

Phase II Trial of Irinotecan Plus Cisplatin in Patients With Recurrent or Metastatic Squamous Carcinoma of the Head and Neck

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BACKGROUND. Patients with recurrent or metastatic HNC have a poor response and survival with currently available chemotherapy agents. Thus, new agents are needed. The authors report the results of a phase II trial of irinotecan and cisplatin in patients with metastatic or recurrent HNC.

METHODS. Patients were treated with irinotecan 65 mg/m² IV over 90 minutes and cisplatin 30 mg/m² were administered intravenously weekly for four weeks, followed by a two week rest. However, after 17 patients were treated with weekly irinotecan at a dose of 65 mg/m², toxicity analysis demonstrated the poor tolerance of that dose in this patient population. Thus, the protocol was amended, and irinotecan was dose reduced to a starting dose of 50 mg/m². Twenty-three additional patients were treated with this dose.

RESULTS. Forty patients were enrolled on study between February 2002 and April 2006, 17 patients at the first dose level and 23 patients at the amended dose level. Overall, 12 of 17 patients (71%) treated with irinotecan 65 mg/m² experienced clinically significant grade 3 or 4 toxicity. Twelve patients required dose reductions. Toxicity was reduced but 17% of patients still experienced grade 3 or 4 toxicity on the lower irinotecan dose. The response rate was 35% for patients treated at irinotecan 65 mg/m² and 22% for patients treated at 50 mg/m². No complete responses were noted.

CONCLUSIONS. The combination of irinotecan and cisplatin is efficacious in a poor prognosis group of patients but toxicity is substantial. *Cancer* 2008; 113:186–92. © 2008 American Cancer Society.

KEYWORDS: concurrent chemoradiotherapy, cisplatin, irinotecan, metastatic-refractory, squamous cell carcinoma of the head and neck.

Approximately 40,000 new cases of squamous cell carcinoma of the head and neck (HNC) are diagnosed each year in the United States. Most patients present with locally advanced but nonmetastatic disease. The increased use of concurrent chemoradiotherapy has resulted in marked improvement in local/regional control and survival. For patients who experience disease recurrence, a few may be cured with salvage surgery or reirradiation. For the patients for whom local therapy is not considered feasible, systemic therapy is the standard treatment option. Even with treatment, their prognosis is poor, and the median survival is less than 1 year.¹

Numerous single agents have demonstrated activity in the recurrent or metastatic setting with response rates ranging from 15% to 35%. However, responses usually are of duration (2–4 months). The use of combination regimens results in improved response rates but no significant improvement in overall survival compared with single

agents.²⁻⁵ New, active agents or combinations of agents that may impact on survival must be identified for the treatment of recurrent or metastatic disease.

Investigators at Vanderbilt University undertook a Phase II trial to evaluate the efficacy and tolerability of irinotecan in patients with recurrent, refractory, or metastatic HNC. In a chemo-naïve patient population, the response rate to single agent irinotecan was 20% at a dose of 125 mg/m² given weekly for 4 weeks followed by a 2-week rest. However, this regimen proved toxic, and the dose subsequently was reduced to 75 mg/m² irinotecan given on Days 1 and 8 of a 21-day cycle. The response rate was 13% using this revised dose and schedule.^{6,7}

Cisplatin remains one of the most active agents for the treatment of HNC, and it is used in the primary treatment of locally advanced tumors as well as in the metastatic or recurrent setting. In vitro and xenograft studies demonstrate a synergistic anticancer effect of cisplatin and irinotecan, possibly related to the down-regulation of topoisomerase I activity by cisplatin. The combination of cisplatin and irinotecan has been evaluated extensively in other tumor types using several differing doses and schedules and has proven to be an active combination.⁸⁻¹³ The chosen dose and schedule of cisplatin in combination with irinotecan were based on Phase I data from Saltz et al. and from several Phase II studies of non-small cell lung cancer that confirmed the tolerability of cisplatin 30 mg/m² and irinotecan 65 mg/m² on a weekly schedule for 4 of 6 weeks for each treatment cycle.^{11,14,15} On the basis of the promising preclinical and clinical data, we designed a Phase II trial to evaluate the efficacy and tolerability of irinotecan in combination with cisplatin.

