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Phase I Trial of Concomitant Hyperfractionated Radiotherapy with Docetaxel and Cisplatin for Locally Advanced Head and Neck Cancer

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BACKGROUND

This study was conducted to determine the maximum tolerated dose of docetaxel when administered concomitantly with radical hyperfractionated radiotherapy and cisplatin in patients with locally advanced head and neck cancer.

PATIENTS AND METHODS

Patients with stage III–IV tumors received radical radiotherapy of 74.4 Gy given in two daily fractions of 1.2 Gy for 6 weeks. Cisplatin was given once weekly on day 1 at a constant dose of 15 mg/m². The starting dose of docetaxel was 10 mg/m² once weekly on day 3, with planned escalation steps of 5 mg/m². Main endpoints of the study were the maximum tolerated dose of docetaxel, acute toxicities, and the preliminary efficacy results.

RESULTS

Twenty-five patients were enrolled. Median follow-up was 15 months (range: 4–40 months). Two of three patients presented with dose-limiting toxicities at the 15-mg/m² dose of docetaxel (one patient presented with multiple grade 3–4 toxicities requiring hospitalization for management and another presented with multiple toxicities including life-threatening bronchoaspiration). Thus, the weekly docetaxel dose of 10 mg/m² was considered the maximum tolerated dose.

Nineteen patients were then treated with the maximum tolerated dose and no dose-limiting toxicities were observed. Radiotherapy was completed in all patients except one (median dose: 74.4; range: 73.2–74.4), and at least 80% of the scheduled cisplatin and docetaxel doses were given in 92% of the patients. Acute toxicities were dominated by grade 3 mucositis (92%) and grade 3–4 dysphagia (68%). The 2.5-year actuarial local control rate was 87.5%, and the disease-free survival rate was 75%. At the time of last follow-up, 23 patients were alive and two had died from cancer. No distant metastases were observed.

DISCUSSION

In patients with locally advanced head and neck cancer, this study determined the maximum tolerated dose of docetaxel to be 10 mg/m² administered once weekly when given concurrently with 74.4 Gy hyperfractionated radiotherapy and a weekly 15-mg/m² dose of cisplatin. The toxicity profile and the encouraging results suggest that this new combination merits further investigation in a multi-institutional phase II trial. (*Cancer J* 2006;12:63–68)

KEY WORDS

Head and neck cancer, radiotherapy, docetaxel, cisplatin

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In patients with advanced head and neck cancer, several randomized trials have demonstrated the superiority of combined treatment (radiotherapy + chemotherapy) over radiotherapy (RT) alone for both locoregional control and, to a lesser extent, overall survival. The results of the successive meta-analyses^{1–3} were consistent in reporting the superiority of the concomitant administration of RT and chemotherapy over other treatment strategies. This increased efficacy is most likely secondary to the radiosensitizing effect of some chemotherapy agents

when administered concomitantly with RT. Although the acute and probably late toxicities are somewhat higher when adding chemotherapy to RT, this strategy is becoming standard in patients with locally advanced disease. However, other studies reported superior locoregional control by altering RT dose fractionation by using either accelerated regimens or hyperfractionated RT.⁴⁻⁶ Despite the use of more aggressive RT schedules or the addition of chemotherapy, locoregional failure remains the principal mode of recurrence after treatment of locally advanced head and neck cancer. Thus, the concomitant use of altered RT fractionation and chemotherapy appears to be the next step in increasing the aggressiveness of treatment, particularly by using drugs that have a potent radiosensitization effect in addition to their cytotoxic properties.

