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Feature Articles

Treatment of Relapse of Breast Cancer After Adjuvant Systemic Therapy — Review and Guidelines for Future Research

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INTRODUCTION

MOST PATIENTS with early breast cancer now receive adjuvant systemic therapy as part of primary treatment. This leads to a significant improvement in survival [1], but there is concern that it may compromise our ability to treat effectively the disease after relapse. The purpose of this review is to examine the available evidence, consider possible mechanisms for an impaired response of advanced disease to treatment and assess the implications for clinical practice.

CLINICAL EXPERIENCE (Table 1)

That adjuvant treatment might be associated with a poor response to treatment on relapse was first suggested in 1981 [2], but, in the same year, others claimed that the response frequency of advanced disease to either endocrine treatment or chemotherapy was not impaired by prior systemic therapy [3]. The first substantial report came from the amalgamated data of two trials of adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) carried out in Milan [4]. After prior CMF, 38/125 (30%) responded to endocrine treatment compared with 10/25 (40%) who had not had adjuvant treatment. The respective figures for first-line chemotherapy for advanced disease were 32/83 (39%) and 21/55 (38%). The conclusion was that adjuvant chemotherapy did not compromise treatment after recurrence.

Although response frequencies similar to the above were seen at the Mayo Clinic, a different conclusion was reached [5]. In a report of 257 patients who had relapsed after previous adjuvant treatment with a combination of cyclophosphamide, 5-fluorouracil and prednisolone with or without tamoxifen, the response to endocrine treatment was 47/161 (29%) of median duration 13 months and for chemotherapy 43/156 (28%) of median duration 8 months; median survival from first relapse was 22 months. The response of advanced disease to endocrine treatment was particularly poor if adjuvant treatment had included tamoxifen. Intervening chemotherapy after relapse lowered the response to hormonal therapy, but the converse did not apply.

Clearer evidence of a low response rate to treatment in advanced disease after adjuvant chemotherapy came from experience at Guy's Hospital [6]. Premenopausal patients with stage II breast cancer were randomised to receive postoperative CMF or no adjuvant treatment. 7/38 (18%) patients who relapsed after adjuvant CMF responded to endocrine therapy compared to 23/61 (38%) ($P<0.05$) who had not had adjuvant treatment. For first-line chemotherapy for advanced disease, the figures were 6/26 (23%) and 24/51 (47%) ($P=0.05$), respectively. Significant differences in favour of no prior CMF were also found for time to progression ($P<0.03$), but survival from first relapse was the same irrespective of whether or not adjuvant chemotherapy had been given.

Similar results were reported by the French Epirubicin Study Group [7].477 patients in two consecutive trials received either epirubicin alone or in various combinations with 5-fluorouracil and cyclophosphamide for advanced disease. Stratifying for prior adjuvant CMF, those who received this treatment had a response frequency of 44/137 (32%) compared to 163/340 (48%) ($P=0.03$) in those without previous adjuvant treatment. In addition to the lower response frequency, prior adjuvant treatment was associated with a significantly shorter time to treatment failure ($P=0.002$), and reduced survival after relapse ($P=0.001$). Similar observations were made in another series [8].

Less information is available on the effect of adjuvant endocrine treatment on the responsiveness of advanced disease to systemic therapy. In the Stockholm Breast Cancer Study Group trial, testing adjuvant tamoxifen 40 mg daily for 2 years against no treatment, 378 patients out of 1159 randomised relapsed, of

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Table 1. Results of systemic therapy following recurrence after adjuvant therapy for primary breast cancer

Reference	Adjuvant therapy	Systemic therapy after relapse: Treatment*	*n*	Responses	Duration (months)	TTP (months)
3	FAC	CT	38	15 (39%)	16	—
	FAC	HT	35	14 (40%)	16	
4	CMF	HT	125	38 (30%)	19	—
	None	HT	25	10 (40%)	17	—
	CMF	CT	83	32 (39%)	17	—
	None	CT	55	21 (38%)	16	—
5	CFP ± TAM	HT	161	47 (29%)	—	13
	CFP + TAM	CT	156	43 (28%)	—	8
6	CMF	HT	38	7 (18%)	—	4
	None	HT	61	23 (38%)	—	5
	CMF	CT	26	6 (23%)	—	2
	None	CT	51	24 (47%)	—	4
7	CMF	CT	137	44 (32%)	—	6
	None	CT	340	163 (48%)	—	9
9	TAM	HT	28	4 (14%)	—	4
	None	HT	26	14 (54%)	—	15
10	TAM	HT	28	3 (11%)	—	—
	TAM	CT	44	13 (30%)	—	—

