The taxanes, paclitaxel and docetaxel, are novel antimitotic agents that are under extensive investigation in clinical trials in patients with various solid tumors. The taxanes have demonstrated significant activity against solid tumors present a significant treatment challenge due to poor overall cure rate. However, increasing use of chemotherapy and radiation may lead to improved local control as well as overall survival of patients with many locally advanced tumors treated traditionally with radiation alone, surgery alone, or chemotherapy alone. Radiation therapy alone may fail due to the inability to deliver higher than standard doses without unacceptable toxicities and the presence of a subpopulation of tumor cells that are relatively insensitive to radiation therapy. Surgery alone may fail due to the presence of disease outside of the surgical bed. In addition, chemotherapy alone has limited activity against many common solid tumors.

The taxanes have several properties that are favorable for combined-modality therapy. Both paclitaxel (Taxol) and docetaxel (Taxotere) are generally well tolerated, with significant activity in the treatment of many tumor types and a high potential for radiosensitization. Extensive clinical experience has been gained with paclitaxel in combined-modality therapy. Recent and ongoing clinical trials are beginning to explore the radiosensitization properties of docetaxel. Both taxanes, paclitaxel and docetaxel, can be administered on an outpatient basis, and extensive clinical experience has enabled the circumvention of anaphylactic reactions. Furthermore, combinations of taxane and radiation therapy may result in less toxicity than other concurrent chemotherapy/radiotherapy regimens (eg, cisplatin [Platinol], etoposide, and irradiation). Major advances in the use of the taxanes in combined-modality therapy for different tumor types are discussed here.

**Taxanes as Radiosensitizers**

Taxanes are mitotic inhibitors that stabilize microtubules by promoting their assembly and retarding their depolymerization. After exposure to the taxanes, cells are arrested in the G2/M phase of the cell cycle, which is the most radiosensitive phase. In addition to enhanced response to radiation, other effects have been observed that depend on factors that are only partially understood at present. For example, stimulation of apoptosis with paclitaxel has been observed in cell cultures and in vivo. Recently, the effects of paclitaxel were evaluated with 16 different murine tumors. With a single dose of paclitaxel at 40 mg/kg, mitotic arrest was induced to some degree in all tumor types, and apoptosis was observed in 50% of the tumors. The kinetics of mitotic arrest and apoptosis were studied in these tumors to determine the possible mechanism of taxane effects. Apoptosis, rather than mitotic arrest, appeared to predict antitumor efficacy (as determined by the delay in tumor growth). Tumor reoxygenation and repopulation occurring with taxanes also may be important in radiation enhancement.

The increased cell radiosensitivity with exposure to the taxanes is evident at very low levels of the agents, below the levels required for cytotoxic effects. Numerous studies have demonstrated the radiosensitizing properties of paclitaxel in various cell lines. Docetaxel also has been shown to enhance response to radiation and induce mitotic arrest and apoptosis in murine tumor cells. The effects of taxane exposure have been studied with numerous human cell lines derived from lung tumors, head and neck tumors, brain tumors, breast tumors, colon tumors, pancreatic tumors, ovarian tumors, cervical tumors, vulvar tumors, prostate tumors, and from melanoma and leukemia cells. A supra-additive effect was observed most frequently, but additive or subadditive effects also were demonstrated under some experimental conditions.
extent of enhancement of the taxane-radiation interaction is dependent on the specific cell line, growth status, and intensity and duration of drug exposure. Most in vivo studies analyzing taxane-induced radiopotentiation focused on paclitaxel and characterized both paclitaxel-sensitive and paclitaxel-resistant tumor types.[16] Radiation-induced inhibition of tumor growth is possible even in tumors that are resistant to single-agent paclitaxel, and the effects of the taxanes on the radioresponse of normal tissues are clearly less significant. The results of preclinical studies also suggest that the timing of exposure to paclitaxel relative to radiation may be critical and that the optimal timing may vary depending on the sensitivity of tumor type to the taxane. Preclinical evidence also indicates possible applications of docetaxel in combined modality therapy. Collectively, these observations form a compelling basis for the continued design of clinical trials including the taxanes in chemoradiation treatment. Combined-modality therapy including paclitaxel or docetaxel results in substantial responses in several tumor types. Extensive experience has been gained with non–small-cell lung cancer, head and neck tumors, and esophageal tumors. Additional information will be required to determine the optimal dose and schedule of taxanes for different tumor types, the exact mechanism of action of taxane-induced radiosensitization, and the most effective use of radiation therapy in combined-modality therapy.

