Role of Taxoids in Head and Neck Cancer

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ABSTRACT

Docetaxel and paclitaxel represent a new class of cytotoxic agents having both a specific chemical structure and mechanism of action. They act to promote tubulin polymerization and the formation of stable microtubules. The microtubules produced in the presence of taxoids are resistant to disassembly by physiologic stimuli, and cells exposed to these agents exhibit an accumulation of disorganized microtubule arrays. This affects the normal mitotic process and eventually results in cell death.

Both drugs are active as single agents in patients with head and neck cancer with response rates ranging from 20% to 40%. They may be combined with other cytotoxic agents, radiotherapy, or both. A review is given of the presently available data.

INTRODUCTION

The taxoids represent a new class of agents having both a specific chemical structure and mechanism of action. Paclitaxel, a natural product derived from the bark of the Western Yew, Taxus brevifolia, was the first agent of this class to be identified and introduced into the clinic in the 1980s. Recently, the natural source has been replaced by laboratory production of the drug by semisynthesis [1].

The analog docetaxel is produced by semisynthesis from 10-deacetylbaccatin-III, an inactive precursor extracted from the needles of the European Yew (Taxus baccata). It differs chemically from paclitaxel in only two molecular sites (the 10\(^\text{\text{-}}\)position on the baccatin ring and in the 3\(^\text{\text{-}}\)-position on the side chain).

Tubulin is the cellular target of both paclitaxel and docetaxel. In contrast to the vinca alkaloids, another class of tubulin-acting agents, taxoids act to promote tubulin polymerization and the formation of stable microtubules. The microtubules produced in the presence of taxoids are resistant to disassembly by physiologic stimuli, and cells exposed to these agents exhibit an accumulation of disorganized microtubule arrays. This affects the normal mitotic process and eventually results in cell death [1].

PACLITAXEL

Preclinical and Clinical Evaluation

Recent preclinical data have indicated that paclitaxel is able to inhibit DNA synthesis, causing cell arrest in G\(_2\)-M phase. Several different pathways control the cell cycle and apoptosis. An oncogene-derived protein, Bcl-2 inhibits the pathway of apoptosis, while a Bcl-2-homologous protein, Bax, promotes cell death by competing with Bcl-2. While Bax-Bax homodimers act as apoptosis inducers, Bcl-2-Bax heterodimer formation evokes a survival signal for the cells. Both Bcl-2 and Bax are transcriptional targets for the tumor suppressor protein, p53, which induces cell cycle arrest or apoptosis in response to DNA damage [2].

Paclitaxel was able to induce Bax expression and decrease Bcl-2 expression in head and neck cancer cell lines [3]. P-glycoprotein (P-gp) overexpression seems to protect cells from paclitaxel but correlates with a higher index of apoptosis [4, 5]. This was also observed in an in vitro study with berberine, an agent used in Chinese herbal medicine that upregulates the P-gp-170 expression and decreases the sensitivity to paclitaxel [6].

In vitro and in vivo interactions between paclitaxel and p53 have also been examined. There was no correlation found between p53 expression and response to paclitaxel in patients with head and neck cancer [7]. When head and neck cell lines were preincubated with paclitaxel, transfection with a wild-type p53 by a viral vector proved to be synergistic [8].

In vitro, the radiosensitizing effect of paclitaxel was demonstrated in squamous cell cancer cell lines by different assays [9-11]. The combination of paclitaxel and radiotherapy proved to be synergistic or additive, depending on the model used [9]. Moreover, there seems to be a dose-dependent
relationship with synergism observed at doses that are readily achievable in the clinical setting [10].

Single-Agent Paclitaxel

Single-agent paclitaxel is active in patients with squamous cell carcinoma of the head and neck. Paclitaxel given as a 3- or 24-h infusion every three weeks in doses of 175 mg/m² to 250 mg/m² with or without hematopoietic growth factors induced a response rate varying from 20% to 40% (Table 1) [12-14]. A direct comparison in a randomized phase II study performed within the EORTC Head and Neck Cancer Cooperative Group showed overlapping 95% confidence intervals of the response rates obtained by standard-dosed methotrexate and two infusion schedules of paclitaxel in patients with recurrent and/or metastatic head and neck cancer [15]. A phase III study comparing weekly methotrexate and weekly paclitaxel is ongoing with the Eastern Cooperative Oncology Group in the United States.

