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Should Surgery Remain the Initial Treatment of "Operable" Breast Cancer?

SURGERY HAS traditionally enjoyed a prominant role in the primary treatment of most stages of breast cancer. The value of surgery in providing diagnostic security and allowing access to important prognostic information appeared unassailable, and the contribution of surgery to the control of local and regional disease was unquestioned. During the past two decades, however, two important developments have led to a reassessment of the breast surgeon's role. Firstly, prospective clinical trials evaluating breast conservation in early stages of the disease have demonstrated convincingly that the use of breast irradiation allows the extent of primary surgery to be drastically reduced, while maintaining adequate disease control [1–4]. Secondly, the appreciation of breast cancer as a systemic illness has led to the scientific investigation and widespread application of adjuvant systemic therapies in high risk patients, promising for the first time to change the natural history of the disease [5]. More recently, the putative successes of hormonal and chemotherapies have prompted their frequent use as adjuvants even in patients traditionally viewed as having a "good" prognosis, e.g. node-negative patients [6, 7], thus at least partially obviating the need for an axillary staging operation.

WHICH TREATMENT SHOULD BE FIRST?

A logical outgrowth of the above considerations is the use of "up front" systemic therapy, following establishment of the diagnosis by fine-needle aspiration cytology or limited biopsy of the primary tumour. Such treatment, variously termed "neo-adjuvant", "induction", "preoperative", or "primary", most frequently involves the administration of several cycles of combination chemotherapy. Based upon excellent response rates observed in the treatment of locally advanced stage III breast cancer [8, 9], primary chemotherapy is now under intensive investigation for less extensive lesions (Table 1). This strategy offers both real and theoretical advantages. Firstly, the objective response of the tumour can be observed, allowing the treatment to be continued in the event of a favourable response, or otherwise to be abandoned or modified. The second concrete advantage is to offer the possibility of breast preservation to patients who are not candidates for classical breast-conserving techniques because of an unfavourable ratio between tumour

Table 1. Summary of objective response rates and rates of breast-conserving treatment in published studies of primary chemotherapy for operable breast cancer

Study [ref.]	*n*	Tumour size	Chemotherapy cycles	Objective response CR/PR (%)	Conservative procedures (%)
Mauriac [10]	134	T>3 cm	3 EVM + 3 MiTVi	33/?	63
Bonadonna *et al.* [11]	165	T>3 cm	3–4 CMF or 3–4 FAC or 3 FEC	17/60	88
Jacquillat *et al.* [12]	250	T1–T4	3–6 VeTMFP +/− A, +/− TAM	30/41	100*
Scholl *et al.* (pp.1668–1671)	95	T>2 cm	2 FAC	13/32	79*
Spielmann *et al.* [13]	119	T>2 cm	3 AVCMF	9/61	53
Hortobagyi *et al.* [14]	128	Stage II–IV	4 FAC	14/60	27

*Treatment included radiotherapy given immediately after primary chemotherapy. A = doxorubicin, V = vincristine, C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, E = epirubicin, Mi = mitomycin, T = thiotepa, Vi = vindesine, Ve = vinblastine, P = prednisone, TAM = tamoxifen.

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size and breast volume. On a more hypothetical basis, the use of primary as opposed to conventional postoperative chemotherapy might prolong survival, in that its early, intensive administration might minimise the appearance of drug-resistant phenotypic variants [15]. In addition, this approach avoids the possible unfavourable influence of primary tumour removal on the growth kinetics of micrometastases [16].

STUDIES OF PRIMARY CHEMOTHERAPY

Evaluation of the existing literature is difficult because of the heterogeneity in patient selection, variability in chemotherapeutic combinations, differing criteria for the use of radiotherapy and surgery, and limited follow-up. Most of the reported experience consists of non-randomised pilot studies, a detailed analysis of which is beyond the scope of this paper. Although some investigators favour the use of primary chemotherapy for patients in all operable stages, the most frequent selection criterion for inclusion into primary chemotherapy programs is a clinical tumour size judged too large for conservative surgery and radiotherapy. A recent survey of 19 French cancer centres indicated that 16 institutions had protocols for the primary chemotherapy of operable breast cancers 3 cm or larger in diameter [17], smaller tumours being treated preferentially by conservative surgery, radiotherapy, and selective adjuvant systemic therapy.

