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Editorial

Prognostic Impact of Amenorrhoea after Adjuvant Chemotherapy

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THE EVIDENCE from a large number of clinical trials, involving tens of thousands of patients, clearly shows a reduction in the risk of relapse and death by use of adjuvant endocrine and chemotherapy for treatment of patients with primary breast cancer [1]. Furthermore, these clinical benefits seem to be having an impact on reducing national mortality from breast cancer in the U.K., in spite of an increase in the incidence of the disease [2, 3]. However, in spite of the very large numbers of patients involved in these clinical trials, it is still difficult to identify the relative merits of the different types of treatment, especially the contribution of cytotoxic chemotherapy versus endocrine treatment.

Although chemotherapy seems to provide a small but real benefit for all categories of patients (in fact, it is difficult to identify any subgroups of patients who do not gain benefit) the results from most trials show a consistently better benefit for premenopausal (under 50 years of age) rather than postmenopausal (over 50 years of age) patients [1]. Chemotherapy will induce amenorrhoea (CIA) by causing ovarian failure in a substantial proportion of premenopausal patients [4] and adjuvant ovarian ablation, after primary breast cancer treatment, will increase relapse-free survival and reduce mortality in premenopausal women [5]. This raises the possibility that part of the chemotherapy benefit could arise from an additional endocrine effect of this treatment [6].

In postmenopausal women the indirect comparisons in the 1990 Oxford overview meta-analysis of adjuvant trials for the non-confounded effects of using tamoxifen alone, chemotherapy alone, or both treatments together, indicated that the addition of endocrine therapy, using tamoxifen, to chemotherapy produced an additional benefit with no evidence of any interaction between the two types of treatment [1]. In premenopausal women, however, the magnitude of the adjuvant chemotherapy benefit appeared larger than for postmenopausal women and the addition of tamoxifen seemed to contribute little extra benefit. This would be in keeping with a chemocastration effect caused by the chemotherapy, which might have compromised any possible additional tamoxifen adjuvant endocrine benefit.

What is the evidence that chemocastration in premenopausal women is a factor in therapeutic benefit? Unfortunately there is very little prospective endocrine data from adjuvant chemotherapy trials. Most of the evidence relates to the incidence of amenorrhoea with the assumption that failure to have cyclical bleeding indicates likely ovarian failure. Periodic bleeding, however, it not necessarily related to the changes in levels of steroid sex hormones, which could influence endocrine sensitive tumour growth and the magnitude of treatment benefit. It is known that various cytotoxic drugs can cause ovarian failure with loss of ovarian follicles progressing to ovarian fibrosis [7]. With CMF (cyclophosphamide, methotrexate, 5-fluorouracil) adjuvant chemotherapy given for more than 3 months, approximately 70% of women develop amenorrhoea. The individual drugs which seem to have most effect on the ovary are cyclophosphamide, doxorubicin and mitoxantrone whereas methotrexate and 5-fluorouracil seem to have little effect on causing ovarian dysfunction. Ovarian failure relates to the total drug dosage and intensity of treatment and is more likely to occur in older than in younger premenopausal patients, with almost all premenopausal women over the age of 40 years having at least temporary amenorrhoea. For review see [4].

Even without adequate endocrine evaluation, many clinical trials have shown that much of the benefit of adjuvant chemotherapy in premenopausal women occurs in those women who develop amenorrhoea on chemotherapy with ER positive primary cancers [8–12]. Similar findings have been reported by Pagani and colleagues in this issue of the *European Journal of Cancer* (pp. 632–640). Curiously, although amenorrhoea is more likely to occur in women over 40 years of age, adjuvant chemotherapy in premenopausal women seems to be more effective in women under 40 years. (Reported but not published in the Oxford Overview meta-analysis, 1995). An important observation in the report by Pagani in this issue (pp. 632–640) is that amenorrhoea does not have to be permanent in order to achieve a benefit on relapse-free survival. It seems that even temporary amenorrhoea for over 6 months is of similar benefit to permanent amenorrhoea, in keeping with other types of adjuvant endocrine therapy. For example, adjuvant tamoxifen given for 2 years seems to give ongoing benefit on relapse-free survival and survival for up to at least 10 years [1]. Similarly, ovarian radiation-induced menopause in premenopausal women has a long ongoing benefit on relapse-free survival and survival extending out to 20 years. Most of these women would have achieved a natural

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menopause only a few years after ovarian radiation and yet, the benefit of relapse and survival only became obvious after many years [13]. These data indicate that a short adjuvant endocrine intervention may be sufficient to provide long-term adjuvant benefit.

