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PHASE I ADJUVANT RADIATION WITH DOCETAXEL IN HIGH RISK HEAD AND NECK CANCER

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Abstract

Background—This phase I study was designed to determine the maximum tolerated dose (MTD) and preliminary efficacy of docetaxel with concurrent radiotherapy, (RT), in high risk squamous cell carcinoma of the head and neck (HNSCC).

Patients and Methods—Eligible patients had resected HNSCC, histologically involved lymph nodes, and/or extranodal disease, and/or involved surgical margins and performance status 0-1. Treatment included weekly docetaxel with concurrent RT in a dose finding study; a subsequent small cohort of patients was treated using the MTD of docetaxel.

Results—Twenty patients were enrolled. Planned accrual was 25, but the study was closed prematurely due to slow accrual. The MTD was 15mg/m². Dose limiting toxicity was oral stomatitis. Therapy was well tolerated. Five patients experienced locoregional relapse at a median follow up of 32 months.

Conclusion—Docetaxel with concurrent RT has acceptable toxicity. This approach warrants further investigation in a phase II trial.

Keywords

Phase I; radiochemotherapy; docetaxel; high risk; head and neck cancer

INTRODUCTION

Squamous cell carcinoma of the head and neck comprise 2-3% of all cancers in the United States and account for 1% to 2% of all cancer deaths¹. Prognosis correlates strongly with stage at diagnosis. Survival for stage I disease exceeds 80%, however for patients with locally advanced disease at the time of diagnosis, specifically stage III and IV, survival drops to below 40%². Development of nodal metastasis reduces survival of a small primary tumor by approximately 50%. Involvement of even a single lymph node is associated with a marked decline in survival. Other high risk features include extracapsular extension of nodal disease and positive surgical margins³. The standard of care for high risk HNSCC includes post operative chemoradiotherapy usually with cisplatin for patients who have high risk features after resection⁴⁻⁵. This approach however, is not without significant toxicity. In an effort to devise a less toxic strategy, we set out investigate the use of weekly docetaxel with concurrent radiotherapy in patients with high-risk HNSCC. The primary end points of this phase one study were to determine the dose limiting toxicity (DLT) and MTD of weekly docetaxel administered concurrently with radiation in the adjuvant setting. We intended to expand this study to a phase II trial, using the MTD, with endpoints including an assessment of locoregional relapse, patterns of first relapse, disease-free survival and overall survival; however the study was terminated early due to slow accrual.

MATERIALS AND METHODS

Patients with histologically proven and completely resected squamous cell carcinoma of the oral cavity, oropharynx or larynx, with histologically involved regional lymph nodes and/or extra nodal disease and/or positive surgical margins were eligible to participate. Other inclusion criteria included: a Southwest Oncology Group performance status, (SWOG PS) of 0 or 1, age ≥ 18 years, absolute neutrophil count $\geq 1500/\text{mm}^3$, hemoglobin $>8.0\text{g/dL}$, platelet count $\geq 100,000/\text{dL}$, and adequate renal and liver function. Patients were required to register within six weeks of surgery, by signed and witnessed informed consent describing the investigational nature of this study. Patients who had prior chemotherapy or radiation therapy to the head and neck, evidence of distant metastasis, synchronous or concurrent head and neck primary tumors, peripheral neuropathy greater than grade 1, or other malignancies within the last five years were excluded. This study was approved by the institutional review boards of each participating institution and informed consent was obtained from each subject.

Treatment Plan

In the phase I portion of the study, a traditional dose escalation schema was planned, evaluating cohorts of six patients each, starting with docetaxel at a weekly dose of $20\text{mg}/\text{m}^2$ for six weeks, administered concurrently with radiation therapy in the postoperative setting. Dose limiting toxicity was defined as any grade 4 neutropenia lasting greater than three

days, grade 4 neutropenia with fever, grade 4 thrombocytopenia, grade 4 stomatitis, or any other grade 3 or 4 non-hematologic toxicity. Toxicities were graded according to NCI CTCAE v 3.0. Due to higher than expected DLT observed at the initial dose level, a dose de-escalation schema was designed such that the next cohort was to be treated with 15mg/m²/week of docetaxel concurrent with radiation therapy. Subsequent cohorts were to be treated at progressively lower doses of docetaxel, decreased by 5mg/m²/week until the MTD was reached, defined as the maximum dose level of docetaxel tolerated such that no more than two of six patients in the cohort experienced DLT. The phase II portion of the trial was then designed to use this MTD of weekly docetaxel in combination with daily radiation therapy in a total of 25 patients with high risk HNSCC.

