Van Dongen reported that there was an intention to cure in 84% of those with local relapse. Success of salvage depended upon the aggressiveness of the tumour. Of those patients who relapsed within 2 years, local control was achieved in only 30%, as compared with 60% of those whose disease-free interval was more than 2 years.

NEW APPROACHES

All successful trials of breast conservation have incorporated axillary clearance and external radiotherapy. Various studies are testing whether these treatments are needed. Chetty reported the Edinburgh trials in which patients were treated with either axillary clearance or axillary sampling (with postoperative radiotherapy if nodal involvement was present). Similar rates of nodal involvement were found in both groups and local control was similar.

The use of a variety of first-line chemotherapy treatments was reported by the Milan Group. After treating 229 patients with cancers > 3 cm, tumour size was reduced in 202 cases (88%) so the QUART technique (quadrantectomy, axillary dissection and radiotherapy) could be used for BCT.

AVOIDANCE OF RADIOTHERAPY

Teleky reported a series of 220 patients with T1 tumours treated by lumpectomy or quadrantectomy and axillary clearance, but given no postoperative radiotherapy. After 4 years median follow-up, 13 (6%) had relapsed locally. Of those aged < 50, 8% relapsed compared with 5% of those aged > 50. Using a combination of T1 tumour, node negativity and age > 50, it may be possible to avoid radiotherapy in selected cases.

The Swedish trial randomised patients who had been treated by sector resection and axillary clearance to observation or radiotherapy (54 Gy). There was a significant improvement in cosmetic outcome rated both subjectively and objectively in the non-irradiated group.

Pilot work at Guy's Hospital has examined the role of implant treatment without external radiotherapy. In the first study, patients with tumours < 4 cm were treated by tumourectomy, axillary clearance and iridium implant giving 55 Gy as a continuous treatment over 5 days to the tumour-bearing quadrant. Local relapse after 4 years is similar to that following standard BCT and no untoward radiation reactions have been seen. However, because of radiation protection requirements, this approach was discontinued and replaced with a medium dose rate intermittent caesium implant delivery 45 Gy in four fractions over 4 days. So far, 32 patients have been treated in this way but follow-up is short. Once the study has been completed, it is hoped to incorporate this type of approach as one arm of a prospective randomised EORTC trial.

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Breast Cancer: Adjuvant Treatment

R.D. Rubens

INTRODUCTION

THE PRESENTATIONS on adjuvant systemic treatment gave the latest information on efficacy and, of more importance to patients, effectiveness. Demonstration of efficacy, whether or not treatment has an effect, comes from prospective randomised clinical trials. Effectiveness concerns the applicability of these effects to routine practice when they have to be balanced against any adverse consequences of treatment.

EFFICACY

Postoperative chemotherapy and endocrine treatment

The meta-analysis of trials of adjuvant treatment has essentially ended the debate on whether or not adjuvant systemic treatment affects survival. It is now clear that in all prognostic subsets of patients with breast cancer the various approaches lead to a reduction in the annual odds of death by about 25%. This results in the avoidance of approximately 10% of deaths at 10 years after diagnosis [1]. The current meta-analysis is based on over 70000 women in 200 randomised trials. These large numbers have not only given firm information on the efficacy of adjuvant treatment, but also enabled separate analyses for different prognostic subsets and different types of treatment.

In younger patients (less than 50 years old), chemotherapy has become established as having the clearest effect by reducing the annual odds of death by a quarter. Prolonged multiple drug treatment, for example cyclophosphamide, methotrexate and 5-fluorouracil (CMF), is more effective than either limited perioperative chemotherapy or prolonged single-agent treatment; treatment beyond 4–6 months does not enhance the effect. It is of interest that, despite the limited duration of chemotherapy, the actuarial survival curves are still seen to be diverging at 10 years. The current meta-analysis also clearly demonstrates an effect of similar magnitude for ovarian ablation, although the standard deviation is wider because of the lower numbers available for analysis. The results of the first trial directly to compare the effects of ovarian ablation and chemotherapy were reported [2]. After a median follow-up of 5.5 years and accrual of 332 patients, the effects of ovarian ablation or an intravenous regimen of CMF are similar. In this factorial design trial, the addition of prednisolone reduced myelosuppression from CMF, but did not affect its efficacy or that of ovarian ablation.