**Non–Small-Cell Lung Cancer**

No single modality of therapy has emerged as clearly most beneficial for stage III non–small-cell lung cancer.[32] Long-term survival is rare (5% to 15% of patients), regardless of whether patients undergo surgical resection or standard radiation therapy.[33] Although chemotherapy results in improved quality of life and modest survival benefits in patients with advanced, recurrent, and metastatic non–small-cell lung cancer, it is rarely effective for cure.[34-36] Several new agents with substantial activity in advanced and metastatic non–small-cell lung cancer are now available.[37] Combined chemotherapy and radiation therapy have been evaluated extensively in patients with locally advanced, unresectable non–small-cell lung cancer.[38-42]

The use of chemotherapy with radiation therapy potentially may improve control of local disease and distant micrometastases in patients with stage III non–small-cell lung cancer.[43] Early trials of chemoradiation therapy included radiation-sensitizing agents, such as hydroxyurea, bleomycin (Blenoxane), 5-fluorouracil (5-FU), and cisplatin,[42,44-47] and did not improve patient survival appreciably. A pivotal Cancer and Leukemia Group B (CALGB) trial, CALGB 8433, determined that sequential chemotherapy (cisplatin and vinblastine) followed by radiation therapy conferred a significant survival advantage over radiation alone in patients with inoperable stage III non–small-cell lung cancer.[38,39] Both taxanes have substantial activity as observed in phase II studies of previously untreated patients with metastatic non–small-cell lung cancer.[48-57] Their radiosensitizing properties stimulate continued interest in combined chemoradiation therapy using these agents.[3]

**Paclitaxel**

Paclitaxel, as a single agent and combined with other chemotherapeutic agents, has been investigated in several phase I and II studies in combination with radiation therapy in patients with unresectable, stage III non–small-cell lung cancer (Table 1). In a series of studies at Brown University and at Vanderbilt University,[43,58,61,70] paclitaxel and concurrent radiation therapy were assessed. The maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of paclitaxel with concurrent thoracic radiation were determined in a phase I study in which paclitaxel was administered weekly as a 3-hour infusion, starting at 10 mg/m² per week.[54] Over a period of 6 weeks, 27 patients were treated with paclitaxel at seven different dose levels, ranging from 10 to 70 mg/m² per week, with concomitant chest irradiation (60 Gy total). The MTD of paclitaxel was 60 mg/m² per week, and reversible esophagitis was the principal DLT. In another phase I trial, Lau et al evaluated paclitaxel administered twice weekly plus concurrent radiation therapy in 26 patients with locally advanced, unresectable non–small-cell lung cancer (Table 1).[59] In 25 evaluable patients, three (12%) achieved a complete response, and 17 (68%) achieved a partial response, for an overall response rate of 80%. The most common toxicity was esophagitis, which occurred in approximately 50% of patients who received paclitaxel doses > 30 mg/m² twice weekly.

In a phase II trial (LUN-27), the response rate, toxicity, and 2-year survival rate were assessed in 33 patients who received weekly paclitaxel and concurrent radiation therapy (Table 1).[43] Previously untreated patients with histologically documented unresectable stage IIIA or stage IIIB non–small-cell
lung cancer received paclitaxel 60 mg/m² administered weekly as a 3-hour infusion with concurrent radiation therapy (60 Gy total) for 6 weeks. Of 27 eligible patients, three patients (10%) achieved a complete response and 22 patients (76%) achieved a partial response, for an overall response rate of 86% (95% confidence interval, 68% to 96%). The median follow-up duration was ≥ 20 months. The 1-, 2-, and 3-year survival rates for all patients were determined to be 61%, 33%, and 18%, respectively, and the median overall survival was 20 months. Esophagitis was the most significant toxicity noted, but this adverse effect was manageable and reversible.

Paclitaxel in combination with platinum agents also has been investigated in the context of combined-modality therapy. A recent phase II trial (LUN-56) of paclitaxel/radiation therapy added two adjuvant cycles of chemotherapy to a regimen of induction chemoradiotherapy and was designed to enhance both systemic and local disease control.[70] This trial added carboplatin (Paraplatin), an agent with radiation-sensitizing potential and systemic activity when used in combination with paclitaxel. Forty previously untreated patients (25 male, 15 female) with stages IIIA and IIIB non–small-cell lung cancer entered the trial. On an outpatient basis for 7 weeks, patients received paclitaxel 50 mg/m² per week as a 1-hour infusion and carboplatin at an area under the plasma concentration-time curve of 2 (AUC in mg/mL · min) weekly as a 30-minute infusion, with radiation to the tumor and regional lymph nodes (44 Gy) followed by a boost to the tumor (22 Gy). Following chemoradiation therapy, patients received an additional two cycles of paclitaxel (200 mg/m² as a 3-hour infusion) and carboplatin (AUC of 6) every 3 weeks.

