Special Article

Rationale of Concurrent Docetaxel Chemotherapy and Radiation to Chest Wall & Peripheral Lymphatics after Four Cycles of AC Chemotherapy in patients with Early Breast Cancer

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Introduction & Study Rationale

Adjuvant setting offers an opportunity to cure early breast cancer. The overview data reveals that patients who receive adjuvant chemotherapy have reduced rates of recurrence and mortality at ten years. The absolute survival at ten years improves from 42 to 53% in node-positive women under 50 years of age[1]. Despite adjuvant treatment a significant number of these women develop recurrence and die of their disease.

CMF and anthracycline based chemotherapies have been the most widely used adjuvant treatments. In a large randomized controlled trial the AC x 4 and CMF x 6 were found equivalent in terms of improvement in disease free survival and overall survival[2]. This led to widespread use of AC adjuvant chemotherapy in North America. However studies comparing higher dose anthracycline regimens with CMF have found better DFS and OS for anthracycline based regimens[3]. Furthermore, longer duration anthracycline regimens are better then shorter duration regimens[4]. Considering the results of these trials there seems to be a strong possibility that AC alone is not an optimal adjuvant treatment for all patients. However, there are no randomized controlled trials directly comparing any of these regimens with AC regimen.

AC chemotherapy could possibly be a sub-optimal treatment for patients with high-risk disease with four or more positive nodes. We already know that with the increasing number of involved axillary lymph nodes, the relapse rate increases and the survival rate decreases[5]. This means that the patients with 4-9 positive nodes or ten or more positive nodes, have the poorer prognosis. For these patients new treatment options need to be explored.

Patients with ten or more positive nodes have recently been treated with high dose chemotherapy and stem cell support but have not been shown to have any significant improvement in event free and overall survival[6]. Other randomized trials have also failed to show significant benefit from high dose chemotherapy and stem cell support[7,8].

Another approach for adjuvant treatment of node positive patients is the sequential use of adjuvant chemotherapies. The additions of four cycles of paclitaxel to four cycles of AC in node positive patients has resulted in a small absolute improvement in survival of 3% at 36 months of follow up[9]. Since then, 4 cycles of AC followed by four cycles of paclitaxel have become a widely accepted programme. Although subsequent MD Anderson hospital trial and NSABP B-28 have not shown any statistical advantage of addition of paclitaxel in adjuvant setting[10,11]. However, the latest report on AC paclitaxel sequential chemotherapy strongly suggests that the administration of a non-cross resistant drug sequentially after treatment with standard chemotherapy can improve disease free and overall survival[12].

Recently, docetaxel has emerged as the most powerful cyto-toxic drug against breast cancer. As a single agent in second line treatment in phase II trials in metastatic breast cancer, it has achieved a response rate of 53-58% at a dose of 100 mg/m^2 given every three weeks[13-15]. As a first line chemotherapy it has shown a response rate of 68% in the phase II trials[16,17]. A subsequent phase III study which compared docetaxel to doxorubicin in metastatic breast cancer patients who had received prior alkyltaing agent containing chemotherapy, docetaxel has produced significantly higher response rates of 47.8% versus 33.3%[18]. Another study revealed a response rate of 47% with docetaxel and 27% with doxoubicin[19].

A dose of 75mg/m^2 of docetaxel has been safely combined with 50 mg / m^2 of adriamycin and both have been combined at a dose of 60 mg / m^2 of each.[20] At a dose of 50 mg / m^2 of adriamycin with 75 mg /m^2 of docetaxel it was tested against AC (60/600) as first line chemotherapy for metastatic breast cancer, and achieved an overall response rate of 60% against 47% of AC[21]. A three drug combination of TAC achieved an overall response rate of 77% with response rate of 82 %, 82 % and 80% for visceral, bone and liver metastasis respectively.[22] This data led to a phase III trial which compared TAC (75 /50/500) with FAC (500 /50/500) and produced significantly higher overall response rate of 55% versus 32%[23]. These trials of docetaxel in metastatic breast cancer provide the strong rationale for its use in adjuvant setting as it has achieved the highest response rates ever achieved against metastatic breast cancer and it has achieved a response rate in second