The article by Scholl *et al.* (pp. 1668–1671) is of particular interest in that it represents the second published prospective, randomised study devoted to primary chemotherapy. A previous study carried out in Bordeaux [10] allocated 272 patients with tumours larger than 3 cm to receive either primary chemotherapy or primary modified radical mastectomy, reserving the same chemotherapy in the latter group as a postoperative adjuvant for patients with positive axillary nodes and/or negative hormone receptors. The short-term results of this study are encouraging, in that primary chemotherapy not only enabled 63% of patients to be treated with preservation of the breast (requiring a reduction of tumour size to 2 cm or less), but resulted in a superior overall survival compared to that of patients treated with mastectomy and selective adjuvant chemotherapy.

In contrast to the Bordeaux trial, the question asked by the Curie Institute study by Scholl *et al.* was almost purely one of timing of chemotherapy. It was planned to administer six cycles of the same chemotherapy to all patients in each arm, with the first two cycles given prior to local-regional treatment in the primary chemotherapy arm; provision was made for modification of the chemotherapy regimen in the event of a poor response to the initial two cycles. Unfortunately, the fundamental questions raised in association with primary chemotherapy remain unanswered by this study, since group discipline apparently did not allow the trial to be carried out as designed. Only 72% of the randomised patients actually received the therapy as assigned, and an unspecified number of postmenopausal patients received hormone treatment. Thus the failure to show differences in overall and disease-free survival must be viewed with caution, as significant differences might have been demonstrated if strict adherence to protocol had been practiced. The results of a new "improved" study from the Curie group is promised for the near future.

Response rates to primary chemotherapy

Nonetheless, this paper should not simply be dismissed as yet another negative study, as it contains interesting observations relevant to the use of primary chemotherapy. First, response rates are documented for patients in this study who actually received primary chemotherapy (clinical stage II and IIIA patients with a mean tumour diameter of 5 cm). After two cycles of doxorubicin, 5-fluorouracil and cyclophosphamide, clinical complete response (CR) and partial response (PR) were observed in 13% and 32%, respectively with a minor response in 45% and only 1 patient showing disease progression. The relatively modest response rates probably reflect the early evaluation after only two courses of therapy. The observation that better response was obtained in patients who received more than 75% of the planned dose suggests that, at least for short treatment courses, dose intensity might be a determining factor in achieving the desired effect. In addition, data from other studies (Table 1) generally indicate higher response rates after more prolonged (if not necessarily more dose-intensive) chemotherapy. After four to six cycles of combination chemotherapy, with or without tamoxifen, CR rates of 30–33% have been observed [10, 12]. The observation of Scholl *et al.* that disease-free survival was superior in patients showing an objective response is consistent with the experience of Jacquillat *et al.*, who showed that tumour regression after primary chemotherapy was an important independent prognostic variable in a multifactorial analysis [12].

Breast preservation after primary chemotherapy

More relevant to the issue of breast preservation is the capacity of primary chemotherapy to reduce the primary tumour to a size which permits a breast-conserving procedure to be carried out. For most investigators, this connotes a tumorectomy or quadrantectomy with axillary dissection in the event of adequate tumour regression [11, 13, 14], or in some centers, radiotherapy alone after clinically complete response [10]. Rates of breast-conserving procedures vary from 27–83% after primary chemotherapy (Table 1), presumably reflecting variability in the distribution of tumour sizes, intensity of chemotherapy, and criteria for "adequate" response. Particularly impressive results were reported by Bonadonna *et al.* [11] in a prospective series of tumours larger than 3 cm in diameter; tumour reduction sufficient to allow quadrantectomy (less than 3 cm), was achieved after three or four cycles of chemotherapy in 86% of patients with tumours between 3 and 5 cm in diameter, and in 59% of patients with larger tumours. This result appeared to be independent of the chemotherapy regimen employed, and was similar for both premenopausal and postmenopausal patients.