In 39 eligible patients, 12- and 24-month survival rates were 55.7% and 40.6%, respectively, with a median overall survival of 20.5 months. The 12- and 24-month progression-free survival rates in 39 eligible patients were 48.3% and 38.6%, respectively, with a median progression-free survival of 8.8 months. The overall response rate (partial plus complete response) of 37 evaluable patients was 75.7%. The major nonhematologic toxicity was esophagitis. Seventeen patients (46%) developed grade 3 or 4 esophagitis at the end of the concurrent phase. However, only two patients developed late esophageal toxicity, with stricture at 3 and 6 months posttreatment. This study demonstrated that combined-modality therapy with paclitaxel, carboplatin, and radiation is a promising treatment for locally advanced non–small-cell lung cancer, by virtue of a high response rate, acceptable toxicity, and survival rates that compare favorably with those in other multimodality studies.[70]

In a Vanderbilt Cancer Center Affiliate Network (VCCAN) phase II study (LUN-63), chemotherapy with concurrent hyperfractionated radiation therapy was investigated.[61] Forty-three patients with unresectable stage IIIA/IIIB non–small-cell lung cancer received weekly treatment with paclitaxel/carboplatin plus hyperfractionated radiation therapy, followed by two cycles of consolidation paclitaxel/carboplatin administered 3 weeks apart. Of the 42 patients evaluable for response, three patients (7%) experienced a complete response and 30 patients (71%) experienced a partial response for an overall response rate of 79%. The 1-year overall survival rate was 63% for all patients. As in previous studies, esophagitis was the principal toxicity; grade 3 or 4 esophagitis occurred in 11 patients (26%). Although a randomized trial is necessary to fully evaluate this regimen, these results with concurrent weekly paclitaxel/carboplatin and hyperfractionated radiation therapy are promising.

Another phase II trial[65] evaluated twice-weekly paclitaxel/weekly carboplatin plus concurrent radiation therapy followed by consolidation paclitaxel/carboplatin in patients with locally advanced, unresectable non–small-cell lung cancer. In 17 evaluable patients, complete responses were achieved in two patients (12%) and partial responses in eight patients (47%), for an overall response rate of 59%. Grade 3/4 toxicities included esophagitis, myelosuppression, and nausea/vomiting; these occurred primarily during the concurrent chemoradiation therapy phase of treatment.

Other trials of chemoradiotherapy with paclitaxel/platinum compounds involved various paclitaxel doses and administration schedules (Table 1).[62,66-68,71-73] Induction chemotherapy was used in some studies, in which concurrent chemoradiation therapy with paclitaxel and platinum combinations was initiated following induction.[54,67,68] Results of these trials also are encouraging, with overall response rates of 59% to 82%, and 1-year survival rates of 60% to 74%.[54,67,68]

Results of recent trials of paclitaxel/carboplatin and radiation therapy demonstrated manageable toxicity and highlight the importance of chemoradiation therapy for locally advanced non–small-cell lung cancer.[63] Several current and proposed trials are being conducted by the large cooperative oncology groups in the United States.[74] Ongoing phase II and III trials are evaluating the utility of continuous infusion of paclitaxel,[75] amifostine mucosal protection,[76,77] as well as induction chemotherapy with paclitaxel plus concurrent chemoradiotherapy.[78-80] In the CALGB 9431 trial,[81] induction chemotherapy with subsequent concomitant chemoradiotherapy is being
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Investigators. Patients with stage IIIB non-small-cell lung cancer are receiving four cycles of cisplatin 80 mg/m², with two cycles being administered concurrently with gemcitabine (Gemzar) 1,250 mg/m² (arm 1), paclitaxel 225 mg/m² (arm 2), or vinorelbine (Navelbine) 25 mg/m² (arm 3), and a total of 60 Gy of radiation. In an early analysis of the results of this trial, the treatments in all three study arms generally were tolerable.

In the CALGB 9531 trial, patients with stage IIIB non-small-cell lung cancer receive two cycles of induction chemotherapy with paclitaxel 200 mg/m² and carboplatin (AUC of 6), followed by paclitaxel 50 mg/m² per week and carboplatin (AUC of 2) weekly with concurrent radiation therapy. The results of this trial will determine the protocol for a randomized phase III CALGB trial in which patients will receive either concurrent chemoradiotherapy with paclitaxel/carboplatin or two cycles of induction chemotherapy with paclitaxel/carboplatin followed by concurrent chemoradiotherapy with paclitaxel/carboplatin.[74] Paclitaxel/carboplatin was evaluated in a recent phase III Eastern Cooperative Oncology Group (ECOG) 1594 study of patients with stage IV (and selected stage IIIB) non-small-cell lung cancer. The ECOG is planning to use a similar regimen of paclitaxel/carboplatin in patients with stage III non-small-cell lung cancer in a trial evaluating two cycles of induction paclitaxel/carboplatin followed by conventional daily radiotherapy (64 Gy/7 weeks) or hyperfractionated accelerated radiation therapy (57.8 Gy/36 fractions/15 treatment days).[74]

The Southwestern Oncology Group (SWOG) is conducting a trial of induction paclitaxel/carboplatin followed by weekly paclitaxel/carboplatin plus concurrent radiation therapy and consolidation paclitaxel/carboplatin in patients with unresectable stage III non-small-cell lung cancer.[74] The Radiation Therapy and Oncology Group (RTOG) is conducting a phase II trial (RTOG 9801) of induction paclitaxel/carboplatin followed by paclitaxel/carboplatin plus concurrent radiation therapy, with or without amifostine for mucosal protection.[77] Results of these ongoing trials should further define the role of paclitaxel-based chemoradiation therapy in patients with unresectable stage III non-small-cell lung cancer.

