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Advanced Breast Cancer—New Approaches to Treatment: a Review

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In Europe, approximately a quarter of a million women die each year from breast cancer. Few, if any, die of primary breast cancer; most die of disseminated, metastatic disease. Much emphasis is placed on the early diagnosis of primary disease, together with effective local and systemic adjuvant therapy. The best that can be hoped for with the drugs and treatments available at the present time is an increase of 10–20% in cure rate of primary breast cancer. This still leaves hundreds of thousands of women who develop disseminated breast cancer each year. The average survival from first relapse for these women is only about 18 months in spite of the introduction of many new treatments effective at causing objective regression of obvious tumour deposits. It would therefore seem appropriate to encourage further developments in the treatment of disseminated breast cancer, not only to help control the symptoms of the many women who have and will continue to develop metastatic breast cancer, but also to attempt to prolong survival and even cure some of these patients. For research purposes, treatment of metastatic breast cancer provides a rapid method for detection of new, potentially active treatments and developments of more effective ways of using established treatments which may be useful as adjuvant systemic therapy. Finally, treatment of metastatic breast cancer with the measurement of objective response, provides the basis for scientific studies into the biological and biochemical mechanisms of tumour growth and effects of treatment.

For these reasons in this review I would like to examine some of the biological aspects of endocrine treatment of advanced breast cancer in post-menopausal women in order to attempt to identify a rational approach to treatment. This will be followed by an assessment of palliative versus curative chemotherapy in order to identify the objectives of treatment of metastatic breast cancer with cytotoxic drugs.

ENDOCRINE THERAPY

Since Beatson in 1896 [1], the established basis for treatment of pre-menopausal patients with advanced breast cancer has depended on ablation of ovarian function by oophorectomy, irradiation of the ovaries or more recently by the use of agents (LHRH analogues) which lower pituitary gonadotrophic secretion. It is likely that the tumour growth stimulating hormone produced by the ovaries is oestrogen, supported by the similar response rate reported when patients are treated with tamoxifen, a synthetic anti-oestrogen [2].

In post-menopausal women it was supposed that the opposite mechanism occurred. The menopause is caused by a natural failure of the ovaries to produce oestrogen, and it was assumed that hormone sensitive cancers which occur in these women have grown in a low-oestrogen environment. On this basis it was not surprising to note that post-menopausal women responded to administration of oestrogen [3] in a similar manner to the response of pre-menopausal women to ovarian ablation. However, the development of new effective treatments for post-menopausal women has made this hypothesis untenable and opens up a more general mechanism of oestrogen dependence for all tumours whether they develop in pre- or post-menopausal women.

For example, in spite of oestrogen being the primary treatment for post-menopausal women, tamoxifen, a supposed anti-oestrogen, was tested for anti-tumour activity and found to be effective [4]. The mechanism of action was not clear because post-menopausal women have relatively low oestrogen levels and the anti-tumour effect of tamoxifen could have been through an oestrogenic rather than an anti-oestrogenic mechanism.

Since the introduction of cortisone, adrenalectomy was possible and found to be an effective, albeit a difficult and sometimes lethal treatment for post-menopausal women [5]. It was assumed that the adrenal produced a steroid hormone other than oestrogen or cortisol which could stimulate tumour growth. Aminoglutethimide, an agent which blocks steroid synthesis by the adrenal glands, could give rise to a 'medical' adrenalectomy. It inhibits the synthesis of cholesterol to progesterone, a prerequisite for all steroid hormone synthesis and is as effective as adrenalectomy at inducing objective regression of tumour in post-menopausal breast cancer patients [6]. Its action is not a generalized inhibition of all steroid synthesis, because levels of androstenedione and testosterone levels are not lowered [7]. However, the levels of oestrogen are lowered, which indicates that the effective activity of aminoglutethimide is to inhibit the conversion of androgens to oestrogens by the aromatase enzymes. This is confirmed using low dosages of aminoglutethimide (125 mg/day) where only the aromatase activity is apparent with lowering of oestrogen levels and objective response of tumour [8]. Although this indicates that oestrogen synthesis may be important for hormone dependent growth in post-menopausal women, it was not possible to exclude inhibition of other enzymes by the non-specific activity of aminoglutethimide particularly within the tumour. Furthermore, low dosages of aminoglutethimide still retained much of the toxicity of full dosage and the search went on for alternative 'aromatase' inhibitors.

