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ORIGINAL ARTICLE

Robert I. Haddad · David A. Van Echo

Phase II study of docetaxel and topotecan combination chemotherapy in patients with advanced head and neck cancer

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Abstract *Purpose*: To evaluate the activity of combination chemotherapy with docetaxel and topotecan in patients with advanced head and neck cancer. *Methods*: Docetaxel was given at 60 mg/m^2 as a 60-min intravenous infusion on day 1. Topotecan at 0.75 mg/m^2 per day was infused over 30 min on days 1, 2 and 3. Cycles were repeated every 21 days. *Results*: There were no responses (CR + PR) seen in the ten patients. Only one patient had stable disease and was able to receive six cycles of chemotherapy. Median survival was 81 days (range 67–161 days). *Conclusions*: The combination of docetaxel and topotecan at these doses and in this schedule is not recommended for patients with locally advanced, recurrent or metastatic squamous cell carcinoma of the head and neck. Other investigational approaches are needed.

Keywords Head and neck cancer · Docetaxel · Topotecan

Introduction

Squamous cell carcinomas of the head and neck (SCCHN) are newly diagnosed in approximately 40,000 patients each year in the US [7]. More than 70% of the patients present with locoregionally advanced disease (stage III and IV). Despite aggressive local therapy with surgery, and radiotherapy with or without chemotherapy, fewer than 30% of these patients remain free of disease at 3 years [19]. Locoregional disease recurs often and metastatic disease develops in approximately 30% of patients. Chemotherapy has been extensively studied in patients who are no longer deemed curable and for whom definitive local therapy has failed. Commonly used single agents including cisplatin, methotrexate, bleomycin, and 5-fluorouracil have shown response rates of approximately 15% to 20% and the most frequently used regimen is the combination of cisplatin and 5-fluorouracil which results in a mean response rate of 32% and a median survival of approximately 6 months [3].

Docetaxel and topotecan have shown activity in patients with recurrent head and neck carcinoma. We have recently reported on the pharmacokinetics and pharmacodynamics of this combination when given in two different sequences of administration [17, 20]. We determined that the administration of docetaxel on day 4 results in an approximately 50% decrease in its clearance and is associated with increased neutropenia. We recommended that docetaxel and topotecan be started on day 1. Based on these results, we initiated a phase II trial of the combination in patients with recurrent or metastatic SCCHN. This was an empirical regimen. The rationale for performing this study was based on the notion that docetaxel and topotecan have different and nonoverlapping mechanisms of action. Some, but not all, in vitro evidence suggests that taxanes and topotecan may have additive or even synergistic activity [2, 10].

Patients and methods

Patient selection

Eligibility criteria for study entry included the following: histologic confirmation of head and neck cancer; locally advanced, metastatic or recurrent disease not curable by standard therapy; ≥2 weeks since prior radiation and or surgery; ≥4 weeks since prior chemotherapy; WHO performance status score of 0, 1 or 2; and an adequate baseline organ function defined as a granulocyte count of ≥1500/mm^3, platelet count ≥100,000/mm^3, and liver and renal function within normal limits. All patients gave written informed consent, and the study was approved by the Cancer Research Committee (CRC) and the Institutional Review Board (IRB) at the University of Maryland.

R. I. Haddad (✉)
Dana Farber Cancer Institute, SW430G,
Harvard Medical School,
44 Binney Street, Boston, MA 02115, USA
E-mail: Robert_haddad@dfci.harvard.edu
Tel.: +1-617-6325530
Fax: +1-617-6324448

D. A. Van Echo
Greenebaum Cancer Center, University of Maryland,
Baltimore, MD 21201, USA

Treatment plan

Docetaxel was given at 60 mg/m^2 as a 60-min intravenous infusion on day 1. Topotecan at 0.75 mg/m^2 per day was infused over 30 min on days 1, 2 and 3. Granulocyte colony stimulating factor (G-CSF) was given on days 4, 5, 6, 7 and 8. Cycles were repeated every 21 days. The doses of docetaxel and topotecan were adjusted to the outcomes of blood counts and blood chemistry immediately before the infusions, and toxicity was recorded during treatment. A 25% decrease in both drugs was mandated for febrile neutropenia, grade 4 neutropenia lasting more than 7 days and for grade 4 thrombocytopenia. Patients who developed grade 3 neuropathy were taken off study. Grade 2 neuropathy also mandated a 25% dose reduction.