Docetaxel

Preclinical data indicate that docetaxel has radiosensitizing properties,[6-9,27] and clinical trials of docetaxel plus radiation therapy have been initiated in patients with non-small-cell lung cancer and esophageal cancer.[82,83] In a recent phase I study[82] designed to determine the maximum tolerated dose and optimal schedule of docetaxel with concurrent radiotherapy, 29 patients (20 with non-small-cell lung cancer and nine with esophageal cancer) initially received docetaxel 40 mg/m² on day 1 of 21-day cycles, docetaxel 20 mg/m² on days 1 and 8 of 21-day cycles, or docetaxel 20 mg/m² each week of 21-day cycles; doses were escalated to 60 mg/m² per 21-day cycle and 75 mg/m² per 21-day cycle, with a weekly administration schedule used in some patients. Concurrent radiotherapy was administered at daily doses of 1.8 to 2.0 Gy to a total dose of 45 to 70 Gy. Within the radiation field, there was an overall response rate of 40% among 20 evaluable patients with non-small-cell lung cancer and 22% among nine evaluable patients with esophageal cancer. Esophagitis and neutropenia were dose-limiting toxicities. The maximum tolerated doses of docetaxel with concurrent radiation therapy were 40 mg/m² per cycle when given as one or two doses per cycle and 60 mg/m² when given as three doses per cycle (ie, 20 mg/m² weekly). Although concurrent docetaxel and radiation therapy appeared to be feasible, the patient group was heterogeneous, and further studies are warranted.

Another phase I trial[83] evaluated docetaxel 20 to 40 mg/m² per week plus concurrent radiation therapy (40-Gy primary dose with 20-Gy boost) in 11 patients with unresectable stage III non-small-cell lung cancer. Response and survival data are not yet available; grade 4 toxicities (including hyperglycemia, esophagitis, and skin toxicity) were observed in all dose groups. An ongoing SWOG phase II trial is assessing docetaxel as consolidation chemotherapy for patients with stage IIIB non-small-cell lung cancer.[74] In this study, patients receive cisplatin/etoposide with 60 Gy of concurrent radiation therapy, followed by three cycles of docetaxel. Further investigation is necessary to determine the role of docetaxel in combined-modality therapy for unresectable stage III non-small-cell lung cancer.

Small-Cell Lung Cancer

Combinations of etoposide and platinum agents are used commonly as standard chemotherapy regimens for the treatment of extensive-stage small-cell lung cancer. For patients with limited-stage disease, radiation therapy has been added to these regimens, resulting in good efficacy and
potential for cure. Small but significant improvements in survival were measured in two meta-analyses of patients who received chemotherapy in addition to radiation therapy.[84,85] No chemoradiotherapy regimen emerged from these studies as clearly superior,[86] and newer chemotherapeutic agents with activity in small-cell lung cancer continue to be evaluated.

**Paclitaxel**

Studies coordinated by ECOG and the North Central Cancer Treatment Group demonstrated the activity of single-agent paclitaxel in small-cell lung cancer.[87,88] Subsequently, paclitaxel in combination with etoposide and/or platinum agents has been evaluated in numerous studies in small-cell lung cancer patients, with encouraging response rates.[89] Studies have evaluated paclitaxel-containing chemotherapy and radiation therapy in patients with limited-stage small-cell lung cancer (Table 2).[90-92] In a phase II trial by Hainsworth et al paclitaxel/carboplatin plus etoposide at two dose levels were evaluated with concurrent radiation therapy in 56 patients with limited-stage small-cell lung cancer.[90] With the low-dose regimen, six of 15 evaluable patients achieved a complete response (40%) and eight patients (53%) achieved a partial response, for an overall response rate of 93%; with the high-dose regimen, 29 of 41 evaluable patients achieved a complete response (71%) and 11 patients (27%) achieved a partial response, for an overall response rate of 98%. Median survivals for the low-dose and high-dose regimens were 17 months and > 16 months, respectively. Both regimens were generally well tolerated, with a higher incidence of myelosuppression observed with the high-dose regimen. Other grade 3/4 toxicities included esophagitis, anemia, and leukopenic fever.

