Docetaxel in Combination With Fluorouracil for Advanced Solid Tumors

Review Article [1] | August 01, 1997
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The results from preclinical studies using murine tumor models show that the combination of docetaxel (Taxotere) and fluorouracil (5-FU) is highly synergistic. Phase I studies in patients

**Introduction**

A number of ongoing clinical trials are investigating the use of docetaxel (Taxotere) in combination with fluorouracil (5-FU) in a variety of solid tumors. Interest in the use of docetaxel in combination regimens was generated by the unique mechanism of action of the taxanes, a single dose-limiting toxicity of neutropenia, and a broad spectrum of antitumor activity.

As first-line therapy in patients with metastatic breast cancer, single-agent docetaxel administered at a dose of 100 mg/m² as an intravenous infusion over 1 hour, once every 3 weeks, has produced a response rate of 59%.[1] Docetaxel also demonstrates a high level of activity in second- and third-line regimens,[1] as well as in patients with anthracycline-resistant or -refractory metastatic breast cancer.[2,3]

Preliminary trials in patients with advanced head and neck tumors show that docetaxel at the same dosage produces a response rate of approximately 31%.[4] Docetaxel appears to have activity in usually chemotherapy-resistant gastric carcinomas as well, with reports of a response rate of 26%.[4]

Fluorouracil (5-FU) has shown activity in a variety of advanced solid tumor types, including metastatic breast cancer.[5] Further, the combination of docetaxel and 5-FU has shown synergistic cytotoxicity in preclinical studies using murine tumor models.[6] A tumor-free survival rate of 60% was noted with this combination using 70% of the highest nontoxic dose in C38 colon adenocarcinoma.[6] Each has a unique mechanism of action; docetaxel promotes microtubule assembly and 5-FU acts as an antimetabolite. Finally, docetaxel and 5-FU possess toxicity profiles that do not completely overlap.

**Docetaxel/5-FU in Patients With Advanced Solid Tumors**

**Phase I Studies**

Three phase I trials have been performed to determine the maximum tolerated dose and tolerability of docetaxel and 5-FU in patients with advanced solid tumors, including metastatic breast, head and neck, and gastric cancers.[7-9] Peacock and colleagues[7] evaluated this combination when administered on a 28-day cycle in 28 patients with advanced solid tumors. Docetaxel was administered as a 1-hour intravenous infusion on day 1, followed by a once-daily intravenous bolus dose of 5-FU for days 1 through 5. The dose-escalation schedule of docetaxel/5-FU started at 25/100 mg/m² and progressed to 35/150, 50/200, 60/200, or 60/300 mg/m². Premedication with 8 mg of dexamethasone was given twice daily for 3 days beginning 1 day prior to the administration of docetaxel. Growth factor support was not provided.

Among the 28 patients, tumor types included gastric, non-small-cell lung, head and neck, colon, sarcoma, and pancreas. The median Karnofsky performance score was at least 60%, with the majority of patients (68%) having received prior chemotherapy. The maximum tolerated dose was 60 mg/m² of docetaxel followed by 300 mg/m² of 5-FU.

This was also the dose the authors recommended for phase II trials. At this dose, grade 3 to 4 neutropenia was noted in 4 of 6 patients, 2 of whom also had fever. At each dose level, grade 1 to 2 mucositis, diarrhea, and asthenia were seen and did not appear to be dose-dependent. The authors noted antitumor activity in patients with breast, gastric, head and neck, and non-small-cell lung cancers. In particular, a complete response was noted in 1 patient with anthracycline-resistant...
breast cancer (personal communication, Peacock and Burris, May 1997). Recently, de Valeriola and colleagues[8] reported their findings in 40 patients with advanced solid tumors using a 21-day cycle of the docetaxel combined with continuous-infusion of 5-FU on days 1 through 5. The dose-escalation schedule of docetaxel/continuous-infusion 5-FU was 60/300 mg/m² and progressed to 75/300, 75/500, 75/750, 85/750, or 85/1,000 mg/m², without prophylactic growth factor support. To date, a median of 2 courses (range: 1 to 10) of each dose level have been administered.

