Eur J Cancer Clin Oncol, Vol. 19, No. 12, pp. 1779–1781, 1983.
Printed in Great Britain.

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

Treatment of Advanced Breast Cancer; Workshop Report

GIANNI BONADONNA* and ALLAN VAN OOSTEROM†
*Istituto Nazionale Tumori, Milan, Italy and †Academisch Ziekenhuis, Leiden, The Netherlands

INTRODUCTION

ADVANCED breast cancer today is an area where little progress is observed in terms of increased response rate and survival. The frequent presence of great tumor cell burden and the high incidence of drug-resistant phenotypes are the main causes preventing the achievement of complete response of long duration [1, 2]. Clinical research is primarily aimed at evaluating new drugs and regimens and new sequences of therapy available thereby trying to meet the need of the individual patient. A number of posters related to this problem and presented at the conference were discussed in this workshop. Together with data mentioned by other discussants, they form the basis of this report.

NEW DEVELOPMENTS IN HORMONAL THERAPY

Aminogluthetimide (AG) has recently been added to the existing forms of endocrine treatment. The problem of the optimal dose was addressed by Stuart-Harris *et al.* The compound acts as a 'medical adrenalectomy' by inhibiting the desmolase conversion of cholesterol to pregnenolone, but *in vitro* studies have shown that AG also inhibits the aromatase conversion of androgens to estrogens at very much lower dosage. The investigators noticed that significant estrone suppression occurred at the starting dose of 62.5 mg b.d. without hydrocortisone, and suppression at 125 mg b.d. was as effective as the conventional dose of 500 mg b.d. with hydrocortisone. Of 17 postmenopausal patients with measurable tumor, three achieved an objective response at 125 mg b.d. Drowsiness and lethargy, common side-effects at conventional dosage, were not observed at the low dosage.

In 201 assessable patients with actively progressive advanced breast cancer, Murray and Pitt have noticed with AG an objective response rate of 35%, with a mean response duration of 12.5 months. They have analyzed the response rate to AG in relation to the prior response to tamoxifen (T). In 58 patients who responded to T, AG induced a further regression in 55%, while failure to respond to T was still associated with a significant response to AG (27% of 71 women). The results of these studies showed that AG can now be safely included in the hormonal manipulations for advanced breast cancer, that therapeutic results can be achieved with very low doses which allow deletion of hydrocortisone and that cross-resistance between T and AG plays no significant role. Although the optimal sequence has not yet been defined, current evidence suggests that T should be tried first and AG reserved for failures.

Buserelin is a potent luteinizing-hormone-releasing-hormone (LHRH) analog whose chronic administration at pharmacological doses causes in animals partial hypophysectomy, chemical castration and antagonism of sex steroid actions at their target organs, as well as regression of spontaneous and DMBA-induced mammary tumors. Klijn *et al.* have reported the endocrine and therapeutic effect of 1200 mg buserelin per day intranasally (after 3–7 days 3 mg i.v. or s.c.) as the first-line agent in 17 menstruating women with metastatic breast cancer. However, in only three patients was buserelin tested alone, in five women the hormone was combined with T and in nine T was added later. Anovulation was reached in all women. Treatment resulted in an objective tumor response in 8 of 17 patients, especially in those showing chemical castration, and no side-effects. The place of buserelin in the sequence of hormonal manipulation remains to be determined.

Trilostane, a substituted C19 steroidal agent which inhibits the 3-β-hydroxysteroid dehydrogenase–Δ-5-isomerase system, was tested by Hindley *et al.* in 23 postmenopausal patients. This new hormonal agent administered at the dose of 240 mg q.i.d. plus dexamethasone 0.5 mg

b.d. and hydrocortisone 10 mg b.d. for a minimum of 8 weeks induced an objective response in 26%, with mild side-effects (nausea, vomiting, diarrhea, drowsiness and hot flushes). This compound should now randomly be tested against AG to see the relative merits.

Powles and Coombes presented the interim results of a prospective randomized trial involving multiple endocrine therapy (TAD: tamoxifen and aminogluthetimide, with hydrocortisone and danazol). In 62 assessable patients TAD induced an objective response in 51%, compared to 34% in 65 women treated with T alone ($P < 0.05$). However, duration of response and survival for both treatment groups were similar. This study failed to show clear superiority of polyhormonal therapy over single hormonal therapy.

COMBINATION CHEMOTHERAPY

The main limits of combination chemotherapy in advanced breast cancer are the lack of complete remissions of long duration and the low response rate of salvage regimens. Both events could be attributed to the presence of drug-resistant phenotypes [1, 2]. Blumenschein *et al.* reviewed their large series of 619 women treated with 5-fluorouracil, adriamycin and cyclophosphamide (FAC) and cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Complete remission (CR) was achieved in 116 patients (18.7%), but only 12 of 619 patients (1.9%) were relapse-free survivors from all forms of therapy at about 5 yr. Similar results were reported by Bonadonna, who showed that following therapy with cytoxan, methotrexate and 5-fluorouracil alternating with adriamycin and vincristine (CMF-AV), 36 (16.5%) of 218 patients entered CR but only 0.9% were alive and disease-free at 5 yr.

From both series there was no evidence that prolongation of treatment after achievement of CR resulted in a longer duration of response. Because treatment failure, therefore, seems to be largely, if not exclusively, dependent on the overgrowth of drug-resistant cell population(s), there is no reason to continue therapy in complete responders after two cycles of consolidation chemotherapy.

Rosner presented the results of a complex study which indicated that recycling previously used drugs in effective non-cross-resistant regimens significantly prolonged the survival by avoiding premature exhaustion of the therapeutic modality. This study confirms that primary or secondary treatment failure does not necessarily indicate that refractory neoplastic cells are indeed resistant to all drugs included in a given regimen.

