*Eur J Cancer Clin Oncol*, Vol. 19, No. 12, pp. 1775–1778, 1983.
Printed in Great Britain.

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

# Therapy of Advanced Breast Cancer; a Review

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## INTRODUCTION

BREAST cancer may be cured by primary treatment in a proportion of the patients. If no cure is achieved, metastatic disease will become manifest sooner or later. Advanced breast cancer is a disease which can be rapidly fatal, but it may also permit a survival of many years. It may present itself in many different ways, depending on the type of spread, the rate of progression and probably on other factors in tumor and host. There are many possibilities for treatment, but advanced disease cannot be cured. The intention of treatment is essentially palliative.

## HORMONE THERAPY

In 1896 Beatson reported objective remission of advanced disease in premenopausal patients after oophorectomy. By 1900 it had become clear that about 30% of the patients would respond to such treatment, and that these remissions were temporary, with an average duration of more than 1 yr. At the present time we have a variety of modalities of hormone therapy listed in Table 1.

Responders to hormone therapy have a good chance to respond again to subsequent hormone treatment. Failure to respond to one treatment does not exclude response to another treatment. Therefore it is important that several modes of hormone therapy are at our disposal.

Additive therapy with pharmacologic doses of estrogens or androgens often produces serious side-effects, but after an objective remission the patients may experience a withdrawal remission when the treatment is stopped. The antiestrogen tamoxifen has largely replaced the sex hormones because of its lack of side-effects. Also, withdrawal remissions after stopping tamoxifen seem to be very rare. This is probably due to the fact that when tamoxifen treatment is stopped the drug is retained in the body for a long time (more than 6 weeks). Progestagens may be used for hormone therapy. Activity has been demonstrated for medroxyprogesterone acetate, megestrol acetate and norethisterone acetate, with various dose schedules.

A number of questions still have to be answered. It is not clear whether 'very high' doses, which may produce unpleasant side-effects, are really more effective than 'low' doses. Several clinical trials are underway to compare different dose levels. It is not clear whether the intramuscular route of administration is more effective that oral use. Serum levels may show different patterns after oral or intramuscular use, but the relevance of serum levels of progestagens for response is still an open question. Correlation of response with receptor status has not yet been finally clarified. There are indications that other receptors than for estrogens and progesterone may be important (androgens, corticosteroids). Corticosteroids in relatively low doses can be effective as an endocrine therapy, with modest remission rates; but corticosteroids have usually been given as second- or third-line therapy. Tamoxifen can be effective in premenopausal patients. A high response rate after subsequent oophorectomy has been reported for responders, whereas tamoxifen failures do not respond to subsequent oophorectomy. These data are rather preliminary, and so far other reports have failed to confirm the

*Table* 1. *Hormone therapy*

| |
|---|
| Oophorectomy, or X-ray castration |
| Adrenalectomy |
| Hypophysectomy |
| |
| Estrogens |
| Androgens |
| Withdrawal of estrogens or androgens after remission |
| |
| Progestagens |
| Corticosteroids |
| |
| Antiestrogens |
| Aminoglutethimide (medical adrenalectomy) |
| LHRH analogues |

suggestion that the response to tamoxifen could be used to decide upon sequential oophorectomy.

Aminoglutethimide (AG) plus hydrocortisone is effective in postmenopausal patients. The drug inhibits adrenal steroid synthesis, and probably also the aromatization of other steroids to estrogens in peripheral tissues. Hydrocortisone is added to prevent the pituitary from responding to lowered cortisol levels with increased ACTH secretion. The side-effects (lethargy, rash) are less if the full daily dose is reached gradually. A randomized study has shown that AG is equally as effective as adrenalectomy. There is some evidence that AG is effective after tamoxifen but that tamoxifen after AG is disappointing. Newer adrenal suppressing agents are being studied; their value in comparison to AG has to be investigated. Trials with combined hormone therapies so far have not produced superior results to single treatment, with the possible exception of addition of corticosteroids.

