Eur J Cancer Clin Oncol, Vol. 19, No. 12, pp. 1771–1773, 1983.
Printed in Great Britain.

0277-5379/83$3.00+0.00
Pergamon Press Ltd.

Breast Cancer—Adjuvant Systemic Therapy; Workshop Report

R. D. RUBENS* and J. W. MEAKIN†

Imperial Cancer Research Fund Breast Cancer Unit, Guy's Hospital, London SE1 9RT, U.K. and †Ontario Cancer Treatment and Research Foundation, 7 Overlea Boulevard, Toronto, Ontario M4H 1A8, Canada

INTRODUCTION

THE WORKSHOP on adjuvant systemic therapy for breast cancer was structured to discuss the following questions: Who should be treated with adjuvant systemic therapy? How should its value be assessed? What is the role of adjuvant systemic therapy? Where do priorities lie for future clinical trials? This report summarises the chairman's and rapporteur's perception of the proceedings of the workshop and not necessarily their own opinions.

The discussions were based largely on the information presented in the review lectures [1]. At the outset it was recognised that in discussing this subject it was necessary to be constantly aware of the two distinct contexts in which this treatment can be used: clinical trials and routine practice.

WHO SHOULD BE TREATED

At the present time the state of involvement of the axillary lymph nodes is the most important prognostic factor in operable breast cancer. There is general agreement that most patients with involved axillary nodes have occult disseminated disease at the time of mastectomy. Furthermore, with an increasing number of nodes involved, there is a proportionate worsening of prognosis. Hence information on axillary node status is essential both for the selection of patients for adjuvant systemic therapy and accurate analysis of clinical trials. It seems that the only way to get complete information on axillary node status is a full axillary clearance and it is contentious whether lesser procedures are sufficient [2]. There is no unequivocal information on the prognostic relevance of internal mammary node involvement and this factor is not taken into account in considering adjuvant systemic therapy.

Patients without axillary node involvement have a relatively good prognosis, but consideration was given to whether high-risk groups could be defined within this category. Recent information suggests that patients without axillary node involvement but with oestrogen receptor (ER)-negative tumours may have a particularly poor prognosis in comparison to those with ER-positive disease. However, current data are conflicting and follow-up relatively short, so that no general consensus is yet available on this point.

Many other prognostic factors can be considered, and histological grade and evidence of blood vessel invasion were suggested as particularly useful indices to predict patients likely to relapse. However, no other markers have been sufficiently validated to be used for predicting prognosis [3]. Virtually all markers studied so far give only an indirect indication of micrometastatic disease, but recent developments suggest that monoclonal antibodies may enable the specific staining and direct identification of micrometastatic disease in the bone marrow.

Major advances are still needed for the accurate selection of patients who will relapse. Clearly, it is unsatisfactory to rely on surgical axillary clearance to achieve this, but axillary node status is still pre-eminent as a predictor of prognosis. Hence patients should continue to be treated and followed in prospective trials in which all putative markers of prognosis are studied so that a sufficient body of experience can be amassed to enable accurate analyses and conclusions to be derived. Given that the ability to predict precise prognosis is eventually achieved, the value of this to patients will then only be realised if effective treatment can be applied.

The conclusions reached on who should be treated may be summarised as follows. It was agreed that for patients without axillary node involvement, there was no place at the present for routine adjuvant systemic treatment. This should be tested only in clinical trials using no treatment controls. Trials would be indicated, especially in high-risk groups, as they became defined.

Regarding patients with positive axillary nodes, there is now general agreement that adjuvant systemic therapy can prolong relapse-free survival (RFS) after mastectomy, but that these patients should still continue to be treated within clinical trials. Disagreement exists on whether or not no-treatment controls should be used. In certain parts of the world it is now accepted that adjuvant systemic therapy is beneficial for patients with involved axillary nodes and that it would not be possible to use no-treatment controls. This view has been engendered by early trial results which have greatly influenced oncological practice. Furthermore, patients in some areas have come to expect adjuvant treatment. Elsewhere, data based only on RFS has not been considered adequate to validate the use of this treatment (see below) and no-treatment controls are still considered essential for trials in patients with positive axillary nodes. More time is needed to resolve this controversy.

ASSESSMENT OF VALUE OF ADJUVANT SYSTEMIC THERAPY

Concern was expressed over problems in evaluating clinical trials because large numbers of patients were needed to identify confidently small differences, there were difficulties in defining accurately time of relapse and the subset analyses were complex. It was argued that there had been a poor return of results from the many thousands of patients studied in clinical trials. Considering the main aim of treatment to be the eradication of micrometastatic disease or, failing this, to delay symptoms due to recurrence, an alternative approach was suggested. This involved the identification of 'test beds' to precede the establishment of large phase III trials. These should include prior identification of agents active for advanced disease and the randomisation of high-risk patients only. Furthermore, the evaluation should be only within well-defined prognostic groups and only patients with 'adequate' treatment should be evaluated. This view was opposed because excessive selection would diminish numbers of patients available for study and so trials based solely on these tenets would become detached from the reality of the generality of breast cancer. There was a consensus that the majority of patients with breast cancer should still be treated in clinical trials with sufficient numbers to enable accurate subset analyses.

