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Adjuvant Systemic Treatment for Early Breast Cancer: a Review

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INTRODUCTION

ADJUVANT SYSTEMIC treatment has been one of the most controversial and closely studied aspects of breast cancer in the past 15 years. Its aim is to eradicate residual micrometastatic disease after the primary local treatment of operable breast cancer. Failing that, worthwhile objectives are to delay the onset of symptoms due to recurrent disease and prolong survival.

1983–1987

Significant progress in our understanding has been made since the 3rd Breast Cancer Working Conference in 1983 and, before reviewing this, we should recall the conclusions that were made then. The review lecturers recognized that adjuvant chemotherapy led to an improvement in relapse-free survival with the possibility of an improved survival in some sub-groups [1]. They were critical of the design of some new trials which assumed benefit from adjuvant chemotherapy prematurely and were no longer using no treatment control arms. There was also concern about small patient numbers and short observation times in some reports. They regarded ovarian ablation with prednisone as being able to prolong both time to recurrence and survival, while tamoxifen appeared to confer a delay in time to first recurrence, but improvements in survival were not then apparent. The reviewers concluded that '... the ultimate effective adjuvant systemic regimen has yet to be demonstrated, and since the superiority of one particular treatment is not evident, such therapy must still be considered experimental and should be administered within the framework of prospective clinical trials. These trials should also further analyse prognostic factors and predictive tests for the efficacy of treatment, the proper drugs or combinations of drugs, the time for and the duration and intensity of therapy, and the acute and long-term toxicities. The trials should also include studies of the psychological and socio-economic implications of adjuvant systemic therapy.'

The workshop reaffirmed these views and it emphasized the continuing importance of axillary node status for the selection of patients for adjuvant systemic treatment [2]. There was general agreement that there was no place for routine adjuvant systemic treatment in women with uninvolved axillary nodes, but that it was important to attempt to define high risk patients within this category. For patients with positive axillary nodes, there was major disagreement. Certain workers had accepted that adjuvant systemic treatment was beneficial and that it was unacceptable to use no treatment control arms in clinical trials. This view had been engendered by early trial results and these had greatly influenced oncological practice in certain countries. Elsewhere, data based on relapse-free survival alone were not considered adequate to validate the long term value of adjuvant systemic treatment. The workshop ended by concluding that 'the subject of adjuvant systemic therapy for breast cancer remains controversial and there has been a considerable polarisation of views'.

Since then, a great deal of information has become available and published. It is not possible to give a comprehensive review of this information here, but even if it was, this would be likely to result in persisting confusion because of the enormous number of variables that need to be considered and which lead to difficulties of interpretation within trials (Table 1). This is why Peto's overview [3] has been of significant value in crystallizing our thoughts, but before considering this further it is appropriate to mention some of the major studies which have influenced our thinking and stimulated a great deal of work in this field.

Table 1. The variables to be considered in the analysis of trials of adjuvant systemic treatment

Prognostic variables
Age
Menstrual status
Extent of axillary involvement
Histology
—grade
—blood vessel invasion
Size of primary
Steroid receptor status
Local treatment
—extent of surgery
—radiotherapy
Treatment variables
Endocrine treatment
—type
—dose
—duration
Chemotherapy
—drugs
—number of drugs
—dose
—schedule
—duration
Combination of endocrine and chemotherapy
Corticosteroids
Response variables
Relapse-free survival
Survival
Toxicity
—acute
—long term
Efficacy of treatment on relapse

TRIALS

Early trials of adjuvant systemic treatment concentrated on an endocrine approach by ovarian ablation [4]. These showed a clear tendency for this treatment to prolong both relapse-free survival and survival, particularly when combined with corticosteroids. More recently, tamoxifen has been extensively investigated in several large trials and has consistently been shown to be able to improve both relapse-free survival and, sometimes, survival [4]. This effect has been observed in patients with either oestrogen receptor positive or negative tumours. Other endocrine treatments have received relatively little attention. A prospective comparative trial of androgens did not show any benefit from this treatment [5], but early results from a trial of aminoglutethimide and hydrocortisone show that this treatment can delay first recurrence [6].