*Only responses to first-line hormonal (HT) or first-line chemotherapy (CT) are given. TTP, median time to progression; FAC, 5 fluorouracil, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; CFP, cyclophosphamide, 5-fluorouracil and prednisolone; TAM, tamoxifen.

whom 54 were evaluable for the response of advanced disease to either tamoxifen alone or in combination with fluoxymesterone [9]. The objective response rate was significantly lower among patients in the adjuvant tamoxifen group compared to the controls, 4/28 (14%) compared to 14/26 (54%) ($P < 0.01$). The median time to progression was also significantly shorter (4 versus 15 months; $P < 0.05$). In an analysis of 673 patients at Guy's Hospital who received adjuvant tamoxifen, 142 relapsed. Response to endocrine treatment for advanced disease was only 3/28 (11%) and to first-line chemotherapy was 13/44 (30%) [10].

The balance of evidence indicates that adjuvant systemic treatment compromises response of the disease to either endocrine therapy or chemotherapy after relapse. It has also been suggested that patterns of relapses may be affected by prior adjuvant treatment with an increased incidence of liver metastases after chemotherapy, and a higher proportion of patients with pulmonary metastases after endocrine treatment [11]. However, the poorer outcome after relapse does not outweigh the benefits from adjuvant chemotherapy in prolonging survival [1]. On relapse after adjuvant tamoxifen, the disease also appears to be less amenable to endocrine treatment. This applies particularly to the use of tamoxifen, but it is less clear if the response to other agents, such as progestogens or aromatase inhibitors, is also impaired. There is no evidence so far to suggest that responsiveness to chemotherapy is lower after adjuvant endocrine treatment.

MECHANISMS OF IMPAIRED RESPONSE

The biochemical mechanisms of resistance of breast cancer to either chemotherapy or endocrine treatment *in vivo* are not known. Considerable evidence points to P-glycoprotein overexpression as a mechanism for resistance to various cytotoxic drugs, such as the anthracyclines and vinca alkaloids [12]. Preliminary data suggest that this could explain resistance of breast cancer to these drugs *in vivo* [13–15], while results from *in vitro* experiments suggest that other mechanisms could also be involved [16,17]. For endocrine treatment, altered secretion of transforming growth factor-β (TGF-β) by stromal cells [18,19], as well as alterations in intracellular drug metabolism and transport [20], have been suggested as possible mechanisms for tamoxifen resistance. Of particular interest is the lack of cross-resistance between different endocrine treatments, for example, that between tamoxifen and aminoglutethimide [21–23], which is difficult to explain on the basis that both treatments act by depriving tumour cells of oestrogenic stimulation.

In the absence of adequate experimental data, consideration of the mechanisms of impaired response following previous treatment has to be based on theoretical considerations and hypothetical deductions from clinical observations. One possibility is that previous adjuvant therapy could induce acquired resistance and so impede the effect of later treatment. An alternative hypothesis is that a reduced response to later treatment may, at least in part, be due to selection of primary resistant cells. Adjuvant chemotherapy and endocrine therapy each improve long-term and disease-free survival [1]. Whether or not some patients have their micrometastases completely eradicated or tumour growth is delayed for a long time, the numbers of patients who relapse is reduced after adjuvant treatment. Such therapy would, therefore, be expected to reduce both the number and the proportion of patients with tumours sensitive to

treatment among those who relapse (Fig. 1). Thus, the finding of a lower response rate among patients relapsing after adjuvant therapy is not in itself evidence of acquired resistance.

FEASIBILITY OF STUDYING DRUG RESISTANCE

Study of the mechanisms of drug resistance is a major challenge. Primary resistance needs to be evaluated in prospective studies which relate response to systemic treatment and biological parameters measured in biopsies and/or plasma samples obtained immediately before treatment. Any delay between the time of sampling and start of treatment may lead to erroneous conclusions. While oestrogen and progesterone receptors, measured in primary tumours, predict response to endocrine treatment in metastases appearing years later, this may not be so for other parameters. Cancer cells undergo evolutionary changes and adjuvant therapy may alter tumour biology.