The relative values of RFS and overall survival as end-points in clinical trials were debated. RFS is to be expected from adjuvant treatment when agents active in the advanced disease are used. Many consider this to be the most sensitive end-point because overall survival may be affected significantly by treatments used after relapse. Furthermore, RFS gives the first identifiable end-point and enables some assessment of trial results before overall survival information becomes available. The exact timing of relapse can be difficult and verifiable physical evidence of recurrence was considered mandatory for assessing clinical trials; also, the records of patients studied should be amenable to critical external review. It is useful to consider separately both loco-regional recurrence and distant metastases. The psychological value of an extension in RFS to patients was recognised because of the dire implications of first recurrence. However, overall survival is considered by many to be the only valid end-point in analysing trials, in order to be sure that extension of RFS is not obtained at the expense of decreasing our ability to effectively treat disease on relapse.

The meaning of 'cure' in individual patients was discussed. This concept could have different meanings. First, in biological terms it implied the total eradication of all malignant cells, but this cannot be identified. A second, more practical meaning was that 'cure' implied extension of RFS to such an extent that death from another cause intervenes before clinical recurrence of breast cancer. Considered in this way, and accepting that adjuvant systemic therapy does extend RFS, then on this definition adjuvant treatment will necessarily increase the probability of cure in some patients. In practical terms a treatment applied to a population of patients may be said to be curative if it restores the survival expectancy to that of the general population of the same age and sex.

Regarding the possibility of second malignancies arising as a consequence of adjuvant systemic treatment, one study was presented which suggested that this is to be expected, but it has not yet been corroborated elsewhere. It is still too early to determine the eventual magnitude of this problem.

The final judgement on the value of adjuvant systemic treatment will depend upon cost–benefit considerations. The size of the beneficial effects of therapy must be weighed against the costs in terms of both acute and long-term toxicity.

THE ROLE OF ADJUVANT SYSTEMIC THERAPY

The value of ovarian ablation in significantly extending both RFS and overall survival has been demonstrated in two independent Canadian trials involving many hundreds of patients with follow-up extending to more than 10 yr. It may therefore be asked why this treatment is not currently considered more often for the routine treatment of

menopausal patients at high risk. The view was expressed that it was particularly justifiable to use such treatment as it was non-toxic and harmless.

Several more recent trials have tested tamoxifen as adjuvant therapy in postmenopausal patients and a consistent trend for an increased RFS has been seen in trials conducted in Denmark, the U.K. and the U.S.A. Although some trials have shown this benefit to be confined to patients with ER-positive tumours, others have shown the same trend in patients with either ER-positive or -negative tumours. This is contrary to our current understanding of the mechanisms of endocrine treatment, and further follow-up is needed both to clarify this issue and to define the effect of adjuvant tamoxifen on actual survival.

Many clinical trials have demonstrated that adjuvant cytotoxic chemotherapy can extend RFS, but this trend has been observed most consistently for premenopausal patients with 1–3 axillary lymph nodes involved. A number of important questions concerning the administration of adjuvant chemotherapy were addressed. One major Scandinavian trial has indicated that a beneficial effect from chemotherapy can only be achieved if it is started immediately after operation and that any delay abolishes the therapeutic effect. However, other trials have suggested that a short delay of some weeks is not detrimental. The question of the optimal timing of chemotherapy remains open. The duration of treatment was discussed and present data do not show any significant differences for chemotherapy given over different time periods. However, small numbers and short follow-up could result in real differences being concealed. Some retrospective analyses suggest that high doses of drugs are important but other data conflict with this and prospective trials are needed to identify any important dose–response relationships.

It was stressed that positive studies need repeating as the initial results are not always confirmed. Such verification of results is essential before any single trial findings are adopted for routine practice. Additionally, all published reports should state clearly the median observation time and the statistical methods used.

PRIORITIES FOR FUTURE TRIALS

Continued efforts aimed at defining high-risk patients are needed in order to enable uniformity for subset analyses with regard to factors such as stage, ER status and other primary treatments. The relative efficacies of chemotherapy and endocrine therapy within defined subgroups now needs elucidation. The role of doxorubicin, the most effective single agent for advanced disease, in adjuvant therapy needs to be determined. The development of methods to overcome drug resistance attributable to both kinetic and biochemical factors are required. The best methods of drug delivery await determination and it should be considered whether they are best administered simultaneously, sequentially or on alternating schedules, as well as what the optimal interval between treatments should be.

CONCLUSIONS

The subject of adjuvant systemic therapy for breast cancer remains controvertial and there has been a considerable polarisation of views. However, workshops such as this allow continual reappraisal as clinical trials mature. During this workshop we were able to observe a gradual changing of attitudes, and we expect that ultimately there will be a general agreement on the role of adjuvant treatment based on clear unequivocal results from well-analysed long-term clinical trials.

Acknowledgements—We acknowledge the contribution to this workshop of the following primary discussants: Drs C. Rose, T. J. Powles, I. C. Henderson and G. Bonadonna.

REFERENCES

1. MOURISDEN H, PALSHOF T. Adjuvant systemic therapy in breast cancer; a review. *Eur J Cancer Clin Oncol* 1983, **19**, 1753–1770.
2. HAYWARD JL, BARTELINK H. Breast conserving therapy in operable breast cancer; workshop report. *Eur J Cancer Clin Oncol* 1983, **19**, 1749–1751.
3. BULBROOK RD. Prognostic factors and tumour markers in early breast cancer; a commentary. *Eur J Cancer Clin Oncol* 1983, **19**, 1693–1697.