MATERIALS AND METHODS

Patient Eligibility and Baseline Assessment

Patients were aged ≥ 18 years and had histologically proven HNC that was considered incurable with surgery or radiation therapy. Measurable disease was required, and patients whose measurable disease was within the prior radiation port must have had a biopsy-proven recurrence at least 8 weeks after the completion of radiotherapy. Patients were excluded if they had received prior chemotherapy for metastatic or recurrent disease. Patients who received chemotherapy as part of primary combined-modality therapy at least 6 months before study entry were considered eligible. Additional inclusion criteria were as follows: an Eastern Cooperative Oncology Group performance status from 0 to 2, adequate hematologic function (granulocytes $\geq 1500/\text{mm}^3$ and platelets $\geq 100,000/\text{mm}^3$), adequate hepatic function (aspartate amino-

transferase < 3 times the upper limit of normal, serum bilirubin < 1.5 mg/dL), adequate renal function (serum creatinine < 2 mg/dL or a creatinine clearance of ≥ 50 mL/minute). All patients provided written informed consent for this study, which was approved by the Institutional Review Board of the Vanderbilt University School of Medicine.

Pretreatment evaluations included history and physical examination, tumor measurements, chest x-ray, and routine blood work. Scans or x-rays to document measurable or evaluable disease were completed within 4 weeks before treatment. All chemistry evaluations were completed within 2 weeks before treatment, whereas complete blood counts with differential and platelet counts as well as potassium, blood urea nitrogen, and creatinine levels were determined within 24 hours of treatment.

Patients received irinotecan 65 mg/m² intravenously 90 minutes and cisplatin 30 mg/m² administered intravenously weekly for 4 weeks followed by a 2-week rest. Patients were treated for a maximum of 6 cycles. Patients received standard antiemetic agents for premedication of cisplatin, including dexamethasone plus a 5-hydroxytryptamine 3 receptor antagonist. Routine use of colony-stimulating factor (CSF) (granulocyte-CSF or granulocyte-macrophage-CSF) was not recommended. Patients were instructed to take loperamide at the earliest signs of diarrhea and/or abdominal cramping that occurred > 8 hours after they received irinotecan. Atropine was used for the first signs of cholinergic syndrome that occurred during or within 1 hour after patients received irinotecan.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Dose modifications were made for grade 3 and 4 toxicities. Patients received a 1-dose-level reduction to irinotecan 50 mg/m² and cisplatin 20 mg/m² given on the same schedule if the absolute neutrophil count was $< 1000/\text{mm}^3$ and the platelet count was $< 75,000/\text{mm}^3$ within 24 hours of treatment. Treatment was held for grade 3 or 4 diarrhea, nausea, or vomiting that occurred despite appropriate supportive medications. Treatment was resumed when the toxicity resolved to a grade ≤ 1 but was restarted at a 1-dose-level reduction. Patients were removed from study for toxicity that did not resolve to grade ≤ 1 within 3 weeks, for toxicity that required > 2 dose reductions, and for > 2 missed treatments in a single cycle.

Tumor measurements were obtained every 3 months for the first 2 years and every 6 months thereafter. A complete response was defined as the complete disappearance of all clinically detectable, malignant disease for at least 4 consecutive weeks. A partial response was defined as a decrease $\geq 50\%$ in

the tumor area or a decrease of 50% in the sum of the products of the greatest perpendicular dimensions of multiple lesions without an increase >25% in the size of any area of known malignant disease and without the appearance of new areas of malignant disease. Stable disease was defined as no significant change in measurable disease for at least 4 weeks, as defined by a decrease <50% in tumor area or an increase of malignant disease <25% at any site without the development of new sites of disease. New lesions or an increase >25% in tumor volume indicated disease progression. For lesions that measured <2 cm², progression was defined as the appearance of new malignant lesions or an increase ≥50% in the area of malignant disease.

Statistical Considerations

This trial was a single-institution, open-labeled, single-arm, Phase II investigation. A 2-stage accrual design, as described by Simon was used.¹⁶ If there was evidence that the true underlying overall response rate (complete and partial responses) was ≥30%, then consideration would be given for further testing of irinotecan and cisplatin. Planned accrual of this first stage was 24 assessable patients. An early stopping rule was used so that, if <5 responses were observed in the first 24 patients, then the trial would be terminated with the conclusion that there was little evidence to suggest that the overall response rate would reach 30%. However, if ≥5 responses were observed in the first 24 patients, then the study would continue to accrue a total of 54 patients, and the combination would be considered interesting if at least 13 of 54 patients demonstrated a response. This dosing provided an 80% statistical power to detect a difference of 15% with a significance level of <.05 (Type 1 error). The trial was to accrue a maximum of 54 patients within a period of no >4 years.