Paclitaxel in Combination with Cytotoxic Agents

Paclitaxel was combined with different cytotoxic agents in several phase I/II studies (Table 2).

Paclitaxel with Platinum Compounds

Paclitaxel with Cisplatin

Several I/II studies examined the combination of paclitaxel with cisplatin [16-21] in patients with head and neck cancer. Cisplatin was administered as a 0.5- to 1-h infusion, mostly preceded by paclitaxel (Table 2). This combination could be administered weekly [16], biweekly [17], or every three weeks [18-21]. In patients with recurrent or metastatic squamous cell carcinoma of the head and neck, a high response rate was seen ranging from 32% [17] to 77% [19]. Main side effects were neurosensory and neuromotor changes [16-20]. Hematologic toxicity was acceptable, and doses could be increased after use of granulocyte colony-stimulating factor [16]. Several studies reported results of combinations of paclitaxel plus cisplatin with other chemotherapeutic agents.

Paclitaxel, Cisplatin with 5-Fluorouracil (5-FU)

Benasso et al. reported on 23 chemotherapy-naive patients with relapsed unresectable squamous cell carcinoma of the head and neck treated with paclitaxel, cisplatin, and 5-FU. Paclitaxel (100-180 mg/m²) was given as a 3-h infusion on day 1 with cisplatin (20-25 mg/m²/d, days 1-3) and 5-FU (200-250 mg/m²/d, bolus, days 1-3) every 21 days. At the dose level of paclitaxel 160 mg/m², cisplatin 25 mg/m²/d, and 5-FU 250 mg/m²/d, one of seven patients developed neutropenic fever. Nonhematological toxicities were diarrhea and stomatitis. The authors concluded that these dosages were recommended for phase II testing [22].

In a preliminary report on 42 evaluable patients with head and neck cancer treated with the combination of paclitaxel (175 mg/m² in a 3-h infusion), cisplatin (100 mg/m²), and 5-FU (500 mg/m²/d, days 1-5) every three weeks, a response rate of 85% was reported. Grade 3 and 4 neutropenia, diarrhea, mucositis, and myalgia were observed in only a minority of patients [23]. Based on these data, a randomized study comparing induction chemotherapy with cisplatin plus infusional 5-FU followed by radiotherapy and cisplatin plus 5-FU and paclitaxel followed by radiotherapy is ongoing in Spain.

Paclitaxel, Cisplatin with Ifosfamide

In a phase I/II study, 52 chemotherapy-naive patients with recurrent or metastatic squamous cell carcinoma of the head and neck were treated with the combination of 175 mg/m² paclitaxel in a 3-h infusion on day 1, 60 mg/m² cisplatin on day 1, and 1.0 g/m²/d ifosfamide in a 2-h

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<td>Inuyama Y [49]</td>
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n eval pts = number of evaluable patients; RR = response rate; G-CSF = granulocyte colony-stimulating factor; q = every.
infusion on days 1-3, repeated every three to four weeks. Major toxicities included neutropenia, cumulative peripheral neuropathy, and fatigue. The overall response rate was 58%, with 17% complete responses [24].

Kosmas et al. performed another phase I study with the combination of paclitaxel (135-215 mg/m² in a 1-h infusion), cisplatin (40-50 mg/m²/d, days 1-2), and ifosfamide (2.25-3 g/m²/d, days 1-2) with granulocyte colony-stimulating factor from days 5-14 in 42 patients with solid tumors. Cycles were given every three weeks. Grade 3 or 4 toxicities were neutropenia in 27% of cycles, neutropenic fever in three patients at the highest dose levels, and thrombocytopenia and anemia in 7% and 13% of cycles, respectively. The major nonhematological toxicity was neuropathy. The response rate was 48%. The doses of paclitaxel, cisplatin, and ifosfamide for phase II testing were 200 mg/m², 50 mg/m²/d, and 2.5 g/m²/d, respectively [25].

