The Role of Docetaxel in the Management of Squamous Cell Cancer of the Head and Neck

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By Bonnie S. Glisson, MD

The activity of docetaxel (Taxotere) as a single agent (overall response rates, 24%-45%) in the treatment of patients with recurrent squamous cell cancer of the head and neck has resulted in the investigation of docetaxel-based doublet and triplet combinations in both the recurrent and neoadjuvant settings. When combined with cisplatin, with or without fluorouracil (5-FU), in the treatment of recurrent disease, response rates of 33% to 44% have been observed for docetaxel, with median survival ranging from 9.6 to 11 months. In the neoadjuvant setting, response rates have been typically greater than 90%, with promising disease-free and overall survival results.

ABSTRACT: The activity of docetaxel (Taxotere) as a single agent (overall response rates, 24%-45%) in the treatment of patients with recurrent squamous cell cancer of the head and neck has resulted in the investigation of docetaxel-based doublet and triplet combinations in both the recurrent and neoadjuvant settings. When combined with cisplatin, with or without fluorouracil (5-FU), in the treatment of recurrent disease, response rates of 33% to 44% have been observed for docetaxel, with median survival ranging from 9.6 to 11 months. In the neoadjuvant setting, response rates have been typically greater than 90%, with promising disease-free and overall survival results. Randomized trials are now under way to assess the value of docetaxel-based therapy relative to that of the standard cisplatin/5-FU combination in both the neoadjuvant and recurrent settings. Preclinical data indicate that docetaxel is a potent radiosensitizer and its initial evaluation with concurrent radiation in patients with locally advanced unresectable squamous cell cancer of the head and neck suggests feasibility. Phase II evaluation of this approach is in progress. [ONCOLOGY 16(Suppl 6):83-87, 2002]

Docetaxel's (Taxotere) notable activity in the treatment of squamous cell cancer of the head and neck was presaged by its activity in vitro and in vivo in squamous cell cancer of the head and neck cell lines.[1] It has since undergone substantial development clinically and is recognized as one of the most active cytotoxins in the current armamentarium against head and neck cancers based on single-agent response rates. Given a mechanism of action that is distinct from cisplatin and fluorouracil (5-FU), two drugs typically used in this disease, and a toxicity profile that is generally nonoverlapping, it has been added to that combination in triplet and to cisplatin and 5-FU individually in doublets. This manuscript will review the results of the clinical development of docetaxel in squamous cell cancer of the head and neck thus far, noting the rationale for, and the design of, ongoing phase III randomized trials and discussing its potential as a radiation sensitizer.

TABLE 1

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<th>Docetaxel Monotherapy in Recurrent Squamous Cell Carcinoma of the Head and Neck</th>
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<td><strong>Table 1</strong> describes the results of four studies evaluating the activity of docetaxel as monotherapy in patients with recurrent or incurable squamous cell cancer of the head and neck at presentation.[2-5] Three studies[2-4] evaluated docetaxel, 100 mg/m² every 3 weeks, and a Japanese study evaluated docetaxel, 60 mg/m² every 3 to 4 weeks.[5] As is true for most single-agent trials, the complete</td>
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Page 1 of 5
response rate is low. However, the average overall response rate of 35% compares favorably with other active drugs in this disease. For example, a pooled average overall response rate to cisplatin, historically the most active single agent in squamous cell cancer of the head and neck, is 28%.\[6\] Only the study of Couteau et al reported overall survival for single-agent docetaxel (median: 6.7 mo).\[4\] Docetaxel monotherapy is well tolerated, with predictable and uncomplicated myelosuppression as the most frequently noted side effect. Nonhematologic toxicities include asthenia, stomatitis, diarrhea, nausea, and vomiting. TABLE 2

Table 2 summarizes the results of five studies with docetaxel-based regimens in varying combinations with cisplatin, 5-FU, or both.\[7-9,12,13\] Two phase II studies investigated docetaxel at doses of 75 mg/m² or 100 mg/m² in combination with cisplatin at 75 mg/m² every 3 weeks for patients with squamous cell cancer of the head and neck that was locally advanced, recurrent, or metastatic.\[7,8\] Survival estimates of 9.6 to 11 months suggest a possible improvement over the median of 5 to 7 months generally observed with the cisplatin/5-FU combination. Janinis et al studied the addition of docetaxel to cisplatin/5-FU in previously treated patients.\[9\] This regimen included docetaxel, 80 mg/m² on day 1, cisplatin, 40 mg/m² on days 2 and 3, and 5-FU, 1,000 mg/m² continuous infusion on days 1 to 3, and granulocyte colony-stimulating factor (G-CSF [Neupogen]) for 5 days following treatment. Cycles were repeated every 28 days. The regimen proved feasible for administration, prompting additional studies of the triplet combination. Phase I studies of the docetaxel/5-FU combination in patients with advanced solid tumors indicated potentially promising activity in head and neck cancers.\[10,11\] However, comparatively low response rates (24%-27%) have been observed with the docetaxel/5-FU combination for squamous cell cancer of the head and neck in phase II studies.\[12,13\] This finding has also been noted in an ongoing randomized trial in which accrual to the docetaxel/5-FU arm has been suspended.