A 25% dose reduction in subsequent doses of docetaxel occurred if patients experienced any one of the dose limiting toxicities described above, or grade 2 peripheral neuropathy, or liver dysfunction defined as total bilirubin, alkaline phosphatase, or AST/ALT > 5 institutional upper limit of normal.

For grade 4 toxicity, docetaxel was to be held for 7 days, and a 25% dose reduction was recommended for subsequent doses. No more than two dose reductions were allowed for any given patient. If a patient required a third dose reduction they were to be removed from the study treatment. Patients were also removed from study if they required greater than three weeks of delay in their treatment secondary to toxicity. All dose reductions were to remain permanent throughout the remainder of the planned concurrent therapy.

The radiation therapy consisted of 60 Gy in 30 fractions over six weeks. In all patients, radiation therapy was planned and delivered with 3-dimensional conformal radiation therapy technique. A minimum of 54 Gy was delivered to low risk sites (e.g. areas requiring radiation that were distant from the region that rendered patient high risk). A conedown boost of up to 6 Gy was delivered in 3 fractions over 3 days was allowed at the discretion of the treating radiation oncologist to the high-risk site(s) only. Radiotherapy was started as soon as adequate healing after surgery had been established, but no longer than 6 weeks after surgery. Daily dose reductions to 1.8 Gy were allowed if a treatment break due to toxicity became necessary.

Statistical Methods

Rules for accrual to the phase I portion of the trial are described above. The phase II portion of the trial was designed, as described, to use the MTD of weekly docetaxel in combination with daily radiation therapy in a total of 25 patients with high risk HNSCC. Because of slow accrual the study was closed early. Conclusions in the phase II portion are therefore not possible. Conclusions on efficacy of this combination were based on 20 evaluable patients. Our original statistical design was followed such that, if less than 3 patients developed locoregional recurrence at 2 years, we would conclude that the recurrence rate in this patient population is highly likely, with 95% confidence, to be less than 33%. If 3 to 7 patients developed locoregional recurrence at 2 years and if the toxicity/feasibility profile appeared acceptable, interest in this drug would be maintained such that further investigation would be considered. If 8 or more patients developed locoregional recurrence at 2 years, we would conclude that this recurrence rate is likely, with 95% confidence, to be greater than 23%

(that observed with cisplatin/RT) and could be as high as 33%. Based on these findings, we would conclude that further investigation of this therapy in this particular patient population would not be warranted.

Descriptive statistics were used to detail the characteristic of the study sample, toxicity profile and patterns of relapse. Disease-free and overall survival were estimated using Kaplan-Meier methods. Time was calculated from the date of study enrollment to the date of first recurrence or death for disease-free and overall survival, respectively. Patients with no event were censored at the last follow-up date with no recorded event.

RESULTS

Over a 3 year period twenty patients were enrolled onto this study. The characteristics of the entire study population are summarized in Table I. Testing for human papilloma virus was not performed. Five patients were enrolled onto the initial cohort, using a dose of docetaxel of 20mg/m²/week. A total of fifteen patients were enrolled onto the next dose de-escalation cohort and subsequent phase II portion of the trial. The median age was 60 years. Fourteen males and 6 females were enrolled. High risk feature included positive margins, lymph node involvement, and extracapsular extension. Table II characterizes the high risk feature and site of relapse in each study patient.

Phase I Safety and Toxicity

Grade 3 and 4 toxicities of the phase I portion of the trial are summarized in Table III. In the first cohort, four of the first five patients treated suffered grade 4 oral stomatitis at 20 mg/m²/week of docetaxel. Each patient received all planned doses of chemotherapy and radiation therapy. All toxicities resolved within 2 to 3 weeks. No patients were gastrostomy tube dependent for nutrition or hydration beyond 8 weeks of completion of therapy. Based on the high rate of grade 4 oral stomatitis, it was decided to dose de-escalate the docetaxel and treat subsequent patients at 15mg/m² per week.