NEW CYTOTOXIC DRUGS

Cornbleet *et al.* and Kolaric *et al.* reported on the testing of new compounds in phase I–II studies in advanced breast cancer: mitoxantrone and *cis*-platinum respectively.

Mitoxantrone is an anthracene-dione with some structural similarities to adriamycin. At the dose of 12–14 mg/m^2 given in a 30-min infusion repeated every 3 weeks, partial response was observed in 32% of 59 patients previously untreated with chemotherapy, with a median duration of 10 months (range: 3–13 months). The drug was well-tolerated, and leukopenia presented the major short-term toxicity. Although in this study endomyocardial biopsy failed to show features characteristic of adriamycin-type toxicity, a safe cumulative dose of mitoxantrone in patients previously treated with one of the anthracycline drugs remains to be demonstrated.

Cis-platinum was tested in 38 women previously untreated with chemotherapy at the dose of 30 mg/m^2 for 4 consecutive days every 3 weeks. The total objective response rate was 54%, and even more impressive was the 37% CR rate. Toxic effects were moderate. Confirmation of these interesting results is urgently needed.

The results of these studies will allow the integration of both of these drugs into the design of potentially effective combination regimens.

COMBINED HORMONE-CHEMOTHERAPY

The main scope of combining hormonal with cytotoxic therapy is to increase the median duration of response and survival. Forbes *et al.* randomly tested, in a phase III trial involving 394 evaluable patients, first-line endocrine therapy (ovariectomy in pre- and tamoxifen (T) in postmenopausal women) vs first-line combination chemotherapy (cyclophosphamide plus adriamycin to the cumulative dose of 450 mg/m^2, followed by vincristine, methotrexate and fluorouracil) vs first-line combined therapy. On treatment failure, patients on endocrine therapy were changed to cytotoxic therapy and patients on cytotoxic therapy were changed to endocrine therapy respectively. Despite the significant inferior response rate with T (24.3%) compared to chemotherapy (41%) and chemotherapy plus T (55.4%), the survival rate did not significantly differ among the three treatment groups. A similar conclusion was presented by Mouridsen *et al.*, who noticed that the superior response rate after CMF plus T (75%) vs CMF (49%) could not be translated into a survival difference. This lack of survival advantage is probably related to the rather infrequent incidence of long-lasting CR following systemic therapy for advanced breast

cancer and to a lack of true synergism between endocrine therapy and chemotherapy which might be ascribable to their different, possibly mutually exclusive, mechanisms of action.

Since the proliferative index of hormone-dependent tumors is decreased under endocrine therapy whereas cytotoxic drugs predominantly kill cells engaged in the mitotic cycles, Parideans *et al.* have designed a new clinical trial based on the principle of estrogenic recruitment of G_0 hormone-dependent cells. A brief estrogenic exposure might amplify the killing effect of cytotoxic drugs administered 24 hr thereafter. After achieving endocrine suppression by surgical castration or AG, the investigators utilized the FAC (fluorouracil, adriamycin and cyclophosphamide) regimen given every 3 weeks exactly 24 hr following the oral administration of ethinylestradiol (50 μg) as a hormonal recruitment agent. The initial clinical results were promising, for in 41 patients 37% achieved CR and 37% PR. The findings will require confirmation through an appropriate randomized trial in estrogen receptor (ER)-rich tumors.

IMMUNOTHERAPY

Two prospective randomized trials involving chemotherapy ± immunotherapy (*C. parvum* and levamisole) were presented by Abel *et al.* and Heuson *et al.* Both trials yielded negative results, without increased response rate and survival in subsets receiving immunotherapy. The findings confirmed the lack of efficacy of immune-stimulation in the treatment of advanced breast cancer.

LOCALLY ADVANCED DISEASE

As a rule, patients with locally advanced breast cancer (stage III) harbor micrometastases to which they ultimately succumb. Two groups have presented the results of a combined modality approach.

Papaioannou *et al.* presented, in a total of 280 patients, a quantitative observation on the primary tumor shrinkage following combined preoperative combination chemotherapy (vincristine, cyclophosphamide, adriamycin, fluorouracil and methotrexate). Premenopausal women also underwent oophorectomy at the same time of mastectomy. They correlated this effect on the primary tumor with recurrence rate. Shrinkage of the primary tumor was shown to be a valuable prognostic index for the effectiveness of systemic therapy, but only in premenopausal women. In general, postmenopausal patients faired better than younger women. They also showed that the addition of postoperative radiotherapy did not improve the results.

Engelsman *et al.* presented the results of a prospective randomized trial comparing radiotherapy (RT) with RT plus CMF and T, and with RT preceded and followed by alternating chemotherapy (CMF and AV). There were 113 evaluable patients. Contrary to their initial observation, there was no significant differences in both relapse-free and total survival among the three treatment arms.

COMMENT

The studies presented in this workshop showed the present difficulty in significantly improving the treatment results in advanced breast cancer by utilizing new drugs or regimens over those achieved with previous therapies. This finding can to a large extent be attributed to tumor heterogeneity and therefore to the presence and emergence of drug-resistant phenotypes [1–3]. However, a criticism can often be made on the trial design in terms of patient selection. In fact, in no study testing hormonal therapy either alone or combined with chemotherapy was patient selection based on ER status. While in clinical practice endocrine treatment can often be applied regardless of this important prognostic parameter, it is highly recommended that in scientific meetings and publications the results of new hormonal treatments be related only to patients with ER-positive tumors. Otherwise it will be practically impossible to document a real improvement from hormonal therapy, the actual results being blurred by the fluctuation of endocrine-sensitive vs -resistant cells.

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