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Editorial

Chemotherapy is Antihormonal Therapy—How Much Proof do Oncologists Need?

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BREAST CANCER is unique among solid tumours as there is a subgroup of patients who successfully respond to a therapeutic strategy other than chemotherapy. We have known for a century that a third of premenopausal patients with advanced breast cancer will respond to ovarian ablation (see Figure 1) [1, 2]. Sensitive tumours are identified by the presence of the oestrogen receptor (ER), but, most importantly, by the end of the 1970s it was clear that any antihormonal strategy, in pre- or postmenopausal patients that denied estrogen to a sensitive tumour, would aid the patient [3]. A clear cut basic principle was established that would subsequently guide the applications of antihormonal therapies to this day, i.e. an ER positive tumour is more likely to respond to antihormonal therapy than an ER negative tumour. Unfortunately, the fact that not all the early adjuvant clinical trials using tamoxifen appeared to obey the principle confused the issue for the practicing clinician. Nevertheless, the process of overview analyses of randomised clinical trial has now demonstrated that the original principles are correct. Antihormonal adjuvant strategies benefit pre- and postmenopausal patients and the main effect is observed in ER positive disease (Figure 1) [4].

However, in a 'parallel universe', cytotoxic chemotherapy was evolving. Twenty-five years ago, the use of adjuvant combination chemotherapy held the promise of a cure for breast cancer. The hopes were pinned on the belief that the remarkable successes of chemotherapy in childhood leukemia and Hodgkin's disease could be extrapolated to solid tumours. The chosen strategy was logical; aggressive, noncross resistant drugs would be given to patients after surgery to destroy the remaining tumour cells. It was known that responses in advanced disease are based on tumour burden, therefore patients with a microscopic tumour burden would undoubtedly be cured. Enormous efforts have subsequently been made to calculate drug scheduling, to estimate cell kill and to provide growth factor support for the patient. Nevertheless, analysis of data from the first reports to the present demonstrate that the control of disease recurrence is related to the menstrual status of the patient. Premenopausal patients have a much better response to adjuvant chemotherapy than postmenopausal patients [5, 6]. Now, at last, in the 1990s chemotherapy and antihormonal therapy are poised to coalesce.

The paper in this issue, from the International Breast Cancer Study Group (pp. 632–640) [7], describes the therapeutic merits of chemotherapy-induced amenorrhea in a large trial of 1554 pre- and perimenopausal women who received different durations of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy. It has been known for 20 years that alkylating adjuvant chemotherapy induces ovarian failure in breast cancer patients [8] but the problem with all trials, which is again illustrated by the present report, is that a 'cytotoxic oophorectomy' is age related and often incomplete. Younger patients are more resistant to this side-effect of chemotherapy than older patients. Thus, irrespective of any other factors, the trial results are complicated by definitions of amenorrhea, the ages of the patients and the proportion of patients who exhibit the 'side effect' of amenhorrea—that is even before the results are appropriately analysed for ER status. Fortunately, unlike other retrospective studies, the authors were prepared to analyse their data based on a description of amenorrhea recorded for each patient. Indeed, this course of action was preplanned as the group, under a different title, had previously demonstrated that chemotherapy-induced amenorrhea can increase disease-free survival [9].

Overall, the conclusions from the clinical trial merit consideration based on what we currently know about the biology of breast cancer. The principle is quite simple. Any procedure that perturbs the hormonal balance will benefit a proportion of patients. These will have ER-positive breast cancer. With this in mind, there are two major points from the paper. First, the authors find that patients who exhibit amenorrhea have a substantially longer disease-free survival compared with patients who do not. In other words, if a woman has a chemically induced oophorectomy then, based on what we know from the overview analysis about increased survival of breast cancer patients following adjuvant oophorectomy [4], we would anticipate a benefit for some patients. Second, the authors find that patients with ER-positive disease are more likely to benefit from chemotherapy induced

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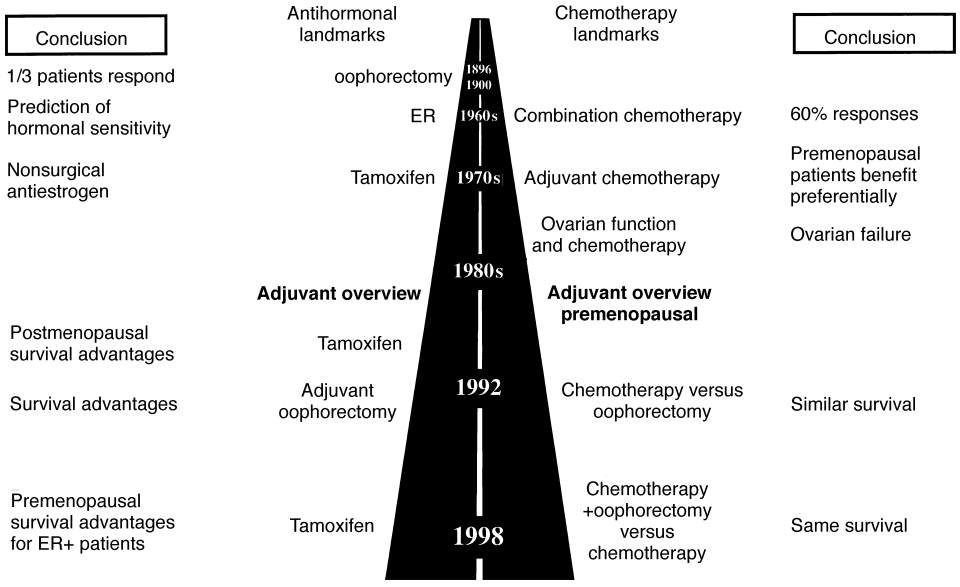

Figure 1. The historical evolution of results and conclusions about antihormonal and chemotherapeutic agents for the treatment of breast cancer.

amenorrhea. Conversely, patients with ER-negative disease do not respond preferentially based on the development amenorrhea. This result is exactly what would be expected based on the past 30 years of research concerning the link between the ER and the regulation of breast cancer growth.