The second cohort of 6 patients enrolled in the phase I portion of the trial experienced slightly less toxicity. Five of these six patients developed grade 3 oral stomatitis, which again resolved within 2 to 3 weeks of discontinuing treatment. Patient 7 developed grade 4 aspiration pneumonia with associated hypoxia requiring hospitalization and intravenous antibiotics, but this was not felt to be treatment related. This patient missed his last scheduled dose of docetaxel as a result but was discharged home after 2 days with his baseline supplemental oxygen therapy and a course of oral antibiotics. Two patients at this dose level experienced grade 3 skin toxicity, defined as dry desquamation in the radiation field, which resolved within 1 to 2 weeks of completion of therapy. Two patients required a dose reduction on the fourth dose. Gastrostomy tube dependence resolved within 6 weeks of completing treatment for all patients. This dose level was therefore determined to be the MTD.

Nine more patients were treated at the MTD, 15mg/m²/week docetaxel, as part of the planned phase II portion of the trial, before the study was closed due to poor accrual. Thirteen of all fifteen patients treated at the MTD, (86.7%; 95% CI 72.0 - 97.6), experienced

grade 3 stomatitis but no grade 4 stomatitis was observed. One patient had the last 2 doses held due to stomatitis. All patients enrolled completed all planned radiation therapy. All remaining patients enrolled had their gastrostomy tubes removed within 3-6 weeks of completion of therapy. No significant myelosuppression, febrile neutropenia, nausea or vomiting or peripheral neuropathy was observed. No treatment related deaths occurred.

Relapse Free survival, Overall Survival, and Pattern of Relapse

Survival and relapse data are based on all twenty patients enrolled onto the trial. Four of the initial five patients enrolled remain alive without relapse. With a median duration of follow up of 32 months, 9 patients have relapsed (table IV). Four patients relapsed locally, including 1 of 5 patients in the initial cohort, 1 relapsed locally and with distant metastases, 4 patients developed distant metastases alone. The probability of 1 year relapse free survival was 59.2% (95% CI 37-81). Two year relapse free survival probability was 52.6% (95% CI 30-76). The mean relapse free survival (RFS) time is 32 months. Kaplan Meier estimates of RFS are shown in Figure 1. The median RFS has not yet been met. One year overall survival probability is 94.4% (95% CI 84-100). Two year overall survival probability is 69.3% (95% CI 47-92) (Figure 2). The mean overall survival time is 41.6 months. The median overall survival has not yet been reached.

DISCUSSION

In 2004, Cooper et al, published the results of RTOG 9501, a large randomized trial demonstrating that adding concurrent cisplatin to postoperative radiotherapy in high risk patients with HNSCC yielded a reduction in local and regional recurrence, as well as improvement in disease free survival over that of standard postoperative radiotherapy alone⁴. A similarly designed European trial revealed similar results as well as an overall survival advantage to the concurrent therapy⁵. Based on these data, postoperative cisplatin administered every 21 days for 3 doses with concurrent radiotherapy became the standard of care in the United States for patients with high risk resected HNSCC.

Unfortunately, the benefit of postoperative concurrent chemoradiotherapy was not without significant toxicity. In RTOG 9501, grade III toxicity occurred in 77% of patients treated with concurrent radiation and cisplatin versus 34% of patients treated with radiation alone³. Most of the increase was due to mucositis, gastrointestinal, and hematologic toxicity. In an effort to obtain similar benefit but less toxicity, other agents warrant investigation in this setting.

Docetaxel has proven to be effective against HNSCC as an induction therapy and in the treatment of metastatic disease⁶⁻¹². There is more limited experience incorporating docetaxel in the adjuvant setting especially when combined with radiotherapy in the treatment of other malignancies¹³⁻¹⁵. A number of trials have shown docetaxel to have radiosensitizing effects and manageable toxicity when administered weekly¹⁶⁻¹⁸. In our pilot phase I/II trial we observed that docetaxel with concurrent radiotherapy is well tolerated with manageable toxicity when administered in the postoperative setting to patients with high risk HNSCC. Most of the toxicity that we observed was oral stomatitis; however there was no grade 4 stomatitis experienced at the 15mg/m²/week dose level. In the phase I

portion of the study we concluded that 15mg/m²/wk of docetaxel was the MTD when administered concurrently with radiotherapy. The phase II portion of this trial could not be completed as planned, but reviewing the toxicity of all 15 of the patients treated at the MTD, we concluded that toxicity was manageable and appears efficacious, although with a very limited patient sample. The degree of stomatitis seen in our study was within the same range of the much larger RTOG study suggesting that docetaxel with concurrent radiation is not any worse than cisplatin with radiation.

