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Reflections on the Development of Resistance During Therapy for Advanced Breast Cancer. Implications of High Levels of Activity of Docetaxel in Anthracycline-Resistant Breast Cancer Patients

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Anthracyclines play a central role in the treatment of breast cancer. They are perhaps the most active single agents available for the treatment of this disease. For patients with primary breast cancer for whom chemotherapy would be appropriate, anthracyclines are often incorporated in adjuvant regimens. For patients with endocrine-therapy-resistant metastatic disease, anthracyclines are nearly always included in the first or second-line therapeutic regimes. Unfortunately, despite the fact that anthracyclines and anthracycline-containing regimens can achieve impressive objective response rates, this impressive activity has not translated into a great improvement in disease-free survival for patients with early stage breast cancer or overall survival for patients with metastatic disease. The addition of anthracyclines to adjuvant therapy regimens in general only modestly improves their efficacy and the use of anthracyclines in metastatic disease does not cure these patients. The clinical utility of anthracyclines would be greatly improved if we could predict which patients would be anthracycline resistant, interfere with the development or expression of anthracycline resistance and predict which anticancer agents would be non-cross-resistant with anthracyclines. Some progress is being made in all these areas. Preclinical studies have identified several intracellular processes that are perturbed by anthracyclines, or that may modulate anthracycline sensitivity of cells. These processes include topoisomerase II activity, drug and toxin transmembrane pumps, intracellular detoxification systems (such as that related to glutathione), stress-related proteins and apoptotic mechanisms. Although measurement of the components of these systems has not yet shown clinical utility in breast cancer, some preclinical work and exploratory studies with small numbers of patients suggest that we may in the future be able to predict which patients will respond or be resistant to anthracyclines. An important avenue of work is the identification of anticancer agents that are non-cross-resistant with anthracyclines in breast cancer patients. These agents would be particularly valuable in patients with metastatic disease who had progressed while on anthracyclines. In general, such patients have a very poor prognosis with a median survival of less than 1 year. Also of importance in non-cross-resistant agents is that they might be used in combination with anthracyclines in regimens with very high response rates. Recently completed work suggests that taxoids might be such agents. This finding opens up exciting possibilities in the treatment of metastatic disease and, even more importantly, in the adjuvant arena. The identification of agents that clinically are non-cross-resistant with anthracyclines depends on the careful interpretation of clinical trial data. Unfortunately, a number of definitions of anthracycline resistance have been used in the medical literature. These range from very weak definitions, which include many patients with only prior anthracycline exposure (for example, in an adjuvant regimen), to more biologically and clinically appropriate definitions, such as documented progression while receiving an anthracycline. This distinction is very important because it is clear that many patients who have relapsed after an anthracycline-based adjuvant therapy will respond to anthracyclines for metastatic disease and are, therefore, not truly anthracycline resistant. In this regard, the recently completed trials with docetaxel in patients with rigorously defined anthracycline resistance are particularly provocative. These trials show that docetaxel maintains much of its excellent first-line levels of efficacy in patients with

anthracycline-resistant breast cancer. Agents with this type of maintenance of efficacy in anthracycline-resistant tumours may find immediate utility in this clinical scenario as single agents but, more importantly, have great potential in future combination regimens including anthracyclines.

Key words: docetaxel, breast cancer, anthracycline resistant
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FRONT-LINE therapies of clinical value exist for most of the major adenocarcinomas; second-line therapies are, however, generally much less effective. Obviously the mechanisms of resistance to therapy of many of the currently available front-line therapies are shared with agents used in second-line therapy. One way forward in the development of new antineoplastic agents is to develop drugs that are, to a large extent, non-cross-resistant with front-line agents. These non-cross-resistant agents would not only be useful in second-line palliative scenarios, but would hold promise in combination with the agents used in front-line therapy, yielding combination regimens of high activity that might be used as front-line regimens for advanced disease or as regimens for primary adjuvant systemic therapy. One of the scenarios where this exploration for non-cross-resistant regimens has led to new therapeutic opportunities is the development of docetaxel (Taxotere®) for the treatment of anthracycline-resistant breast cancer.