As reviewed above, adjuvant therapy influences the response of breast cancer to later treatment, and a high proportion of primary drug-resistant cells in metastases is not likely to be representative of the biology of the untreated primary tumour. There is also the possibility that the metastatic process itself could select cells with particular characteristics such that certain parameters are expressed differently in primary and secondary tumours [24]. Any difference in the expression of biochemical parameters among tumours subsequently responding or not responding to a particular treatment provides no certainty that they represent the mechanism underlying primary resistance. It is well known that expression of certain tumour characteristics such as receptor status, thymidine labelling index, ploidy, genetic alterations, growth factors and histological grading can correlate with each other statistically [25–29], and expression of the *mdr* phenotype in cells has also been related to biochemical mechanisms of resistance not due to P-glycoprotein overexpression [17,30,31].

Acquired resistance develops over time, and to study it we must assess alterations in tumour biology developing during treatment in individual patients. While primary systemic therapy of primary tumours appears to be an excellent model in which to study primary drug resistance, the treatment of advanced disease is probably a better one for the study of acquired resistance. For this we need to obtain sequential samples both before starting and during the treatment in order to study biological changes when acquired resistance evolves. In practice, this is difficult to achieve as many patients do not have accessible metastases or it is clinically inappropriate to subject them to repeated biopsies.

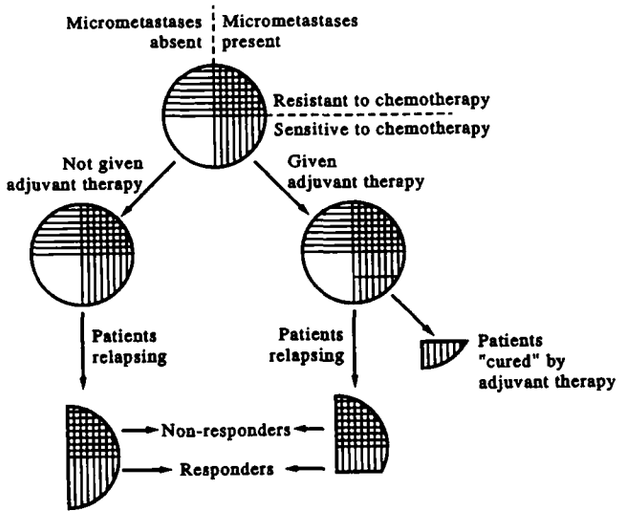

Fig. 1. Illustration of the hypothesis of how adjuvant systemic therapy may lower the proportion of patients responding to later treatment by reducing the incidence of relapse in patients with drug-sensitive tumours.

Two subgroups of patients with locoregional relapses are suitable for sequential biopsies: patients with multiple, small nodules that may easily be removed, or patients with a single, large tumour suitable for sequential needle biopsies. However, there is always the problem of intratumour variation in the expression of biochemical parameters. While the possibility exists that different nodules may have different biological characteristics, such variation may also exist between different areas within a single tumour mass.

Considering endocrine treatment, many tumours lack oestrogen receptors and are not apparently under endocrine control [31]. These tumours are not expected to respond either to oestrogen deprivation or to anti-oestrogen treatment, but this still occurs in 5–10% of cases. Yet some receptor-positive tumours do not respond to primary endocrine therapy [32–34], and so it is unclear whether or not the mechanisms of primary resistance and acquired resistance in receptor-positive tumours could be similar.

Ideally, studies on the mechanisms of either primary or acquired resistance should be limited to patients treated with single agents given at optimal dosage. This also offers the opportunity to study cross-resistance if a sequential design is used. Biochemical observations in patients treated with combined chemotherapy and hormone therapy would be particularly difficult to interpret. This approach does not conflict with good practice in the management of advanced breast cancer for which the different treatments are generally used alone, sequentially. A particular problem in studying the effects of endocrine treatment is that many patients with advanced disease would have had prior adjuvant tamoxifen, or, if not, tamoxifen is generally given as first-line therapy on relapse. This is likely to impair the study of subsequent forms of endocrine therapy, such as aromatase inhibitors. Apart from possible modifications in tumour biology caused by tamoxifen therapy, a major problem is the long retention time of this drug and its metabolites [35], detectable tissue levels being found in patients several months after terminating treatment [36]. Thus, while it may be important to obtain samples in relation to treatment with aromatase inhibitors or high-dose progestins from patients who have been off tamoxifen for sufficient time, this is not usually practical.

