Docetaxel in Breast Cancer and a Rationale for Combination Therapy

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Development of the taxoids has progressed rapidly in the 1990s. In vitro studies have demonstrated that docetaxel (Taxotere) has a longer residence time and higher accumulation within tumor cells than paclitaxel (Taxol), possibly accounting for its greater cytotoxicity.

Introduction

Clinical development of the taxoids began in 1983, when paclitaxel (Taxol) was first used in cancer patients, but progressed slowly until the 1990s. Docetaxel (Taxotere) first entered clinical trials in 1990, with phase II studies beginning internationally in 1992.[1] Increasing in vitro, in vivo, and clinical experience indicate that the two taxoids, although related, are different and should not be considered interchangeable.

In Vitro Studies

The cellular distributions of the taxoids differ in vitro for the same extracellular concentration. At equilibrium, docetaxel achieves an intracellular concentration triple that of paclitaxel, with one-third the rate of cellular efflux (Figure 1).[2] The resulting longer cell residence time and higher intracellular accumulation may account for its greater in vitro cytotoxicity. As shown in Figure 2, docetaxel is a highly potent inhibitor of cell replication in in vitro murine and human models.

Animal Models

In vivo comparative data also suggest a higher degree of antitumor activity for docetaxel. In the rapidly growing murine B16 melanoma model, known to be sensitive to the taxoids, the increase in tumor burden, following subcutaneous implantation of tumor cells in mice, was delayed after treatment with docetaxel when compared with treatment with paclitaxel or control (Figure 3).[3]

Clinical Studies of Docetaxel as Monotherapy

Docetaxel has demonstrated high activity as a single agent in first-line therapy for metastatic breast cancer, as shown in Table 1. Its efficacy is comparable with or higher than that of paclitaxel, doxorubicin and other anthracyclines, and vinorelbine (Navelbine).[4-6] Docetaxel is also highly effective in anthracycline-resistant disease. The historical data are complicated by changes in the definition of resistance over the past two decades. However, five recent trials demonstrate that the taxoids, and docetaxel in particular, are more active than other, older agents (Table 2).[5,6,15-21]

Clinical Studies of Docetaxel in Combination Therapy

Requirements for Combination Chemotherapy

- Criteria for using a drug in concurrent combination chemotherapy include the following:
- High activity against the disease
- Different mechanism of action from other agents in the combination
- No cross-resistance
- No overlapping toxicity
- Capacity to enhance the activity of other components of therapy
- Doses as near as possible to the full dose

Docetaxel demonstrates activity against breast cancer as high as or higher than that of many commonly used agents, and toxicity is manageable. Preclinical studies have demonstrated its unique mechanism of action: Docetaxel enhances formation of microtubules and stabilizes the polymerization process. No other agent attacks tumors in this way except paclitaxel, which has small
but important differences in its specific mechanism of action. Except for paclitaxel, no cross-resistance has been found to any other antineoplastic agent used in breast cancer treatment, and the cross-resistance between docetaxel and paclitaxel is incomplete.

Docetaxel combinations were shown to be highly active in preclinical models. Synergies, or at least additive effects, were observed in studies with two- and even three-drug combinations, including docetaxel, cyclophosphamide (Cytoxan, Neosar), fluorouracil (5-FU), vinorelbine, methotrexate, and etoposide (VePesid).[7]

Some of the clinical trials have combined drugs at near their individual maximum tolerated doses with relatively little increase in overall toxicity. Docetaxel has been combined with the Vinca alkaloids, vincristine, vinblastine, and vinorelbine (at 80% to 100% of the optimal dose), or with doxorubicin, etoposide, cyclophosphamide, 5-FU, and methotrexate (at 60% to 70% of the optimal dose).[8-11]

**Resistance**

The mechanisms of resistance to the taxoids are not completely understood, although the mdr gene, abnormal tubulin, and perhaps other factors may be responsible. Cell lines resistant to 5-FU, vincristine, cisplatin (Platinol), etoposide, or paclitaxel are not necessarily cross-resistant to docetaxel.

Some mechanisms of resistance to docetaxel and anthracyclines are shared, eg, increased drug efflux and defective apoptotic mechanisms.[8] Others differ, eg, increased topoisomerases and altered tubulin structure.[8] As shown in Table 2, docetaxel exhibits high activity in anthracycline-resistant metastatic breast cancer, suggesting partial cross-resistance between docetaxel and the anthracyclines.

**Ongoing and Future Trials**

**Anthracycline Combinations in First-Line Therapy**

A phase I trial, reported more fully in this supplement by Diéras et al, defined the maximum tolerated doses in women with advanced or metastatic breast cancer as 50 mg/m² of doxorubicin, followed by 85 mg/m² of docetaxel. The dose-limiting toxicity was febrile neutropenia.[13] Side effects were tolerable, with no reported congestive heart failure. Responses were observed at all dose levels, with response rates as high as 90% at the recommended dose levels, 50 mg/m² of doxorubicin followed by 75 mg/m² of docetaxel.

A phase III study of first-line therapy has been initiated to compare 50 mg/m² of doxorubicin plus 75 mg/m² of docetaxel, with 60 mg/m² of doxorubicin plus 600 mg/m² of cyclophosphamide, a standard regimen in metastatic and primary breast cancer.

In another phase III trial, 75 mg/m² of docetaxel will be compared with 500 mg/m² of 5-FU, each in combination with 50 mg/m² of doxorubicin and 500 mg/m² of cyclophosphamide. Nabholtz et al describe preliminary results of a pilot feasibility study for the docetaxel arm of this trial in this supplement.[14]

The scheduling of docetaxel/doxorubicin combination therapy will be explored in a three-arm trial. The first group of patients will receive 60 mg/m² of docetaxel plus 60 mg/m² of doxorubicin. The second group will receive 100 mg/m² of docetaxel followed by 75 mg/m² of doxorubicin in a sequential schedule. The third group will receive the two agents at the same doses as the second group, but in an alternating schedule.

**Non-Anthracycline-Containing Combinations**

There are also trials in development that do not involve anthracyclines. In one trial, 85 mg/m² of docetaxel will be combined with 20 mg/m² of vinorelbine on days 1 and 5 of the course of therapy. In others, docetaxel will be evaluated in combination with 5-FU, in continuous infusion or as a bolus, and with cisplatin.

**Summary**

This overview of the clinical development of docetaxel summarizes some of the combination chemotherapy studies that have been conducted or are ongoing. The challenge is not only to find effective combinations, strategies, and regimens, but also to determine the optimal role for this agent in relation to many other active agents in development today.

Early results from phase I combination chemotherapy studies in metastatic or advanced disease demonstrate manageable toxicity at all dose levels of docetaxel (25 to 100 mg/m²). The most frequent hematologic toxicity was neutropenia, the incidence of infection was low, and there was generally no significant cardiotoxicity. Response rates were observed in all studies, ranging from

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