The median age of patients was 52 years (range: 28 to 72) and there was a median World Health Organization performance status of 1 (range: 0 to 2). A total of 83% of patients had received prior chemotherapy for advanced disease. Preliminary analysis indicates that the maximum tolerated dose was 85 mg/m² of docetaxel and 1,000 mg/m² of 5-FU. The dose-limiting toxicities were mucositis and complications of neutropenia. Antitumor activity was seen at each dose level. The authors recommended a dose of docetaxel/continuous-infusion 5-FU for phase II trials of 85/750 mg/m².

**Preliminary Results**

The third phase I trial[9] also used a 21-day cycle of docetaxel administered as a 1-hour intravenous infusion on day 1 followed by continuous infusion of 5-FU on days 1 through 5. Lorholary and colleagues[9] reported preliminary results in 20 patients with metastatic breast cancer who had failed previous anthracycline-based chemotherapy. The dose-escalation schedule of docetaxel/5-FU started at 60/250 mg/m² and progressed to 75/250, 75/350, 75/500, 85/500, or 100/500 mg/m². Premedication with 8 mg of dexamethasone was given twice daily for 3 days beginning 1 day prior to the administration of docetaxel. Growth factor support was not provided.

The median age of patients was 58 years, with 60% of the patients having a World Health Organization performance status of 0 and 40% having a WHO performance status of 1. A total of 83% of patients had received prior chemotherapy for advanced disease. Visceral metastases consisted of those associated with bone (65%), soft tissue (5%), and bone and soft tissue (30%). Approximately 60% of the patients had metastasis in more than 2 sites.

The median cumulative dose of docetaxel and 5-FU was 571 mg/m² (range: 196 to 1,045 mg/m²) and 14 mg/m² (range: 5 to 35 mg/m²). Preliminary analysis indicates an overall response rate of 40% and stable disease in 45% of patients. The authors noted that the maximum tolerated dose has not yet been reached. Grade 4 neutropenia was noted in 90% of the patients; however, febrile neutropenia developed in only 1 patient.

**Phase I/II or II Studies**

A number of phase I/II or II trials have been conducted to evaluate the use of docetaxel/5-FU-based combinations in previously treated and untreated patients with advanced solid tumors.[10-13] The inclusion criteria used in these studies were consistent with other similar studies and included patients with metastatic or locally advanced disease; Karnofsky performance status of at least 60% or a World Health Organization performance status of 2 or less; adequate bone marrow, hepatic, and renal function; no chemotherapy or radiation therapy within 4 weeks of study entry; and no prior exposure to taxanes.

Watanabe and colleagues[10,11] reported the results of a phase I/II trial in previously treated patients with advanced or recurrent breast cancer. Patients with measurable and/or evaluable metastatic sites received docetaxel administered as a 1-hour intravenous infusion on day 1 followed by a continuous intravenous infusion of 5-FU on days 1 through 5. The cycle was once every 3 to 4 weeks. The dose-escalation schedule of docetaxel/continuous-infusion 5-FU was 40/150, 40/300, 50/300, 50/500, or 60/500 mg/m². Premedication with dexamethasone or growth factor support was not provided.

Data from 19 patients were analyzed in the phase I portion of this trial. Preliminary analysis indicates an overall response rate of 47%. The maximum tolerated dose of docetaxel/continuous-infusion 5-FU was 60/500 mg/m². Severe neutropenia and diarrhea were the primary dose-limiting toxicities. Pharmacokinetic analysis revealed no interaction between docetaxel and continuous-infusion 5-FU when administered according to stated schedule. The phase II portion of this trial is currently evaluating 60 mg/m² of docetaxel administered as a 1-hour intravenous infusion on day 1, followed by a continuous intravenous infusion of 500 mg/m² per day of 5-FU on days 1 through 5.