As already mentioned, the use of combination chemotherapy makes it difficult to determine which drug could be responsible for an observed alteration. Some conclusions may be drawn from results obtained *in vitro* where certain drugs, for example the anthracyclines and vinca alkaloids, have been found to be associated with the *mdr* phenotype [37], while resistance to other drugs, like the alkylating agents, relates to an increased expression of glutathione sulphotransferases (GSTs) [38]. However, we should be cautious about extrapolating such results to patients. The possibility that a drug may have several mechanisms of action, and that more than one may be responsible for clinical resistance to a drug should always be considered. The anthracycline group of drugs may be used as an example to illustrate this. While these drugs are thought to exert their cytotoxic effect at the DNA level [39–41], other actions have also

been suggested [16,42]. Anthracyclines have been considered to be substrates for the P-glycoprotein pump [43,44], but recent *in vitro* investigations have related doxorubicin resistance to other mechanisms [45].

An indirect approach could be to compare alterations caused by different drug combinations (like combinations A+B versus combinations A+B+C). However, such comparisons assume the action of the different drugs simply to be additive, and the possibility of pharmacokinetic as well as pharmacodynamic drug interactions should always be kept in mind. However, the use of single agents to treat advanced disease is often justified. Treatment with doxorubicin alone at high dose (70–75 mg/m^2 every 3 weeks) gives similar response rates to combination chemotherapy, and is suitable for many patients with advanced disease [46,47], providing a more satisfactory opportunity to study the development of resistance which can also be related to dose intensity.

IMPLICATIONS FOR CURRENT PRACTICE

For locoregional relapse after mastectomy and adjuvant treatment, prognostic factors are the disease-free interval, initial clinical stage, histological grade, extent of axillary nodal involvement, the number and location of recurrences, effectiveness and type of local therapy, the use of adjuvant systemic and radiation therapy [48]. Local treatment with surgery or radiation therapy, according to the clinical characteristics of the tumour and previous treatment, is appropriate, but the risk of further recurrence is high, and prognosis is generally poor [48]. Given this poor prognosis after local relapse, it may be reasonable to give adjunctive chemotherapy or hormone treatment to these patients. This approach needs evaluating in clinical trials in which multivariate analyses take note of relevant prognostic factors, including prior adjuvant treatment.

The prognostic significance of local recurrence after mastectomy is worse than after breast conserving treatment; in the latter case, it is often confined to the breast, and there is still the possibility of potentially curative mastectomy [49]. Prognostic factors are the histological type, tumour size at recurrence, diffuse infiltration of the breast or lymphatic involvement. Local treatment is surgical, usually mastectomy, but wide local excision is sometimes possible. As for locoregional relapse after mastectomy, the indications for systemic therapy are ill-defined. Systemic therapy could be considered for poor prognosis patients, preferably within a clinical trial.

Treatment of disseminated disease is medical, and whether to choose chemotherapy of hormone therapy depends on many factors: age and general status of the patient, duration of the relapse-free interval, oestradiol and progesterone receptors, sites of metastatic disease, the presence of clinical symptoms and previous adjuvant cytotoxic or hormone treatment.

For patients relapsing after adjuvant hormonal therapy, the most important clinical parameters to consider are probably the duration of hormonal therapy and disease-free interval. The possibility of further endocrine therapy, for example, with an aromatase inhibitor, should first be considered. When patients have relapsed within 2 years of starting adjuvant endocrine treatment, the responsiveness to another hormonal approach is likely to be poor, although absolute refractoriness is not definite. The clinical decision to use either endocrine therapy or chemotherapy should be based on all available clinical data, particularly the location of metastases and total tumour burden. Extensive visceral involvement is generally an indication for chemotherapy.

After adjuvant chemotherapy, options include either endocrine or further chemotherapy. Important parameters are the disease-free interval, the intensity of prior adjuvant chemotherapy, the drugs used and performance status. In addition to these clinical parameters, oestrogen and progesterone receptors may help in the decision process, but it should be remembered that prior tamoxifen may interfere with the dextran-coated charcoal assay [50,51]. The use of new techniques, utilising monoclonal antibodies recognising receptors irrespective of whether they are bound or unbound to ligand, are to be preferred [52]. It should also be noted that tamoxifen may increase levels of oestrogen and progesterone receptors [53]. If this is a reversible effect, receptor measurements shortly after stopping tamoxifen therapy could give inaccurate predictive information.