CONCLUSION

We conclude this dose and schedule of concurrent docetaxel and radiotherapy has acceptable toxicity and that preliminary efficacy data are promising, thus further investigation in a larger phase II setting is warranted.

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Figure 1.
Kaplan Meier estimate of relapse free survival.

Figure 2.
Kaplan Meier estimates of overall survival.

Table I

Baseline demographics and disease characteristics of all study patients (N=20)

<i>Age, years</i>	
Median	60
Range	26-83
<i>Sex</i>	
M	14
F	6
<i>SWOG PS</i>	
0	12
1	8
<i>Primary Tumor Location</i>	
Oral cavity	8
Oropharynx	7
Hypopharynx	2
Larynx	2
Unknown	1
<i>Stage</i>	
II	1
III	3
IVa	15
IVb	1
<i># with Positive Nodes</i>	18
<i>Extracapsular spread</i>	17
<i>Positive Margins</i>	11

SWOG PS – Southwest Oncology Group performance status

Table II

Individual Patient Characteristics

Patient #	Positive nodes	Extracapsular	Margin	Site of relapse
1	1/32	Yes	+	-
2	1/45	Yes	-	locoregional
3	1/66	Yes	+	-
4	3/30	No	+	-
5	2/19	Yes	-	-
6	4/22	No	+	locoregional
7	--	Yes	+	distant
8	1/22	Yes	-	locoregional
9	7/21	Yes	-	distant
10	1/24	Yes	-	-
11	4/34	Yes	-	Locoregional and distant
12	2/10	Yes	-	distant
13	X	X	+	-
14	8/25	Yes	-	-
15	2/46	Yes	-	-
16	19/21	Yes	+	distant
17	6/55	Yes	+	-
18	8/23	Yes	+	-
19	3/27	Yes	+	distant
20	1/23	Yes	+	-

-- - patient 7 had matted lymph nodes dissected, number was not discernible

X – patient 13 had stage II disease and no neck dissection

Table III

Phase I grade 3/4 toxicity

Pt #	Age	Primary site	T	N	Stage	Dose (mg/m)	# doses received	Toxicity	Duration of toxicity
1	49	Tonsil	1	2a	IVa	20	6	Grade 3 stomatitis	2 weeks
2	26	Tongue	2	1	III	20	6	Grade 4 stomatitis	3 weeks
3	47	Larynx	2	2b	IVa	20	7	Grade 4 stomatitis	3 weeks
4	64	Soft palate	3	2c	IVa	20	6	Grade 4 stomatitis Grade 4 skin reaction	Stomatitis –2 weeks skin – 2 weeks
5	43	Tonsil	2	2b	IVa	20	6	Grade 4 stomatitis	3 weeks
6	68	Tongue	1	2b	IVa	15	6	Grade 3 stomatitis Grade 3 skin reaction	Stomatitis –3 weeks skin – 2 weeks
7	67	Base of tongue	3	2c	IVa	15	5	Grade 3 stomatitis Grade 4 aspiration pneumonia *	Stomatitis –2 weeks pneumonia –2 days
8	65	Larynx	3	2b	IVa	15	6	Grade 3 stomatitis	2 weeks
9	61	Tongue	3	2b	IVa	15	6	(Grade 2 transaminitis)	5 days
10	50	Oropharynx	1	1	III	15	6	Grade 3 stomatitis Grade 3 skin reaction	Stomatitis –2 weeks skin –1 week
11	58	Oral cavity	4a	2b	IVa	15	6	Grade 3 stomatitis	2 weeks

Grade 3 stomatitis defined as dysphagia / odynophagia and/or painful erythema, edema or ulcers and cannot eat requiring intravenous hydration.

Grade 4 stomatitis defined as dysphagia / odynophagia and/or painful erythema, edema or ulcers requiring enteral or parenteral nutritional support.

Grade 3 skin reaction defined as radiation induced confluent dry desquamation other than skin folds.

Grade 4 skin reaction defined as radiation induced wet desquamation.

Grade 2 transaminitis defined as increase in transaminases 2.6 – 5.0x upper limit of normal.

* Not felt to be treatment related.

Table IV

Relapse free survival by site of relapse.

	Relapse Free Survival (n = 20)		
Site of Relapse	n	%	Months (mean)
No Relapse	11	55	32
Local	4	20	8
Local & Distant	1	5	8
Distant	4	20	13