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Comments and Critique

Can we Increase Survival in Breast Cancer With Innovative Applications of Conventional Drugs?

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THE TREATMENT of metastatic breast cancer is frustrating at best. On the one hand, we are tantalised by high initial response rates, on the other, discouraged by the eventual death of the patient with unresponsive metastatic disease. The palliative nature of our treatment of malignancy is not dissimilar to our treatment of patients with heart disease or chronic pulmonary disease. The difference lies in the oncologist's ability to reduce the size of tumours for substantial periods of time. This response to treatment is visible and measurable. With heart disease, little change is made in the atherosclerotic process, and in pulmonary disease, fibrosis or emphysema is irreversible. This should give us all some hope that by continuing to modify our treatment regimens, we will one day hit a home run.

In this issue, Hug *et al.* present a study on the treatment of patients with metastatic breast cancer with a modified standard doxorubicin-containing chemotherapy regimen. They attempt hormonal recruitment (priming) with the use of high doses of oestrogen. In addition, they modify the administration of 5-fluorouracil, delivering it by continuous infusion, as it is known that the drug is strongly schedule dependent. Finally, they limit the number of cycles given, hypothetically to reduce the emergence of drug-resistant cells and to improve quality of life. The response rate was 76%, with a median overall survival of greater than 29 months, which is on the upper end of known efficacy for most conventional regimens [1]. Complete response rate was 13%. The results included two toxic deaths, one related to neutropenic sepsis and the other to congestive heart failure. The question then arises whether this regime demonstrates a significant increase in efficacy over conventional regimens.

As the authors point out, it is difficult to determine which of the factors may be responsible for the favourable response rates and overall survival observed. Let us examine each of the premises under which the trial was conducted. The first refers to the experimental observation that breast cancer cells, both *in vitro* and *in vivo*, can be synchronised into a proliferative phase by oestrogen [2]. These cells, once induced into the synthetic cycle, can then be rendered more vulnerable to chemotherapy. While their report indicates that follicular range levels of oestradiol were achieved, a problem exists with the hypothesis that this dose of Premarin increases the efficacy of cycle-dependent drugs. In a previous study by Conte and colleagues, using biopsies performed on patients with addition of oestrogen, the thymidine labelling index was increased by only a few per cent in 8 of 16 patients [3]. This is unlikely to make a substantial difference in treatment response. Although Hug *et al.* did not find any association between time to progression (TTP) and oestradiol levels, it is possible that the pharmacological doses of Premarin given in their study may have had a tumoricidal effect in some patients. The use of tamoxifen and Premarin in a previous attempt at hormonal synchronisation in a non-randomised clinical study showed improved outcome in locally advanced breast cancer [4]. Although early studies such as this were promising, more recent randomised trials have not confirmed increased efficacy using hormonal synchronisation [5–7]. Thus, it seems unlikely that this aspect of the study accounts for the apparently higher response and overall survival rates.

The second approach used to improve treatment was the use of infusional rather than bolus 5-fluorouracil (5-FU). There is experimental evidence that bolus schedule (short-term exposure) works by blocking RNA synthesis, whereas the infusional schedule (prolonged exposure) inhibits thymidylate synthesis and consequently, DNA synthesis [8]. Numerous studies in colon cancer have shown the superiority of infusional administration [9]. In refractory breast cancer, phase II studies document a 30% response rate (range 17–53%) to this regimen, even in patients previously exposed to bolus 5-FU [10]. Hug *et al.*'s use of 5-FU 3000 mg/m^2 delivered over 72 h in this chemotherapy-naive population may have led to higher response rates, and lends support to this form of drug delivery.

The optimum length of treatment duration in metastatic breast cancer patients has not been defined. Although it has been shown that continuous chemotherapy produces a longer TTP than interrupted courses, overall survival is not improved [11]. This is not surprising if the demise of the patient is finally determined by the rate of growth of the resistant clone of cells, as predicted by certain experimental models [12]. The question of optimum palliation is raised. The ability to deliver a circumscribed period of chemotherapy and maximise time off treatment without deleterious effect on TTP or overall survival is encouraging. Indeed, any attempt at improvement of quality of life in the palliative setting should be seriously considered.

