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Introduction

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While much of the attention of clinical research has focused lately on the primary therapy of breast cancer, metastatic disease is still a major concern, deserving considerable thought and allocation of resources. The 10-year results of the worldwide overview, and even longer follow-up of individual seminal trials, have confirmed an appreciable impact of systemic adjuvant therapy on both disease-free and overall survival [1,2]. Nevertheless, most patients who would have developed stage IV disease without such treatment will continue to do so even with the best adjuvant drug therapies [3]. Metastatic breast cancer is the most common cause of death in women in their fifth decade in Western Europe and North America, and the continuing toll of human misery and loss caused by this disease are just cause for public and professional concern.

Advanced breast cancers that are unresponsive to hormonal therapy, or that demonstrate resistance after initial response, may often be palliated by the form of cytotoxic drug treatment popularly called 'chemotherapy.' In spite of high response rates, however, response durations are limited for most patients, producing long-term survival rates that are low, even after the most aggressive application of such treatment. The reasons for relapse after chemotherapy, in both the adjuvant setting and after treatment for advanced disease, are hypothesized to be multiple and complex, involving biochemical drug resistance, privileged sanctuaries, stromal factors and various forms of kinetic resistance [4]. The consequence is that populations of cancer cells remaining after chemotherapy are capable of growth during further chemotherapy, leading almost inevitably to disease of life-threatening volume.

Preventing lethal breast cancer will depend on keeping the tumour volume small enough to be below the fatal threshold. This could, theoretically, be accomplished by eradicating all cancer cells, where possible, or by combining cytotoxic influences with antigrowth manipulations to prevent regrowth of residual cancer cells [5]. To optimize cell kill we will need to improve our understanding of cytokinetic dynamics. It is already evident, from observations of relapse times in the unperturbed state and after adjuvant drug therapy, that slow-growing tumours like breast cancer do not follow the exponential growth kinetics of acute leukaemias. The simplest model that fits clinical data is the Gompertzian curve, in which the relative growth rate slows down as the tumour becomes larger. Gompertzian growth curves are ubiquitous in nature, and may be the consequence of fundamental mathematical laws relating the cancer cells geometrically to their stroma [4,5].

A basic property of Gompertzian growth is that the more a population is reduced in size by a noxious influence, the faster is its recovery. The durability of this pattern of growth over the eons of evolution may be because it acts as a homeostatic mechanism for maintaining tissue integrity. For example, epidermal growth rates would be higher in response to a large abrasion of the skin than in response to a small abrasion, thus ensuring rapid repair in both cases. A frustrating result of Gompertzian growth, when applied to anticancer therapy, is that mere cytoreduction is not enough to assure clinical success: every single cancer cell must be eradicated and the regrowth of even the smallest residual collections of cells must be perturbed significantly to accomplish our goals.

Many investigational approaches to optimizing cell kill have been employed. Most have focused on increasing the dose level of a drug, so-called 'dose escalation', in an effort to kill more cells with each administration. Other lines of investigation are focusing on 'dose density', the more frequent administration of drugs at conventional or escalated dose levels. In both means of dose intensification, combinations of agents, as well as single agents, have been employed. In the future, such optimized schedules may be combined with antigrowth influences, antigrowth factor antibodies, signal transduction inhibitors and vaccines, in order to maintain the gains from the cytotoxic activity of the induction chemotherapies. Nevertheless, the heart of all presently conceivable anticancer drug strategies is composed of drugs that kill cancer cells.

The above discussion underscores the importance of introducing new cancer-killing agents into the oncologic armamentarium. The past few decades have seen relatively few new agents that have inspired more enthusiasm than the taxoids. Both paclitaxel (Taxol®) and docetaxel (Taxotere®) have shown exceptional

activity against breast cancer and other neoplastic diseases [6,7]. Paclitaxel has been used in many dose schedule combinations, and the optimal method of administration remains an active area of interest. For docetaxel, less heterogeneity of dose scheduling is evident. At the recommended initial dosage of 100 mg/m^2 intravenously over 1-h every 3 weeks, the drug is now licensed worldwide for the treatment of breast cancer that has recurred during or after, or failed to respond to, cytotoxic therapy which included an anthracycline or anthracenedione.

The first group of reports in this supplement describes the encouraging activity and improved toxicity profile associated with the use of docetaxel as a single agent. In her introduction, Dr M Piccart reminds us that responses to chemotherapy decline with increasing numbers of regimens, and drug resistance is a serious medical problem.

