E8. Primary medical treatment – current status and future applications

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Adjuvant chemotherapy has been traditionally administered exclusively in the post-operative setting [1]. However, numerous studies have evaluated its use preoperatively [2]. This approach has been variously denominated neoadjuvant chemotherapy, primary chemotherapy, preoperative chemotherapy, up-front chemotherapy, and proto-adjuvant chemotherapy. The potential benefits of neoadjuvant chemotherapy include downstaging of the primary tumour to allow breast-conserving surgery and assessment of a tumour's *in vivo* sensitivity to individual chemotherapeutic regimens [2-4]. The largest study evaluating the impact of neoadjuvant chemotherapy was the National Surgical Adjuvant Breast Project (NSABP) B-18 [5] In this study, 1523 women were randomised to receive four cycles of doxorubicin and cyclophosphamide, either prior to or after surgical resection. The timing of chemotherapy did not affect the disease-free or overall survival for the entire cohort, although more patients who received preoperative therapy were able to undergo breast conservation rather than mastectomy in comparison to those treated postoperatively. However, an important finding in this study was the clear correlation of pathological complete response (pCR) in the breast (absence of invasive cancer cells) with survival [5]. In this study, using a single chemotherapy regimen, the pCR rate was 13%. However, this did not include absence of lymph node involvement, but did include residual ductal carcinoma *in situ* in the breast. The pCR rate has become one of the most important intermediate trial endpoints in assessing the efficacy of new adjuvant chemotherapy regimens [6,7]. A second large randomised clinical trial had an identical design, and was implemented by the European Organisation for Research and Treatment of Cancer (EORTC) [8]. This study, while half the size of NSABP B-18, confirmed the findings of B-18, with equivalent survival rates and an increased rate of breast-conserving therapy after neoadjuvant chemotherapy.

A similar association between pathological response and survival was shown when axillary lymph nodes were cleared after neoadjuvant 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) chemotherapy at the M.D. Anderson Cancer Center [7]. Published studies of anthracycline-based pre-operative chemotherapy demonstrate pathological complete response rates of up to 17% [6–9]. Several recently reported studies, including the sequential use of anthracycline-based regimens and taxanes, have achieved significantly higher pathological responses ranging from 25 to 34% [10–14]. For instance, the NSABP B-27 compared neoadjuvant chemotherapy with 4 cycles of doxorubicin and cyclophosphamide (AC) with the same followed by 4 cycles of docetaxel (AC+T). pCR rates were twice as high in the AC+T arm as in the AC arm. Another smaller study by Smith and colleagues, using an AC-like regimen followed by docetaxel suggested that both responders and non-responders to the AC-type regimen benefited from crossover to the taxane, in terms of higher response rates and longer time to progression and survival [12]. Whether these results can be confirmed in B-27 and other trials remains to be seen. Longer follow-up is necessary to determine whether these high pathological response rates seen from the sequential use of the taxanes in the preoperative setting will translate into a favourable impact on survival.

However, should pCR be validated by additional trial results as an accurate surrogate marker of long-term outcome, and, even more importantly, if improvements in the pCR rates can be shown to have a commensurate effect on long-term survival, we could short-cut the process of evaluation of adjuvant systemic therapies and accelerate the assessment of new systemic interventions by converting to the systematic use of neoadjuvant chemotherapy.

However, there are several questions remaining related to the use of this strategy. Some relate to optimal local-regional therapies: when should axillary assessment be performed in relation to neoadjuvant chemotherapy, what should the criteria be for the administration of post-mastectomy radiation therapy following neoadjuvant chemotherapy, and how to optimally perform breast-conserving surgery following neoadjuvant chemotherapy [15–18]. The role and relative timing of neoadjuvant hormone therapy is also under intensive evaluation at this time. This is solely relevant to the group of patients with hormone receptor-positive tumours, but has potential impact on the type and sequence of local, regional and systemic therapies.

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