Radiosensitization has been demonstrated in both *in vitro* and *in vivo* studies using cisplatin.^{7,8} However, its use as a single agent is likely to have only a modest effect on the ultimate clinical outcome after hyperfractionated RT, as experienced in our hands.⁹ Consequently, the hypothesis that treatment intensity may be important in improving patient outcome has given rise to studies testing the value of concurrent multidrug combinations.¹⁰ Recently, there has been significant interest in the use of taxanes (docetaxel and paclitaxel) in concurrent treatment programs. The rationale for using taxanes is based on their well-known *in vitro* and *in vivo* radiosensitizing effect^{11,12} as well as their proven efficacy as single agents or as components of multiagent chemotherapy programs.^{13,14} Because treatment intensity tends essentially to improve locoregional disease control, the use of weekly concurrent low-dose drugs may prove to be the optimal schedule, because it maximizes drug-radiation interaction at the cost of limited systemic toxicity. We have performed a phase I study to determine the maximum tolerated dose (MTD) of docetaxel when administered weekly with concomitant radical hyperfractionated RT and weekly cisplatin in patients with locally advanced head and neck cancer. The secondary endpoint was early oncologic results.

PATIENTS AND METHODS

After being informed and having given their written consent, 25 patients from one institution (Geneva University Hospital) were enrolled in this prospective trial. Eligibility criteria included the following: 1) biopsy-proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; 2) clinical stage III-IV (T3-4N0M0 or any TN1-3 M0); 3) World Health Organization performance status of

0-1; 4) age \leq 70 years; 5) no prior (in the last 5 years) or concurrent malignancy (except nonmelanoma skin cancers or *in situ* carcinoma of the cervix); 6) no prior RT or chemotherapy; 7) hemoglobin $>$ 10 g/dL; 8) white blood cell count $>$ $3.5 \times 10^9/L$; 9) an adequate renal function [serum creatinine \leq 120 $\mu\text{mol/L}$ (1.4 mg/dL), and if values are $>$ 120 $\mu\text{mol/L}$, creatinine clearance should be \geq 60 mL/min]; 10) normal bilirubin level; 11) levels of aspartate aminotransferase or alanine aminotransferase $<$ 2.5 times the upper limit of normal; 12) and an alkaline phosphatase level $<$ 5 times the upper limit of normal. Patients were excluded if they presented with \geq grade 2 (Cancer Institute of Canada-Clinical Trials Group) or clinically impaired hearing.

Pretreatment work-up consisted of medical history and physical examination, chest X-ray, computed tomography, and/or magnetic resonance imaging of the head and neck region, as well as a panendoscopy. For tumor classification, the International Union Against Cancer staging system (1997) was used. Patients were scheduled to have a monthly clinical examination for the first 2 years, and then every 3-4 months along with imaging examination in the case of suspected persistent or recurrent disease.

Radiotherapy

The RT schedule has been previously described in detail.⁹ The planned total dose was 74.4 Gy, delivered in 62 fractions of 1.2 Gy, twice per day over a period of 43 days. The minimum interval between the two daily fractions was 6 hours. The basic course was given to a total dose of 50.4 Gy, and the boost to initial sites of macroscopic tumor involvement consisted of 24 Gy. Most patients were treated with two opposed laterals and one anterior field for the large volume, while an individualized conformal technique was used for the boost according to the tumor location and extent. All patients were treated with 6-MV photon beams, and irradiation of the posterior neck was then continued with electrons of appropriate energy after spinal cord exclusion at the dose of 39.6 Gy.

Chemotherapy

The scheduling of chemotherapy allowed it to be given in an ambulatory setting. Thus, cisplatin was to be administered weekly at a constant dose of 15 mg/m² *i.v.* immediately before the RT sessions on days 1, 8, 15, 22, 29, 36, and/or 43. Before each cisplatin treatment, 1000 mL of normal saline *i.v.* was given over 90 minutes. Cisplatin was administered as a 30-minute infusion. Docetaxel was to be administered at

a weekly starting dose of 10 mg/m² i.v. on days 3, 10, 17, 24, 31, and 38 in escalating doses of 5 mg/m² per step. The intravenous infusion was to be performed over 15 minutes. Dexamethasone 8 mg was administered 45 minutes before the 30-minute docetaxel infusion.

