Docetaxel and Radiation as Combined-Modality Therapy

Review Article [1] | June 01, 2002
By Edward S. Kim, MD [2] and Fadlo R. Khuri, MD [3]

Combined-modality approaches for the treatment of non-small-cell lung cancer (NSCLC), head and neck cancer, and esophageal cancer offer survival benefits by improving locoregional control and treating micrometastatic disease. The taxanes are active, tolerable drugs in these solid tumors and have radiation-sensitizing activity.

The treatment of solid tumors including non-small-cell lung cancer (NSCLC), head and neck cancer, and esophageal cancer continues to be challenging and associated with a poor overall survival. Traditional treatments have included single modalities such as surgery, radiation, or chemotherapy. Combined modality approaches offer a theoretical benefit by improving locoregional control and treating micrometastatic disease. Among the various chemotherapeutic agents administered concurrently with radiation therapy[1] are the platinums, taxanes, and gemcitabine (Gemzar).[2-5] The taxanes, in particular, are active, tolerable drugs for the treatment of solid tumors, and they possess radiation-sensitizing activity. Docetaxel (Taxotere) has been studied in combination with radiation with favorable results. This report will focus on the treatment of solid tumors with docetaxel and radiation as combined-modality therapy.

Background

The taxanes are a class of antineoplastic agents, derived from plants, that have demonstrated efficacy in various malignancies.[6-9] Taxanes are potent mitotic spindle poisons that bind to beta-tubulin, increase tubulin polymerization, and promote microtubule assembly. The microtubules remain stabilized because the taxanes inhibit depolymerization.[10-15] The first taxoid was discovered in the 1960s when it was determined that the bark of the Pacific yew tree, Taxus brevifolia, had activity against several murine tumors. Paclitaxel became the first commercially available taxane in 1992. Docetaxel, which was semisynthetically produced in 1986, is derived from 10-deacetyl-baccatin III, a noncytotoxic precursor extracted from the needles of the European yew, Taxus baccata. Docetaxel has several properties that are different from paclitaxel, including a higher uptake and accumulation in tumor cells and a greater affinity to microtubules.[16]

Preclinical Data

The radiation sensitizing effects of the taxanes are seen at drug levels well below those required for cytotoxicity. Studies of docetaxel have shown an enhanced response to radiation with induced mitotic arrest and apoptosis in murine tumor cells.[17,18] During the cell cycle, the G2/M phase has been found to be the most radiosensitive. Docetaxel exposure arrests cells in the G2/M phase, thus rendering them susceptible to radiation.[11,12,19-23] In addition, docetaxel induces apoptosis as well as direct cytotoxicity against radioresistant S-phase cells.[17,23] In vitro data have demonstrated the putative role of the taxanes in phosphorylation of the bcl-2 antiapoptotic oncoprotein, suggesting that these agents may further enhance the efficacy of radiation by facilitating the triggering of the apoptotic pathway after DNA damage by radiotherapy.[24] The effects of the combination of docetaxel and radiation have suggested a synergistic effect on tumor cell radiosensitivity.[7,11,13,14] This synergy has been demonstrated in vitro as well as in vivo in murine models.[17] Docetaxel may also have immunomodulating properties as well as antiangiogenic effects.[25,26] Based on these preclinical results, phase I investigations of docetaxel with concurrent radiation therapy were initiated.

Phase I Trials

Multiple phase I trials have been conducted to assess the combination of single-agent docetaxel chemotherapy and radiotherapy in patients with non-small-cell lung cancer (NSCLC) and other solid tumors (Table 1).
Non-Small-Cell Lung Cancer

The Choy et al Trial

Choy et al[27] conducted a phase I study of weekly docetaxel with concurrent thoracic radiation therapy in patients with unresectable stage III NSCLC. Docetaxel was administered as a 1-hour infusion every week for 6 weeks at an initial dose of 20 mg/m², escalated in increments of 10 mg/m² as tolerated to each successive cohort of three patients. Thoracic radiation therapy was administered 5 days a week for 6 weeks to the primary tumor and regional lymph nodes (40 Gy) followed by a boost to the tumor and involved nodes (20 Gy). A total of 15 patients (11 males and 4 females) with a median age of 61 years were enrolled in the study. Patients had stage IIIA (nine) or IIIB (six) disease and had a performance status of 0 or 1. The principal dose-limiting toxicity was esophagitis and the maximum-tolerated dose of docetaxel with concurrent radiation therapy was 30 mg/m². Seven patients achieved a partial response for an overall response rate of 47%.

