Docetaxel: Overview of an Active Drug for Breast Cancer

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ABSTRACT
Docetaxel and paclitaxel differ in their precise molecular targets and pharmacokinetics. Docetaxel is more avidly taken up by tumor cell lines than paclitaxel, and its efflux is slower. Comparative cytotoxicity data suggest greater potency. These factors may help explain the clinical differences that have been observed between the taxanes in patients with breast cancer. The Oncologist 2001;6(suppl 3):1-4

INTRODUCTION
Docetaxel is now generally recognized as one of the most active agents, and possibly the most active drug, currently available for the treatment of metastatic breast cancer [1]. Current research efforts center on defining its role in adjuvant therapy and on exploring the clinical significance of the reported preclinical synergy between it and trastuzumab in HER-2-overexpressing breast cancer.

PHASE III TRIAL DATA
In a randomized trial conducted in patients who had prior exposure to alkylating agent-based chemotherapy (adjuvant, metastatic, or both), docetaxel was compared with doxorubicin [2]. Docetaxel produced a statistically significantly superior response rate (RR) than doxorubicin (48% versus 33%) (p = 0.008). Patients treated with docetaxel also had a statistically significantly longer time to treatment failure. The toxicity profile of docetaxel was also superior to that of doxorubicin. In Figure 1, the performance of the comparator drugs is expressed relative to that of doxorubicin in terms of both RR and time to progression or treatment failure. Bars above the central line indicate performance superior to doxorubicin, while values below the line show inferiority. Paclitaxel administered as a 3-hour infusion achieved an RR significantly lower than that of doxorubicin [3]. When given as a 24-hour infusion, paclitaxel was roughly equivalent in performance to the smaller doxorubicin dose of 60 mg/m² [4]. In the final study, doxorubicin was somewhat superior to mitoxantrone [5].

In the absence of data from a direct comparison between docetaxel and paclitaxel, no firm conclusion can be drawn. However, the information which is available suggests docetaxel is the more active agent in metastatic breast cancer. Docetaxel has also been systematically studied in patients who have failed anthracycline-containing chemotherapy. Nabholtz et al. of the Breast Cancer International Research Group, compared docetaxel with a regimen of mitomycin/vinblastine, a combination widely used at the time for patients following doxorubicin failure [6]. The RRs were 42% with

![Figure 1. Comparison to doxorubicin-relative differences [2-7]. All dosages shown are mg/m². TTP = time to progression; TTF = time to failure; MST = mean survival time.](attachment:figure1.png)
docetaxel and 21% with mitomycin/vinblastine. Median progression free survival was 19 weeks among patients randomized to docetaxel and 11 weeks among those in the control arm \((p < 0.001)\). Remarkably, this study also revealed a statistically significant difference in overall survival (OS) (median 11.4 months for docetaxel and 8.7 months for mitomycin/vinblastine, \(p = 0.0097\) by log rank test). Such a difference in survival is a rare finding in randomized studies in metastatic breast cancer and less common still in the salvage setting.

In a further study, Sjostrom et al. compared docetaxel versus an intensive regimen of methotrexate and 5-fluorouracil (5-FU) [4]. Docetaxel produced a statistically significantly superior RR and time to treatment failure. In this study, no difference in OS was observed between the two treatment arms, a fact attributed to the cross-over provision built into the trial design.

Preclinical Data

Despite assumptions sometimes made to the contrary, the taxanes (docetaxel and paclitaxel) are not near-identical agents. Accumulating evidence suggests that the particularly high activity of docetaxel reflects the unique character of the drug molecule.

The preclinical data on docetaxel and paclitaxel show several well-established differences. In part these relate to molecular targeting.

Mechanism of Action

The binding affinity of docetaxel for the beta-tubulin subunit is greater than that of paclitaxel (relative potency 1.9 versus 1.0) [8-10]. The two drugs have subtly different binding sites: the tau site in the case of docetaxel and the N-terminal 31 amino acids in the case of paclitaxel. The potency of docetaxel, measured at the pharmacological level by the ability to inhibit depolymerization, is twice that of paclitaxel [11]. Whereas paclitaxel interacts with the mitotic spindle, the structure affected by docetaxel is the centrosome. While docetaxel does not change protofilament numbers, paclitaxel does; and the cell cycle specificity of the two agents is also somewhat different.

Pharmacokinetics

In explaining the clinical observations that have been made with the two agents over the past decade, differences in pharmacokinetics are also relevant. The pharmacokinetics of docetaxel are largely linear, while those of paclitaxel are not [12, 13].