Patient evaluation

A complete history, physical examination, complete blood cell count with differential, serum chemistry, EKG, and a chest radiograph were obtained at baseline. Tumor measurements were recorded prior to starting treatment with physical examination, Computed tomography (CT) or magnetic resonance imaging (MRI). A complete response (CR) was defined as the complete disappearance of all tumors for a minimum of 4 weeks. Partial response (PR) was defined as a 50% or greater decrease in the sum of the products of two perpendicular diameters of measured lesions for a minimum of 4 weeks. Stable disease (SD) was defined as any response less than PR or tumor progression less than 25%. Progression was an increase of at least 25% in the size of any measurable lesion. Tumor measurements were obtained prior to every other course of treatment.

Assessment of feasibility and sample size

In order to limit the number of patients treated in the event that the regimen proved to be ineffective, a three-stage design was used for patient accrual. It was assumed that the new combination therapy would be of no further interest in patients with head and neck cancer if the true response rate was less than 10%, but would be of interest in these patients if the rate was 30% or more. For the purpose of early stopping, "response" refers to CR + PR.

A three-stage test procedure was used [1]. In stage 1, ten patients were entered into the study. If no responses were seen, accrual would be stopped and the combination would not be recommended for this indication. If at least one response was seen, an additional 9 patients would be accrued in stage 2 to a total of 19. If no more than two responses were seen, the study would be stopped. If three or more responses were seen, an additional 7 patients would be accrued in stage 3 to a total of 26. If five or more responses were seen in the final 26 patients, the combination therapy would be considered promising unless other considerations indicated otherwise.

This procedure tested the null hypothesis that the true response rate was 10% or less versus the alternate hypothesis that the true response rate was greater than 30%. The significance level of the test was 10% with a power of 90%.

Results

Patients

From October 1998 to June 2000, ten patients were enrolled onto the study. The characteristics of the ten patients (listed in Table 1) included a median age of 60.5 years, squamous cell carcinoma as a predominant histology and advanced stage disease in all patients. All patients had previously received radiation therapy either in an adjuvant form or as part of a chemoradiation approach. Seven patients had had previous surgery and seven had had previous chemotherapy that included cisplatin, 5-fluorouracil, carboplatin and paclitaxel.

Table 1 Patient characteristics at baseline ($n = 10$)

Age (years)	
Median	60.5
Range	48–84
Sex	
Male	8
Female	2
Performance status	
1	6
2	4
Primary disease site	
Oropharynx	5
Nasopharynx	1
Larynx	2
Paranasal sinuses	2
Prior therapy	
Surgery	7
Radiotherapy	10
Chemotherapy	7
Disease status at study entry	
Local-regional	8
Local-regional + metastasis	1
Metastatic disease only	1
Number of cycles delivered	
One	2
Two	6
Four	1
Six	1

Table 2 Common toxic side effects in ten patients

	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	0	2	1	0
Anemia	0	3	4	0
Thrombocytopenia	3	0	0	0
Neutropenic fever	–	–	1	0
Mucositis	0	0	1	0
Diarrhea	4	1	0	0
Hypersensitivity	0	0	0	0
Nausea/vomiting	1	2	0	0
Neuropathy	0	0	0	0
Anorexia	1	4	0	0
Fatigue	1	2	0	0

Toxicity

Toxic effects are listed in Table 2. Overall, 24 courses of chemotherapy were administered to the ten patients (median 2 per patient). The treatment was well tolerated with no grade 4 toxicity encountered. Only one patient had neutropenic fever and the dose had to be reduced in this patient. His blood cultures were positive for streptococcus and he was treated with intravenous antibiotics. Four patients had grade 3 anemia that required blood transfusion. Thrombocytopenia was limited to grade 1.

Non-hematologic toxicities were limited and never reached grade 4. They included grade 1/2 nausea/vomiting, diarrhea, anorexia and fatigue. One patient whose tumor invaded the brain stopped his seizure medications and had to be admitted for status epilepticus that resolved with appropriate antiseizure medications. His seizures never recurred subsequently. One patient had a cardiac arrest and died at home 21 days after receiving her first cycle of chemotherapy. An autopsy could not be obtained from the family.

Response assessment

There were no responses (CR + PR) seen in the ten patients. Only one patient had stable disease and was able to receive six cycles of chemotherapy; his follow-up scans after the sixth cycle showed PD. Median survival was 81 days (range 67–161 days). Based on the three-stage design described above, the study was closed to accrual and the regimen deemed to be ineffective in this patient population.