**Docetaxel in the PFL Regimen**

The impact of adding docetaxel to the active PFL regimen (cisplatin [Platinol]/5-FU/leucovorin) in previously untreated patients with locally advanced, curable squamous-cell carcinoma of the head and neck was reported by Posner and co-workers.[12] In this phase I/II trial, patients received varying doses of docetaxel (25, 45, or 60 mg/m²) as a 1-hour intravenous infusion prior to a modified...
PFL regimen--continuous Platinol, 25 mg/m² per day, and leucovorin, 500 mg/m² per day, for days 1 through 5, and 700 mg/m² per day of 5-FU for days 2 through 5. A total of 3 cycles were administered at 4-week intervals before patients underwent twice-daily radiotherapy. Growth factor support was provided with granulocyte colony-stimulating factor (G-CSF) (filgrastim [Neupogen]). To date, data from 17 patients are available for analysis. The median age was 51 years (range: 32 to 66 years). The overall response rate and complete response rate were 100% and 67% respectively. All 15 patients who had primary-site disease that underwent surgery had a pathologic complete remission. Of the 14 patients who had nodal disease, 8 had a complete remission and 6 had a partial remission.

The maximum tolerated dose was 60 mg/m² of docetaxel, which was administered to 12 patients for a total of 34 cycles. The dose-limiting toxicities consisted of febrile neutropenia, a renal tubular concentrating defect, and/or mucositis. Despite aggressive home care with intravenous hydration, hospitalization was required for 44% of cycles due to febrile neutropenia, a renal tubular concentrating defect, and/or mucositis in the 12 patients who received the maximum tolerated dose. The risk/benefit ratio appears favorable, however, considering the overall short treatment interval and impressive antitumor activity. The authors concluded that additional studies with docetaxel as part of the modified PFL chemotherapy regimen are warranted in selected patient populations.

Janinis et al[13] reported preliminary results from a phase II study evaluating the efficacy and tolerability of docetaxel combined with cisplatin and 5-FU in 21 patients with advanced squamous-cell carcinoma of the head and neck and nasopharyngeal carcinoma. The treatment plan of the 28-day cycle consisted of 80 mg/m² of docetaxel administered as a 1-hour intravenous infusion on day 1, followed by 40 mg/m² of cisplatin given intravenously on days 1 and 2, and 1,000 mg/m² per day of 5-FU as a continuous intravenous infusion on days 1 through 3. Premedication with 8 mg of dexamethasone was given twice daily for 5 days beginning 1 day prior to the administration of chemotherapy. Growth factor support was provided on days 4 through 8 with 150 µg/m² per day of G-CSF.

A total of 63 courses have been administered to date. The overall response rate was 75%, with 25% of patients achieving a complete response. The primary toxicities of grade 3 to 4 severity included neutropenia (11%) and nausea (4%). Febrile neutropenia was noted in 5% of cycles. Based on these preliminary data, the authors concluded that docetaxel in combination with Platinol and 5-FU is highly active and well tolerated in patients with advanced squamous-cell carcinoma of the head and neck and nasopharyngeal carcinoma.

Commentary

Initial phase I studies with the use of docetaxel and 5-FU indicate that it is a feasible combination regimen with antitumor activity in a number of cancers, particularly breast, head and neck, and gastric cancer. Because docetaxel is schedule independent, it may be used with a number of agents in varying regimens. In phase I/II studies, the addition of docetaxel to the modified PFL regimen plus radiation therapy produced an overall response rate of 100% in patients with advanced squamous-cell carcinoma of the head and neck.

Although substantial toxicity was associated with this three-drug combination, the initial benefits achieved support further investigation. Docetaxel combined with cisplatin and 5-FU achieved impressive results in patients with advanced squamous-cell carcinoma of the head and neck and nasopharyngeal carcinoma. Taken in total, the clinical experience to date with docetaxel- and 5-FU-containing chemotherapy regimens justifies the further study in patients with advanced solid tumors, including head and neck cancer, metastatic breast cancer, and gastric carcinoma.

References:


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