The Aamdal et al Trial

Aamdal et al[28] conducted a phase I study of docetaxel combined with radiation in 12 chemotherapy and radiotherapy-naive patients with inoperable stage III NSCLC. Docetaxel at 20 to 40 mg/m² was administered as a 1-hour infusion on days 1, 8, 22, and 29. Radiation therapy was administered in fractions of 2 Gy daily for 5 days over 5 weeks. The maximum tolerated dose of docetaxel was 40 mg/m² and the dose-limiting toxicity was reversible esophagitis-related dysphagia. The median survival was 15 months, with four patients still alive at 20 to 26 months' follow-up. The recommended phase II dose was 30 mg/m² of docetaxel.

The Koukourakis et al Trial

A similar trial was conducted by Koukourakis et al,[29] who investigated the radiosensitizing effects of docetaxel and concomitant radiotherapy in 30 patients (all male) with advanced NSCLC, 18 of whom had stage IIIB disease and 12 who had stage IV disease. The median age was 65 years. Patients were treated with a 20-minute infusion of docetaxel, 20 to 40 mg/m²/wk for 5 weeks to a total dose of 60 to 64 Gy using a concomitant boost technique. Esophagitis, asthenia, and anorexia were the dose-limiting toxicities noted at the docetaxel dose of 40 mg/m². Complete responses were seen in 8 (27%) patients and partial responses in 15 (50%) for an overall response rate of 77%. The recommended phase II dose was 30 mg/m² of docetaxel.

Other Solid Tumors

The Mauer et al Trial

Mauer et al[30] studied different schedules of the combination of docetaxel and concomitant thoracic radiation in 29 patients with NSCLC (20) or esophageal cancer (9). All patients had no prior history of taxane exposure or radiotherapy. Docetaxel was administered either once every 3 weeks (1 dose per cycle); 2 of 3 weeks (2 doses per cycle); or weekly. The total dose of docetaxel per 3-week cycle was escalated from 40 to 75 mg/m². Standard concomitant chest radiotherapy was delivered in 1.8- to 2.0-Gy daily fractions to a total dose of 60 Gy over 6 weeks. The median age of the patients was 64 years and most had a performance status of 0/1. Dose-limiting esophagitis and neutropenia were encountered in the 1- or 2-dose per cycle schedules at 60 mg/m² per cycle. The maximum tolerated dose for these schedules was 40 mg/m² per cycle. No patients on the weekly schedule developed neutropenia although dose-limiting esophagitis was observed. The maximum tolerated dose for the weekly schedule was 60 mg/m² per cycle or 20 mg/m² weekly. The weekly schedule allowed administration of the the highest total dose of docetaxel with concomitant chest radiotherapy. Of 21 patients who were assessable for response, two achieved a complete response and eight a partial response.

The Koukourakis et al Trial

Koukourakis investigated twice-weekly docetaxel with conventionally fractionated radiotherapy in a phase I trial in 27 patients with lung, brain, and pelvic cancer.[31] The median age of participants was 64 years and included 16 males and 11 females. Among enrolled patients, nine had brain glioblastoma, nine had stage IIIB NSCLC, three had stage IVA cervical cancer, three had endometrial adenocarcinoma, two had bladder carcinoma, and one had an unknown pelvic primary. Docetaxel was administered twice a week starting at 15 mg/m² and escalated in increments of 4 mg/m² in three-patient cohorts. Radiotherapy consisted of 2 Gy/d, 5 days a week for 6 weeks with a boost to a total of 60 Gy in patients with chest tumors and 64 Gy in those with pelvic tumors. Patients with brain tumors received hyperfractionated radiotherapy (1.4 Gy × 2 fractions per day) to a total dose of 74 Gy. The maximum tolerated dose of docetaxel for chest and pelvic cancer patients was 15 mg/m² twice a
week with radiotherapy. The dose-limiting toxicities were asthenia and mucosal toxicity. In patients with glioblastomas, no toxicity was seen with a docetaxel dose of 23 mg/m² administered twice a week. Encouraging response rates were observed. In patients with NSCLC, three of nine patients achieved a complete response and four of nine a partial response, for an overall response rate of 78%. Among patients with glioblastoma, three had a partial response and four of nine patients with pelvic malignancies had a complete response.