Discussion

The taxanes, paclitaxel and docetaxel, have been used extensively in oncology and have shown inherent activity against SCCHN [5]. Between the two agents, docetaxel has the advantage of a longer intracellular half-life leading to higher intracellular levels in the steady state. In addition, in vitro, docetaxel is 100 times more potent than paclitaxel with respect to bcl-2 phosphorylation and inactivation, which is another mechanism by which taxanes may act in addition to tubulin stabilization [8]. Docetaxel undergoes primarily hepatic metabolism via cytochrome P450 (CYP) 3A4 [11]. Couteau et al. have recently reported [4] that docetaxel is active as a single agent given every 3 weeks in patients with metastatic SCCHN. They reported an overall response rate of 20.8% with a median duration of 11 weeks. Several authors have evaluated docetaxel in combination chemotherapy regimens in the treatment of advanced SCCHN. In a multicenter EORTC Early Clinical Studies Group phase II trial, docetaxel was administered as an infusion at 100 mg/m^2 followed 3 h later by cisplatin 75 mg/m^2 as a 3-h infusion [14]. Cycles were repeated every 3 weeks; 31 patients were evaluable for disease response. An overall response rate of 54% was reported. Docetaxel combined with either cisplatin, 5-fluorouracil or both have been evaluated in several other studies. Tubiana-Mathieu et al. [18] evaluated docetaxel 75 mg/m^2 on day 1 followed by 5 days continuous-infusion 5-fluorouracil 1000 mg/m^2 and reported a response rate of 27%. The combination of the three drugs in 48 locally advanced, therapy-naive patients yielded an impressive 71% overall response rate [15].

Topotecan, a topoisomerase I inhibitor, is a camptothecin analog that undergoes primarily renal elimination and may also undergo clinically significant oxidative metabolism via CYP [6]. It has demonstrated a high degree of activity in a broad spectrum of tumor models that are relatively refractory to a wide variety of anticancer drugs, including B16 melanoma, colon carcinomas 38 and 51, HT 29 colon cancer and multidrug-resistant P388 leukemia [9]. The Southwest Oncology Group (SWOG) was the first to report the use of topotecan in head and neck cancer patients [16]. Among 29 patients treated at 1.5 mg/m^2 per day for five consecutive days, no responses were seen. Robert et al. [13] treated 26 patients with the same dose every 3 weeks. The overall response rate was 14%. Six additional patients experienced stabilization of their tumor parameters. The median survival for all patients entered was 4 months.

The clinically significant oxidative metabolism of docetaxel and topotecan via CYP suggests that their coadministration might produce clinically significant alterations in the pharmacokinetics and clinical effects of each agent. Thus as part of a phase I trial, we recently reported on the pharmacokinetics and pharmacodynamics of docetaxel and topotecan when administered in combination in two schedules that altered their sequence of administration. Administration of topotecan for 3 days before the combination of topotecan and docetaxel resulted in an approximately 50% decrease in clearance and increased the severity of neutropenia. We recommended that docetaxel be given on day 1 along with topotecan [20].

Based on these results we initiated this phase II study. We used the three-stage design described by Chen [1] in order to limit the number of patients exposed to this regimen in case it turned out to be ineffective. Indeed, among the ten patients entered in the first stage of the study, no responses were seen. Only one patient had stable disease. The treatment was overall well tolerated with no grade 4 toxicity or treatment-related deaths. Among these ten patients, four had a PS of 2; these patients are frequently excluded from participating in clinical trials. Moreover, seven patients had previously received palliative chemotherapy. All patients had previously received radiation therapy and the majority had previously undergone surgery. These patients are known to be quite resistant to chemotherapy with a very poor prognosis and an overall survival of approximately 3–6 months. It is unlikely that the sequence of administration affected the response rate given our phase I results. It is more likely that these poor results were due to the fact that this was a group of patients with highly resistant tumors.

We conclude that the combination of docetaxel and topotecan, given at these doses and in this schedule, cannot be recommended for patients with locally advanced, recurrent or metastatic SCCHN. Other approaches to the treatment of these patients need to be investigated. Indeed the advent of several novel potentially noncytotoxic agents such as the signal transduction inhibitors, growth factor receptor inhibitors, gene

therapy and antiangiogenic agents given with or without chemotherapy and/or radiation has generated much excitement over a novel treatment approach for SCCHN [12]. Clinical trials integrating these novel agents with and without chemotherapy are urgently needed. Patient participation in these trials must be encouraged to determine the optimal treatment.

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