Patients had to be treated at the same dose level of docetaxel in groups of three. If no dose-limiting toxicity (DLT) (defined as grade 4 local mucocutaneous toxicity in the radiation field and/or grade 4 hematologic toxicity with fever [single oral temperature > 38.5°C or three elevations to 38°C during a 24-hour period], and/or life-threatening toxicity) occurred, the next three patients would be treated at the next higher dose level. If one DLT occurred at a given level, three additional patients would be treated at the same dose level. If two or more DLTs occurred at a given dose level, the dose escalation would be stopped, and the dose just below that level would be considered the MTD for the purposes of further investigation.

Acute toxicities were to be graded using the National Cancer Institute Common Toxicity Criteria Version 2.0. The major expected dose-limiting toxicities were hematologic, mucosal, and cutaneous. The following recommendations for docetaxel and cisplatin dose reduction were applied. For grade 4 neutropenia without fever, only docetaxel was to be stopped and then continued upon recovery at 25% below the original dose. For grade ≥ 3 neutropenia plus fever or grade 4 thrombocytopenia, docetaxel and cisplatin were to be stopped and then continued upon recovery at 25% below the original dose. For grade 4 mucosal and/or cutaneous toxicity, docetaxel, cisplatin, and RT were to be stopped; upon recovery, docetaxel and cisplatin were to be continued at 25% below the original dose, while RT was to be continued at the planned dosage.

Surgery

According to institutional policy, three patients underwent planned neck dissection prior to radiotherapy without primary tumor resection. Otherwise, surgery was reserved for salvage of locoregional failures.

Statistics

Rates of acute toxicities were calculated as simple proportions. Actuarial local control, and overall and disease-free survival rates were calculated by using the product-limit method (Kaplan-Meier method).

RESULTS

Between June 2001 and August 2004, 25 patients were accrued. Pretreatment patient and tumor characteristics are displayed in Table 1.

Docetaxel Dose Escalation and DLTs

Three patients were treated at the dose level of 10 mg/m² with no observed DLT. At the second dose level of 15 mg/m², two of three patients presented with DLTs (one with multiple grade 3–4 toxicities requiring hospitalization for management and another with multiple toxicities, including life-threatening bronchoaspiration). Docetaxel dose escalation was subsequently stopped, and the following 19 patients were treated at the inferior dose level (10 mg/m²) without additional DLTs being observed. Thus, the weekly docetaxel dose of 10 mg/m² was considered the MTD and the recommended dose.

Toxicities and Treatment Compliance

All patients presented with at least one grade 3 acute toxicity. Table 2 displays the main acute toxicities observed for all patients. The severe acute toxicities (grade 3–4) mainly concerned organs located in the RT fields, such as mucosa and skin. The first patient with DLTs presented with grade 4 dysphagia, grade 3 mucositis, grade 3 fatigue, and grade 3 fever requiring hospitalization for management. The combination of such severe grade 3–4 acute toxicities has been considered dose limiting in this patient. The second patient with DLTs presented with grade 4 bronchoaspiration, grade 3 renal failure, and grade 3

TABLE 1 Patient Characteristics

N	25
Age, years	57 (49–68)
Gender (male/female)	21/4
Performance status (WHO) 0/1	24/1
Tumor location	
Oropharynx	15
Hypopharynx	4
Larynx	6
T stage (UICC 1997)	
T2	4
T3/T4	13/8
N stage	
N0/N1	7/2
N2	16
UICC stage	
III/IV	7/18

Abbreviations: WHO, World Health Organization; UICC, Union Internationale Contre le Cancer.

Acute Toxicities According to the NCI-CTC Scoring System for All Patients

Organ/Symptom	Grade 1	Grade 2	Grade 3	Grade 4
Mucosa	0	2	23	0
Dysphagia	1	7	13	4
Skin	9	10	6	0
Xerostomia	13	12	0	–
Hematologic				
Leucopenia	11	5	1	0
Neutropenia	2	4	1	0
Anemia	9	2	1	0
Thrombocytopenia	1	0	0	0
Infection/fever	2	1	1	0
Others				
Myelitis	–	1	–	–
Bronchoaspiration	–	–	–	1

Abbreviations: NCI, National Cancer Institutes; CTC, Common Toxicity Criteria.