The primary endpoint was the response rate. Onset of response was defined as the time from the date of initial treatment until the first objective documentation of disease progression. Duration of response was defined as the time from the first objective documentation of response to the first objective documentation of disease progression. The time to tumor progression was defined as time from the date of initial treatment to the first objective documentation of disease progression. Response rates were reported with the 2-sided 95% confidence intervals for the response rate on the basis of the multi-stage test method.

Survival and response analyses were performed on all treated patients. Survival was estimated by using the Kaplan-Meier method. In addition, for life-

TABLE 1
Patient Characteristics

Characteristic	No. of patients (N = 40)
Median age (range), y	58 (33-79)
Sex	
Men	33
Women	7
Performance status	
0	3
1	27
2	10
Primary disease	
Oral cavity	4
Oropharynx	16
YHypopharynx	2
Larynx	10
Nasal septum	1
Nasopharynx	1
Unknown	6

time data analysis, the possible risk factors were compared for survival with Kaplan-Meier estimates and log-rank tests. A proportional hazards model was used for adjusted tests of significance and estimates of odds ratios.

However, after 17 patients were treated at the 65 mg/m² irinotecan dose, toxicity analyses demonstrated the poor tolerability of that dose in this patient population. Thus, the protocol was amended, and the irinotecan dose was reduced to a starting dose of 50 mg/m². Because the original dose level demonstrated a significant response rate, a decision was made to enroll 23 patients at the second dose level to assess efficacy and toxicity. If toxicity was reduced substantially and efficacy was maintained, then accrual would continue to 54 patients for the second dose level.

RESULTS

Forty patients were enrolled on the study between February 2002 and April 2006, including 17 patients at the first dose level and 23 patients at the second dose level. Most patients were men, and the median age was 58 years. The patient characteristics are listed in Table 1. Forty patients were evaluable for toxicity, and 32 patients were evaluable for response. The reasons that patients were not evaluable for response included 7 patients who did not receive at least 1 full cycle of therapy apiece and 1 patient who had incomplete records. In total, 40 chemotherapy cycles were delivered, including 17 cycles at a starting dose of irinotecan 65 mg/m² and 23 cycles at a starting dose of irinotecan 50 mg/m². Each patient received an average of 2.15 cycles of therapy.

TABLE 2
Common Grade 3 or 4 Toxicities

Dose level (Irinotecan mg/m ² /Cisplatin mg/m ²)	No. of patients
65/30	17
50/30	23
Toxicity	
Neutropenia	
65/30	9
50/30	6
Nausea/vomiting	
65/30	6
50/30	2
Diarrhea	
65/30	3
50/30	3
Fatigue	
65/30	3
50/30	4

Toxicity

Common grade 3 and 4 toxicities are listed in Table 2. Six of 17 patients experienced grade 3 or 4 neutropenia for a rate of 35%. Eight of 17 patients (47%) who were treated at this dose experienced grade 3 or 4 gastrointestinal toxicity, which manifested as nausea, vomiting, or diarrhea. Overall, 12 of 17 patients (71%) who received irinotecan 65 mg/m² experienced clinically significant grade 3 or 4 toxicity. Twelve patients required dose reductions.

Twenty-three patients were enrolled at the second dose level. Although toxicity was diminished, it remained substantial. Five of 23 patients (22%) demonstrated grade 3 or 4 neutropenia, and 4 of 23 patients (17%) demonstrated grade 3 or 4 gastrointestinal toxicity. Seven patients required a dose reduction.