The Tishler et al Trial

Tishler et al[32] studied concurrent docetaxel and radiation therapy in head and neck cancer patients with a poor prognosis. Patients were eligible to enroll if they had received induction chemotherapy with cisplatin/fluorouracil (5-FU)/leucovorin or cisplatin/5-FU and failed to achieve a complete response or had a positive postinduction biopsy. Docetaxel was given at doses of 20, 25, or 30 mg/m² weekly for 6 weeks concurrently with daily radiation, 2 Gy/d to a total dose of 66 to 74 Gy. Twenty-one patients with stage III/IV head and neck cancer were treated, including patients with T3/T4 tumors (16 patients) and N2/N3 disease (11 patients). The dose-limiting toxicities were mucositis, dermatitis, and 2-week treatment interruptions. The maximum tolerated dose of docetaxel was 25 mg/m² weekly.

The overall response rate was 86%, with 12 patients (57%) achieving a complete response and 6 patients (29%), a partial response. At a median follow-up of 35 months, 17 patients were alive, 14 of whom had no evidence of disease. Late toxicities included percutaneous endoscopic gastrostomy in nine patients, tracheostomy in four patients, and esophageal stenosis in one patient.

These phase I trials,[27-32] helped establish the basis for phase II trials, which are discussed below (Table 2).[33-36] Encouraging activity was observed with both in the 3-week and weekly schedules.

Phase II Trials

Docetaxel and Radiation Therapy

The Koukourakis et al Trial

A phase II trial of docetaxel and radiation therapy in 35 patients with stage IIIA or IIIB NSCLC was conducted by Koukourakis et al (Table 2).[33] The dose of docetaxel, 30 mg/m²/wk, was established from their previous phase I trial.[29] In contrast to the phase I study, conventionally fractionated radiotherapy was used in hopes of achieving better tolerance, fewer side effects, and similar efficacy. Patients were required to have a performance status of 0 to 2 and adequate bone marrow, and hepatic, renal, and pulmonary function. Patients who received prior treatment were included in the trial: chemonaive (20 patients), prior taxane (6 patients), prior platinum (10 patients).

Study patients received docetaxel, 30 mg/m², as a 1-hour infusion weekly for 6 weeks with concurrent radiation therapy (2 Gy/d for 5 days a week for a total dose of 64 Gy over 6.5 weeks). The median age of participants was 64 years, and 33 of the 35 patients were male. Squamous cell carcinoma was the predominant histology (21 patients). The main side effects were asthenia and radiation-induced esophagitis, which required 2-week treatment delays in 6 patients and minor delays of less than 1 week in 11 patients. Complete responses were seen in 12 of the 35 patients (34%) and partial responses in 16 (46%), for an overall response rate of 80%. The overall and local progression-free survivals at 1 year were 60% and 48%, respectively.

The Aamdal et al Article

Aamdal et al reported the results of a phase II trial of docetaxel combined with concurrent radiation therapy in 33 patients with locally advanced NSCLC.[34] Based on their previous phase I study, docetaxel was administered at 30 mg/m² on days 1, 8, 22, and 29 of a 5-week schedule.[28] Concurrent thoracic radiation of 2 Gy, 5 days a week for 5 weeks was administered to patients who were chemo- and radiotherapy-naive with inoperable stage III NSCLC. The median age of patients was 57 years, with 18 (55%) women and 15 (45%) men. Histologies included squamous cell (14 patients), adenocarcinoma (13 patients), and other types (6 patients). Esophagitis was the main toxicity, and was mild or moderate in 90% of patients. No grade 3/4 neutropenia was observed. Of 30 patients who were evaluable for response, 8 (27%) achieved a complete response and 7 (23%) a partial response, for an overall response rate of 50%. Stable disease was seen in one patient, and seven patients progressed. The median overall survival of all 33 patients was 13.6 months, and the median time to progression was 12 months. Based on these encouraging data, a phase III trial is currently under way to compare the above chemoradiotherapy regimen to radiation alone.