Paclitaxel with Methotrexate

The dose of paclitaxel given as a 24-h infusion and preceded by methotrexate could not be increased over 135 mg/m² because of neutropenic fever, even after addition of G-CSF [30]. This combination yielded only a 10% response rate.
Paclitaxel with 5-FU

Results of a phase II study of weekly 1-h paclitaxel 60 mg/m² and 24-h infusion of high-dose 5-FU (1,800 mg/m²) with leucovorin (500 mg/m²) in chemotherapy-naive patients with advanced squamous cell carcinoma of the head and neck were reported by Constenla-Figueiras et al. Thirty-six patients with chemotherapy-naive inoperable advanced (26 patients) and/or recurrent (10 patients) head and neck cancer were treated weekly for three of four weeks. Grade 3 neutropenia developed in one patient. Nonhematological toxicities included mild mucositis, diarrhea, and vomiting in addition to irritation at the venous infusion site. Responses were observed in 4 of 10 (40%) patients with recurrent and metastatic disease and in 11 out of 22 (50%) patients with locally advanced disease. The authors concluded that the toxicity of this combined chemotherapy was minimal, but they considered the 18% complete response rate in patients with locally advanced disease as disappointing [31].

Paclitaxel with Gemcitabine

The combination of paclitaxel and gemcitabine was used in 28 patients with solid tumors [32]. Dose-limiting toxicity was not seen at doses of 150 mg/m² of paclitaxel and 3,000 mg/m² of gemcitabine biweekly. Hematologic toxicities were grade 4 neutropenia and thrombocytopenia in a minority of patients. Only grade 3 mucositis and asthenia were reported as nonhematological toxicities. One partial response was reported in a patient with bladder cancer.

In a Greek phase II study, 44 patients with recurrent or metastatic head and neck cancer were given first-line therapy with paclitaxel (200 mg/m² in a 3-h infusion, day 1) and gemcitabine (1,000 mg/m² in a 30-min infusion, days 1 and day 8) every three weeks. Grade 3 and 4 toxicities included neutropenia (21%), thrombocytopenia, anemia, infection, flu-like symptoms (all 5%), and peripheral neuropathy (2%). The overall response rate was 41%, with 11% of patients achieving a complete response [33].

Paclitaxel in Combination with Radiotherapy

Different study groups [34-38] reported results of the combination of radiotherapy and paclitaxel in different schedules.

Paclitaxel (30 mg/m²/d, days 1-5 and days 29-33) given concomitantly with a split-course accelerated radiotherapy (2 × 1.5 Gy/d with a rest period of nine days after 30 days) was feasible in 9 of 12 patients having head and neck cancer with neutropenic fever. The overall response rate was 100% in 10 evaluable patients [34].

Hoffmann et al. [35] studied the combination of conventional radiotherapy with a weekly 1-h infusion of paclitaxel in 18 patients with unresectable or incompletely resected squamous cell carcinoma of the head and neck. Paclitaxel was given at a starting dose of 20 mg/m², and subsequent dose escalations of 10 mg/m² were applied. Radiotherapy was administered over six to seven weeks with 2.0 Gy daily fractions, up to total doses of 60 to 70 Gy. The maximum tolerated dose of paclitaxel in this setting was 30 mg/m²/week, with mucositis being dose-limiting.

Serious toxicity was observed in a small study of 14 head and neck cancer patients who were treated with paclitaxel every three weeks in a dose of 100 mg/m² concurrently with external beam radiation [36]. Most patients needed a percutaneous gastrostomy. Twelve of 13 evaluable patients achieved a complete response at the primary site with this approach.

Another phase I trial studied the simultaneous treatment of continuous 24-h paclitaxel (75 mg/m²/d) concomitant with radiotherapy in 24 patients with advanced head and neck cancer. The dose-limiting toxicities in this study were febrile neutropenia and stomatitis. All patients had major responses [37].