An ongoing phase II trial is evaluating the addition of paclitaxel to cisplatin/etoposide plus radiation therapy in patients with limited-stage small-cell lung cancer (Table 2).[91] In 20 evaluable patients thus far, 16 achieved a complete response (80%), and three achieved a partial response (15%), for an overall response rate of 95%. The regimen was generally well tolerated; the most common grade 3/4 toxicities included leukopenia and thrombocytopenia. Grade 3 esophagitis was observed in two patients.

Other trials evaluating chemoradiation therapy in limited-stage small-cell lung cancer are ongoing by RTOG and ECOG. The results of these trials should contribute to a better understanding of the importance of dose and schedule of paclitaxel in chemoradiation therapy for small-cell lung cancer.

**Docetaxel**

To date, no data on docetaxel in combined-modality therapy for small-cell lung cancer have been published. Only one new chemotherapeutic agent (topotecan [Hycamtin]) and one new biologic treatment (marimastat) are currently being evaluated in randomized clinical trials in small-cell lung cancer.[86] The current status of research in this area reflects the need for evaluation of new treatments.

**Head and Neck Cancer**

Although radical neck dissection previously was preferred in the treatment of neck metastases,[93] a combination of surgery and radiation therapy improves local and regional control of stages III and IV head and neck cancers.[94,95] However, 5-year survival rates remain below 40% and do not differ significantly from those in patients who undergo surgery alone.[95,96] The addition of chemotherapy to the treatment of locally advanced head and neck cancers may improve prospects for long-term survival. Chemotherapeutic agents used in the treatment of squamous cell carcinoma of the head and neck in the past included methotrexate, bleomycin, cisplatin, 5-FU, and carboplatin, with single-agent response rates of 15% to 31%.[97,98] Newer chemotherapeutic agents (eg, paclitaxel, docetaxel) result in single-agent response rates of approximately 38%.[97,98] Randomized trials also demonstrated that chemoradiation therapy results in increased time to progression and increased overall survival rates.[99,100]

**Paclitaxel**

Numerous phase I and II trials have evaluated paclitaxel (as a single agent and in combination with other chemotherapeutic agents) plus radiation therapy in patients with locally advanced head and neck cancer (Table 3). Phase I trials evaluated various paclitaxel doses and administration schedules with radiation therapy.[101-104] Grade 3/4 toxicities included mucositis, skin toxicity, and myelosuppression; toxicities generally were manageable. Response rates were encouraging, with complete response rates ranging from 50% to 75% and overall response rates of 90% to 100%. Two phase II trials evaluated paclitaxel/platinum chemoradiation regimens in patients with locoregionally advanced head and neck cancers.[105,107] One phase II trial[105] assessed weekly paclitaxel/carboplatin with concurrent radiation therapy, and one phase II trial[107] assessed...
induction chemotherapy with paclitaxel/carboplatin and concurrent radiation therapy followed by
follow-up chemotherapy with 5-FU, interferon alfa, and cisplatin. Results of these trials were
encouraging, with complete response rates of 57% to 78%. Principal toxicities included mucositis,
skin toxicity, and myelosuppression.

A regimen of 5-FU/hydroxyurea plus radiation therapy (FHX) was developed at the University of
Chicago for the treatment of patients with locally advanced head and neck cancer, which has
resulted in encouraging response and survival rates, with good tolerability.[108] Additional studies
demonstrated that this widely used regimen was effective even in previously irradiated
patients.[109] Recent trials evaluated the feasibility of adding other agents, such as cisplatin or
paclitaxel, to the FHX regimen in poor-prognosis patients who had failed to respond to earlier
surgery or radiation therapy.[108,110] The addition of cisplatin to the FHX regimen was generally
tolerable with granulocyte colony-stimulating factor (G-CSF) support, and the regimen resulted in a
high locoregional control rate and a long failure-free interval.[110]

More recently, paclitaxel was added to the FHX regimen to enhance locoregional control and treat
systemic micrometastatic disease. In a phase I trial, 55 patients with poor-prognosis head and neck
cancer received 14-day cycles of 5-FU (600-800 mg/m²/day for 5 days), hydroxyurea (500 mg or
1,000 mg twice daily for 11 days), and escalating paclitaxel doses (5 to 25 mg/m² per day for 5 days)
plus concurrent radiation therapy (2 Gy on days 2 through 6 or 1.5 Gy twice daily) and G-CSF
support.[108] The addition of paclitaxel to the FHX regimen is feasible, and patients generally
experienced less toxicity with this regimen than with the cisplatin-FHX regimen. Consequently, a
phase II study of the paclitaxel-FHX regimen was initiated in previously untreated patients with
looceregionally advanced head and neck cancer.[111] At a median follow-up of 10 months, 29 of 57
patients had achieved a complete response and 14 of 57 patients had achieved a partial response,
for an overall response rate of 75%. Therefore, this intensive concurrent chemoradiotherapy regimen
resulted in encouraging locoregional control in patients with advanced disease.

