Primary chemotherapy of breast cancer followed by perioperative chemotherapy: feasible, but are there clinical benefits?

Systemic chemotherapy administered within a few days following surgery is often referred to as ‘perioperative’ chemotherapy [1]. While primary (preoperative) systemic chemotherapy and adjuvant postoperative chemotherapy are standard treatments for early breast cancer, perioperative chemotherapy is not. Relatively few randomised trials have evaluated either single agents or combination chemotherapy given during the perioperative period. A meta-analysis, based on five clinical trials and 6093 randomised patients, found perioperative polychemotherapy reduced the hazard ratio for disease-free survival by 18% (95% confidence interval 0.72–0.92), when the control groups received no systemic therapy. However, no reduction (0%) in the hazard ratio was observed when perioperative chemotherapy was added to postoperative systemic therapy. Of note, perioperative chemotherapy did not improve overall survival in this analysis [1]. Although perioperative chemotherapy has generally been well tolerated with the regimens used, there have been concerns of more frequent and severe postoperative complications and impaired wound healing following perioperative chemotherapy. Because preoperative chemotherapy has not improved survival compared with postoperative chemotherapy despite earlier timing [2], it seems unlikely that the few weeks time period between breast surgery and initiation of conventional postoperative systemic therapy plays any larger role. Thus, at present, perioperative chemotherapy appears to be associated with few or no proven benefits when added to another adjuvant systemic therapy. A recently reported randomised trial found a single perioperative dose of 14 mg/m² mitoxantrone ineffective in a series of 552 breast cancer patients, which merely serves to strengthen this view [3].

Yet, a closer look may make perioperative chemotherapy more appealing. The growth factors that initiate and maintain tissue healing after surgery might stimulate residual cancer cells, which may be detected at the time of surgery in the bone marrow of a considerable proportion of breast cancer patients [4]. A surgery-driven release of growth factors, such as tumour necrosis factor-α (TNF-α) [5], platelet-derived growth factor (PDGF), epidermal growth factor (EGF), heparin-binding EGF-like growth factor (HB-EGF) [6] and vascular endothelial growth factor (VEGF) [7], may be involved in growth stimulation of residual cancer. In a few rodent models, surgery-associated enhancement of residual tumour growth is more effectively inhibited by pre- or perioperative chemotherapy than by postoperative chemotherapy [8, 9]. Major surgery may also impair immunosurveillance and increase tumour cell shedding into the systemic circulation [10, 11]. Perioperative chemotherapy might be particularly effective in the prevention of locoregional recurrent tumours by inhibiting formation of implant metastases at the time of surgery. Interestingly, a meta-analysis found a single cycle of perioperative polychemotherapy to reduce the rate of breast cancer local recurrence by 26%, even when the control group patients received systemic adjuvant chemotherapy, while it failed to reduce the rate of distant metastases in the same studies [1]. One randomised study found a single course of 5-fluorouracil (5-FU), doxorubicin and cyclophosphamide given within 36 h of breast surgery reduced the locoregional recurrence rate as much as 50% [12].

In this issue, Colleoni et al. report results from a series of 54 breast cancer patients, with T2–3 N0–2 M0 disease, treated with primary chemotherapy followed by perioperative chemotherapy [13]. Therapy consisted of six preoperative 3-weekly cycles of ViFuP (vinorelbine 20 mg i.v. bolus on days 1 and 3, continuous 5-FU 200 mg/m²/day and cisplatin 60 mg/m² on day 1). Patients who responded to ViFuP were given perioperative chemotherapy consisting of single-agent continuous infusion 5-FU 200 mg/m²/day until breast surgery. 5-Fluouracil infusion was discontinued only 30 min prior to surgery, restarted immediately after surgery and then administered postoperatively for 15 days. A central infusion line and a portable elastomeric infusion system were used, and prophylactic antibiotic therapy was given at the time of surgery. The authors report a high pathological complete response (pCR) rate of 29% to this non-taxane, non-anthracycline regimen among the 49 patients evaluable for response, and a pCR rate as high as 33% among the 36 patients treated with both pre- and perioperative chemotherapy. They found perioperative 5-FU to be well tolerated with no detrimental effect on wound healing, and the entire treatment regimen was associated with moderate toxicity. Five (9%) patients discontinued preoperative chemotherapy because of deep venous thrombosis or venous port displacement, three (6%) further patients preferred to discontinue perioperative 5-FU before breast surgery, and 12 (22%) had grade 3 or 4 neutropenia.