Discussion of clinical resistance to chemotherapeutic drugs in oncology to some extent hinges on definitions of resistance. The schematic illustration in Figure 1 shows some of what we know about clinical resistance. As illustrated, many tumours are initially sensitive to antineoplastic agents but, with repeated exposure to therapy, they acquire resistance. Other tumours are intrinsically resistant to chemotherapeutic agents. We would expect that the intrinsically resistant tumours would be the more resistant to therapy. These tumours might have intrinsic levels of resistance far above the treatment failure line. Tumours with acquired resistance would be less resistant, with levels of resistance near the treatment failure line threshold. Treatment responses might be recaptured (even if transiently) by dose intensification. Finally, the least resistant tumours would be those that had only been exposed to a therapy given as an adjuvant. Many of these tumours would not have been given the multiple cycles of therapy necessary to drive the tumours to a highly resistant state.

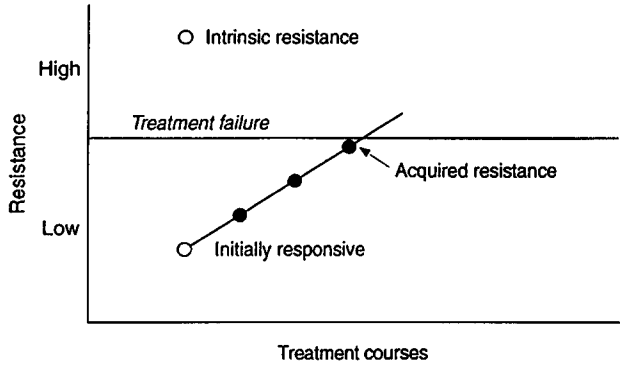

Figure 1. Types of clinical resistance.

These observations on the paths leading to treatment resistance have implications for how definitions of treatment resistance are used. The least important of these definitions would be merely prior exposure to an agent. Many of these previously treated patients would not have developed high degrees of resistance to an agent. Patients who developed progression during treatment or who had intrinsic resistance would have a more clearly defined minimal level of resistance to an agent. The definition of clinical resistance is, of course, not absolute in that in patients failing an agent, response can often be recaptured by increasing the dose. However, the degree of resistance in such patients progressively increases and will again become clinically manifest. An anticancer agent that showed high levels of activity in a population of resistant patients could be meaningfully defined as at least partially non-cross-resistant with the front-line agent.

Using these definitions docetaxel has been shown to maintain excellent levels of activity in anthracycline-resistant breast cancer patients. The results from trials utilising docetaxel as front-line therapy for metastatic breast cancer are impressive; the overall response rate was 61% [1]. This high level of activity would be of less interest if the high levels of efficacy were not maintained in patients with anthracycline-resistant breast cancer.

Three phase II trials were carried out in patients with stringently defined anthracycline-resistant breast cancer (Table 1) [2–4]. The trials used the same dose and schedule of docetaxel (100 mg/m^2 over 1 hour every 3 weeks) and all used stringent definitions of anthracycline resistance. All patients must have shown either no clinical benefit or progression while taking an anthracycline. Patients who had prior exposure to anthracyclines but no evidence of clinical failure of anthracycline-based therapy (such as patients who completed treatment but did not show recurrence of disease during anthracycline-based adjuvant therapy, or patients with metastatic disease who stopped treatment with anthracyclines while in partial or complete remission and who had no evidence of progression) were not eligible for inclusion. The European study used an even more stringent definition of

Table 1. Treatment efficacy in three phase II trials using single-agent docetaxel in patients with anthracycline-resistant breast cancer

Parameter	Study 1 [2]	Study 2 [3]	Study 3 [4]	Overall
Number of patients	41	42	51	134
PR (%)	46	43	29	39
CR (%)	0	7	0	2
CR+PR (%)	46	50	29	41
Median duration of response (weeks)	27	28	24	

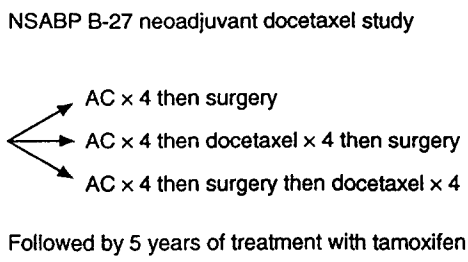

Figure 2. NSABP B-27 trial. Ongoing neoadjuvant trial designed to take advantage of the non-cross-resistance between anthracyclines and docetaxel. (AC, doxorubicin and cyclophosphamide).

anthracycline resistance, not allowing patients who had any evidence of initial response to anthracycline treatment, only allowing patients with intrinsic resistance to participate in the study.