Encouraging results in trials including paclitaxel-containing regimens stimulated further investigation
of novel administration schedules and investigation of other new chemotherapeutic agents. A phase
II study recently was initiated to evaluate a simplified paclitaxel/FHX regimen with paclitaxel
administered over 1 hour on day 1 of chemoradiotherapy between the two daily radiation
fractions.[112]

Docetaxel

Docetaxel has substantial activity in squamous cell carcinoma of the head and neck.[113,114] Two
phase II studies including a total of 74 patients evaluated the activity, safety, and tolerability of
docetaxel 100 mg/m² infused over 1 hour every 3 weeks in patients with locoregional or metastatic
squamous cell carcinoma of the head and neck.[113,114] Docetaxel was generally tolerable and
could be safely administered on an outpatient basis.[114] Overall response rates for single-agent
docetaxel in these trials ranged from 32% to 42%.[113,114] In a recent phase II study, a combined
regimen of docetaxel with cisplatin was investigated in locally advanced, recurrent, and/or
metastatic squamous cell carcinoma of the head and neck.[115] Analysis of this study has not been
completed yet.

A phase I/II trial explored the use of induction chemotherapy followed by radiation therapy in 23
previously untreated patients with advanced squamous cell carcinoma of the head and neck.[116]
Induction chemotherapy consisted of docetaxel (25 mg/m², 45 mg/m², or 60 mg/m² with and without
growth factor support) plus cisplatin (25 mg/m²), 5-FU (700 mg/m²), and leucovorin (500 mg/m²)
(PFL) every 28 days for up to three cycles; 72 to 74 Gy of radiation therapy was administered to the
primary site following induction chemotherapy. The maximum tolerated dose of docetaxel was 60
mg/m² when combined with the PFL regimen. The dose-limiting toxicity was neutropenia; other major
toxicities included nausea, mucositis, diarrhea, peripheral neuropathy, and nephropathy. In 22
evaluable patients, clinical complete responses at the primary site were observed in 19 patients
(86%), and clinical partial responses were observed in three patients (14%), for an overall response
rate of 100%. The encouraging results of this study merit further evaluation of this combination. An
ongoing phase I study is evaluating induction chemotherapy followed by weekly 1-hour docetaxel
infusions and concurrent radiotherapy for 6 weeks in previously untreated patients with advanced
squamous cell carcinoma of the head and neck.[117]

Esophageal Cancer

Radiation therapy plays an important role in the management of esophageal cancer, mainly as a
component of multimodality therapy. Chemoradiation currently is considered the nonsurgical
standard of care for local-regional esophageal cancer and may prolong survival and increase cure
rates when administered prior to surgical resection. Chemoradiation therapy has been the focus of many studies in esophageal cancer because several chemotherapeutic agents active against this tumor are known radiosensitizers (eg, paclitaxel, 5-FU, and cisplatin).[118]

**Paclitaxel**
Paclitaxel has substantial single-agent activity in advanced or metastatic esophageal cancer, with acceptable toxicity. Paclitaxel is therefore under investigation in neoadjuvant chemoradiation regimens in combination with cisplatin[119] or cisplatin or carboplatin plus 5-FU (Table 4).[120,121,123,124] Paclitaxel was evaluated at various doses and administration schedules. Preliminary results of these trials are encouraging, with overall response rates in phase II trials ranging from 42% to 81%.[119,121,123] Principal grade 3/4 toxicities included esophagitis and myelosuppression. Additional phase I and II trials are in progress to explore the use of paclitaxel in combination with cisplatin or carboplatin as neoadjuvant therapy in patients with potentially resectable esophageal cancer[125] and in patients with unresectable locally advanced or metastatic esophageal cancer.[126,127] Results of these trials should further define the role of paclitaxel-containing chemoradiation therapy in esophageal cancer.

**Docetaxel**
Data on docetaxel in combined-modality therapy for esophageal cancer are limited. Two recent phase I trials evaluated docetaxel 40 to 75 mg/m² per 21-day cycle with concurrent radiation therapy at 2 Gy/day in patients with advanced unresectable malignancies, including esophageal cancer.[82,128] The MTDs in one trial[82] were 40 mg/m² per cycle when administered once every 3 weeks or for 2 weeks of every 3 weeks and 60 mg/m² per cycle when administered weekly for 3 weeks (ie, 20 mg/m² per week). Similarly, the MTDs of docetaxel in the other phase I trial was 20 mg/m² per week in combination with radiation therapy.[128] Esophagitis and neutropenia were the DLTs.[82,128] Partial responses were observed in both studies, encouraging further investigation of docetaxel in combined-modality therapy for esophageal cancer.