The Sistermanns et al Trial

Researchers from Germany conducted a study of the combination of weekly docetaxel and radiotherapy in 32 patients (10 females, 22 males) with locally advanced, unresectable NSCLC.[35]
The average age of patients was 53 years. Docetaxel at 25 mg/m² was administered as a 15-minute infusion on days 1, 8, 22, and 29 concurrently with thoracic radiation at 1.8 Gy/d over 6 weeks, for a total dose of 50.4 Gy. Histologies included squamous cell (14 patients), adenocarcinoma (9 patients), and large cell (9 patients).

The overall response rate in this trial was 34%, with seven patients (22%) achieving a complete response and four (12.5%), a partial response. The responses were durable and lasted a median of 250 and 145 days for the complete responses and partial responses, respectively. One patient had stable disease and 20 patients had progressive disease.

The most severe toxicities included grade 3 esophagitis and pneumonia; otherwise, treatment was well tolerated. Based on these results, a randomized phase III study is currently comparing chemoradiotherapy with either cisplatin/radiation or docetaxel/radiation in patients with locally advanced, inoperable NSCLC.

The Mauer et al Trial
Mauer et al performed a trial of induction chemotherapy followed by chemoradiation in 54 patients with locally advanced adenocarcinoma of the esophagus and gastric cardia whose median age was 61 years.[36] Eligibility criteria included stage II or III cancer of the esophagus or gastroesophageal junction, performance status of 0 to 2, adequate bone marrow, hepatic and renal function, and no prior chemo- or radiotherapy. Patients initially received induction therapy with docetaxel at 75 mg/m² and cisplatin at 75 mg/m² on day 1 every 3 weeks for 3 cycles. Prophylactic granulocyte colony-stimulating factor (G-CSF, Neupogen), 5 µg/kg/d, was administered beginning on day 3 until the white blood cell count rose above 10,000/µL. The chemoradiotherapy treatment included weekly docetaxel at 20 mg/m², with chest radiotherapy delivered in fractions of 2 Gy/d, 5 days per week for 5 weeks, in resectable patients, to a total dose of 50 Gy. Patients who were deemed unresectable received a total dose of 70 Gy over 7 weeks.

Most patients had a performance status of 0 (59%) and a histology of adenocarcinoma (74%) or squamous cell (20%). Of 44 patients evaluable for toxicity during induction chemotherapy, 17 experienced grade 3/4 neutropenia, including 6 with neutropenic fever. Of 36 patients evaluable for toxicity during the chemoradiotherapy phase, one developed neutropenic fever. Grade 3/4 esophagitis (33%) and vomiting (8%) were the most common nonhematologic toxicities. Of 31 patients who received induction therapy followed by chemoradiotherapy, seven (23%) achieved a complete response and nine (29%), a partial response, for an overall response rate of 52%.

After the completion of chemoradiation, 23 patients were able to undergo surgical resection and 12 (52%) achieved a complete pathologic response, with 8 (35%) having microscopic residual disease and 3 (13%) having gross residual disease. Analysis to explain the dropout rate and/or why patients were not able to complete the regimen (54 patients enrolled, 31 who completed chemoradiotherapy) are awaited, as are survival data.

Docetaxel/Cisplatin Therapy With Radiation
The combination of chemotherapeutic agents with radiation therapy has been shown to be effective and improve survival compared to radiotherapy alone.[37] Phase III studies have demonstrated improved response and median survival rates in patients with NSCLC who receive concurrent chemotherapy and radiotherapy compared to sequential treatment schedules.[38,39] The combination of docetaxel and cisplatin is well tolerated and effective in patients with advanced NSCLC.[40-44] The following studies helped to establish the optimal doses and schedules for docetaxel combined with platinum and radiation therapy.

The Segawa et al Trial
A phase I/II trial conducted by Segawa et al[45] from Japan evaluated docetaxel and cisplatin with concurrent thoracic radiation therapy in patients with locally advanced NSCLC and no prior therapy. Patients received a 1-hour infusion of docetaxel followed by a 1-hour infusion of cisplatin on days 1, 8, 29, and 36 of a 6-week schedule. Concurrent thoracic radiotherapy was administered in fractions of 2 Gy/d for 5 consecutive days per week over 6 weeks, to a total dose of 60 Gy. The phase I portion escalated the doses of both docetaxel and cisplatin in three-patient cohorts. Doses of docetaxel/cisplatin were 20/30 mg/m², 25/30 mg/m², 30/30 mg/m², 30/35 mg/m², 30/40 mg/m², 35/40 mg/m², 40/40 mg/m², and 45/40 mg/m², respectively. Dose-limiting toxicities included esophagitis, leukopenia, neutropenia, and liver dysfunction for the 33 evaluable patients. The maximum tolerated dose was docetaxel, 45 mg/m², with cisplatin, 40 mg/m²; thus, the recommended phase II dose was docetaxel, 40 mg/m², and cisplatin, 40 mg/m².