Comparison of pCR rates achieved in uncontrolled studies of primary chemotherapy is difficult due to variations in the inclusion criteria, tumour sizes, thoroughness of pathological evaluation of the resection specimen and inclusion of in situ residuals in the category of pCR. The pCR rates obtained with primary anthracycline-containing systemic therapy regimens have generally varied between 6 and 19% (reviewed in [2]), but rates exceeding 20% have been obtained with regimens containing both a taxane and an anthracycline [14–16] or with a regimen containing an anthracycline and protracted continuous 5-FU for 6 months [17]. The pCR rate of the present combined pre- and perioperative approach compares well with these results, since the intention-to-treat pCR rate in the study reported by Colleoni et al. is 25% (14 out of 54 patients). If the patients with in situ cancer in the
resection specimen \(n = 2\) are not considered to have achieved a pCR, the intention-to-treat pCR rate is still 22% \(12\text{ out of } 54\). It is not known to what extent the perioperative component contributed to the high pCR rate achieved.

Patients entered on to the Colleoni et al. study were required to have cancer with a Ki-67 labelling index \(\geq 20\%\). The authors used this study inclusion criterion based on their previous results, according to which a Ki-67 labelling index \(\geq 20\%\) identified tumours with a greater chance of responding to primary chemotherapy. There are also other data suggesting that patients with hormone receptor negative cancer and those with a high Ki-67 labelling index respond more frequently to primary or perioperative chemotherapy \[18–20\]. Thus, the study entry requirement of a high Ki-67 labelling index makes it difficult to compare the response rate obtained with those of other studies where a high Ki-67 index has usually not been required. Selection of patients for chemotherapy based on a high Ki-67 labelling index may not be generally justified, because many patients with well differentiated and hormone receptor positive cancers also benefit from systemic chemotherapy \[21\], though achievement of response may take longer and responses may be more infrequent in such patients. According to two recent randomised studies, an attempt to improve the response rate of estrogen receptor-positive patients to primary chemotherapy by giving tamoxifen concomitantly with other chemotherapy resulted in no demonstrable improvement in benefit compared with the same chemotherapy alone \[18, 22\].

Finally, the study adds an interesting finding regarding the putative systemic growth factor burst that might make perioperative chemotherapy attractive. The authors measured serum VEGF concentrations the day before surgery, immediately after surgery and 1 day after surgery in the peripheral blood of 16 of their patients using an ELISA. The median serum VEGF values turned out to be similar, and the authors interpret this to support the possible favourable effect of perioperative chemotherapy on growth factors. The majority of patients who received perioperative chemotherapy were treated with conservative breast surgery \(29\text{ out of } 36; 81\%\), and according to one study, even major surgical operations requiring thoracotomy or laparotomy were associated with only small and transient elevations in the serum VEGF levels, and minor surgery such as tonsillecctomy was associated with no detectable elevations \[7\]. Although more research data are needed, conservative breast cancer surgery may not cause any marked and long-lasting rise in systemic VEGF and other growth factor levels, which would not argue for the routine use of perioperative chemotherapy.

In summary, the results of the Colleoni et al. study suggest that giving 5-FU at the dose of 200 mg/m²/day until breast surgery and immediately following surgery is feasible, and is not associated with severe toxicity or impairment of wound healing. Although neither anthracyclines nor taxanes were used, this novel approach was found to be effective, though efficacy comparisons with other regimens are difficult without a randomised study. The same goals might be possible to achieve in a practical and better tolerated manner using orally administered drugs, such as capecitabine. The clinical benefit of perioperative chemotherapy and the combined approach in comparison to standard systemic chemotherapy need to be demonstrated in controlled studies before their adoption into clinical practice.

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References