line setting which is only slightly lower than response rate seen in first line.[13-15] Furthermore docetaxel frequently induces responses in liver metastases[22.24]. Adjuvant chemotherapy trials incorporating docetaxel in combination chemotherapy with both anthracyclines and non-anthracyclines are underway and some are being reported[25,26]. However, it would be interesting to explore the role of sequential use of docetaxel after four cycles of AC adjuvant chemotherapy in high-risk patients. Although the sequential use of paclitaxel after AC chemotherapy has been reported previously, the docetaxel appears to be a better choice than paclitaxel for use in adjuvant setting after four cycles of AC for a variety of reasons. Firstly, as mentioned earlier, the high response rates in metastatic breast cancer merits its use in adjuvant setting. Secondly, the differences observed in the mechanism of action and in vitro cyto-toxicity patterns of docetaxel and paclitaxel are important. Docetaxel is approximately twice as potent as paclitaxel in inhibiting the micro-tubular de-polymerisation[27,28]. Docetaxel is 1.3 to 12 times more potent than paclitaxel in a variety of murine and human tumor cell lines including breast cancer cell lines[29-31]. There is a partial resistance to the P-glycoprotein positive P388/DOX cell lines resistant to doxorubicin while for paclitaxel, this resistance is complete[31]. This is also observed in clinical studies in known anthracycline resistant disease where paclitaxel achieves a variable response rate of 6-53 % and docetaxel achieves a stable response rate of 60%[32-35]. All this data makes it a better candidate than paclitaxel for testing in adjuvant setting.

Recently, a feasibility study has evaluated docetaxel based sequential and combination regimens in the adjuvant setting in node-positive breast cancer patients and has shown that the adriamycin docetaxel sequential chemotherapy is feasible though it is associated with some increase in docetaxel specific side effects[36]. The increased incidence of docetaxel specific side effects are seen with a dose of 100 mg/m^2 given sequentially after adriamycin chemotherapy.

A dose of 100mg/m^2 in adjuvant setting has been derived from its efficacy in metastatic setting in patients who had massive gross disease in multiple organs. A dose of 75mg/m^2 can also achieve a reasonably high response rate of 52% in these patients with gross metastatic disease.[37] At this dose colony stimulating factor support is seldom required. A dose of 75mg/m^2 can be expected to produce significant cell kill in the adjuvant setting where total cancer cell number is small and the growth fraction is large. This high cell killing at lower part of Gompertzian growth curve will increase the possibilities of total cell kill and a possible cure. Sequential AC-Docetaxel adjuvant chemotherapy with radiotherapy given concurrently holds other advantages which can help in achieving a cure. Firstly it provides the longest duration of treatment based on two most active drugs available so far. Secondly, the use of a stronger drug after the weaker drug increases the chance of eliminating the strains resistant to or made resistant to weaker drugs used first. Finally, the radiation eliminates any remaining foci of disease, in chest wall and peripheral lymphatics. Radiotherapy to chest wall and peripheral lymphatics has shown to improve the rates of relapse free survival and overall survival in patients with positive nodes[38,39].

In Danish Breast Cancer Cooperative Group (DBCG) trial 82b, the addition of radiotherapy to adjuvant chemotherapy reduced the ten year rate of local recurrence from 32% to 09% and improved the overall survival from 45 % to 54%[37,38]. In DBCG trial 82c, the addition of radiotherapy also reduced ten year local recurrence rate from 35 % to 08 % and improved overall survival from 36% to 45%[40]. A small British Columbia study produced similar results.[41] Subsequent meta-analysis published in 2000 confirmed the survival benefit for local and regional radiotherapy in node positive women treated with modified radical mastectomy and adjuvant systemic therapy[42].

There is not enough data on effect of sequencing of chemotherapy and radiotherapy on outcome. The trial specifically designed to address this issue suggested that the local recurrence was greater with delayed radiotherapy and the distant recurrence was greater with delayed chemotherapy[43]. Therefore there is a necessity to use radiotherapy and chemotherapy simultaneously, eliminating the delay of either of the modalities. CMF chemotherapy has been successfully combined with radiotherapy[44]. It has also been feasible to use radiotherapy concurrent with paclitaxel after four cycles of AC chemotherapy[45]. However there is no published data on the concurrent use of radiotherapy and docetaxel after four cycles of AC chemotherapy.

Concurrent radiotherapy with docetaxel after AC chemotherapy will possibly add many specific benefits. Firstly it will maximize the local control. Secondly, by eliminating the residual foci it will possibly reduce the chances of metastatic spread from residual foci. It is of interest to note that there is no scientific arguments or published data against the possibility of metastatic spread from the residual microscopic disease in chest. We continue to believe that there is a strong possibility that local disease, recurrent or residual, does contribute to distant spread in some patients. This is also evident from the fact that many local recurrences are followed by distant relapse.

With the above consideration it seems appropriate in our setup to evaluate the feasibility of AC chemotherapy followed by concurrent docetaxel chemotherapy and radiation to chest wall and peripheral lymphatics in high-risk patients with operable breast cancer. High-risk patients include those with positive nodes and those with negative nodes and negative receptors, age <35, T2-3 primaries, grade II-III lesions and possibly lympho-vascular invasion. But as the increased relapse rate and decreased survival rate correlates better with increasing

number of lymph nodes, it is appropriate to include patients with four or more positive nodes only in this study.

Therefore, the Cancer Research Group Pakistan has started this phase II study with the objectives to assess the feasibility of this regimen.

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