In the phase II portion of the study, 42 patients were evaluated, including 6 from the the phase I study. Patient characteristics included a median age of 67 years, 86% males, 43% with a performance status of 0, and 83% with stage IIIB disease, with squamous cell the most prevalent
histology (62%). The most common hematologic toxicities were grade 3/4 leukopenia (71%) and neutropenia (60%). Grade 3/4 esophagitis developed in 19% of patients.

One patient achieved a complete response and 32 had a partial response, for an overall response rate of 79%. One patient's disease progressed while on therapy. Early survival data indicate an actuarial 1-year survival rate of 80% in these patients. The regimen proved effective in combination with radiotherapy in patients with locally advanced NSCLC. Although there was considerable toxicity, compliance analysis of the study showed the regimen was well tolerated.

The Moriyama et al Trial
A phase I trial conducted by Moriyama et al evaluated weekly docetaxel and cisplatin with concomitant thoracic radiation in 21 patients (19 males, 2 females) with locally advanced NSCLC, who had no prior chemo- or radiotherapy.[46] The median age of patients was 65 years, and most had a performance status of 0 or 1. The predominant disease histology among these patients was squamous cell (76%). Chemotherapy was initially administered on a split schedule (docetaxel at 20 mg/m², cisplatin at 25 mg/m² on days 1, 8, 15, 29, 36, and 43) and then a continuous, once weekly schedule was initiated, with docetaxel at 20 mg/m² as a 1.5-hour infusion and a constant dose of cisplatin at 25 mg/m² as a 1-hour infusion. The dose of docetaxel was escalated in increments of 5 mg/m² in successive cohorts of three patients. Thoracic radiation was administered concurrently at 2 Gy/d, 5 d/wk for 6 weeks, for a total of 60 Gy.

Grade 3 neutropenia did not occur in the first cohort, but two patients in the second cohort experienced grade 3 neutropenia. One episode of grade 3 esophagitis was reported in the first cohort and two cases of grade 3 esophagitis in the second cohort. Seven patients were treated on the continuous schedule. Grade 3 neutropenia developed in four patients and two patients experienced grade 3 esophagitis. Only four of seven patients completed chemoradiotherapy. Based on toxicity, the split schedule with docetaxel at 20 mg/m² and cisplatin at 25 mg/m² was best tolerated. All 21 patients were evaluable for response. Complete responses occurred in 5 patients and partial responses in 14 patients for an overall response rate of 90%. The two remaining patients had stable disease. The 1-year survival and median progression-free survival rates were 48% and 52 weeks, respectively.

The Mudad et al Trial
Mudad et al conducted a phase I study of docetaxel and cisplatin with concomitant thoracic radiation in patients with locally advanced unresectable NSCLC.[47] All patients had stage IIIA or IIIB (no pleural effusion) disease and were deemed unresectable. Treatment comprised docetaxel at 15 mg/m², escalated in increments of 5 mg/m² per cohort, and cisplatin at 25 mg/m² administered weekly for 6 weeks in combination with standard thoracic radiation delivered at 1.8 Gy/d, 5 d/wk, to a total dose of 64 Gy. Thus far, 8 of 11 patients have completed therapy. No grade 3/4 toxicities have been observed in the first cohort. In the second cohort, among six patients, one patient experienced grade 4 diarrhea, and one patient died of progressive disease. None of the remaining patients experienced any grade 3 or 4 toxicities. This dose escalation study is ongoing.

Based on the current studies, the combination of docetaxel and cisplatin administered concurrently with radiation is an effective regimen for locally advanced NSCLC. The recommended dose of docetaxel is 20 mg/m² and cisplatin, 25 mg/m², administered once weekly concomitantly with radiation therapy at standard doses.

