Neoadjuvant Therapy in Breast Cancer: Can We Define Its Role?

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Abstract
It remains unclear whether neoadjuvant therapy increases disease-free survival when compared with an approach in which chemotherapy is delayed until after surgery. However, the current rationale for neoadjuvant therapy is based on its usefulness in quickly evaluating the likely benefit of new approaches to treatment and tailoring therapy to the biological characteristics of the individual tumor. In the primary therapy of breast cancer, the Aberdeen study shows that patients unresponsive to an anthracycline-based neoadjuvant regimen may achieve a response when switched to docetaxel. Further, patients with an initial clinical response to CVAP were more likely to show a pathological complete response (pCR) at final assessment when four cycles of CVAP were followed by four of docetaxel than when CVAP was maintained for eight cycles (pCR rate 34% versus 16%). Early data suggest that this difference translates into significantly lengthened progression-free survival. As in other disease settings, it may be possible to devise non-anthracycline-containing neoadjuvant regimens which are at least as effective as those in current use. The Oncologist 2001;6(suppl 3):36-39

Introduction
Historically, neoadjuvant therapy was undertaken with the aim of shrinking the tumor in patients who were not candidates for primary surgery, and in the hope of allowing greater conservation of the breast. Evidence then emerged suggesting that induction of a pathological complete response (pCR) was at least to some extent predictive of long-term clinical response [1, 2].

Today, the rationale is different: neoadjuvant therapy is viewed as a means of testing the activity of a therapeutic approach or the potential importance of biological factors in determining disease outcome. Patients can be treated de novo, results are available quickly, and valuable information can be gathered from proof-of-concept studies involving a relatively small number of patients.

Randomized Phase III Studies of Primary Chemotherapy
Initial indications that primary therapy could favorably affect prognosis were followed by a series of randomized controlled studies in which patients were managed using either the adjuvant or neoadjuvant approaches [3-7] (Table 1).

Two of three relatively small studies (271-414 patients) showed in the published reports that use of the neoadjuvant approach led to a significant or near-significant increase in the

<table>
<thead>
<tr>
<th>Study</th>
<th>n of pts.</th>
<th>Median follow-up</th>
<th>% Disease-free survival at 5 yrs</th>
<th>% Surviving at 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mauriac [3]</td>
<td>272</td>
<td>47 mo.</td>
<td>50</td>
<td>75</td>
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<tr>
<td>Scholl [4, 5]</td>
<td>414</td>
<td>66 mo.</td>
<td>65</td>
<td>78</td>
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<tr>
<td>Semiglazov [6]</td>
<td>271</td>
<td>53 mo.</td>
<td>72</td>
<td>78</td>
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proportion of patients disease-free at 5 years [4-6]. However, the third study showed no difference in the proportion of patients who were disease-free, and this was also the case with the far larger (1,523 patients) National Surgical Adjuvant Breast and Bowel Project (NSABP) study of Fisher et al. [2, 7]. In the latter study, the outcome among patients randomized to four cycles of doxorubicin plus cyclophosphamide (AC) followed by surgery was exactly the same as that among patients in whom surgery preceded AC chemotherapy [7]. This was true both for disease-free and overall survival. Indeed, none of the studies cited found a statistically significant advantage for the neoadjuvant approach when looking at the proportion of patients alive at 5 years. A possible explanation for some of these results could be that early chemotherapy may be of major importance only for patients whose tumor is not hormone-dependent and thus not treated with tamoxifen. The International Breast Cancer Study Group has recently shown that timing of adjuvant therapy is a crucial factor for estrogen receptor (ER)-negative premenopausal patients [8].

Neoadjuvant Therapy: The New Rationale

Given these uncertain data, the historical justification for neoadjuvant therapy besides the proven decrease of mastectomies, while it cannot be dismissed, cannot be considered convincing. Happily, a new and sound rationale for the neoadjuvant approach is available.

Molecular biologists have now provided the clinical oncologist with an extraordinarily rich and powerful range of new tools with which to improve our understanding of breast cancer and enhance its treatment. The promise is that in the near future it will be possible to tailor therapy to the particular characteristics of an individual tumor, so bringing an end to the era in which a particular therapy was administered blindly to all comers.

The work of Colleoni et al. stands as an example of how the importance of biological determinants can be established [9, 10]. Prospectively derived data suggest that response to either AC chemotherapy or the 5-fluorouracil/leucovorin/vinorelbine combination is predicted by factors such as p53 and c-erbB-2 positivity and a high or decreasing Mib1/Ki67 percentage in the tumor sample. According to these data, relative resistance to the chemotherapy regimens cited is predicted by ER and progesterone receptor (PgR) positivity.