**Brain Tumors**
Progress in the treatment of brain tumors since the early 1980s has been limited, and standard radiation treatments frequently fail to achieve local control of the disease.[129] Despite the need for newer therapeutic approaches, little information is available concerning treatment of primary brain tumors with paclitaxel, which is effective against a wide range of solid tumors.[129] Brain tumor sensitivity to single-agent paclitaxel appears to be dependent on histology. Newly diagnosed or recurrent glioblastomas multiforme are relatively resistant to single-agent paclitaxel, while gliomas and brain metastases with oligodendroglial components appear to be sensitive to the effects of paclitaxel. The in vitro radiosensitizing properties of paclitaxel and activity against glioma cell lines stimulated the design of several recent trials of multimodality therapy for primary brain tumors (Table 5).

In addition to these trials, a phase III study coordinated by RTOG is evaluating the use of paclitaxel with conventional cranial irradiation for newly diagnosed malignant astrocytomas or with stereotactic radiosurgery for recurrent tumors.[133] Concurrent chemotherapy and radiation therapy also may be effective in the treatment of metastatic brain tumors. Further study of the pharmacokinetics of paclitaxel in patients with brain tumors is important, and the optimal dose and schedule of administration are critical questions in the treatment of this tumor type, as for others.[133] In a phase I/II investigation of combined-modality therapy including conventional cranial irradiation, a weekly schedule of paclitaxel was used.[129,131] When pharmacologic properties and safety are considered, a weekly paclitaxel administration schedule is preferable, but additional studies are required for confirmation of its utility.

Docetaxel has not been used extensively in the treatment of brain tumors, either in chemotherapy or chemoradiotherapy regimens. In a phase II trial of docetaxel 75 mg/m² (when prior adjuvant therapy was administered) or 100 mg/m² (when no prior chemotherapy was administered) in 18 patients with recurrent malignant gliomas (five with glioblastoma multiforme and the remainder with other malignant gliomas), no complete or partial responses were observed.[134] A lack of central nervous system penetration was observed in a single case study of a patient with leptomeningeal carcinomatosis.[135] While these data are limited, docetaxel does not appear to have significant activity against brain tumors.

**Pancreatic and Gastric Cancers**
More effective means of local disease control are needed in the treatment of pancreatic, gastric, and
Taxanes in Combined-Modality Therapy for Solid Tumors
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Gastroesophageal Adenocarcinomas. Most patients with pancreatic cancer have extensive, unresectable disease at the time of diagnosis. Historically, attempts to use combined-modality therapy (eg, 5-FU, mitomycin, and radiation therapy) in the treatment of pancreatic cancer did not yield encouraging results,[136] and newer, less toxic agents with good activity are needed to treat this disease. The incidence of gastric and gastro-esophageal junction adenocarcinomas is rising. In patients with gastric cancer, local recurrence of disease after surgical resection is an important cause of treatment failure. Newer approaches, including more effective neoadjuvant regimens, are needed for the treatment of these upper gastrointestinal malignancies.

A trial similar to that conducted for non-small-cell lung cancer[58] was completed recently for the treatment of gastric-pancreatic cancer.[137] Paclitaxel 30 to 60 mg/m² IV over 3 hours was administered weekly for 6 weeks with concurrent radiation therapy (50 Gy delivered in 28 fractions of 1.8 Gy each) in patients with locally advanced pancreatic (n = 18) or gastric (n = 16) cancer. Substantial activity was observed in this study against both pancreatic and gastric cancers. Among the 13 patients with pancreatic cancer evaluable for response, there were no complete responses and four partial responses, for an overall response rate of 31%. Among 10 evaluable patients with gastric cancer, there were no complete responses and seven partial responses, for an overall response rate of 70%. The dose-limiting toxicities in this study were abdominal pain within the irradiated field, nausea, and anorexia, which occurred at a paclitaxel dose of 60 mg/m².

Two phase II studies were initiated to evaluate paclitaxel 50 mg/m² per week with concurrent radiation therapy (at a total dose of 50 Gy) in patients with locally advanced pancreatic and gastric cancers.[138] After enrollment of 25 patients in the pancreatic cancer trial, six of 18 evaluable patients achieved a partial response, for a preliminary response rate of 33%. Grade 3/4 toxicities included hypersensitivity reactions, neutropenia, and nonneutropenic biliary sepsis. Among the first 16 patients with gastric cancer, one complete response and eight partial responses were observed, for an overall preliminary response rate of 56%. In this trial, grade 3/4 toxicities observed included nausea, anorexia, esophagitis, and gastritis. In 24 patients with adenocarcinomas of the gastroesophageal junction, there were four complete responses and 14 partial responses, for an overall response rate of 75%. Grade 3/4 toxicities included neutropenia, nausea, and dehydration. These trials demonstrated that chemoradiation including paclitaxel is well tolerated and has substantial activity against locally advanced upper gastrointestinal malignancies.