The data of Scholl *et al.* do not provide as clear a picture of the contribution of primary chemotherapy to the possibilities of breast conservation, since they introduce an important new element into the equation. True to the traditions of the Curie Institute [18], the primary local-regional treatment used in both arms was not surgery, but radiotherapy delivered to both the breast and regional nodal areas. Surgery, intended to be "as conservative as possible," was implemented only after completion of radiotherapy, although decision-making criteria were not provided by the authors.

When should radiotherapy be implemented?

This raises the question of the precise role of radiotherapy in a strategy designed to avoid mutilating surgery in patients with tumours considered too large for primary tumorectomy. Although it is clear from retrospective studies that breast preservation can be achieved in a variable percentage of stage II–IIIA cancers by radiotherapy alone without surgery [18–20], this approach has never gained wide acceptance outside of France. In the study of Scholl *et al.*, breast preservation could

be attempted in all but 36% of patients in the primary radiotherapy arm, and in 34% a surgical intervention could be avoided altogether. The addition of two cycles of primary chemotherapy prior to radiotherapy improved the breast conservation rate from 64% to 77%, suggesting that the contribution of chemotherapy in this regard was real, but relatively modest.

Jacquillat *et al.* [12] have also evaluated reponse, local control, and survival in 250 stage I–IIIB patients after a full course of radiotherapy administered following a more intensive programme of primary chemotherapy. One of the stated aims of this combined treatment programme was to reserve surgery exclusively for the treatment of local recurrence. Clinically complete tumour disappearance was noted in all patients after chemo-radiotherapy, which resulted in a breast preservation rate of 94% at 5 years. Grade 2 or 3 toxicity was observed in 9% of patients, and cosmetic results were judged excellent or good in 88%.

CONCLUSIONS

It is too early to judge to what extent the possible advantages of primary chemotherapy translate into real benefits for the breast cancer patient. Nonetheless, over a period of less than 10 years, much has been learned about primary chemotherapeutic approaches to operable breast cancer, but many unanswered questions remain. A certain number of general conclusions can be drawn from existing studies. Firstly, primary chemotherapy results in tumour regression in a large majority of patients, with clinical CR in 9–33%, depending upon case selection and intensity of treatment. Secondly, disease progression during primary chemotherapy is observed in 0–2% of patients. Thirdly, similar results have been achieved with a variety of chemotherapeutic regimens. Fourthly, objective response to primary chemotherapy translates into superior disease-free survival in comparison with that of non-responders. Fifthly, if selection criteria of tumour size are respected, primary chemotherapy allows increased use of conservative surgery in conjunction with radiotherapy for patients not considered candidates for classical breast-conserving treatment. Finally, the use of radiotherapy immediately after primary chemotherapy is under investigation with regard to increasing the frequency of breast-conserving procedures.

The unanswered questions may be summarised as follows.

What are the true disadvantages of dispensing with the prognostic information, particularly the lymph node status, traditionally provided by analysis of the primary surgical specimen? Will treatment decisions become less objective? Will the comparability of therapy results be made more difficult? Will the conduct of clinical trials be jeopardised? Such questions seem legitimate, despite the availability of nuclear grading, hormone receptor assessment, flow cytometric studies, and other analyses from fine-needle aspirate or drill biopsy material.

Given the potential toxicity of chemotherapy, on the basis of what criteria should patients be selected for such treatment?

What is the influence of primary chemotherapy on long-term disease control and survival compared with those associated with "adjuvant" postoperative chemotherapy, assuming similar criteria for choice of operation in each group? This question is currently under investigation in a large, multicentric study [21].

What is the optimal regimen, dose intensity, and number of cycles of primary chemotherapy? What is the role of additional chemotherapy after local-regional treatment? What is the role of hormone therapy?

How should response be evaluated, and at what point in time should this assessment be performed? What strategy should be proposed for non-responders?

At what point and according to what criteria should the choice of local-regional treatment be made? Should patients in CR after chemotherapy be treated by radiotherapy alone?

Does the use of radiotherapy after primary chemotherapy enable most patients to be safely treated without resorting to any kind of surgical intervention?