Treatment with anthracyclines has improved the outcome for patients with breast cancer, but anthracycline resistance has now become an increasing problem in treating recurrent disease. Dr ME Trudeau reports on the five multicentre studies using docetaxel for first-line treatment of locally advanced or metastatic disease. The response rate was 61% for women initially given docetaxel at the current recommended dosage. The response rate was somewhat lower, 48%, for women initially treated at the lower dose of 75 mg/m^2.

Dr P Ravdin details the impressive results of studies using docetaxel in poor-prognosis women whose disease had progressed during, or recurred after, cytotoxic therapy involving an anthracycline or anthracenedione. The overall response rate, among three phase II multicentre studies, was 41%, and response duration was around 6 months.

Dr V Valero reports preliminary results of a study using docetaxel in patients whose disease had failed to respond to the other taxoid drug, paclitaxel. As suggested by preclinical results that indicated biochemical differences between these two agents, incomplete cross-resistance was seen in the clinic.

One of the worst prognostic factors in patients with metastatic breast cancer is the presence of liver metastases. Dr P Fumoleau's analyses of results in patients with and without liver lesions illustrate that the response rate to docetaxel is maintained in patients with liver lesions. This observation suggests that full-dose docetaxel will be helpful in the management of patients with liver metastases if hepatic function is not impaired, since, as Dr HA Burris reports, even moderate hepatic impairment can hamper docetaxel metabolism and increase febrile neutropenia, severe mucositis and toxic death. All of the investigations cited above, however, have indicated that the rates of severe toxicity are very low in patients with normal hepatic function. In these patients the most common dose-limiting toxicity is transient neutropenia, while peripheral oedema is reduced by the recommended schedule of steroid administration.

Dr A-R Hanauske introduces us to some of the other cytotoxic compounds which are being developed for the treatment of cancer and points us in the direction of novel approaches to therapy that do not depend on classical cytotoxicity. Dr M Aapro details the preclinical development of docetaxel as a prototypical taxoid, its potent effects on microtubule dynamics, and its cytotoxic activity at concentrations comparable with readily achievable plasma concentrations. Dr JP Armand describes how the recommended dose–schedule of docetaxel was established by phase I studies, to be carried through consistently in phase II trials.

Dr D Khayat describes the complexities associated with the use of combinations of agents and the heterogeneity of clinical opinion with regard to the treatment of metastatic breast cancer. The theme of combination drug therapy is continued by Dr JR Eckardt. He introduces the rationales behind the choice of drugs to use in combination, and gives some elegant examples of modulation of the activity of one drug by another. Dr V Dieras provides further illustrations in the form of studies in which paclitaxel and docetaxel have been used in combinations with either doxorubicin or vinorelbine. Preliminary results suggest high response rates, but ongoing trials will need to be analysed before conclusions may be drawn regarding optimal combinations, or even the preferability of combinations over well-designed single-agent schedules.

Even at this relatively early stage of clinical development, the taxoids have emerged as the most active, most promising class of agents for the management of advanced breast cancer. This symposium captures some of that excitement, summarizes many of the key areas of discovery and points out hopeful directions for further progress.

References

1. Early Breast Cancer Trialist's Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet* 1992; **339**: 1–15, 71–85.
2. Bonadonna G, Valagussa P, Moliterni A, *et al.* Adjuvant cyclophosphamide, methotrexate, and fluourouracil (CMF) in node positive breast cancer: the results of 20 years of follow-up. *N Engl J Med* 1995; **332**: 901–906.

3. Hudis C, Norton L. Systemic adjuvant therapy for breast cancer. *Curr Opin Oncol* 1993; **5**: 782–990.
4. Gilewski T, Norton L. Cytokinetics of Neoplasia. In: Mendelsohn J, Howley P, Israel MA, Liotta LA, eds. *The Molecular Basis of Cancer.* Philadelphia: WB Saunders; 1995: 143–159.
5. Norton L. Introduction to Clinical Aspects of Preneoplasia: A Mathematical Relationship Between Stromal Paracrine Autonomy and Population Size. In: Marks PA, Turler H, Weil R, eds. *Challenges of Modern Medicine, Volume 1. Precancerous Lesions: A Multidisciplinary Approach.* Milan: Ares-Serono Symposia Publications; 1993: 269–275.
6. Reichman B, Seidman A, Crown J. Taxol and recombinant human granulocyte colony stimulating factor as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 1993; **11**: 1943–1951.
7. Hudis C, Seidman A, Crown JPA, *et al.* Phase II and pharmacologic study of docetaxel as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996; **14**: 58–65.