For the integration of new cell biological prognostic factors into daily clinical practice, we not only need to know their prognostic power for prediction of relapse-free and overall survival, but also any possible relationship with response to endocrine treatment or chemotherapy, in order for them to be used optimally to select treatment for an individual patient [29,54]. A large number of cell biological parameters are currently available to predict the prognosis of patients with breast cancer, but it is still difficult to predict accurately the response to treatment. A valuable prognostic factor may be a worthless predictive factor to endocrine or chemotherapy, or *vice versa*. High tumour levels of oestrogen, progesterone and androgen receptors, and PS_2 protein predict a relatively good response to endocrine therapy, while epidermal growth factor receptor positivity, HER2/*neu* positivity, aneuploidy, high proliferation indices, and possibly high urinary plasminogen activator levels, indicate a likelihood of a poor response to endocrine therapy in metastatic breast cancer. With respect to chemotherapy, a high proliferation rate and HER2/*neu* amplification predict a good response to therapy in metastatic disease, while *mdr* gene expression and possibly c-*myc* amplification are related to a worse response. Thus, we anticipate that the newer cell biological parameters should become increasingly useful in the identification of prognostic subsets of patients and the selection of systemic treatment, and they could also be targets for new approaches to treatment.

Combining endocrine therapy and chemotherapy may yield higher response rates than either used singly [55,56], but in practice such combinations provide additive results at best, and are sometimes partially antagonistic. Thus, endocrine treatments and chemotherapy should preferably be used independently in sequence [57,58]. New promising hormonal or cytotoxic agents could, except in circumstances of clinical urgency, usefully be tested as first-line treatment, standard regimens being used later when needed. This strategy has proved efficient and safe in the development of doxorubicin, epirubicin, mitoxantrone and cisplatin [59–61]. Other clinical studies are needed to define the place of aromatase inhibitors as first-line treatment at the time of relapse in postmenopausal patients, and the role of intensive chemotherapy in selected patients.

CONCLUSIONS

The response of advanced breast cancer to systemic therapy is modified by prior adjuvant treatment. This is, at least in part, a consequence of the selection of primary resistant cells, but the induction of acquired resistance may also be important. Whatever the mechanisms, it is important that prior adjuvant treatment should be used as a covariate in the analysis of clinical trials in advanced breast cancer. After adjuvant chemotherapy,

investigational agents should be considered for study earlier rather than later in the clinical course of advanced disease, and the reduced benefits from established drugs should be borne in mind when selecting potentially toxic treatments for palliative use.

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Measurement and Valuation of Quality of Life in Economic Appraisal of Cancer Treatment

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In the economic evaluation (EE) of technologies in cancer treatment at least three endpoints are relevant: costs, survival and quality of life (QoL). This article is focused on QoL. EE requires the use of generic and valuation QoL instruments at a disease non-specific level, but the inclusion of cancer-specific instruments may be advisable, particularly for reasons of explanation if changes in dimensions are small or conflicting. Given the pros and cons of the available questionnaires, we advocate the use of the Nottingham Health Profile, the EuroQol and the Rotterdam Symptom Checklist. In our experience the QoL issue in EE linked with cancer trials is associated with practical problems like questionnaire composition, follow-up time, interviewing schedule, patients' compliance and doctors' acceptance. These problems are discussed and some practical guidelines for the design of QoL measurement in cancer trials are given.
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INTRODUCTION

CANCER IS a major cause of illness and death, responsible for almost a quarter of total mortality in Western countries. During the last few decades cancer treatment has shown a rapid evolution. It is now a multidisciplinary treatment strategy incorporating surgery, radiotherapy, chemotherapy and/or immunotherapy. Treatment usually has important side-effects, especially radiotherapy and chemotherapy. For example, radiotherapy causes tiredness, skin injury and emotional discomfort. Chemotherapy, often considered even more burdensome, is given over longer periods and its toxicity causes hair loss, nausea and vomiting, fatigue and emotional problems. Consequently, those involved in the care and treatment of cancer patients have wondered whether improvements in survival probabilities outweigh the burden of these severe side-effects in all cases [1]. Not only life years gained, but also the quality of years alive is at issue.

The high incidence and prevalence of cancer make it a major