What are the potential problems associated with surgery (particularly conservative sugery) after chemotherapy or chemo-radiotherapy (localisation of residual tumour, control of adequacy of excision, problems of wound healing, etc)?

Which radiotherapy techniques are best suited for use after primary chemotherapy (volume, dose, fractionation, type of boost therapy)?

What are the clinical problems presented by the follow-up of such patients, and what are the long-term results and compliations?

Although surgery continues for the present to be considered the standard initial step in the treatment of operable breast cancer, strategies using primary systemic therapy represent an exciting area of clinical research that deserves to be pursued further. It is apparent that such complex treatment programmes require close collaboration among all members of a multidisciplinary breast cancer team, in order to best define the optimal contribution of each modality. To this end, it is essential that further controlled clinical trials be designed to address the important questions raised by this radically new approach to one of the most common oncological problems.

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New Anthracycline Derivatives: What For?

ANTHRACYCLINES ARE probably the most utilised antitumour drug worldwide, and a majority of patients needing systemic treatment for cancer receive either daunorubicin or doxorubicin at some time during their clinical course. There is a difference of only a single hydroxyl group between the chemical structures of daunorubicin and doxorubicin (Fig. 1). Despite only a minor difference in chemical structure, there is a marked difference in their antitumour efficacy. Daunorubicin is one of the major drugs for the treatment of acute leukaemias [1] and doxorubicin is a major drug for the treatment of malignant haematological diseases as well as for the treatment of solid tumours [2, 3]. The clinical success of doxorubicin and this disparity between daunorubicin and doxorubicin in spectrum of antitumour effect resulting from a minor molecular change has been the impetus for a diligent search for other effective or less toxic anthracycline analogues.

Anthracyclines are polyfunctional molecules, both chemically and biologically. The current thinking is that these structures have access to multiple mechanisms, which can act in concert, but in varying patterns with structural changes. Unraveling these chemical reactions into those that are desirable (toxicity to the cancer cell) and into those that are not (toxicity to the organism) is an enigma, recently rendered less inscrutable.

A logical site of biochemical action in the anthracycline molecule is the quinone = ring C in Fig. 1, which is known to undergo reduction and reoxidation processes involving one or two electrons. Single-electron redox cycling leads to enhanced production of cytotoxic free radicals, two-electron reduction can lead to quinone methide structures that function as alkylating agents [4, 5]. There is preliminary progress indicating that catalytic redox turnover contributes a significantly greater extent to the host cytotoxicity, rather than to the antitumour activity. Tumour cytotoxicity does not involve any redox event [6]. Furthermore, the present understanding of anthracycline structure–activity relationship does not demand intercalation as a necessary event of the tumour cytotoxicity [7] as it was thought before [8]. As it now stands DNA damage via aerobic degradation, covalent labelling by the quinone methide, or even related to the topoisomerase cleavable complex provide reasonable explanations for the anticancer activity although the exact molecular lesions involved have not been determined exactly up to now.

Analogues of daunorubicin or doxorubicin might be less myelotoxic, less cardiotoxic, less emetogenic, less toxic to the gastrointestinal tract (stomatitis/mucositis), have a broader range of activity, and ideally and clinically important, lack of crossresistance to the parent compound. Of all toxicities mentioned, most attention is called to cardiotoxicity. In the case of curability, it is an important aspect; in case of palliation it is not. Cardiotoxicity is a major problem of anthracycline therapy if the patient can be cured by intensive anthracycline treatment. There is a clear indication that the treatment for a potential fatal childhood cancer (e.g. acute lymphoblastic leukaemia) may cause another serious or fatal disease. A high incidence of late cardiovascular abnormalities in children who received anthracyclines were observed [9]. There has been a growing tendency to associate anthracycline redox cycling and radical production with chronic anthracycline cardiotoxicity [10, 11]. Myocardial alteration due to free radical generation was described in experimental settings [12, 13] and such alterations are similar or even identical to those observed after anthracycline therapy [14], a fact which might be related to the fact that the biochemical equipment to defend the heart cells to free radical attacks by free radical scavengers and by enzyme systems for detoxification (catalase, superoxide dismutase, glutathione) is reduced in heart cells.

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