The 4-hydroxy-synthetic analogue (4OHA) of androstenedione, a precursor of oestrogen synthesis, was found to be an effective and specific inhibitor of aromatase with virtually no inherent steroid activity [9]. This agent is as effective as aminoglutethimide for treatment of endocrine sensitive post-menopausal breast cancer [10] which strongly supports the hypothesis that the relatively low levels of oestrogen in post-menopausal women as a result of non-ovarian aromatase activity, is sufficient to stimulate growth of hormone dependent breast cancer, similar to that seen in pre-menopausal women.

This raises the paradox that post-menopausal endocrine sensitive breast cancer may respond to oestrogen deprivation or oestrogen treatment [11]. In part, this discrepancy can be resolved by consideration of dose levels. For hormone replacement therapy for post-menopausal women the dose of ethinyl oestradiol (0.03 mg/day) or of premarin (0.625 mg/day) is very much less than for treatment of breast cancer (1.5 mg/day and 15 mg/day respectively). The plasma levels of oestradiol for oestrogen therapy are > 10,000 pmol/l compared with normal levels of 100–1000 pmols/l for pre-menopausal and about 100 pmol/l for post-menopausal women. These very high levels of oestrogen may have a different anti-tumour effect to oestrogen deprivation. This could account for the commonly observed tumour flare seen with oestrogen therapy when levels of oestrogen are rising through a stimulatory phase before achieving high anti-tumour levels. Successful treatment with an aromatase inhibitor requires the normal levels to be reduced to less than 50 pmol/l.

In conclusion, it would therefore seem that endocrine response depends on reducing the endocrine stimulation to growth either by high levels of oestrogen (oestrogen therapy) or by very low levels (< 50 pmol/l) using inhibitors of oestrogen synthesis in post-menopausal women or ablating the ovaries in pre-menopausal women. This would indicate that pre-menopausal patients could respond to oestrogen therapy as has been reported [12, 13]. The anti-tumour effects of other hormones such as androgens and progestins could be as 'physiological' opponents of oestrogen stimulation through their relevant receptors.

Within this hypothesis the mechanism of action of tamoxifen remains unclear. It could act as an anti-oestrogen, blocking the oestrogenic stimulus to growth by binding to the oestrogen receptor. Alternatively, it could act as an impeded oestrogen inhibiting growth in a similar manner to oestrogen therapy. This would account for the occasional 'flare' seen with this agent. These questions will be answered with the development of relatively pure anti-oestrogens where the anti-tumour effect may be lost even though receptor binding is maintained.

In conclusion, studies of the effects of different types of endocrine therapy help to elucidate the basis of hormone dependence of tumour growth. This is essential to the understanding of the mechanisms of endocrine response and relapse and to the development of new and better types of endocrine therapy.

CHEMOTHERAPY

In the past, much emphasis has been placed on objective response of tumour to chemotherapy often without any palliative relief of symptoms or prolongation of survival. Although objective response may be a good comparative measure of the anti-tumour activity of different cytotoxic agents [14], it does not necessarily reflect any therapeutic benefit of treatment. Much controversy has arisen about the relative merits of various types of treatment because the objectives of successful therapy have not been clearly defined. Two objectives which would generally be considered worthwhile are: (1) palliative relief of symptoms caused by tumour and (2) prolongation of survival or cures.

1. *Palliative*

Metastatic breast cancer objectively responds to many cytotoxic agents including anthracyclines, alkylating agents, anti-metabolites and vinca alkyloids. The ceiling of objective response rate for assessable patients appears to be about 60% whether a single agent or combinations of agents are used. With the agents available at present no patients are cured.

Palliation depends on a balance between objective regression of symptomatic tumour and toxicity of treatment. There is much debate as to whether single agent treatment is more effective than combinations of drugs. The most effective single agent at the present time is probably adriamycin (although mitoxantrone looks promising). At a bolus dose of 70 mg/m^2 given every 3 weeks a 57% objective response rate has been reported [15] but at the expense of significant toxicity (79% nausea and vomiting, 100% alopecia, 51% stomatitis). The palliative benefit of this treatment is doubtful. When the dose is dropped to 35 mg/m^2 the response rate fell to 25%, with similar toxicity [16] and no palliative benefit. Attempts to reduce the toxicity of single agents by infusion have been disappointing, although there may be some reduction in cardiotoxicity, nausea and vomiting if adriamycin infusions are extended to 72 h [17]. Unfortunately, it is not possible to prevent alopecia by scalp cooling with these infusions and this, together with the inconvenience of repeated long duration infusions, makes palliative benefit unlikely.