It is already known from the adjuvant studies with chemotherapy alone in postmenopausal patients that there is only a modest direct effect [4]. Clearly, if the main effect of chemotherapy in premenopausal patients in ovarian ablation (Figure 2), then there is probably a smaller direct antitumour action of chemotherapy that is equivalent is both pre- and postmenopausal patients. By contrast, the major therapeutic effect in postmenopausal patients is observed with at least 5 years of tamoxifen in ER-positive disease. The duration of tamoxifen is extremely important and this critical treatment strategy has slowly been unraveled over the past 20 years. Additionally the concern that tamoxifen is ineffective in pre-

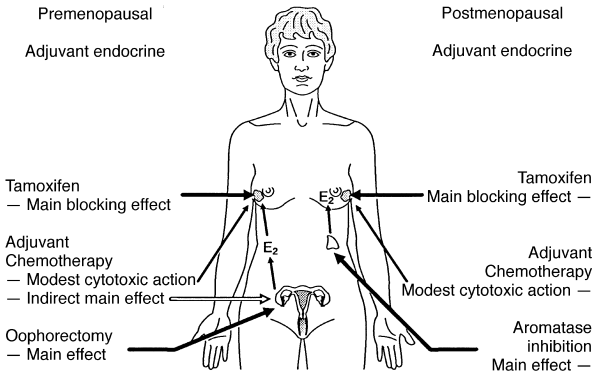

Figure 2. Antihormonal strategies for the treatment of pre- and postmenopausal patients in ER-positive (+) breast cancer. Combination chemotherapy has a modest direct action as an adjuvant in postmenopausal women but the main effect in premenopausal woman is to precipitate a chemical oophorectomy. If the direct antitumor effect of chemotherapy in pre- and postmenopausal women is the same then the completeness of the chemical oophorectomy will determine outcome in the premenopausal patient with ER + disease.

menopausal woman has been resolved. It is now known that short term (1 y) tamoxifen therapy is virtually ineffective compared with long term therapy (5 y). It therefore follows that if adjuvant chemotherapy is antihormonal therapy in the premenopausal patient, then simultaneous short term adjuvant tamoxifen (1 y) would never be expected to add much to prognosis. This was found to be true in the overview analysis [4, 10] and started the myth that 'tamoxifen did not work in premenopausal patients'. Obviously, this was untrue based on the results from National Surgical Breast and Bowel Project (NSABP) protocol B_{14} alone [11]. No chemotherapy was given and tamoxifen was equally effective in both pre- and postmenopausal patients with ER-positive disease. The myth is now laid to rest as the current overview analysis (1998) will show that tamoxifen is effective for control of ER-positive disease in premenopausal patients (see also Powles, pp. 603–605).

The value of antihormonal therapy is the precision of the approach. Testing in the laboratory was hypothesis driven and a heterogeneous population of laboratory animals was not randomly observed for effects. This unfortunately is what confronts the clinical community with the heterogeneity of breast cancer. One treatment will not do all. What we find is that agents are, in general, not very active and often only subgroups produce benefits. In this case [7], it is a hormone responsive subgroup of premenopausal women.

More that 10 years ago Professor Tagnon told me that clinical trials serve the purpose of confirming a hypothesis based on good laboratory data. For the breast cancer patient it has taken 2 decades to refine Jensen's original hypothesis [12] that some patients can be preselected for antihormonal therapy. At that time, in the late 1960s, there was no antihormonal therapy other than endocrine ablation. Now that has all changed and the physician has a broad range of different agents to regulate the access of oestrogen to the receptor (Figure 2) [13]. These non toxic agents should be used to provide optimal benefit for specific patients whether they are pre- or postmenopausal. There is no need to use chemotherapy as an antihormonal therapy in the premenopausal patient with ER-positive disease. Nevertheless, the quest to

understand specific tumour targets for chemotherapy continues. Until that time comes, through the miracle of molecular biology, it is claimed that all ER-positive node negative patients can derive some additional benefit from the ubiquitous application of combination cytotoxic chemotherapy along with tamoxifen [14]. On close examination of the data, there is an important additional observation of note. The summary of the NSABP study states that 'the risk of treatment failure was reduced after chemotherapy ... however, the reduction was greatest in patients 49 years or less.' [14]. Could it be that chemotherapy has really produced an oophorectomy in the premenopausal patients and reduced the high levels of circulating oestrogen known to occur in response to tamoxifen [15]? If the principle is again being served, one wonders what a medical Luteinising Hormone Releasing Hormone (LHRH) oophorectomy, tamoxifen and selective chemotherapy would accomplish in the premenopausal patient with ER-positive disease.

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