## CHEMOTHERAPY

A number of single agents have shown activity in advanced breast cancer. The drugs listed in Table 2 are effective in 25–35% of the patients. Prednimustine, in which chlorambucil is linked with prednisone, was more active than both single drugs given together in one randomized study, but the mode of action is not clear yet. Nor is it clear where the drug might be placed in a treatment schedule. Cyclophosphamide seems to be the most active alkylating drug. Table 3 shows a number of single agents under investigation.

*Table 2. Active single agents for chemotherapy*

| |
|---|
| Cyclophosphamide |
| Methotrexate |
| 5-Fluorouracil |
| Adriamycin |
| Mitomycin-C |
| Vinblastine (infusion) |
| Vindesine |
| Prednimustine |

*Table 3. Single agents under investigation*

| |
|---|
| Cisplatin |
| Ellipticinium |
| Procarbazine |
| Mitoxantrone |
| VP 16-213 (etoposide) |
| Dibromodulcitol |
| Ifosfamide |
| Bleomycin |
| High-dose methotrexate |

They have some activity, but their value has not yet been established. Among drugs tried for activity in advanced breast cancer and found ineffective are actinomycin-D, 6-thioguanine, *m*-AMSA, PALA and hexamethylmelamine. Combination chemotherapy was first reported to achieve higher response rates than single agents, by Greenspan in 1962. The interest in combination chemotherapy has grown rapidly since about 1970, after it had become clear that in advanced Hodgkin's disease combination chemotherapy could be curative. Many combinations have been tried, the most widely used being CMF, CMFP, CMFVP, AV and CAF. With CMF-like combinations response rates of about 50% can be achieved; if adriamycin is included, remission rates may be as high as 70%. Addition of prednisone seems to increase response rates somewhat. Most responses are partial, complete response rates being 20–30%. On the supposition that the development of resistance could be postponed, CMF and AV have been alternated in maximal doses (plus tamoxifen). Toxicity is serious, and although some complete remissions of very long duration (up to 4 yr) have been achieved, it has become clear that cure of advanced disease is not within reach. Other studies have shown that combining more than three drugs did not improve results. Combining adriamycin with vincristin (AV) increases toxicity (neurotoxicity) but not the response rate. If CMF has previously been used for adjuvant therapy, this combination can still be effective later in case of recurrent disease if the free interval has been at least 1 yr. The response rate, however, is lower than the 50% which can be expected if CMF is used as a first-line chemotherapy.

## HORMONOCHEMOTHERAPY

Hormones and chemotherapy have been combined. It was conceivable that effective hormone treatment might render the tumour less sensitive to chemotherapy, but there is no evidence for this from several trials. Combining CMF with estrogens or androgens and AC with androgens does not seem to be advantageous. Oophorectomy plus CMF and oophorectomy followed by CMF after failure or relapse gave equal results. By combining CMF with tamoxifen response rates of about 70% can be reached, but the increase in response rate is restricted mainly to the older patients. No clear advantage in survival has been demonstrated.

## IMMUNOMANIPULATION

Combining chemotherapy with some types of immunostimulation (levamisole, BCG, MER, *C. partum*) has not produced any advantage so far;

one report on a small series of elderly patients claimed remissions for BCG orally as a 'single agent'.

## OTHER MEASURES

Patients with progressive advanced breast cancer may often benefit from measures directed to specific lesions (Table 4). Local radiotherapy is very helpful for painful bone lesions, especially in weight-bearing areas such as the spine and pelvis. For patients with extensive bone disease with multiple painful lesions predominantly in the upper or lower body half, a half-body irradiation may render the patient pain-free for up to half a year. By an orthopedic operation a patient with a (threatening) fracture in the spine, pelvis or femur may become ambulatory again in a week, whereas without intervention she might have remained bed-ridden for the rest of her life. The neurosurgeon has a place in a pain-team, but he can also contribute to palliative treatment by implanting an Ommaya reservoir, thus enabling the neuro-oncologist to conduct intrathecal chemotherapy for meningeal carcinomatosis. Some patients with arm edema, or peritonitis with ascites, will profit from lymphovenous or peritoneovenous shunt operations.