When administered as a 3-hour infusion, a decrease in paclitaxel dose of 30% (from 175 mg/m^2 to 135 mg/m^2) is associated with a 68% decrease in \(C_{\text{max}}\) and an 89% decrease in area under the concentration time curve (AUC). Given as a 24-hour infusion, dose proportionality is more linear over the range 135 mg/m^2 to 175 mg/m^2. Since myelosuppression relates to the period of time plasma levels exceed a certain threshold, the uptake of the two agents by target cell lines and their binding are clearly different. In general, docetaxel is taken up more avidly than paclitaxel and bound more tightly. However, probably of greatest relevance to clinical activity are differences in drug efflux: docetaxel is retained intracellularly for a longer period than paclitaxel [8, 14].

This phenomenon may account both for the fact that paclitaxel appears to be more active when given as a 24-hour rather than a 3-hour infusion, and that docetaxel given over 1 hour seems clinically to be at least as active as paclitaxel infused over 24 hours [2-5, 15].

Cytotoxicity

Milligram for milligram, docetaxel is a more potent cytotoxic agent than paclitaxel when the two drugs are compared using a variety of murine and human tumor cell lines, as shown in Figure 2 [8, 16].

Drug Interactions

Data suggest that there are clinically relevant differences between docetaxel and paclitaxel in the way they interact with anthracyclines.

Pharmacokinetic studies have demonstrated that the administration of paclitaxel increased the AUC of doxorubicin and therefore exposure to the drug [17]. This effect is sequence- and schedule-dependent, the increase in AUC being greater when paclitaxel precedes doxorubicin, when the interval between drugs is less than 1 hour, and when paclitaxel is infused over a shorter (3 hours or less) rather than longer period [18, 19]. This fact may explain why certain trials in which paclitaxel was used in combination with doxorubicin have reported troubling levels of cardiac toxicity [20, 21]. Docetaxel, in contrast, appears to have no effect on the pharmacokinetics of doxorubicin, even when the drugs are administered with no interval between them [22].

Figure 2. Taxane antitumor activity: in vitro comparative cytotoxicity. Adapted with permission [8].
ADJUVANT THERAPY

It is in early rather than advanced disease that an impact on survival can most readily be made. Despite this, the development of adjuvant therapy over the past 30 years has been slow. The length of time taken for anthracyclines to become standard treatment in node-positive and node-negative patients is evidence of this.

It would therefore not have been surprising to find that new drugs like the taxanes were difficult to incorporate into adjuvant strategies. It is greatly to the credit of oncology investigators and a tribute to their disciplined approach and quality of their trials that we are as far advanced as we are. An example of this is the work of the Cancer and Leukemia Group B in the United States. In study 9344, doxorubicin/cyclophosphamide (AC) was compared with AC followed by paclitaxel. This large and well-conducted trial provided compelling evidence that the addition of paclitaxel improved not only disease-free survival rates (which were 90% versus 86% with AC alone, \( p = 0.0077 \)) but also OS (97% with AC followed by paclitaxel and 95% with AC alone, \( p = 0.039 \)) [23]. It is hoped that the studies in which docetaxel is added to anthracycline-based adjuvant regimens will demonstrate at least similar advantage.

Of considerable relevance to the adjuvant setting are the recent data from Pegram and Slamon suggesting that docetaxel has an unanticipated synergistic interaction with the novel biological treatment Herceptin [24]. This combination (with the addition of cisplatin or carboplatin) will soon be in clinical trial in both the metastatic and adjuvant settings.

DISCUSSION

Data from the Southwest Oncology Group study of docetaxel versus paclitaxel will not be available for some time since accrual to the study is still incomplete. In their absence, we must make decisions on candidates for combination therapy using the information available. Clinical trial data suggest that docetaxel is likely to be the most active single agent available in metastatic breast cancer. The drug is therefore a clear candidate for use with doxorubicin.

This judgment would also be supported by toxicity considerations. There are grounds for concern that the pharmacokinetic interaction between paclitaxel and doxorubicin may exacerbate anthracycline cardiotoxicity. Data from the European Organization for Research and Treatment of Cancer study suggest that a physiological difference in cardiac function can be detected between patients administered anthracyclines plus paclitaxel and those given anthracyclines alone. Such a finding is particularly important when combination therapy is considered in the adjuvant setting in which even minor cardiac toxicity would not be acceptable. Neither pharmacokinetic studies nor clinical experience to date suggest that the combined administration of doxorubicin and docetaxel increases anthracycline cardiotoxicity.

REFERENCES


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