Dowell et al. [38] treated patients with locally advanced solid tumors of the lung and head and neck with intensive radiotherapy concurrently with seven weeks of paclitaxel administered by continuous infusion. In 43 evaluable patients, no dose-limiting toxicity was observed at a dose of 17 mg/m²/d. Further dose escalation is anticipated.

Three studies reported the combination of paclitaxel and carboplatin with radiotherapy in patients with head and neck cancer.

A weekly scheme of paclitaxel (45-40 mg/m²) and carboplatin (100 mg/m²) together with conventional radiotherapy was studied in 18 patients with unresectable squamous cell carcinoma of the head and neck [39]. Toxicities were manageable. Chemotherapy dose reduction was needed in 10 patients. Only 53 of 100 doses were administered as planned; 23 were reduced; and 24 were withheld due to neutropenia or mucositis. There were no toxic deaths, and no patient discontinued treatment for toxicity. In 11 evaluable patients, two achieved a complete and six a partial response.

A study reported by Wanebo’s group of operable patients with squamous cell carcinoma of the head and neck showed that the combined use of eight weekly cycles of paclitaxel (60 mg/m²), carboplatin (AUC 1), and conventional radiotherapy (45 up to 72 Gy) had a high potential for organ preservation. Of 33 evaluable patients, 20 (60%) had a complete response and 10 (30%) a partial response. A pathological complete response at the primary site occurred in 94% of 18 evaluable patients. Grade 3 and 4 mucositis occurred in 90% of patients; other grade 3 and 4 toxicities were dermatitis, candidiasis, neutropenia, and dehydration [40].
Eckhardt et al. treated 12 patients with five cycles of weekly paclitaxel (40 mg/m²) and carboplatin (AUC 1.5) in combination with preoperative radiotherapy (40 Gy) in stage III and IV squamous cell carcinoma of the oral cavity or oropharynx. A complete response was seen in 66% of patients, and 60% of 10 operated patients had a pathological complete response [41].

Paclitaxel and carboplatin were also combined with 5-FU during radiotherapy. Thirty-eight patients with head and neck or esophageal cancer were treated with the combination of paclitaxel (200 mg/m² in a 1-h infusion, days 1 and 21), carboplatin (AUC 6, days 1 and 21), and 5-FU (225 mg/m²/d in continuous infusion, days 1-42) in combination with radiotherapy as first-line treatment and were evaluated at week 6. The overall response rate was 86% in 29 evaluable patients. Of 16 patients with head and neck cancer, 75% had a major response. No serious toxicity was observed except for stomatitis [42].

The combination of paclitaxel, 5-FU, and hydroxyurea was evaluated by Vokes’s group. They defined a schedule for phase II testing as paclitaxel 20 mg/m²/d, 5-FU 600 mg/m²/d for five days, and hydroxyurea 0.5 g orally twice daily for 11 doses every other week with twice-daily radiotherapy (2 × 1.5 Gy). At this dose level, 81% of 20 evaluable patients achieved a complete and 10% a partial response. Grade 3 and 4 neutropenia occurred in 15% and 10%, respectively, at this dose level. Two patients, one of whom died, experienced neutropenic fever. Nonhematological toxicities were grade 4 mucositis (20%), dermatitis (10%), and gastrointestinal bleeding in three patients at the recommended dose level [43].

**DOCETAXEL.**

**Preclinical Data**

Docetaxel showed significant antitumor effect in vitro against different human tumor cell lines. On a concentration basis, docetaxel was more cytotoxic in the majority of human primary tumor specimens than paclitaxel [1].

Docetaxel is active against squamous cell carcinoma of the head and neck xenografts [44, 45]. Docetaxel proved to be active at doses of 20 mg/kg i.v. [44] and 30 mg/kg intraperitoneally in nude mouse models [45]. It was also active in cell lines less sensitive to cisplatin indicating that no cross-resistance exists [44].