The overall response rate seen in these three trials was 41%. This result is remarkable for several reasons. The results were remarkably reproducible: the two North American trials had nearly identical results; the European trial, which used the most stringent definition of resistance, found a somewhat lower response rate. The response rate of 41% is the highest ever reported for a single agent in the treatment of patients with anthracycline-resistant breast cancer. The overall response rate was also high in visceral sites of disease, with objective responses being achieved in 12 of 24 (50%) patients with metastatic disease to the lung and in 12 of 39 (31%) patients with metastatic disease to the liver [5]. Finally, the response rate of 41% suggests that nearly two-thirds of the activity of docetaxel as a front-line agent was retained in an anthracycline-resistant population, which demonstrates a high level of non-cross-resistance between docetaxel and anthracyclines and suggests that these agents can be used in a complementary way.

This non-cross-resistance between docetaxel and doxorubicin was expected from the work carried out in preclinical systems. After the discovery of the unique mechanism of action of the taxoids—abnormal stabilisation of microtubule assembly [6, 7]—it was possible to use simple laboratory methods to screen taxoids for those that might have especially favourable features [8]. Docetaxel was discovered using such a screening programme. In preclinical models docetaxel perturbed microtubular assembly kinetics at lower concentrations than did paclitaxel, the first taxoid to be studied in clinical trials. In addition, in some preclinical systems docetaxel accumulated in higher concentrations in cells and had a slower rate of efflux from cells than did paclitaxel. Slower efflux might suggest that docetaxel was a less efficient substrate for drug efflux pumps, although this was not directly investigated. Additional preclinical evidence that docetaxel would be an effective agent in anthracycline-resistant patients came from experiments with cultures from primary human tumours, which showed instances of non-cross-resistance between docetaxel and doxorubicin [9, 10].

Our better understanding of the mechanisms of action and the mechanisms of resistance to anthracyclines and taxoids has strengthened the expectation that these agents would be at least partially non-cross-resistant. In laboratory models anthracycline resistance has been demonstrated to result from a number of mechanisms, such as drug efflux pumps (for example, MDR1, LRP, MRP), alterations in the level of topoisomerase II (the major target enzyme for anthracyclines) [11] and perhaps less well defined but important mechanisms such as alterations in apoptotic control [12]. Taxoids, because of their different major mechanism of action, would be expected to be non-cross-resistant with anthracyclines, although some cross-resistance would be expected because taxoids would be expected to have low levels of activity in tumours with high levels of MDR1 or defective apoptotic mechanisms.

Trials to exploit the non-cross-resistance between docetaxel and doxorubicin are planned or are under way. The largest of these trials is NSABP B-27, in which patients will receive a neoadjuvant regimen consisting of four cycles of the combination of cyclophosphamide and doxorubicin and will then receive either no additional therapy or four cycles of docetaxel as a single agent, either as a neoadjuvant regimen or as a post-surgical adjuvant regimen (Figure 2). If the two regimens have a high degree of non-cross-resistance in patients with early breast cancer, then one would expect the docetaxel-treated patients to gain a particularly high level of benefit.

A second phase I/II trial of docetaxel and doxorubicin has recently been reported [13]. The response rate in patients in this trial was 89%. This result is consistent with docetaxel and doxorubicin being largely non-cross-resistant or perhaps even synergistic. One of the important aspects of this trial is that no cases of congestive heart failure were seen, which is of particular interest because of the suggestion in clinical trial data that the combination of paclitaxel and doxorubicin may be particularly cardiotoxic [14].

The results of the clinical trials completed to date show that docetaxel has a high level of efficacy in anthracycline-resistant breast cancer patients, opening a new and important treatment option for women with this disease. The high degree of non-cross-resistance opens an important new avenue for exploration of the use of these agents in sequence or in combination. This work will probably lead to improvement of adjuvant therapy regimens and overall better treatment regimens for patients with advanced breast cancer.

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