The first trials of adjuvant cytotoxic chemotherapy studied perioperative treatment on the supposition that malignant cells were disseminated during primary surgery. Delay in both first recurrence and death were demonstrated [7]. Subsequently, it was presumed that breast cancer is often disseminated at the time of primary surgery and trials of prolonged intermittent adjuvant chemotherapy were started and based on the assumption that cytotoxic drugs act by first order kinetics. The principal trials which pioneered this approach were those from the National Surgical Adjuvant Breast Project in the United States [8] and from the Istituto Nazionale Tumori in Milan [9]. These pioneering trials led to many others being undertaken and there was soon agreement that such treatment led to a prolongation of relapse-free survival [10].

OVERVIEW

Agreement on the precise effect of adjuvant systemic therapy on actual survival was less easily reached. Because this may have been due to the results of individual trials, with relatively small numbers of patients, being considered in isolation, a major overview of adjuvant systemic treatment was undertaken [3]. This involved the provision of data from the major randomized trials worldwide for central collation. The method entails the comparison of patients within defined groups within trials ('like with like') to provide a summation of differences of observed from expected results and their variances. This overview is less subject to random errors than in individual trials and facilitates the study of major subgroups.

Over 20,000 women in numerous trials were studied in the overview. The trials variously investigated adjuvant chemotherapy or endocrine therapy against no treatment controls, comparisons of single with multiple agents, and the use of combined chemotherapy and endocrine therapy. For chemotherapy, melphalan, cyclophosphamide and thiotepa had been the principal single agents, while most combinations have included cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with the addition of vincristine and/or prednisolone; a few doxorubicin-based regimens have also been studied. For endocrine therapy the overview considered trials of adjuvant tamoxifen which have involved mainly postmenopausal women. Some of these trials have investigated duration of treatment.

The overview has confirmed conclusions tentatively deduced from individual trials. It has been demonstrated that combination chemotherapy leads to a highly significant reduction in early mortality in premenopausal patients, but is less effective in postmenopausal women. Adjuvant tamoxifen leads to a significant decrease in mortality in postmenopausal women. It is not known whether these results are due to a large effect in a few patients or a small effect in many. The recognition that

adjuvant systemic therapy leads to a decrease in mortality is an important development since the last conference in 1983.

MECHANISM OF ACTION

A literature survey of trials of adjuvant ovarian ablation has been subjected to the statistical methodology of the overview. This confirms that ovarian ablation can also lead to a significant decrease in mortality. These data and the predominant effect of adjuvant chemotherapy in premenopausal, rather than postmenopausal patients, have led to the hypothesis that a major part of the effect of chemotherapy could be mediated by ovarian suppression [11]. Further data support this contention. Adjuvant chemotherapy induces permanent cessation of menstruation in 70% of premenopausal patients by 6 months of treatment. This is accompanied by a concomitant decrease in circulating oestrogens and a rise in gonadotrophins. Furthermore, the beneficial effect of chemotherapy is seen only in those premenopausal patients who achieve permanent amenorrhoea. Moreover, the effect of chemotherapy is confined to patients with progesterone receptor positive tumours. These observations suggest that much, possibly most, of the effect of adjuvant chemotherapy is mediated by ovarian suppression, but they do not exclude an additional useful, but small, direct cytotoxic effect of chemotherapy. We need data from clinical trials to test the precise roles of chemotherapy and ovarian ablation and their respective contributions in different prognostic subgroups of patients.

DOSE INTENSITY

Other important issues include the dosage of agents used for adjuvant treatment and the duration of therapy. Undoubtedly, dose intensity is important [12] and, when this is as high as possible commensurate with acceptable side-effects, better therapy results can be expected; firm prospective data confirming this have recently become available in metastatic disease [13, 14]. As far as duration of adjuvant chemotherapy is concerned, no advantage has been demonstrated in any prospective trial for prolonged treatment [15] and regimens lasting not more than 6 months would appear to be adequate with present regimens. For endocrine treatment with adjuvant tamoxifen, it seems likely that the duration of treatment should be longer and the precise definition of this must await long-term trials.