Response

Six of 17 patients (35%) who received irinotecan 65 mg/m² demonstrated a partial response to treatment. Five of 23 patients (22%) who received irinotecan 50 mg/m² demonstrated a partial response to treatment. No complete responses were noted in either group. Eight of 11 patients who responded to therapy had received prior chemotherapy as part of first-line, curative treatment. Six of 32 patients demonstrated stable disease (18%) as their best response. Fifteen patients demonstrated progressive disease as their best response. For all patients on study, the average progression-free survival was 2.3 months, and the median progression-free survival was 1.6 months. The average overall survival was 7.2 months, and the median overall survival was 6.3 months. Five patients remain alive with a range of survival from 378 days to 1228 days. Four of those patients received irinote-

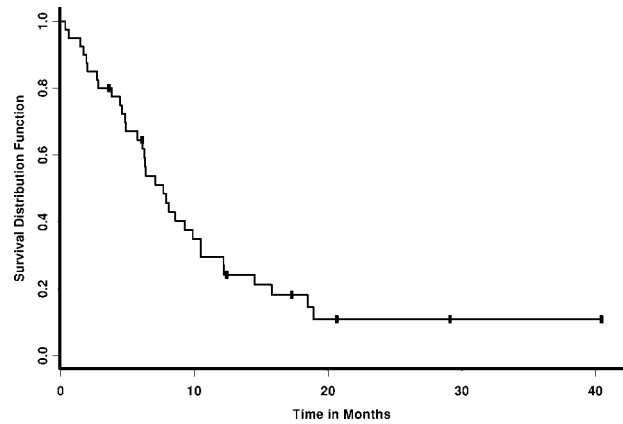


FIGURE 1. Overall survival.

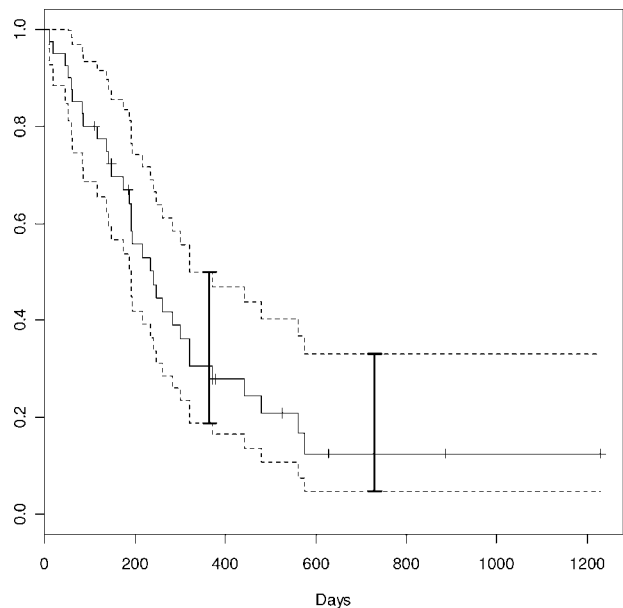


FIGURE 2. Kaplan-Meier survival.

can 50 mg/m², and 1 patient received irinotecan 65 mg/m². The 1- and 2-year survival rates were 50% and 37%, respectively (see Figs. 1, 2). No pretreatment or treatment characteristics were correlated significantly with response or survival. Given the substantial toxicity of the treatment regimen and the modest efficacy at the lower dose level, the study was closed.

DISCUSSION

In this article, we report the results from a Phase II trial that explored the efficacy and toxicity of irinote-

can and cisplatin in patients with metastatic and recurrent HNC. The combination resulted in an overall response rate of 35% at the 65 mg/m² irinotecan dose level and 22% at the 50 mg/m² irinotecan dose level. The median survival and progression-free survival for this combination of agents was not strikingly different from historic controls. However, the combination was associated with significant hematologic and gastrointestinal toxicity. Greater than 70% of patients who were treated at the original dose level experienced grade 3 and 4 toxicity. At the 50 mg/m² irinotecan dose level, the toxicity was diminished but remained substantial. Although the combination had reasonable efficacy, the high levels of toxicity argue against its routine use as first-line therapy for metastatic or recurrent HNC. However, at the time this report was written, 5 patients remained alive, and 2 of those patients had survived for approximately 3 years. Whether this is an effect of the study regimen, subsequent therapy, or underlying disease biology is unknown.