**Single-Agent Docetaxel**

Several phase II studies showed activity of docetaxel in patients with squamous cell carcinoma of the head and neck [46-49] (Table 1). Most studies used docetaxel 100 mg/m² in a 1-h infusion every three weeks [46-48]. In patients without prior chemotherapy for recurrent disease, the overall response rate varied between 21% and 42%. The main toxicity was neutropenia, which was rarely complicated with fever. Other toxicities observed were alopecia, fatigue, anorexia, stomatitis, diarrhea, peripheral neuropathy, and fluid retention [46-48].

In Japan, a similar response rate was obtained with docetaxel 60 mg/m² every three weeks with acceptable toxicity and responses were seen in patients previously treated with chemotherapy for recurrent disease [49].

**Docetaxel in Combination with Cytotoxic Agents**

Combinations of docetaxel with other chemotherapeutic agents are reported in Table 3.

**Docetaxel with Platinum Compounds**

**Docetaxel with Cisplatin**

Schöffski et al. reported results of the combination of docetaxel and cisplatin. Docetaxel, 100 mg/m² administered as a 1-h infusion followed three hours later by cisplatin, 75 mg/m² by 3-h infusion was given to 41 eligible patients with locally advanced, unresectable, and/or metastatic squamous cell carcinoma of the head and neck. Grade 3 toxicities both hematologic and nonhematological were common. There were six complete responses (15%) and 16 partial responses (39%), resulting in an overall response rate of 54% in the intent-to-treat population [50].

Other groups reported preliminary results on the combination of docetaxel and cisplatin [51-54] in patients with head and neck cancer. Response rates observed in these studies varied from 42% to 73%. Main side effects were hematologic toxicity, infectious [51-54] and gastrointestinal complications (nausea, vomiting, and diarrhea) [53], and renal toxicity [53].

**Docetaxel, Cisplatin with 5-FU**

The combination of docetaxel, cisplatin, 5-FU, and leucovorin was examined in chemotherapy-naive patients with locally advanced squamous cell carcinoma of the head and neck [55, 56].

In a first phase I/II study, docetaxel was given in doses of 25, 45, or 60 mg/m² one hour before continuous cisplatin (25 mg/m²/d), leucovorin (500 mg/m²/d) on days 1-5, and 5-FU (700 mg/m²/d) on days 2-5 (TPFL-5). Chemotherapy was repeated every four weeks for three cycles, after which patients were treated with radiotherapy. Neck dissection was performed after radiotherapy in case of partial response of cervical lymph nodes. The maximum tolerated dose of docetaxel was 60 mg/m², with neutropenic fever despite G-CSF, renal tubular concentration...
defects, and/or acute mucositis as dose-limiting toxicities. Of 34 cycles given to 12 patients, 15 led to hospitalization due to neutropenic fever (44%), renal failure (15%), and/or mucositis (18%). The overall response rate in 23 patients was 100% with 61% complete responses. It was concluded that docetaxel did add substantially to the efficacy of the combination of cisplatin/5-FU/leucovorin but at the cost of dramatic toxicity [55].

Therefore, a TPFL-4 regimen was developed in the same patient population. In this regimen, docetaxel (60 mg/m²) was given on day 1 as a 1-h infusion and cisplatin (31.25 mg/m²/d), 5-FU (700 mg/m²/d), and leucovorin (500 mg/m²/d) on days 1-4 as a continuous infusion. Hematologic growth factors and quinolones were used starting 6 h after chemotherapy until absolute neutrophil count exceeded 10.0 × 10⁹/l. Cycles were repeated every four weeks for three cycles. The overall response rate with this regimen was 100% with 61% complete responses. It was concluded that docetaxel did add substantially to the efficacy of the combination of cisplatin/5-FU/leucovorin but at the cost of dramatic toxicity [55].

