

RATIONALE OF SEQUENTIAL AC – DOCETAXEL NEO-ADJUVANT CHEMOTHERAPY FOLLOWED BY MODIFIED RADICAL MASTECTOMY AND POST-OPERATIVE RADIATION TO CHEST WALL AND PERIPHERAL LYMPHATICS IN LOCALLY ADVANCED BREAST CANCER

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Locally advanced breast cancer (LABC) is uncommon in developed countries, where it constitutes only 5% of cases in major centers and less than 20% in other areas.¹ This relative infrequency has seriously limited clinical research and consequently no large-scale studies on treatment of LABC have been reported from the west. It is more common in the developing countries where it constitutes up to 50% of all cases.¹ In Pakistan, according to a population based tumour registry in Karachi, it constitutes 47% of the cases.²

Surgery and radiotherapy have been used for the treatment of LABC for many decades, but surgery or radiation treatment alone results in a high rate of metastases, local recurrences and a 5-year survival of less than 20%.³ Combination of surgery and radiotherapy however improves local control (79-89%), but the survival still remains modest i.e. from 33 to 50%.⁴⁻⁶ Chemotherapy has been introduced for the treatment of LABC in late 1970s. Systemic nature of the disease, high metastatic rate in LABC, and effectiveness of chemotherapy prior to removal of tumour in pre clinical models have provided the rationale of this new form of treatment in which chemotherapy is given first as neoadjuvant (NACT)⁷. Neoadjuvant chemotherapy followed by surgery and radiotherapy have now become the standard of care, and the most widely practiced form of treatment for LABC.^{8,9}

RATIONALE OF SEQUENTIAL AC – DOCETAXEL NACT

The NACT not only provides an early start of systemic treatment in a disease with a high rate of distant failure, but also gives an opportunity to reduce the size of primary tumour. Many inoperable lesions can be rendered operable and even breast conserving surgery is made possible. It allows measurement of in vivo sensitivity of chemotherapeutic drugs and also permits the evaluation of

biological markers in predicting the response, however, the most significant clinical benefit is the opportunity to achieve and document pathological complete response.

Pathological Complete Response (PCR) is the best indicator of efficacy of NACT. It is difficult to predict the probability of PCR on the basis of biological parameters of disease. Oestrogen receptor negativity is predictive of PCR,¹⁰ but DNA ploidy, mitotic index, differentiation antigens and microvascular density do not predict responses.¹¹

Pathologic complete response is also a strong predictor of eventual disease free survival (DFS) and overall survival (OS) in locally advanced breast cancer^{10,12,13} as well as in early breast cancer as seen in NSABP-18 and NSABP 27 studies.^{14,15} Patients who achieve a PCR have better overall and disease free survival. Therefore the current and future therapies shall aim at increasing the rate of PCR to improve the DFS and OS.

Paclitaxel and docetaxel have both been incorporated in most of the recent strategies developed for the improvement of the rate of PCR. But after the demonstration of superiority of docetaxel over paclitaxel in metastatic breast cancer^{16,17} it is important to include docetaxel in neoadjuvant setting for the treatment of locally advanced disease in the best possible way.

Docetaxel can be combined with other drugs conventionally, in a dose dense fashion or in a sequential way. Combinations of docetaxel with doxorubicin or epirubicin have been studied as neoadjuvant therapy but the PCR rates range from 8-28% only.¹⁸⁻²¹ Sequential dose dense use of adriamycin followed by docetaxel has also been studied but has shown to increase the incidence of grade 3/4 hand foot syndrome to a very high level (42%).²²

However the sequential use of docetaxel after anthracycline based chemotherapy at standard do-

ses not only increases the PCR rate but also improves the OS in patients with large and locally advanced breast cancer. In Aberdeen trial, docetaxel after CVAP chemotherapy yielded a 31% PCR rate on intent to treat analysis and a 93% survival at a median follow up time of 63 months.²³ This sequential use of docetaxel after anthracycline has a strong theoretical rationale as well. The use of stronger drug after weaker drug increases the chances of eliminating the strains resistant to or made resistant to the weaker drug used first. The most active drugs in CVAP protocol include adriamycin and cyclophosphamide and this combination of AC has been very extensively studied. It would be another appropriate treatment option to treat LABC with sequential AC-docetaxel chemotherapy. However, mature data on a large scale use of AC-docetaxel sequential therapy in neoadjuvant setting is not yet available.

In GEPARUO study sequential AC-docetaxel was indeed used in neoadjuvant setting and was compared against dose dense adriamycin – docetaxel combination in a mixed population of T2-3, N0-2 patients. It yielded a higher PCR rate of 22.4% in sequential arm vs. 11.5% in dose dense arm.²⁴ Only a few patients were of locally advanced disease in this study, majority being early breast cancer as 60% of these patients were node negative and median tumour diameter was 4 cms.

Similarly in Aberdeen trial, only 92 patients received sequential docetaxel and even these comprised of both large and locally advanced breast cancer patients. Aberdeen and GEPARUO trials are the two most frequently cited trials representative of LABC but both have only a few patients of LABC alone to realistically provide the PCR rate in this setting. Therefore there is a need to evaluate AC-Docetaxel sequential neoadjuvant chemotherapy in LABC to establish the rate of PCR.

With this background it seems appropriate to study AC-D sequential NACT followed by MRM and RT in patient population solely comprising of LABC. A dose of 75 mg/m² shall be reasonable for sequential use after standard AC chemotherapy considering that this dose has shown to yield a high response rate of 52% in metastatic breast cancer.²⁵ Furthermore, the tolerance of chemotherapy in our patients is relatively poor owing to the poor nutritional status and lack of a good bone marrow reserve. Even this dose of docetaxel after AC chemotherapy in adjuvant setting has yielded a grade 3/4 neutropaenia in 47% of our patients with good Karnofsky's performance status.²⁶

There is little prospective data on the rates of locoregional control in LABC after NACT and MRM and RT. One retrospective review on NACT and MRM and RT revealed a 10% locoregional

relapse at 5 years but only 12% of these patients had received a taxane.²⁷ Therefore, it is expected that such an approach will not only provide PCR rates but will also document the efficacy of sequential AC-docetaxel neoadjuvant chemotherapy in locoregional control.

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