arrhythmia requiring hospitalization in an intensive care unit starting 4 weeks after the end of RT. The treatment was completed in an ambulatory setting in 12 of 25 patients (48%). Beside the two patients referred to earlier, 11 patients (52%) were hospitalized due to acute toxicities, mainly for pain management and nutritional support. The median duration of hospitalization was of 27 days (range: 3–95). A nasogastric tube or a gastrostomy was required in 13 patients (52%), and maintained for a median duration of 79 days (range: 18–354). The median weight loss during RT was 5.8 kg (range: 1–15 kg). One patient presented with grade 2 acute myelitis 3.5 months after the end of RT (total dose of docetaxel: 40 mg/m²; total dose of cisplatin: 60 mg/m²). No treatment-related deaths occurred.

With the exception of one patient who missed one session, all patients completed the RT schedule (median dose: 74.4 Gy; range: 73.2–74.4). RT was interrupted in three patients due to acute toxicities for a median duration of 2 days (range: 2–5 days). In one patient, chemotherapy was stopped after 2 weeks due to transient alteration in renal function and liver enzymes. In all other patients (24/25), chemotherapy was given at the planned dose for the first 4 weeks. Due to local toxicities and/or neutropenia/fever, chemotherapy was withheld during the sixth week in three patients and the fifth week in one patient. Altogether, at least 80% of the scheduled cisplatin and docetaxel doses were given in 92% of patients.

Early Oncologic Results

At a median follow-up of 15 months (range: 4–40 months) from the start of RT, two patients had died,

both from head and neck cancer. The 2.5-year actuarial overall survival rate for all patients was 84% (95% confidence interval [CI]: 63%–100%). Two patients presented with locoregional failure and two others with isolated nodal failure, while no distant metastases were observed. The 2.5-year actuarial local control and disease-free survival (Fig. 1) rates were 87.5% (95% CI: 70%–100%) and 75% (95% CI: 52%–97%), respectively. The two patients who presented with locoregional failure underwent salvage surgery and were without evidence of disease at last follow-up.

DISCUSSION

The addition of chemotherapy to RT proved to be superior to RT alone for the treatment of advanced head and neck cancers and is becoming standard therapy despite the higher rate of acute, and probably late, toxicities. Although initially most of the studies used standard RT fractionation or split-course RT and/or single-drug chemotherapy to limit acute toxicities, altered RT fractionation as well as multidrug combinations have recently been used in an attempt to improve patient outcome.^{10,15,16} In a recent randomized trial, the Swiss collaborative group reported a significant improvement in locoregional control when adding two cycles of cisplatin to hyperfractionated RT.⁹ However, even in the combined treatment arm, the locoregional failure rate remained quite high (45%), leading to the consideration that treatment intensity should be increased further. We designed the present study with the aim of advancing a step further in treatment intensification by combining hyperfractionated RT and two chemotherapeutic agents with demonstrated radiosensitizing properties, namely cisplatin and docetaxel. Although the RT schedule is the same as that used in the Swiss collaborative trial, both drugs were given on a weekly basis to allow their de-

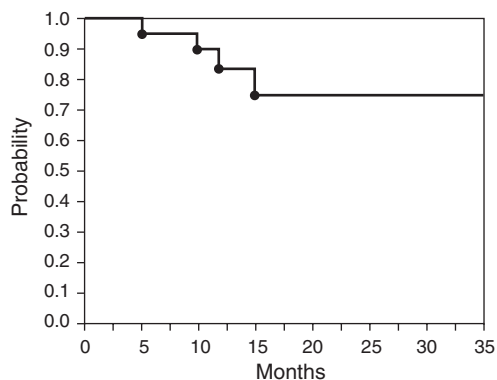


FIGURE 1 Actuarial disease-free survival (without salvage surgery).

livery in an ambulatory setting and to avoid their simultaneous administration. To our knowledge, this is the first study evaluating the effect of docetaxel when added to hyperfractionated RT and cisplatin in a series dedicated exclusively to curative treatment of head and neck cancer.