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The experience with the triple combination, both in the US and in Europe, has led to large phase III trials comparing the triple combination and the standard cisplatin/infusional 5-FU regimen in patients with locally advanced head and neck cancer. These studies are presently ongoing on both sides of the Atlantic Ocean.
Docetaxel with Antimetabolites

Docetaxel with 5-FU

Docetaxel was also combined with 5-FU in three phase I studies in patients with variable solid tumors [59-61] and in one phase II study in patients with head and neck cancer [62]. When 5-FU was administered as a five-day continuous infusion after a 1-h infusion of docetaxel every three to four weeks, the recommended doses of docetaxel and 5-FU were 50 mg/m² and 500 mg/m²/d, respectively. Dose-limiting toxicities in 19 patients with advanced or recurrent breast cancer were neutropenia and diarrhea. The response rate in these patients was 50% [59].

A second group tested the same treatment regimen in a phase I study with variable solid tumors. Again, the regimen was given every three weeks. The recommended doses for phase II testing were 85 mg/m² of docetaxel given as a 1-h infusion on day 1 immediately followed by a five-day continuous infusion of 5-FU (750 mg/m²/d). Dose-limiting toxicities in that study were reversible secretory diarrhea, stomatitis, and febrile neutropenia. Overall, grade 3 and 4 neutropenia and febrile neutropenia were seen in 63.4% and 9.8% of 41 patients, respectively. Four patients experienced grade 3 and 4 infection, which led to toxic death in one of them. Partial responses were documented in 5 of 39 evaluable patients [60].

The third study group evaluated a regimen of docetaxel followed by a daily bolus injection of 5-FU for three or five days every four weeks. The recommended doses for phase II testing were 60 mg/m² of docetaxel and 300 mg/m²/d of 5-FU. Dose-limiting toxicity was grade 4 neutropenia lasting longer than seven days with or without fever and/or severe mucositis. Three of 37 patients had a response [61].

In 44 patients with head and neck cancer, a combination of docetaxel 75 mg/m² on day 1 and 5-FU 1,000 mg/m²/d during five days every four weeks was tested. The dose of 5-FU had to be reduced from 1,000 mg/m²/d to 750 mg/m²/d due to neutropenic fever and mucositis [62]. The response rate in these patients with no prior chemotherapy for recurrent disease was 34%.

The data on both the docetaxel/cisplatin regimen and the docetaxel/5-FU regimen have led to a large, multicenter, three-armed phase III trial comparing both regimens with cisplatin/infusional 5-fluorouracil in patients with recurrent and/or metastatic head and neck cancer.

Docetaxel with Other Spindle Poisons

Docetaxel with Vinorelbine

Preliminary results of a phase II study in heavily pretreated patients with head and neck cancer showed that the combination of docetaxel (80 mg/m²) and vinorelbine (20 mg/m²) every 17 days was feasible, with a response rate of 44% in 27 evaluable patients. Toxicity was grade 3 and 4 neutropenia, infections, and mucositis [63].

Docetaxel in Combination with Radiotherapy

Different investigators [64, 65] also examined the feasibility of the combination of docetaxel and radiotherapy. Mauer et al. showed that it was possible to associate doses of docetaxel up to 20 mg/m²/week in combination with conventional radiotherapy with 1.8 to 2.0 Gy/d to a total dose of 60 Gy in patients irradiated at the thorax [64]. Toxicity was mild, with esophagitis and neutropenia as dose-limiting toxicities.

Koukourakis et al. tested in a phase I setting the combination of docetaxel, irinotecan, and conventional radiotherapy [65]. Combination of weekly docetaxel 20 mg/m² and irinotecan 25 mg/m² induced grade 2 mucositis, while at higher doses (docetaxel/irinotecan: 20/40; 25/55) severe asthenia and mucositis were dose-limiting. The overall response rate in 12 patients with locally advanced head and neck cancer was 100%, with 75% complete responses.

CONCLUSION

The use of taxoids, both paclitaxel and docetaxel, as single agents or in combinations with other cytotoxic agents and/or radiotherapy, has been successfully tested in patients with squamous cell carcinoma of the head and neck. High response rates have been reported in some studies, but with an increased toxicity, in particular in the combined setting. Randomized phase III trials should determine the ultimate place of these treatments in the future.

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