# Neoadjuvant chemotherapy for breast cancers: Current recommendations and future directions

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## Current recommendations for daily practice

### *Efficacy of neoadjuvant chemotherapy*

Allowing breast conservation without increased risk of breast cancer death is the primary goal of neoadjuvant chemotherapy in daily practice. A metaanalysis [1] has shown that neoadjuvant chemotherapy is not associated with an increased risk of death (hazard ratio = 1.00, 95% confidence interval (CI): 0.90 to 1.12), but was associated with an increased rate of breast conservation in five of these trials. Based on these randomised trials, most of the guidelines [2,3] consider neoadjuvant chemotherapy as a standard of care for women presenting a breast cancer that cannot be treated with breast conserving surgery. The clinical guidelines exclude patients with multifocal tumours from neoadjuvant chemotherapy.

### *Optimal regimen*

Several randomised trials have addressed the question of optimal regimen in the preoperative setting. Most of the trials that evaluated the efficacy of taxanes have reported improvement in pCR rates [4–7]. Based on these randomised trials, most of the guidelines recommend the use of both anthracyclines and taxanes for an overall 6 to 8 cycles.

### *Use of preoperative setting as a research tool*

Based on the observation that pathologic complete responses highly correlate with outcome [8], the setting of preoperative chemotherapy has been developed as a model to identify predictive biomarkers for treatment efficacy and to allow quick assessment of drug activity [9].

Overall, current guidelines recommend the use of neoadjuvant chemotherapy in patients with unifocal breast cancer who are not candidates for breast-conservative surgery. In addition, a panel of experts [9] recommends using the preoperative setting to identify predictive biomarker of efficacy.

## Integrating new technologies and new drugs in the preoperative setting: Does it change daily practice?

### *Molecular classifiers to predict the efficacy of preoperative chemotherapy*

A large body of evidence has been reported showing that women with a luminal A cancer, defined either by gene expression array [10] or immunohistochemistry [11], are unlikely to present a pathologic complete response after optimal neoadjuvant chemotherapy. Consistent with these studies, some papers have reported that the rate of breast conservation is lower in this molecular subset [12]. Based on these findings, and considering the risk of early progression, some experts currently consider that patients who belong to the luminal A subset (ER+/Her2−/grade I or Ki67low) are not eligible for preoperative chemotherapy.

Besides classifiers that identify patients who benefit from chemotherapy, several molecular classifiers have been generated in an attempt to predict the efficacy of a specific regimen (drug-specific predictors). As an illustration, a 30 genes-classifier has recently been shown to predict the efficacy of a preoperative paclitaxel-FEC regimen [13]. This classifier is being evaluated in a prospective randomised trial (Remagus 04). It must be emphasised that drug-specific predictors are currently suboptimal, due to the fact that they are usually generated from single arm trials. Biomarker analyses from randomised trials should generate more specific predictors.

### *New radiological tools*

Several studies have evaluated whether breast MRI and PET could better select patients for treatment. In a metaanalysis [14], MRI detected additional disease in 16% of women with breast cancer ($N = 2610$). Although this exam could better identify women who

are definitively not candidates for a breast conserving approach, its use is hampered by a high rate of false positivity. An MRI-based assessment of multifocality is now recommended, pending that this exam does not delay the start of treatment.

Several studies have evaluated the use of PET to identify early the patients who will not present a treatment response. In a study reported by Rousseau and colleagues [15], the sensitivity and specificity of PET to detect responders early were 61% and 96%, respectively.

### *Integrating new drugs with preoperative chemotherapy*

#### *Do new chemotherapy agents improve pCR rates?*

The efficacy of capecitabine has been assessed in several randomised phase II/III trials. In a phase II randomised trial [16], the pCR rates were 20% and 13% in the CEX (cyclophosphamide, epirubicin, capecitabine) and standard FEC arms, respectively. In the GEPARQUATTRO trial [17], capecitabine did not significantly improve the rate of pCR.

The combination of vinorelbine and capecitabine has been evaluated in the GEPARTRIO trial, in patients who did not respond to two cycles of TAC [18]. In this study, the NX combination did not improve the rate of pathologic complete response, but showed a better tolerability.

Several other new drugs have been evaluated in the context of phase II trials, including ixabepilone, gemcitabine and cisplatin. All these trials reported a significant rate of pCR in patients with ER-negative disease.

#### *Integration of targeted agents into a preoperative chemotherapy regimen*

Trastuzumab is the first targeted agent that has been integrated into a preoperative chemotherapy regimen. Randomised trials have shown that the addition of trastuzumab to chemotherapy improves both the rate of pathologic complete response and disease-free survival [19,20].

Several other targeted compounds are being integrated with chemotherapy, including lapatinib, bevacizumab and sunitinib. Further studies will define whether these compounds improve efficacy endpoints, are compatible with surgery, and to what extent pCR is still the most appropriate surrogate to assess their efficacy.

## Conclusion

Neoadjuvant chemotherapy is recommended for women presenting with unifocal breast cancer not eligible for breast conservation. Recent advances have allowed a better selection of patients either by increasing the rate of multifocal detection (MRI) or by identifying patients who are unlikely to benefit from chemotherapy (post-menopausal, luminal A cancer). Further trials will aim at integrating new agents into chemotherapy regimens, developing drug-specific predictors and assessing the medical usefulness of early detection of resistance (PET scan).

## Conflict of interest statement

None declared.

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