Based on previous studies reporting high rates of acute toxicities when combining docetaxel and RT, we started the present study with the low dose of 10 mg/m² administered weekly. After treating three patients at this dose level, no DLTs were observed. At the next dose level of 15 mg/m², two of three patients presented with DLTs. Consequently, the recommended dose of docetaxel, when administered with the present RT and cisplatin combination, was 10 mg/m² to a cumulative total dose of 60 mg/m². The MTD found in the present study is slightly lower than the MTDs reported when using weekly docetaxel as a single agent or when associated with standard fractionated RT (15–25 mg/m²).^{13,17,18} There is only scarce reported experience using continuous altered fractionation RT combined with multidrug therapy incorporating docetaxel. Such a program was reported in only one series¹⁹ of patients presenting with non-small cell lung or head and neck carcinomas, and the recommended dose was of 10 mg/m².

As expected, grade 3–4 acute toxicities were observed in all patients. The latter concerned the toxicities routinely observed in the treatment of this tumor location, namely mucosal reaction and dysphagia. No treatment-related deaths were observed, although hospitalization was required in 52% of patients for management of toxicities. This rate of hospitalization and the rate of nutritional support by nasogastric tube or gastrostomy (52%) were not different from what we reported in our previous study using accelerated RT and concomitant cisplatin-based chemotherapy.¹⁶ Concerning the patient who presented with grade 2 acute myelitis, no RT overdose was found upon review of the technical charts (spinal cord dose below 44 Gy for the full RT course), and the total dose of both drugs were well below the planned doses. Whether this toxicity was directly related to the addition of docetaxel or due to other contributing factors (e.g., particular hypersensitivity) remains debatable. Nevertheless, it would be wise for further investigations to keep the total RT dose (direct and scattered irradiation) below 40 Gy when multidrug chemotherapy and RT are administered concomitantly.

Adherence to the treatment schedule was satisfactory, with only three patients requiring interruption of RT for a few days (2–5) due to acute toxicities and essentially all patients receiving the prescribed RT dose. In addition, more than 80% of the scheduled cisplatin and docetaxel doses were given in 92% of patients

which is in the range of what is expected with such a treatment combination.¹⁰

The early oncologic results are of particular interest, even though the follow-up is short. With a median follow-up of 15 months, only four patients presented with locoregional failure, two of whom underwent salvage surgery for nodal failure and were without evidence of disease at last follow-up. This yielded a 2.5-year actuarial disease-free survival rate of 75% and a local control rate of 87.5% before salvage surgery. These results seem superior to those obtained when using RT with single-agent chemotherapy^{9,20} and appear comparable to the impressive results (80% 3-year progression-free survival rate) reported by Vokes et al¹⁰ using a more intensive chemotherapy-RT combination. In the latter study, induction chemotherapy using carboplatin and paclitaxel was used, and a three-drug combination (paclitaxel, fluorouracil, hydroxyurea) was administered concurrently with split-course hyperfractionated RT. Although the optimal chemoradiation schedule is not yet defined, some investigators argue that induction chemotherapy may be of crucial importance for increasing organ preservation and reducing the rate of distant metastasis. The results of our study do not lend support to this point of view. Our local control rate is quite encouraging, and no distant metastases have been observed thus far. In addition, our patients appear to have been spared both the 3%–4% risk of acute toxic death associated with regimens using intensive full-dose chemotherapy and the 25% rate of tube feeding dependency at 1 year, as observed in the study by Vokes et al.¹⁰

In conclusion, in patients with locally advanced head and neck cancer, our study determined the MTD of docetaxel to be 10 mg/m² administered once weekly concurrently with 74.4 Gy hyperfractionated RT and weekly 15 mg/m² cisplatin. The toxicity profile and the encouraging results suggest that this new combination merits further investigation in a multi-institutional phase II trial. Although further intensification with a third cytotoxic agent would not appear reasonable, a therapeutic window may exist to explore new agents that do not contribute substantially to local toxicities, with a particular emphasis on epidermal growth factor receptor targeted molecules, such as monoclonal antibodies or tyrosine kinase inhibitors.

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