The neoadjuvant approach has been criticized in some quarters since it is held to prevent use of lymph node status as a guide to prognosis. It is argued that eradication of tumor from lymph nodes that were positive before neoadjuvant therapy might lead certain patients to receive insufficiently intensive adjuvant treatment. However, surgeons experienced in the field may be able to use sentinel lymph node biopsy to determine whether nodes were initially positive. The issue is being investigated in the European Organization for Research and Treatment of Cancer-AMAROS study. This trial should enable biological data from the tumor sample to be correlated with primary clinical and lymph node response.

Neoadjuvant Docetaxel: The Aberdeen Study

The Aberdeen study provides important information to guide further therapy both in patients who respond to an initial four cycles of the anthracycline-containing CVAP regimen and those who show no initial response [11, 12]. The rationale of the study is based on the available evidence that docetaxel has activity in anthracycline-resistant disease.

In this trial, nonresponders to CVAP received four cycles of docetaxel. Responders to CVAP were randomized to either four cycles of docetaxel or a further four cycles of CVAP before final assessment and surgery.

One of the complicating factors in the neoadjuvant literature is the variety of classifications employed to establish pCR [13]. The Aberdeen study used the Miller and Payne classification in which pCR (i.e., grade 5 on the five-point scale) is defined as “no invasive cells identifiable in sections from the site of the previous tumor” [13, 14]. The prognostic significance of pCR by this definition for overall survival has now been established.

Of the 145 patients entered into the first phase of the study, 16% showed an objective clinical response (CR) to CVAP and a further 51% had a partial response (PR) [12]. Of the initial responders randomized to docetaxel in the second phase of the study, 62% were converted to a CR. Of those randomized to continuing CVAP, only 34% achieved a CR. A further 32% of patients in both arms of the study showed a clinical PR at final assessment.

The key finding shown in Table 2 is the pCR of 34% among clinical responders to initial CVAP who were then switched to docetaxel [11, 12]. This is more than double the final rate of pCR seen in responders to CVAP who were maintained on CVAP therapy.

Also intriguing are the data on progression-free survival obtained at a median follow-up of 104 weeks (Fig. 1). The curves for initial responders who are randomized to either docetaxel or continued CVAP diverge substantially and significantly (p = 0.022) and suggest clear clinical benefit is derived from switching to the taxane. Mature data are eagerly awaited, and the NSABP B-27 (comparing: AC→docetaxel→surgery, versus AC→surgery→docetaxel, versus AC→surgery) data will be determinant in this setting.

A similar approach using the non-cross-resistance characteristics of taxanes and anthracyclines has been assessed by workers at the M.D. Anderson Cancer Center (Houston, TX) in patients with locally advanced breast cancer [15]. In this study, patients were randomized to either FAC for four courses
or paclitaxel, followed by local therapy, and then four further courses of FAC (with tamoxifen administered in women aged 50 or more with ER-positive tumors). By intent-to-treat analysis, the estimated disease-free survival at 4 years is 81.5% among patients randomized to FAC-only treatment and 85.2% among patients whose neoadjuvant therapy included paclitaxel. This difference is non-significant ($p = 0.2$).

**Nonanthracycline Neoadjuvant Regimens**

The advent of active nonanthracycline agents such as the taxanes and platinum salts raises the question of whether doxorubicin or epirubicin is any longer “the” essential component of neoadjuvant regimens, just as either one may no longer be a “must” in the adjuvant setting.

As an example of such an approach, Hurley et al. recently reported a study in which 25 patients with locally advanced breast cancer received a combination of docetaxel plus cisplatin [16]. The clinical response rate was 96%, and 20% of patients had a pCR. Treatment was well-tolerated, and the combination is to be explored further in the neoadjuvant setting.

**DISCUSSION**

The neoadjuvant context provides a potentially highly useful model through which to increase our understanding of the biology of breast cancer and the likely impact of innovative therapies when used in other disease settings (including adjuvant treatment).

More specifically, the Aberdeen data provide intriguing support for the view that sequential therapy including docetaxel is superior to maintained therapy with an anthracycline combination as a means of inducing pCR in the neoadjuvant setting. The evidence from this trial is important since it suggests that widespread current practice (which is to continue to give anthracyclines to patients who show an initial response) can be improved upon. It provides support for the general concept of using alternating non-cross-resistant regimens, although the trial does not demonstrate that use of such agents in sequence is superior to their simultaneous use from the outset of neoadjuvant therapy.

Although further studies are needed to define the optimal treatment regimen, there is now a case for saying that docetaxel should be considered in the management of all patients receiving primary chemotherapy. Among other unanswered questions is whether inclusion of an anthracycline is an essential component of neoadjuvant regimens.

The use of neoadjuvant studies to understand rapidly the true efficacy (obtained by pCR) of various therapeutic approaches will also have to take into account biological variables, starting simply from tumor ER positivity and menopausal status of the patient.
REFERENCES