The findings from phase II studies led to the development of the TAX 322 trial, originally a three-arm phase III trial with standard cisplatin/5-FU compared with two experimental arms of docetaxel/cisplatin and docetaxel/5-FU. As noted above, accrual to the latter arm has been suspended due to a low response rate. The study continues to accrue patients to the two remaining arms (Figure 1).

**Docetaxel in the Neoadjuvant Setting**

**TABLE 3**

**Docetaxel / Cisplatin / Fluorouracil in the Neoadjuvant Setting**
In the neoadjuvant therapy for patients with squamous cell cancer of the head and neck, clinical and pathologic complete response rates at the primary site have been shown to predict locoregional control following definitive radiation. The low primary site complete response rates achieved with established chemotherapy regimens (eg, cisplatin, 5FU) have led to the investigation of new agents and combinations. The work of Janinis et al demonstrated the feasibility of adding docetaxel to cisplatin and 5-FU, albeit with dose reduction, in the recurrent setting.[9] This triplet combination has also proven feasible as neoadjuvant therapy for patients with locoregionally advanced squamous cell cancer of the head and neck in three separate trials, TAX 017 (European), TAX 708 (US), and a Greek trial, recently reported in abstract form.[14-16] The regimens and the results of these studies are summarized in Table 3. Based on the high overall response rates and the high primary site clinical and pathologic complete responses, the TPF (docetaxel [Taxotere]/cisplatin [Platinol]/fluorouracil [5-FU]) regimen is now being tested in the TAX 324 study, a randomized trial of cisplatin/5-FU vs the same combination plus docetaxel as induction chemotherapy in the neoadjuvant setting. All patients who achieve response proceed to concurrent chemoradiation with weekly carboplatin. This trial is ongoing in North and South America and Europe (Figure 2).

![Phase III Randomized Trial (TAX 324)](image)

In a series of trials, Colevas et al at Dana-Farber Cancer Institute have investigated this same base combination (docetaxel, cisplatin, and 5-FU) with the addition of leucovorin, the so-called TPFL (docetaxel [Taxotere]/cisplatin [Platinol]/fluorouracil [5-FU]/leucovorin) regimen, in patients with locally advanced disease deemed curable.[17-19] Table 3 summarizes the results of these studies following the TPF reports.[15-18] The earliest study, TPFL-5 [17], reported a 100% overall response rate and a 61% complete response rate; however, the regimen was associated with significant toxicity most commonly related to febrile neutropenia and mucositis. The TPFL-5 regimen required hospitalization for drug administration and, subsequently, for toxicity in greater than 40% of patients, despite prophylactic antibiotics and growth factor support. Therefore, Colevas et al modified TPFL-5 to a 4-day regimen that maintained the dose intensity of the original regimen but allowed G-CSF treatment 1 day earlier (TPFL-4).[18] This regimen was associated with reduced hospitalization rates (14%) for toxicity. Similar to the TPFL-5 regimen, the overall clinical (93%) and complete (63%) response rates were notably high. An additional TPFL regimen has been evaluated in phase I trials, and preliminary results were reported in abstract form.[19] The regimen was designed to be administered in the outpatient setting using ambulatory infusion pumps for the 5-FU. Docetaxel was able to be dose escalated to 90 mg/m². Response rates remained high with this approach, and hospitalization rates were reduced. Mature data are not yet available from this third regimen in the TPFL series. Because leucovorin is not universally accepted as adding benefit to cisplatin/5-FU and because it adds to mucosal toxicity, it is unlikely that the TPFL regimens will gain broad acceptance. Further, the results of TAX 708[15] suggest that leucovorin does not add to the efficacy of the TPF regimen.

**Docetaxel as a Radiation Sensitizer**

Preclinical data, both in vitro and in vivo, demonstrate the potent radiosensitizing activity of docetaxel and suggest independence of this effect from pure chemosensitivity.[20] Initial exploration of docetaxel with concurrent radiation for the treatment of squamous cell cancer of the head and neck has been preliminarily reported by Tishler et al at Dana-Farber Cancer Institute.[21] Patients in this trial had received induction chemotherapy and had persistent biopsy-positive disease at the primary site. Patients were treated with conventionally fractionated radiation and escalating doses of docetaxel, given weekly. With experience in 21 patients, a maximum tolerated dose of docetaxel at 25 mg/m²/wk was reported, with the major dose-limiting toxicity of severe and prolonged mucositis. Fourteen patients of the initial 21 treated were alive and without progressive disease at the time of this preliminary report in abstract form. Further investigations of concurrent approaches with docetaxel in altered fractionation regimens and in combination with cisplatin are ongoing.
Conclusion

Docetaxel has shown significant activity as a single agent in squamous cell cancer of the head and neck, adding to the therapeutic armamentarium of agents in the treatment of the disease. Given its mainly nonoverlapping toxicity profile and differing mechanism of cytotoxicity, docetaxel in combination with the established standard of cisplatin and 5-FU has proven feasible and promising in the neoadjuvant setting. Based on phase II evaluation, the combination of docetaxel and cisplatin can be considered as a reasonable option for therapy for recurrent disease. Ongoing phase III trials will further define the role of docetaxel in both the recurrent and/or metastatic setting, and as neoadjuvant chemotherapy for patients with cancer of the head and neck. Additional research initiatives will provide insights on how best to use docetaxel in concurrent chemoradiation approaches for patients with locally advanced disease.

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