In our previous trial, we demonstrated that single-agent irinotecan was effective in both chemonaive and previously treated HNC.¹⁷ However, the toxicity is significant in the head and neck population whether it is used as a single-agent or combined with another cytotoxic chemotherapy. The reason for this is unclear, because irinotecan was tolerated well in a multiagent regimen for recurrent/metastatic colon cancer and because a Phase I trial by Saltz et al. demonstrated good tolerability of this regimen. One possible explanation may be that patients with HNC cancers frequently have a history of tobacco and alcohol use and have multiple comorbidities that may contribute to decreased tolerance of therapy in general. Moreover, most patients with recurrent or metastatic disease have received aggressive therapy for primary disease and may have diminished reserve. Although the Phase I study by Saltz et al. and the Phase II study by Jagasia et al. enrolled patients with the equivalent of a performance status of 2, toxicities were not evaluated in relation to performance status. Our study also did not perform this analysis. In hindsight, such an analysis may have been better for identifying a subgroup of patients with improved tolerance of this regimen. Moreover, the current study was carried out at both the Vanderbilt Ingram Cancer Center and in community oncology clinics in the Vanderbilt Ingram Associated Network. One observation from this trial may be that, in the HNC population, this regimen requires very close clinical monitoring, early recognition of toxicities and toxicity syndromes, and aggressive therapeutic intervention. Therefore, the regimen may

be impractical in a community setting. It also may be hypothesized that the inferior tolerability of this regimen, compared with the same regimen in other cancer populations, stems from the production of proinflammatory cytokines by the HNC tumors. Overexpression of nuclear factor (NF)- κ B leads to cytokine expression on HNC tumors.^{18,19} Proinflammatory cytokines are elevated in the blood of patients with HNC and may serve as a biomarker for recurrence and prognosis.²⁰ Cytokines are associated with multiple symptoms of advanced cancer and its treatment, perhaps leading to a lower threshold for develop toxicities in an already cytokine-enriched milieu.²¹ In addition, cytokines may effect drug metabolism. Cytokines like interleukin-6, tumor necrosis factor, interleukin-1, and interferon lead to a decrease in liver cytochrome P450 in tumor-bearing animals. In addition, an inverse correlation between inflammation and metabolism has been demonstrated in metabolism and cytochrome P3A4 activity in cancer patients.²² Thus, drug exposure may differ between cancer patient populations.

The current study has several limitations. First, the dose was changed after 17 patients were enrolled because of excessive toxicity. Second, the study was closed after an additional 23 patients were enrolled on the adjusted dose schedule. Thus, the current study is subject to both Type 1 error and Type 2 error. Several factors contributed to the decision to close the trial early, including excessive toxicity at the adjusted dose and slowing accrual because of interest in less toxic, targeted agents. Despite the limitations, the results do confirm the activity of the regimen, although the toxicity makes it unsuitable for the general head and neck population.

Further development of irinotecan in this population will require 1 of 2 things: identification of patients who are likely to have significant toxicity or the identification of less toxic combinations. The uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) polymorphism in irinotecan metabolism has been associated with drug-related toxicity. Laboratory testing for high-risk polymorphisms currently is available and may allow clinicians to prospectively determine which patients will have the best risk/benefit ratio with the use of this drug either alone or in combination with other agents.²³⁻²⁵ In addition, the combination of irinotecan with targeted agents remains an attractive combination because of the relatively favorable toxicity profile of these agents.

Cetuximab, a recombinant human/mouse chimeric monoclonal antibody, is one of the most promising targeted agents for the treatment of advanced HNC. Cetuximab is the first agent to demonstrate a

survival advantage for patients with refractory or metastatic HNC.²⁶ As a single agent, cetuximab monotherapy has an objective response rate of 13% and a median survival of 5.9 months in a platinum refractory group of patients.²⁷ Both preclinical and clinical data suggest that the addition of cetuximab to irinotecan can overcome cellular resistance to irinotecan. This resistance may be related in part to the overexpression of NF- κ B; in HNC.²⁸ Clinically, the combination of cetuximab and irinotecan demonstrates encouraging results in colorectal cancer and should be evaluated in metastatic/refractory HNC.²⁸⁻³¹

In summary, the combination of cisplatin and irinotecan has some efficacy in patients with recurrent or metastatic HNC. However, the high levels of toxicity argue against its routine use as first-line therapy for metastatic or recurrent HNC. In the future, trials of irinotecan in HNC should take away several points from this investigation: 1) Appropriate patient selection should be considered carefully, and 2) a priori identification of patients at risk for toxicity secondary to UGT1A1 polymorphisms or use of irinotecan in combination with targeted agents may provide for a better toxicity/benefit ratio.

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