Short communication

Neoadjuvant/presurgical treatments

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Introduction

In this article the term 'neoadjuvant' is used to describe pre-operative treatment for 3 months or more for large (usually ≥3 cm) operable cancers before surgery. Clinical response and pathological response are important end-points. The term 'presurgical' refers to treatment of short duration (around 2 weeks) before surgery, sometimes referred to as a 'window of opportunity' study. This approach can be used for any size of cancer provided it can be core biopsied, and the end-points are molecular markers.

Traditional goals of neoadjuvant therapy include the following:

- to improve survival;
- to downstage so that inoperable cancers become operable or so that conservative surgery can replace mastectomy;
- to identify short-term clinical or molecular markers of response to predict long-term outcome as a prelude to (or as a substitute for) adjuvant trials;
- to predict outcome and plan further treatment in the individual patient; and
- to identify the molecular mechanisms that underlie response and resistance to treatment.

Short-term presurgical therapies can have similar aims with the proviso being that this treatment will not lead to downstaging and that clinical and pathological response rates are unrealistic end-points.

Current evidence suggests that there is no survival benefit from neoadjuvant chemotherapy [1]. The question has not thus far been addressed in a large neoadjuvant endocrine therapy trial. Neoadjuvant chemotherapy has been shown to downstage and reduce the need for mastectomy in some but by no means all women [1]. The same is true for neoadjuvant endocrine therapy; about 40% of mastectomies can be avoided with preoperative aromatase inhibitor therapy [2].

Short-term surrogate clinical and pathological markers for outcome

Clinical response

Clinical response is widely used as a primary or secondary end-point in current neoadjuvant chemotherapy trials (Table 1). This, however, is misguided.

In our own series of 995 patients treated with neoadjuvant chemotherapy at the Royal Marsden Hospital, London, over the past 15 years, there was no significant correlation between clinical response (including clinical complete remission) and long-term disease-free survival or overall survival. Similar findings were reported for the National Surgical Adjuvant Breast and Bowel Project (NSABP)B-18 trial, in which 1,500 patients were randomly assigned to receive neoadjuvant or adjuvant chemotherapy [3]. In the subsequent NSABPB-27 trial, which involved almost 2,500 patients, neoadjuvant adriamycin/cyclophosphamide (AC) alone, four courses, was compared with the same treatment followed by docetaxel for four courses prior to surgery. The sequential arm achieved a significantly higher complete clinical remission rate than AC alone (64% versus 40%; $P < 0.001$) but there was no significant difference in survival [4,5].

In our own experience, neoadjuvant chemotherapy involving cisplatin or carboplatin achieved a significantly higher complete clinical remission rate in patients with triple negative breast cancer than in others (88% versus 51%; $P < 0.005$), but there was no improvement in overall survival, and indeed the triple negative group exhibited a trend toward inferior survival [6].

A clinical response to neoadjuvant chemotherapy is therefore encouraging for the doctor and the patient, but its prognostic and predictive value are unreliable.

AC = adriamycin/cyclophosphamide; HER = human epidermal growth factor receptor; IMPACT = Immediate Preoperative Anastrozole Tamoxifen or Combined with Tamoxifen; NSABP = National Surgical Adjuvant Breast and Bowel Project; pathCR = pathological complete remission.

Table 1

End-points in current neoadjuvant chemotherapy trials

Trial	*n*	Primary end-point	Secondary end-point
GEPARDUO	913	Clinical OR	PathCR
NeoTANGO	800	PathCR	Clinical OR
NSABPB-40	1,200	PathCR	Clinical OR
GEPAR4	1,500	PathCR	Clinical OR
NOAH	288	PathCR	Clinical OR
PREPARE	733	DFS	PathCR
AGO	679	PathCR	Clinical OR
neoALTTO	450	PathCR	Clinical OR

Presented are some current neoadjuvant chemotherapy trials using clinical response and pathCR as primary or secondary end-points. DFS, disease-free survival; OR, overall response; pathCR, pathological complete remission.

A similar uncertainty exists for neoadjuvant endocrine therapy. Neoadjuvant letrozole was shown in a randomized trial to achieve a higher clinical response rate than neoadjuvant tamoxifen [7], and a large similar adjuvant trial, the Breast International Group 1-98 trial [8], confirmed superior long-term outcome for letrozole over tamoxifen. In contrast, the Immediate Preoperative Anastrozole Tamoxifen or Combined with Tamoxifen (IMPACT) trial, which compared neoadjuvant anastrozole versus tamoxifen versus the combination, found no significant difference in complete response [2], whereas the identical treatments in the large adjuvant Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial [9] identified a long-term benefit for anastrozole.