Ongoing trials are evaluating paclitaxel with concurrent radiotherapy for pancreatic and gastric cancers.[139-141] Results of these trials should further define the role of paclitaxel-based chemoradiation therapy for these tumor types.

Breast Cancer

Standard therapy for locally advanced breast cancer consists of systemic neoadjuvant chemotherapy followed by surgery and then radiation therapy.[142] The toxicity of some chemotherapy regimens (eg, anthracycline-based regimens) limit their utility in combined-modality therapy. Chemoradiation therapy has demonstrated efficacy in the treatment of other tumor types, and newer radiosensitizing agents (eg, paclitaxel) that are effective against breast cancer are now available.[143,144] The effects of preoperative chemoradiation were assessed in a pilot trial evaluating 5-FU (200 mg/m² as a continuous infusion) plus radiation therapy (50 Gy at 2-Gy/fraction) in 35 patients with locally advanced breast cancer.[145] Treatment resulted in an overall response rate of 72% (complete and partial responses) and was well tolerated; furthermore, all patients could then undergo modified radical mastectomy.

PACLITAXEL IS HIGHLY ACTIVE AS A SINGLE AGENT AGAINST BREAST CANCER,[143,146,147] AND ITS RADIOSENSITIZING PROPERTIES WERE DEMONSTRATED BOTH IN VITRO AND IN VIVO.[5,12,17,20,21] PRELIMINARY RESULTS OF A TRIAL ASSESSING PACLITAXEL PLUS RADIATION THERAPY IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER WERE REPORTED RECENTLY.[142] PATIENTS INITIALLY RECEIVED PACLITAXEL 60 MG/M² PER WEEK PLUS RADIATION THERAPY 50 Gy (IN 2-Gy FRACTIONS) OVER 5 WEEKS. DUE TO TOXICITY EXPERIENCED BY THE FIRST TWO PATIENTS, THE CHEMOTHERAPY REGIMEN WAS MODIFIED TO PACLITAXEL 30 MG/M² TWICE WEEKLY. PATIENTS WERE THEN RESECTED AND RECEIVED ANTHRACYCLINE-CONTAINING FOLLOW-UP CHEMOTHERAPY. OF THE 13 PATIENTS ENROLLED FOR BREATHER, EIGHT PATIENTS WERE EVALUABLE FOR RESPONSE AND TOXICITY. THE TWICE-WEEKLY SCHEDULE WAS MORE EASILY TOLERATED, AND FOUR PATIENTS (50%) ACHIEVED A PATHOLOGICAL RESPONSE.

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(including complete and partial responses). Correlation of biomarkers with response will be attempted in a subset of patients in this trial. Loss of p53 function confers sensitivity to paclitaxel in several cell types,[148] and identification of relevant tumor characteristics may lead to better patient selection for taxane-based treatment. Although docetaxel is highly active against breast cancer,[4] no results of clinical trials evaluating docetaxel in combined-modality therapy for breast cancer have been reported to date.

**Summary**

In recent studies, the activity of taxanes (as single agents and in combination with other chemotherapeutic agents) plus radiation therapy has been evaluated in a variety of tumor types. For locally advanced non-small-cell lung cancer, results available from phase I and II trials indicate that combined-modality therapy including paclitaxel is generally well tolerated and achieves control of local and metastatic disease. Novel paclitaxel administration schedules, including weekly and twice-weekly infusions, are being evaluated in combination with standard and hyperfractionated radiation therapy. Trials adding platinum compounds to paclitaxel-based regimens are also yielding encouraging results. Ongoing trials are evaluating docetaxel plus radiation therapy in patients with locally advanced unresectable non-small-cell lung cancer. Taxane-based chemotherapy plus radiation therapy is being explored for small-cell lung cancer, poor-prognosis squamous cell carcinoma of the head and neck, esophageal cancer, brain tumors, pancreatic and gastric cancers, and locally advanced breast cancer. Ongoing trials also are beginning to evaluate concurrent paclitaxel and radiotherapy for pelvic malignancies.[149-152]

Molecular genetic alterations in tumor cells are the focus of a growing number of studies. Tumors with p53 gene mutations may respond in unique ways to radiation and chemotherapy, possibly requiring cytotoxic agents with novel mechanisms of action. An evaluation of the response of tumors with p16INK4a gene product mutations to paclitaxel and radiation therapy also is of interest. A better understanding of the role played by biomarkers should lead to more effective treatment and patient selection. Much of the current research should help define critical doses and administration schedules and should lead to better treatment and patient selection methods for many of these common solid tumors.

**References:**


77. RTOG-9801: Phase III randomized study of amifostine mucosal protection in patients with favorable performance inoperable stage II, IIIA, or IIIB non-small cell lung cancer receiving sequential induction and concurrent hyperfractionated radiotherapy with paclitaxel and carboplatin. Study


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