*Table 4. Other measures*

| |
|---|
| Local irradiation |
| Half-body irradiation |
| Orthopedic surgery |
| Neurosurgery |
| Neuro-oncology |
| Lymphovenous shunt |
| Peritoneovenous shunt |

## TREATMENT SCHEDULE

It is possible to design a number of treatment schedules in which choice and sequence of different treatments are prescribed. Since advanced breast cancer is still an incurable disease, all treatment is essentially palliative: the patient should experience the maximum benefit that can be achieved by the present treatment modalities, with the least possible toxicity. Toxicity in the broadest sense also includes unpleasant social side-effects. The actual clinical pattern will always play an important role in the choice of a treatment. Table 5 lists some factors which should be taken into consideration before a decision can be made. If ER status is unknown, factors such as old age, long post-operative disease-free interval, predominantly soft tissue or bone disease are predictive, to a certain extent, of hormone sensitivity of the disease. A low performance status reduces the probability of a response to intensive chemotherapy.

*Table 5. Clinical pattern and expectations*

| |
|---|
| Age |
| Performance status |
| Free interval |
| Type of spread |
| Rate of progression |
| Hormone receptor status |
| Pathology grading |
| |
| Probability of response |
| Probability of side-effects |

Table 6 gives a crude indication of the probability of response with different treatment modalities. The 10% chance of a response with hormone therapy in patients with ER-negative tumors can make it worthwhile to try a non-toxic endocrine therapy for a few weeks in elderly patients with slowly growing metastases of a non-life-threatening character (e.g. skin metastases). If chemotherapy had been the first choice, some potential responders would have missed a very useful remission (possibly free of side-effects). On the other hand, if there is rapidly progressive disease with threatening localizations, there is no time to lose: one should direct the choice of therapy to the maximum probability of response, by combining hormone and chemotherapy regardless of ER status. In the intermediate situations one should carefully weigh the different possibilities of obtaining response against the probabilities of side-effects.

*Table 6. Probability of response*

| Therapy | Probability of response (%) |
|---|---|
| Hormone therapy: | |
| ER-positive | 60 |
| ER unknown | 30 |
| ER-negative | 10 |
| | |
| Chemotherapy: | |
| CMF | 50 |
| CAF | 70 |
| Hormonochemotherapy: | 70+ |

Abbreviations: ER = estrogen receptor status; C = cyclophosphamide; M = methotrexate; F = 5-fluorouracil; A = adriamycin.

## FUTURE ASPECTS

If we have quite a number of possibilities for treatment of advanced breast cancer, this is so because breast cancer happens to be more sensitive

to treatment than many other tumours. There is no reason to be content with what can be achieved now. Research is imperative in order to increase the effectiveness and to reduce the side-effects of present therapy. Better understanding of the mechanisms of hormone sensitivity and of the actions of cytostatic drugs may lead to more effective treatment, or to more effective application of the present treatment modalities. New, better, less toxic drugs would be most welcome. More sensitive tests for the efficacy of cytostatic drugs would diminish unnecessary toxicity. Hormones could possibly be used as vehicles to carry drugs into the target cells (cytostatic drugs, cell poisons, $\beta$-emitters); monoclonal antibodies with the required specificity might be used either directly or as a vehicle. A promising field of research seems to be the hormonal stimulation, or recruitment of the tumour, hopefully rendering it more sensitive to chemotherapy: such treatment schedules might really have an effect on survival.

## REFERENCES*

1. RUBENS RD. Breast cancer. In: PINEDO HM, ed. *Cancer Chemotherapy, the EORTC Cancer Chemotherapy Annual.* Amsterdam, Excerpta Medica, 1979, Vol.1, 376–411; 1980, Vol. 2, 351–379; 1981, Vol. 3, 360–396; 1982, Vol. 4, 339–363.
2. HENDERSON IC, CANELLOS GP. Cancer of the breast: the past decade. *N Eng J Med* 1980, **302**, 17–30, 78–90.

*These comprehensive reviews provide the original references upon which this lecture was based.