Likewise, in both these neoadjuvant trials the aromatase inhibitors letrozole and anastrozole were each very selectively superior to tamoxifen in terms of clinical response in tumours that were human epidermal growth factor receptor (HER)-2 positive [2,10], yet this selective benefit was not seen in either of the respective adjuvant trials in patients with HER-2-positive cancer.

Pathological complete remission

In contrast to clinical response, pathological complete remission (pathCR) is well established as being associated with significantly improved outcome. The problem with this end-point is that it is late, and it is available only at the time of surgery after neoadjuvant therapy has been completed. In addition, it is achieved only in a minority of patients, usually around 10% to 15%, with neoadjuvant chemotherapy in large series, and is extremely rare with neoadjuvant endocrine therapy, occurring in 1% of patients or fewer.

Furthermore, pathCR does not always correlate with improved outcome. In the Royal Marsden Series we found no correlation between pathCR and improved outcome in patients with oestrogen receptor positive cancers [11]. Likewise, in a recent study based on molecular subtypes, the highest pathCR rate of 29% was seen in basal-like breast cancers, as compared with only 6.5% in luminal cancers; in contrast, luminal cancers had a significantly better long-term outcome than did basal-like cancers [12].

In the NSABPB-27 trial described above, the sequential combination of AC followed by docetaxel achieved a significantly higher pathCR rate than did AC alone (26% versus 13%; $P < 0.001$), yet no survival difference was seen between the two arms.

PathCR rate is widely used as a primary or secondary end-point in current neoadjuvant chemotherapy trials (Table 1), but its correlation with improved outcome, although frequent, is not always seen.

Molecular markers: Ki67

In the IMPACT neoadjuvant endocrine therapy trial referred to above, the percentage reduction in the proliferation marker Ki67 at 2 weeks after starting treatment, compared with baseline, was significantly greater for anastrozole than for tamoxifen or the combination [13]. This exactly predicted the outcome of the Taxotere as Adjuvant Chemotherapy Trial (TACT), suggesting that a short-term change in this important proliferation marker could predict long-term outcome in clinical trials.

Long-term outcome from the same neoadjuvant trial revealed that the Ki67 level in the individual tumour 2 weeks after starting endocrine therapy predicted long-term outcome and was a more effective predictor than baseline Ki67 [14]. If confirmed, then Ki67 at 2 weeks after starting endocrine therapy could predict outcome in the individual patient and could be used to determine who might need further adjuvant therapy (and in particular adjuvant chemotherapy) and who would not.

This hypothesis is being tested in the large UK national trial POETIC (PreOperative Endocrine Therapy: Individualising Care). In this trial 4,000 postmenopausal women with hormone receptor positive breast cancer will be randomly assigned to 2 weeks of preoperative aromatase inhibitor or to no preoperative treatment. The first end-point of the trial will be relapse-free survival, determining whether this approach might have a long-term outcome benefit. The second aim is to validate whether 2-week Ki67 (measured at the time of excision surgery) does indeed predict long-term outcome in the individual patient. The third aim is to determine whether multiple changes in gene expression after 2 weeks of treatment with an aromatase inhibitor may provide further insight into the prediction of long-term outcome and into mechanisms of response and resistance to endocrine therapy.

In our own experience with neoadjuvant chemotherapy at the Royal Marsden, we have shown that the level of Ki67 in the

excision biopsy after 4 months of chemotherapy likewise predicts long-term outcome in the individual patient [15]. This raises the important question of whether a similar change after one course of chemotherapy would predict long-term outcome. If so, then this could be used as a basis for continuing effective chemotherapy or discontinuing ineffective treatment after one course in the individual patient.

Conclusion

Neoadjuvant chemotherapy and endocrine therapy trials are only appropriate for a minority of patients with large cancers, and their current standard end-points - pathCR and clinical response - are inconsistent in predicting long-term outcome. Their value is therefore limited, although the clinical benefit of neoadjuvant therapy in downstaging to avoid mastectomy remains valid.

In contrast, short-duration presurgical trials are applicable to many more patients, including those with smaller cancers, and the study of molecular marker changes in such trials may provide information valuable to efforts to individualise adjuvant treatment.

Competing interests

The author declares that they have no competing interests.

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