Docetaxel/Carboplatin Therapy With Radiation
The Skarin et al Trial
Skarin et al[48] conducted a phase I trial of docetaxel and carboplatin as induction chemotherapy, followed by weekly docetaxel/carboplatin with concurrent radiotherapy in 23 patients (14 female and 9 male) with stage III NSCLC and a median age of 62 years (Table 3). Stage IIIA disease was present in 65% of patients and stage IIIB in 35% including 30% with squamous cell and 30% with adenocarcinomas. Patients had received no prior chemo- or radiotherapy and had inoperable disease.

The induction regimen included docetaxel, 75 mg/m², with carboplatin at an AUC of 6, administered once every 3 weeks. After completing two cycles of induction chemotherapy, patients began chemoradiotherapy. Patient cohorts received weekly chemotherapy consisting of docetaxel in escalating doses from 10 to 30 mg/m² with carboplatin at an AUC of 2. Concurrent radiotherapy was administered at 1.8 Gy/d, 5 d/wk, to a total dose of 54 Gy, over a 6-week course. Responding patients went on to surgical resection.

Toxicities among the 21 patients completing induction chemotherapy included grade 3/4 neutropenia in 95% and grade 3/4 allergic reactions in 14%, with 15 patients completing chemoradiotherapy. The maximum tolerated dose of docetaxel/carboplatin has yet been reached.
Dose-limiting toxicities included atrial fibrillation and transaminitis.
This trial has not been fully reported; to date, two partial responses (10%) were observed after induction chemotherapy. Responses to chemoradiotherapy included two complete responses and three partial responses, for an overall response rate of 33%. Of the seven patients with stage IIIA disease who underwent surgery (five complete and two incomplete resections), two achieved a pathologic complete response. Thus far, the median survival and median progression-free survival were 12 and 10 months, respectively.

**The Choy et al Trial**

A phase I dose-finding trial conducted by Choy et al[49] combined docetaxel at 20 mg/m² or 30 mg/m² per week with weekly carboplatin at an AUC of 2 and radiotherapy in patients with stage III unresectable NSCLC. A total of eight patients were treated in the 20 mg/m² group and three in the 30 mg/m² group. Radiotherapy was delivered in 2.0-Gy fractions, 5 d/wk, to a total dose of 60 Gy over 6 weeks. The dose-limiting toxicity was esophagitis, which was reported in one patient in the 20-mg/m² group and three patients in the 30-mg/m² group. Grade 3 leukopenia developed in three patients in the docetaxel 20 mg/m² group and grade 3 anemia in one patient in the docetaxel 30 mg/m² group. Of nine evaluable patients, one achieved a complete response (11%) and five, a partial response for an overall response rate of 67%. The maximum tolerated dose was docetaxel at 20 mg/m²/wk with weekly carboplatin at an AUC of 2 along with a 60-Gy total dose of radiotherapy.

**The Murakami et al Trial**

Murakami et al[50] conducted a phase I trial of weekly docetaxel and carboplatin with concomitant radiotherapy in patients with untreated locally advanced NSCLC. Cohorts of six patients received docetaxel at a fixed dose of 20 mg/m²/wk with weekly carboplatin starting at an AUC of 1 with dose escalation. Radiotherapy was administered 5 d/wk to a total dose of 60 Gy over a 6-week period. The characteristics of the 12 patients enrolled in the study included a median age of 60 years, 10 males and 2 females, stage IIIA (5 patients) and stage IIIB (7 patients) disease, and a performance status of 1 (12 patients). Dose-limiting toxicities included radiation pneumonitis, which was grade 4 in two patients, esophagitis, and liver dysfunction. A partial response was achieved by 11 patients for an overall response rate of 92%. The maximum tolerated dose was found to be docetaxel 20 mg/m²/wk and carboplatin at an AUC of 1.5 per week with 60-Gy radiation therapy delivered over 6 weeks. Because of the pulmonary toxicity reported in this trial, no phase II study is planned.