PRE-OPERATIVE TREATMENT

Delaying treatment for cancer is likely to decrease its effectiveness. Hence, consideration has been given to using adjuvant chemotherapy as soon as possible, even before, definitive loco-regional treatment [16]. Theoretically, this could lead to an improved effect against micrometastases, but possibly could compromise the effective treatment of the primary complex. On the other hand, the ability to observe the response of the primary tumour to systemic treatment could be valuable. A particular problem with pre-operative adjuvant treatment is that important prognostic information, particularly axillary node status, would not be available at the time this treatment is given. This would make selection of patients for such treatment difficult and lead to difficulties in the interpretation of clinical trial results. However, it may become possible to identify powerful prognostic factors in due course which could be used instead of axillary node status. Such factors could also be helpful in selection of patients with axillary node negative disease for adjuvant chemotherapy (Table 2).

Table 2. Factors that may assist in identifying patients with uninvolved axillary nodes at high risk of relapse

High risk factors
Negative steroid receptors
Large size
Histology
—poorly differentiated
—vascular invasion
High labelling index
Bone marrow infiltration
Oncogene expression

COST AND BENEFIT

In deciding on the value of adjuvant systemic treatment, it is necessary to judge the size of the effect of treatment against its costs in terms of both acute and long-term toxicity. A serious disadvantage of adjuvant chemotherapy is the occurrence of unpleasant side-effects. Although there is much individual variation in the experience of these effects and they can often be mitigated to a large extent, many patients do have distressing, sometimes incapacitating, side-effects from chemotherapy. When they occur, the use of relapse-free survival can be criticized as a useful end point. In such circumstances, perhaps we should deduct from relapse-free survival the duration of treatment and so arrive at an 'illness-free interval' to use as a basis for comparing treatments (Fig. 1). With non-toxic treatments, such as tamoxifen, such a deduction is unlikely to be necessary with relapse-free and illness-free survival being equivalent. These considerations underline the need for good indices of quality of life in deciding on the value of treatments for cancer.

CONCLUSIONS

For patients with axillary node negative breast cancer there is no place for routine adjuvant sys-

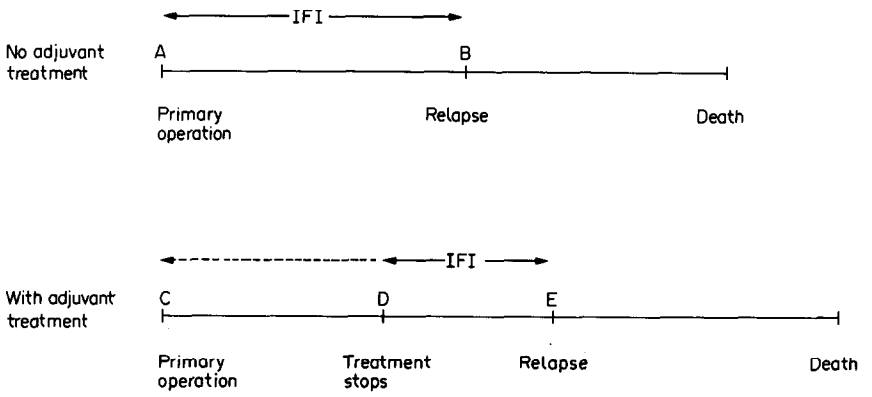

Fig. 1. 'Illness-free survival'. Without adjuvant treatment, the post-operative disease-free interval can be considered free from symptoms giving an 'illness-free interval' (IFI) of length AB. With a toxic adjuvant treatment, the symptom-free interval may be shortened (DE), while a non-toxic treatment may extend it (CE).

temic treatment. Within this group, we should attempt to define patients at high risk of recurrent disease and these should be included in trials of adjuvant treatment in which a no treatment control group is employed.

All patients with axillary nodes involved should now be considered for some form of adjuvant systemic treatment. For premenopausal patients, the National Institutes of Health Consensus Development Panel concluded that combination chemotherapy should become standard care [17]. But, it is not certain if this is significantly better than ovarian ablation and clinical trials should now address this question. For postmenopausal patients with axillary nodes involved, tamoxifen should be standard adjuvant treatment, probably irrespective of steroid receptor status. The precise role of corticosteroids in both pre- and postmenopausal patients requires elucidation.

Many outstanding questions remain, including the optimal timing of treatment, its duration, and the best combination of agents and dosage. At present, the use of adjuvant treatment will be based on the individual clinician's interpretation of available data and judgement of cost–benefit factors. Confident conclusions on the best adjuvant treatment in defined subgroups will be reached only if patients continue to be treated within clinical trials.

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