The meta-analysis shows tamoxifen to result in a highly significant reduction in the annual odds of death by a quarter in women aged 50 years or more. The size of this effect increases with rising levels of oestrogen receptor concentration in the

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primary tumour. The optimal duration of tamoxifen is not yet known, but present results favour prolonged usage, at least 2 years. An effect of chemotherapy in postmenopausal women is demonstrated in the most recent analysis, but the size of the effect is only about half that of tamoxifen. However, it is contended that, with adequate doses of chemotherapy, effects do not differ according to menstrual status [3]. Nevertheless, direct comparison of tamoxifen against CMF reinforces the opinion that tamoxifen is the preferred treatment for postmenopausal patients [4]. Addition of chemotherapy to tamoxifen did not enhance its efficacy in these patients [4].

Peri-operative chemotherapy

Prompt use of adjuvant chemotherapy at the time of surgery is being tested in EORTC trial 10854 [5]. Experimental models have shown that increased proliferative activity of residual tumour after surgical cytoreduction is associated with increased chemosensitivity. There is also a correlation between low residual tumour cell numbers and chemotherapeutic cure rate. Other reasons in support of early adjuvant chemotherapy include the prevention of proliferation of resistant cells and the destruction of tumour cells in circulation. The trial has accrued 2795 patients. Patients were randomised to receive either peri-operative cyclophosphamide, doxorubicin and 5-fluorouracil intravenously within 36 h of surgery or no perioperative chemotherapy. Only premenopausal patients subsequently found to have involved axillary nodes received additional chemotherapy. Early results indicate that relapse-free survival is extended significantly by perioperative chemotherapy, but data on survival are not yet available.

Locoregional control

The principal intention of adjuvant treatment is to extend survival by decreasing the incidence of distant metastases. It is necessary to ensure that locoregional control is adequate, to enquire if this can be satisfactorily achieved by adjuvant systemic treatment and what the consequences of inadequate local control might be for survival. These questions were addressed in a large Danish trial comprising 3986 patients accrued between 1982 and 1989 [6]. Premenopausal patients were randomised after mastectomy to radiotherapy plus CMF or CMF alone or CMF with tamoxifen, while postmenopausal patients had either radiotherapy plus tamoxifen or tamoxifen alone or CMF with tamoxifen. Disease-free survival was significantly improved in irradiated patients because of a lower locoregional recurrence rate; this was associated with a small survival advantage in postmenopausal patients. This study emphasises the importance of aiming for both locoregional and systemic tumour control. Another study reaffirmed the reduced locoregional recurrence rate with post mastectomy radiotherapy, but did not show this to be associated with an improved survival [7].

Although radiotherapy is of questionable value after mastectomy and axillary clearance, it is essential after breast-conserving surgery. The optimal scheduling of radiotherapy and adjuvant chemotherapy in these circumstances has been evaluated in a non-randomised retrospective study [8]. The actuarial 5 year breast recurrence rate was 4% in 99 patients receiving all radiotherapy before chemotherapy, 8% in 54 receiving some chemotherapy then radiotherapy before further chemotherapy; and 6% in 116 having concurrent chemotherapy and radiotherapy. However, the failure rate rose to 41% in 26 patients receiving all chemotherapy before radiotherapy. For those irradiated within 16 weeks of breast-conserving surgery, the actuarial 5 year breast recurrence rate was 5% compared with 35% for patients irradiated after that time. These results indicate that delaying radiotherapy after breast conserving surgery increases the likelihood of local failure. Randomised controlled trials are needed to confirm these results and to define the optimal integration of surgery, radiotherapy and chemotherapy. A small study suggests that combining adjuvant radiotherapy and chemotherapy synchronously is practicable and does not necessitate reduction in the dose intensity of chemotherapy [9].

Immunotherapy

Meta-analysis of the immunotherapeutic approaches to adjuvant systemic treatment shows this approach to be ineffective. EORTC trial 10761 was part of this analysis. After modified radical mastectomy, internal mammary node irradiation and commencing adjuvant CMF, patients were randomised to receive either levamisole or a placebo [10]. At a median follow-up of 8 years, the results show that levamisole has no significant effect on the prognosis of these patients.