One must keep in mind that the investigation by Hug *et al.* is a phase II study in a relatively well-selected population [previously untreated with chemotherapy, oestrogen receptor (ER) positive or unknown, 48/63 postmenopausal] which may

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well account for the favourable outcome. Indeed, response rates in untreated patients to doxorubicin-based regimes are often quoted in the 50–80% range [13]. Median survival from first metastasis for ER-positive patients is significantly longer than ER-negative patients (34 versus 14 months) [14]. Against this possibility is the fact that 60% of patients had visceral disease, and 50% of patients had previous hormonal therapy. Nevertheless, the results from this study, although interesting, do not represent a quantum leap in our treatment of metastatic breast cancer.

How many other ways are there to manipulate our drugs? It is clear that we have reached a plateau in the treatment of metastatic breast cancer with conventional drugs in standard doses. This has led many investigators to use higher doses of conventional drugs with bone marrow peripheral stem cell rescue in an attempt to climb the steep dose–response curve of most drugs. However, the trials in metastatic disease, using very high dose therapy, do not show a survival benefit when compared to trials using standard doses. Most of the early trials treated patients with a large tumour burden, and now it is accepted that patients need to be responsive to chemotherapy with standard doses and have low tumour burden before proceeding to high dose therapy. Patients with a high risk of relapse, such as those with greater than 10 positive nodes or locally advanced inflammatory breast cancer, are groups that are ideal for evaluation of dose-intensive regimens. Two large randomised cooperative group studies are ongoing in the U.S.A., and are designed to answer the question of dose intensity.

Where do we go from here? Breast cancer proliferation, invasion and metastasis include a large number of processes. Loss of regulation or growth control, basement membrane degradation, angiogenesis, immune response, DNA repair, drug resistance, growth and attachment factors all play a role in the metastatic process. As we learn more about the molecular biology of breast cancer, we should be able to more specifically test innovative therapies.

Current strategies include targeting specific sites located on breast tumours. Examples include epidermal growth factor receptor and *erb*B2. Immunotoxin conjugate trials have been initiated.

Other avenues of research include targeting angiogenic factors. There is evidence that tumour growth is angiogenesis-dependent [15]. In addition, endothelial cells do not normally proliferate unless stimulated by a wound or tumour. Therefore, the proliferation of endothelial cells offers a specific target for treatment of cancer. This can be accomplished either by inhibition of an angiogenic factor (ligand) which binds to a receptor, or by inhibition of endothelial cell proliferation. Examples of drugs used for inhibitors of angiogenic factors include pentosan polysulphate and suramin. Other inhibitors of angiogenesis include platelet factor 4, thrombospondin, steroids + B-cyclodextrin tetradecasulphate, fumgallin and its derivatives.

Recently, a phase I study of pentosan polysulphate in advanced refractory cancer patients was completed at the Lombardi Cancer Centre. 19 patients were treated, with 3 patients maintaining stable disease. Anti-heparin binding growth factor activity was present in patient serum even at a dose level which did not produce anticoagulation. This therapy is promising for future development of prevention studies or adjuvant therapy of breast cancer.

A novel antiproliferative and antimetastasis agent developed as a coccidiostat has been shown to inhibit thymidine incorporation and clonogenic growth of a hormone-independent breast cancer cell line, MDA-MB-231 [16]. It is postulated that the mechanism of action is by inhibition of receptor-mediated stimulation of certain enzymes, using guaninine nucleotide binding protein signal transduction. This agent is now being tested in a phase I clinical trial at the National Cancer Institute.

In conclusion, although Hug and Clarke have shown a moderate improvement in outcome using innovative approaches to drug delivery and treatment scheduling, it is not the final answer for this devastating disease. By understanding the biological and molecular basis of cancer we hope one day to be discussing 'cure rates' rather than 'response rates' in metastatic breast cancer.

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