Similarly, low dose weekly injections reduce the acute toxicity of individual injections. Although the objective response is relatively low and it involves frequent hospital visits, there have been encouraging reports of good palliation with this type of regime.

An alternative approach is to attempt to develop relatively low toxicity, effective combinations of drugs. This depends on using drugs of different mechanisms which have relatively low individual side-effects with a variable distribution of toxicity.

In general, patients with metastatic breast cancer respond to a maximum of two or three treatment regimes whether it be single agent or combinations of drugs. The response rate is not increased by using more than three drugs in any combination and therefore, with the number of effective drugs available, at least two combinations of three drugs can be used per patient. In combination the dosages of individual drugs can be reduced while maintaining an objective response rate of 50–60%, a rate which is required for significant palliation. The toxicity for the individual drugs is low, with minimal overlap and the frequency of injection of 3–4 weeks acceptable to the patient. Using these criteria we have evaluated a combination of mitomycin C, an alkylating antibiotic (7 mg/m^2 every 6 weeks), mitozantrone, an anthracenedione (7 mg/m^2 every 3 weeks) and methotrexate, an antimetabolite (30 mg/m^2 every 3 weeks).

For first line cytotoxic therapy, we have reported an assessable objective response rate of 61% with low subjective toxicity (nausea and vomiting 28%, alopecia 5% and stomatitis 11%). Palliation of symptoms caused by tumour was good and better than for other combinations [18].

If palliation is the main objective for treatment consideration of the duration of treatment is required. Unfortunately, very few clinical trials of chemotherapy in breast cancer have addressed this question and most have continued treatment until evidence of failure with a duration of response of about 8–12 months. We have gradually adopted a policy of stopping treatment of patients in remission after 4–6 months, and although this is not randomized, retrospective analysis shows no evidence that either duration of remission or survival is shorter for those who stopped treatment early. Furthermore, continued treatment may compromise the bone marrow for subsequent chemotherapy regimes.

Finally, to achieve maximum palliation adequate symptomatic support is required. This involves appropriate use of antinauseants such as dexamethasone, metoclopramide, domperidone and the new 5-HT3 receptor antagonists, together with scalp cooling to prevent alopecia and folinic acid to prevent methotrexate induced stomatitis.

In summary, it would seem that palliation by chemotherapy is best achieved by use of low toxicity combinations of three cytotoxic drugs for 4–6 months with no maintenance therapy once in remission and adequate symptomatic support during treatment.

2. *Curative*

Long term remission and survival in patients with metastatic breast cancer is unusual. Of over 1000 patients only 42 survived for more than 5 years and most of these had had a good endocrine response to bone metastases [19]. A few patients have responses to chemotherapy of 1–2 years. To test whether any patients could be cured by cytotoxic chemotherapy we decided to give treatment intensification by high dose chemotherapy with autologous bone marrow rescue to patients in good remission on standard chemotherapy. Of 128 possible patients, 15 were selected as eligible whilst in good remission and given 200–250 mg/m^2 of melphalan with autologous bone marrow rescue. There were three treatment related deaths. Otherwise the duration of response (7 months) and survival were identical to matched patients in remission not receiving treatment intensification. Relapse was at the site of

previous tumour and no patients were cured [20].

These results indicate that, with the present drugs and techniques available, few if any long term remissions or cures can be achieved with cytotoxic chemotherapy.

GENERAL CONCLUSIONS

In Europe, at any one time, there are about 500,000 women with metastatic breast cancer. At some time most of these patients will receive two or three different types of endocrine therapy and two or three types of chemotherapy regime according to their age, general condition, sites of metastases and responses to treatment. None will be cured.

At the present time, it is hoped that a better understanding of the mechanisms of endocrine response and relapse, and the interaction with other mechanisms of growth regulation, will allow development of more effective endocrine therapy, with improvement in the response rate and duration of remission. Development of curative endocrine therapy seems unlikely.

Similarly, cure by cytotoxic chemotherapy with the presently available drugs is not possible. However, good palliative remission can be achieved by using low toxicity combinations.

Management of metastatic breast cancer is as difficult for the physician, nurse and support staff as it is trying and often desperate for the patient.

It is possible that new methods of treatment with growth regulating agents will be developed and that new, more effective cytotoxic drugs will become available. It seems likely that metastatic breast cancer will be with us for many years to come and every effort must be made to relieve the symptoms and improve the survival of these unfortunate patients.

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