EFFECTIVENESS

Risk evaluation and selection of treatment

The meta-analysis demonstrates that proportional reductions in mortality from adjuvant systemic treatment are similar in different prognostic subsets of patients. Hence, the absolute benefits of treatment will be greater when prognosis is poor and less in patients with a good prognosis. To achieve the best effectiveness from treatment, it is necessary to evaluate individual patients' risk of relapse [11]. It has been accepted that adjuvant systemic treatment is indicated in patients with axillary node positive disease, but its place in node negative disease has been less certain. What constitutes node negative disease and the extent of axillary dissection needed to characterise such patients has been questioned [12]. In a large Danish study of 13 851 patients a nearly linear relationship between the number of excised lymph nodes and designated node negativity was found for up to 10 lymph nodes excised; above this number there was no additional contribution to the establishment of axillary node status. It was concluded that at least 10 lymph nodes have to be excised from the axilla for precise staging.

Although patients with axillary node negative disease have a relatively good prognosis in comparison with those with node positive disease, they still have a relapse rate of about 20% at 5 years. To separate these patients into different risk groups, attention has been given to tumour size and indices of tumour cell proliferative activity such as histological grade or S-phase fraction measured by flow cytometry [11]. This has enabled three subsets to be identified (i) a group with a good prognosis having survival expectancy similar to that of the unaffected age-matched female population; (ii) an intermediate risk group with a 20% chance of recurrence at 5 years; (iii) a poor prognosis group similar to those with 1–3 nodes positive having a 50% chance of recurrence at 5 years. For the first group, adjuvant treatment is not needed; with the second, endocrine treatment may be preferred; for the third, chemotherapy can be considered for premenopausal and tamoxifen for postmenopausal patients. For patients with more than four nodes involved, examination of histological type and grade can select a group at particularly high risk of relapse—those with ductal carcinomas of grade 2 and 3 or lobular cancer; these patients have an 80% chance of recurrence at 5 years and may be considered for clinical trials of intensive chemotherapy.

Safety of adjuvant treatment

The lack of severe subjective toxicity has made tamoxifen an ideal drug for adjuvant treatment, but its anti-oestrogenic action has caused concern about potential adverse effects on lipid and bone metabolism. Fortunately, it has been shown that, for these metabolic activities, tamoxifen has an oestrogen agonist rather than antagonistic effect [13]. It decreases serum cholesterol and preserves bone density, the latter effect even protecting against corticosteroid-induced osteoporosis. However, one study reported 7 patients who developed pulmonary embolism, one fatal, during adjuvant treatment with tamoxifen [14]. These patients all had predisposing factors such as varicose veins, hypertension or illness requiring bed rest. These observations high-light the importance of omitting treatments in subsets unlikely to benefit and the need to define the indications for either avoiding or temporarily suspending tamoxifen treatment. Anti-thrombin III levels have been noted to be below normal in women taking tamoxifen [15].

The incidence of new primary cancers has been reported to be influenced by adjuvant tamoxifen by decreasing the risk of contralateral breast cancer but increasing the risk of endometrial cancer. Neither of these observations was confirmed in studies reported at the conference [16, 17].

The potential acute toxic effects of chemotherapy detract from its desirability for adjuvant treatment, but methods to mitigate toxicity have improved greatly. Hitherto, fears of long-term morbidity from, or the induction of new malignancies by, adjuvant chemotherapy have not been fulfilled. Possibly, with the increasing use of anthracyclines, care must be taken to avoid cardiotoxicity.

Assessment of benefit

While we improve our ability to establish the precise efficacy of adjuvant treatment in prognostic subsets, further analysis is needed to determine the actual benefit derived by individual patients. This requires quality of life measurements to facilitate comparison between treatments having different degrees of toxicity [18]. One method has been to estimate time without symptoms of recurrent disease or toxic effects of therapy (TWiST). In this technique, time spent on toxic treatment and time after relapse is deducted from survival to enable comparison between treatments. The method has been refined further to allow quality adjustments by applying utility co-efficients to each time component (Q-TWiST). Further study is needed to work towards the integration of survival and quality of life data to formulate a meaningful expression of the true benefits of treatment for patients.

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