There is considerable conflict on whether shorter or longer courses of chemotherapy have a maximum effect on the ovaries. Most data indicate that the total dose of the drug is important [4] and the data in this report by Pagani, that most benefit occurred in those patients with CIA who received suboptimal chemotherapy is surprising. There is no clinical or experimental basis for the supposition that the endocrine benefit is more likely to occur if the chemotherapy effect is suboptimal. These differences in results may relate to the relatively small subset numbers which have not been prospectively determined which makes interpretation difficult.

Where do we go from here? Various trials are underway at present looking at the use of adjuvant chemotherapy with or without ovarian ablation by other means. If part of the benefit from adjuvant chemotherapy is due to chemocastration, then there should be little added benefit in also causing ovarian ablation by other means (see Jordan, pp. 606–608). Any additional benefit should be confined to those patients who do not develop chemocastration. It is, therefore, important for future trials to monitor FSH prospectively rather that menstrual history in order to identify which subpopulation of patients may still have intact ovarian function after chemotherapy. It is these patients who could still gain benefit from subsequent ovarian ablation after adjuvant chemotherapy.

There are many questions which still remain unanswered. For example, is the timing of each cycle of chemotherapy important in relation to the menstrual cycle, especially with classical CMF in a 4 weekly cycle given predominantly in the luteal phase rather than the follicular phase, when it is more likely to have an effect on the ovary? Does the concomitant use of an LHRH analogue with chemotherapy protect the ovaries against chemotherapeutic damage? Does the level of oestrogens after chemotherapy affect the chemosensitivity of endocrine sensitive cancer cells? After permanent loss of ovarian function caused by chemotherapy, could hormone replacement therapy be used to control menopausal symptoms without loss of benefit?

Some of these questions may be directly or indirectly answered by further analysis of ongoing clinical trials. Most will never be answered even by very large adjuvant clinical trials and we may have reached as far as we can go with this approach.

At this time what do we advise our patients? It is obviously only possible to advise an individual patient on treatment options in the very broadest terms, based on large clinical trials. It would seem that most premenopausal patients gain a modest but real benefit from adjuvant chemotherapy. Those with ER positive tumours probably gain part of this benefit by a temporary or permanent ovarian failure. Whether it is safe to give hormone replacement therapy to patients with ER negative tumours who develop early menopause, or to others who have had ovarian failure for more than 1 year, but who now have unacceptable early post-menopausal symptoms, remain unanswered.

One possible approach, which may help to monitor the effects of these treatments on micrometastases, follows the increasing use of primary medical treatment. It seems likely that the response of the primary tumour mimics the micrometastatic response and indicates likely adjuvant benefit with improved relapse-free survival and survival [14]. Changes in molecular markers within the primary tumour such as indicators of proliferation and apoptosis, may predict and monitor likely response to cytotoxic chemotherapy [15, 16]. Changes in hormone receptors and other endocrine markers may help to predict and monitor endocrine response.

Evaluation of these molecular markers in the primary tumour could help differentiate between an endocrine response and a cytotoxic response. This would allow us to determine the respective endocrine and cytotoxic components of adjuvant chemotherapy in premenopausal women and also enable us to identify the therapeutic effects of other endocrine treatments such as tamoxifen, pure anti-oestrogens and LHRH analogues. The time has come for us to attempt to individualise and monitor adjuvant treatment in premenopausal women using the primary tumour as an *in vivo* marker of therapeutic effect. These changes need to be linked with changes that occur in measured hormone levels in the patients rather than crude clinical parameters of age or menstrual history.

In conclusion, it seems likely that we have gained important therapeutic indications for adjuvant treatment of premenopausal patients with breast cancer from the large multicentre clinical trials which have been reported. There is no doubt that there is a small, but real, benefit by giving chemotherapy to premenopausal breast cancer patients and that part of this benefit arises from an indirect effect of chemotherapy on ovarian function. Further clarification of the respective endocrine and cytotoxic component of this treatment will need more refined methodology involving measurements of hormone changes in individual patients and perhaps changes in molecular markers in the primary tumour. This would eventually allow us to individualise and monitor treatment for the patients, rather than relying on broad based general conclusions from population-based research and large indiscriminant clinical trials.

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