**The Nishimura et al Trial**

A phase II study of induction docetaxel and carboplatin with concomitant radiotherapy in patients with early-stage (IB, IIA, IIIB) NSCLC was conducted by Nishimura et al.[51] The 30 enrolled patients (18 male, 12 female) had a median age of 58 years, performance status of 0 or 1, varied clinical stage (15 IB, 2 IIA, 13 IIIB) disease and histology (21 adenocarcinoma, 8 squamous cell, 1 large cell). Patients received two 28-day cycles of carboplatin (AUC 5) on day 1 and docetaxel (60 mg/m²) on day 1, with concurrent radiotherapy delivered in fractions of 2 Gy/d, 5 d/wk, to a total dose of 40 Gy over 4 weeks. The predominant toxicity was grade 3/4 neutropenia (87%), with two cases of grade 2 esophagitis observed. All 30 patients completed the induction chemoradiotherapy, and the preoperative response rate was 70%. Among the 27 patients who underwent a complete resection, 6 pathologic complete responses were reported. All patients treated with surgery were disease-free after a median follow-up of 14 months.

**The Sakai et al Trial**

Sakai et al[52] conducted a phase I/II trial of docetaxel and carboplatin with concurrent radiotherapy followed by consolidation docetaxel/carboplatin in patients with unresectable stage III NSCLC. Successive cohorts of at least 3 patients received docetaxel/carboplatin at the following dose levels (mg/m²/AUC): 20/2.5, 20/3.0, 30/2.5, 30/3.0, and 40/3.0, administered every 2 weeks (starting in week 1) over an 11-week period. Concurrent radiotherapy was administered in 2-Gy fractions 5 d/wk, to a total dose of 60 Gy over 6 weeks. The phase I portion of the trial treated 23 patients. The maximum tolerated dose of docetaxel was 40 mg/m² and carboplatin at an AUC of 3. Neutropenia was the dose-limiting toxicity.

The phase II recommended doses were 30 mg/m² of docetaxel and AUC 3 for carboplatin, administered every 2 weeks. Of 16 patients entered into the phase II portion of the study, 14 were evaluable for response. A partial response was seen in 11 patients, for an overall response rate of 79%; two patients had stable disease and one patient had progressive disease. The regimen was well tolerated and showed promising efficacy.

The combination of weekly docetaxel and carboplatin with radiation therapy demonstrates efficacy in patients with stage III NSCLC (Table 3).[48-52] When administered on a weekly basis, docetaxel at 20 mg/m² and carboplatin at AUC 2 are well tolerated. Some notable pulmonary toxicity was
observed, and ongoing trials will help to further delineate this effect.

**Discussion**

Docetaxel is an active agent in the treatment of NSCLC, as demonstrated by previously reported randomized phase III studies.[40,53-55] Because of its significant in vitro radiosensitizing properties, clinical investigations of docetaxel with radiotherapy have been conducted.[56] Docetaxel combined with radiation therapy resulted in encouraging response rates of up to 80% in phase II trials. The most commonly used schedule has been docetaxel at 20 to 30 mg/m² weekly with concomitant radiation administered in fractions of 1.8 to 2.0 Gy, 5 days a week over 5 to 6 weeks. Esophagitis has been the most common dose-limiting toxicity seen in both phase I and II trials. Studies of docetaxel and platinum combinations have been conducted, predominantly in patients with NSCLC. Early results show good activity with acceptable toxicity, with the dose-limiting toxicities being esophagitis or mucositis. Although many studies are still ongoing, the combination of docetaxel, 20 mg/m²/wk, combined with cisplatin, 25 mg/m², or carboplatin at an AUC of 2 with concomitant radiation, appear to be well tolerated and active. Docetaxel-based chemotherapy with concomitant radiation therapy is a well tolerated and effective regimen, particularly in patients with NSCLC. Future investigations are encouraged including phase III trials in patients with locally advanced NSCLC. Current trials are evaluating different designs including concurrent chemotherapy with radiation followed by consolidation docetaxel. Additional trials of docetaxel-based chemoradiotherapy in the neoadjuvant and adjuvant settings in early NSCLC are warranted. Furthermore, it is essential that future studies of docetaxel include the use of novel biological agents, both as treatment enhancers and as posttreatment maintenance therapy, especially in NSCLC, in order to provide improved patient outcome.

**References:**


26. Dicker AP, Williams T, Grant D: Inhibition of angiogenic processes in endothelial cells by docetaxel (Taxotere) and paclitaxel (Taxol) induced radiosensitization: A potential antiangiogenic strategy. Presented at the 42nd Annual Meeting of the American Society of Therapeutic Radiation Oncology, Boston, MA, 2000.


Source URL:
http://www.diagnosticimaging.com/docetaxel-and-radiation-combined-modality-therapy

Links:
[1] http://www.diagnosticimaging.com/review-article