meta-analysis.[20]

NACT in Her 2 positive Breast Cancer:

Her2 positive breast cancer forms about 15–20% of all breast cancers. It's very aggressive with higher risk of developing brain and visceral metastases. Targeted therapy with Trastuzumab (Herceptine) has produced significant improvement in survival in early and metastatic breast cancer, the Cochrane meta-analysis of 6 randomized studies, showed overall reduction in mortality by one third and in the risk or relapse by 40% .[20–23]

NACT sequential (Taxanes, anthracyclines, Cyclophosphamide) has become the standard for patients with stages II and III. Trastuzumab is added in patients with Her2 positive disease. They resulted in PCR rates of 20-50%, however the majority of patients with TNBC or Her2 positive disease who don't achieve PCR, develop distant metastases within 3 years.[6,24]

Adding additional drugs to the mentioned routinely used drugs e.g. Gemcitabine, Bevacizumab or Capecitabine, didn't increase the PCR rate significantly but increased toxicity.[25–28]

NACT in Inflammatory breast cancer:

Inflammatory breast cancer is a rare form of breast cancer, forming about 1-4% of all breast cancers, it has a high prevalence of hormone receptors negative disease, more Her2 positive disease and shorter survival, usually treated with NACT first then surgery followed by radiotherapy and adjuvant therapy, NACT usually results in PCR rate of 12-23%.[27] The addition of a Taxane to chemotherapy in inflammatory breast cancer, was investigated by Cristofanilli, who reviewed 240 patients treated in 6 trials, 178 patients had inflammatory breast cancer and were treated with (FAC) regimen alone, 62 patients treated with (FAC followed by Paclitaxel). The PCR rate was significantly higher in those treated with FAC and Paclitaxel compared with those treated with FAC alone, (25 vs. 10%), and improvement in DFS of (27 vs. 18months), and a

median survival of 54 vs. 32 months.[28,29]

Neoadjuvant Hormonal Treatment:

This is used in elderly women with ER and PR hormone receptors positive disease and significant co-morbidities. A study has shown the greater efficacy of the Aromatase inhibitor, Letrozole (Femara) vs. Tamoxifen.[30] A recent meta-analysis study had confirmed the higher rates of PCR in these patients.[31] The optimal duration of neoadjuvant Aromatase inhibitor is still debatable, but may be between 4-6 months,[32] most studies used letrozole, comparisons between the 3 Aromatase inhibitors suggest similar efficiency,[33] Direct comparison between chemotherapy NACT and neoadjuvant hormonal treatment is rare, however, in postmenopausal women with hormone receptors positive disease response rate and time to response achieved are similar.[34]

In conclusion, Giving NACT in locally advanced breast cancers and inflammatory breast cancer is an effective treatment as patients who achieve complete pathological response, have a significantly better overall survival and disease free survival, and it allows more breast conservative surgery, so it's particularly needed for our patients in Sudan as most of them present with locally advanced disease. [35]

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