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Docetaxel and irinotecan in recurrent or metastatic head and neck cancer: a phase II trial of the Eastern Cooperative Oncology Group

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Abstract

Background—Docetaxel and irinotecan have single-agent antitumor activity in squamous cell carcinoma of the head and neck (SCCHN). We sought to evaluate their combination in the treatment of patients with recurrent or metastatic SCCHN.

Methods—Eligibility criteria included recurrent or metastatic SCCHN with measurable disease, good performance status, and adequate laboratory parameters. Patients received docetaxel 35 mg/m^2 and irinotecan 60 mg/m^2, intravenously, on days 1 and 8, every 21 days, until disease progression. We assessed UGT1A1 genotype, vascular endothelial growth factor (VEGF) in serum, and cyclooxygenase-2 and VEGF in baseline tumor tissue.

Results—52 patients were analyzable: 20 chemotherapy naive (group A) and 32 previously treated with 1 chemotherapy regimen (group B); 73% of patients had distant metastasis and 60% were paclitaxel-exposed. In group A, 3 patients (15%) achieved a partial response; in group B, 1 patient (3%) achieved a partial response. Median progression-free survival (PFS) and overall survival were 3.3 and 8.2 months in group A and 1.9 and 5.0 months in group B, respectively. Common serious toxicities were diarrhea, fatigue, and anorexia. Patients with high serum VEGF had a median PFS of 2.8 months versus 1.7 months for patients with low VEGF (p=0.085).

Conclusions—Docetaxel and irinotecan had acceptable toxicities but efficacy results in unselected patients with recurrent or metastatic SCCHN did not suggest an advantage over taxane alone or platinum-based regimens.

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Keywords

irinotecan; docetaxel; head and neck cancer; vascular endothelial growth factor

Introduction

More than 45,000 new cases of head and neck cancer are diagnosed annually in the United States [1]. Patients with recurrent or metastatic squamous cell carcinomas of the head and neck (SCCHN) have a poor prognosis [2]. Cisplatin-based combination regimens given as first-line treatment of recurrent or metastatic SCCHN result in objective response rates of about 30% and median overall survival (OS) of 8–9 months [3]. More recently, the epidermal growth factor receptor inhibitors were introduced in the systemic therapy of SCCHN [4]. However, at present time, there is no standard regimen for the second-line treatment of recurrent or metastatic SCCHN.

Docetaxel is a semisynthetic taxane that acts as a mitotic spindle poison by promoting microtubule assembly but inhibiting tubulin depolymerization, which disrupts cell division. The major toxicity with the 3-week scheduling of docetaxel is neutropenia which is ameliorated by weekly administration [5]. Clinical studies have documented the efficacy of docetaxel in many solid tumors, even after previous treatment with paclitaxel [6]. Weekly docetaxel at a dose of 30 mg/m^2 was highly active in a phase II trial in chemo-naïve recurrent or metastatic SCCHN with a reported a response rate of 42% and median OS of 11.3 months [7]. A phase II randomized study of weekly docetaxel versus methotrexate showed higher response rates for docetaxel but comparable survival rates [8].

Irinotecan is a water-soluble analogue of camptothecin that inhibits topoisomerase I, a critical enzyme for DNA replication and transcription. Irinotecan is metabolized in the liver to SN-38, an active metabolite, that undergoes glucuronidation in the liver through uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A1) to the relatively inactive SN-38G (SN-38 glucuronide). The major toxicities of irinotecan are neutropenia and diarrhea. Polymorphisms in UGT1A1 have been reported to result in increased incidence of irinotecan-related toxicities [9,10]. A phase II study of irinotecan given weekly at 125 mg/m^2 for 4 weeks followed by 2 weeks of rest in recurrent or metastatic SCCHN reported a response rate of 26% in 19 evaluable patients [11]. Due to toxicity, 14 subsequent evaluable patients were treated at a lower dose of 75 mg/m^2 and the schedule altered to 2 weeks on, 1 week off. The response rate in this cohort was 14%. However, irinotecan had no significant activity when given in the second-line therapy setting [11].

The combination of irinotecan and docetaxel is supported by preclinical observations and showed promising activity in early clinical investigations in solid tumors [12]. A phase I clinical trial established the recommended phase II dose as irinotecan 60 mg/m^2 and docetaxel 35 mg/m^2 on days 1 and 8, repeated every 21 days [13]. Based on these observations, we designed a phase II study to investigate the antitumor activity and toxicities with irinotecan and docetaxel in patients with recurrent or metastatic SCCHN. We also examined the potential correlation between UGT1A1 genotype and toxicity of the regimen. Cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF) are overexpressed in SCCHN [14–16]. Therefore, we also sought to evaluate the expression of cyclooxygenase-2 (COX-2) and VEGF in tumor tissue as well as serum VEGF as predictors of antitumor efficacy.

Patients and Methods

Patient Selection

Eligible patients were 18 years of age or older with recurrent or metastatic SCCHN considered incurable by means of locoregional therapies, ECOG performance status of 0 or 1, and measurable disease according to RECIST [17]. Patients were enrolled simultaneously in 2 groups. Group A: patients could not have received prior chemotherapy for locally recurrent or metastatic disease but may have received chemotherapy as part of primary curative therapy, if completed > 6 months prior to registration. Group B: patients had to have received one prior chemotherapy regimen for locally recurrent or metastatic disease, or chemotherapy as part of primary curative therapy < 6 months prior to registration. Prior paclitaxel was permitted but prior docetaxel or irinotecan at any time was not allowed. Other inclusion criteria included adequate hematologic and liver function test parameters and no peripheral neuropathy of grade 2 or worse. All patients signed informed consent and the protocol was approved by each institution's Human Investigations Committee.

Treatment plan

Docetaxel (Aventis Pharmaceuticals/Sanofi) was administered as a 60-minute intravenous infusion at a dose of 35 mg/m^2 followed by the administration of irinotecan (Pharmacia Corporation/Pfizer Inc) intravenously over 30 minutes at a dose of 60 mg/m^2. Chemotherapy was given on days 1 and 8 of a 21-day schedule and continued until progression of disease, unacceptable toxicity, or patient withdrawal. Patients received antiemetics and dexamethasone for a total of 3 doses, 12 hours prior to, 30 minutes prior to and 12 hours after docetaxel. All toxicities were graded according to the NCI Common Toxicity Criteria (version 2.0). A dose reduction of docetaxel to 30 mg/m^2 and irinotecan to 50 mg/m^2 was allowed. High-dose loperamide, tincture of opium, and octreotide were used for treatment of delayed diarrhea.

Patient Assessments and Monitoring

Patients were evaluated by computed tomography (CT) of the chest and abdomen and CT or magnetic resonance imaging of the neck at baseline, within 4 weeks of registration, and then after every 3 cycles (9 weeks). Bone scan was performed at baseline and then as clinically indicated. When a patient was deemed to have an objective response, tumor measurements were to be repeated 4–6 weeks later to confirm the response. Complete blood counts were obtained on days 1 and 8 and serum chemistry tests were on day 1 of each cycle.

Statistical Methods

The primary endpoint was the overall objective response rate which was defined as the proportion of patients with complete or partial response defined by RECIST [17] among eligible, treated patients, including patients not evaluable for response. In the first stage of a two-stage design, 14 eligible patients (16 total to allow for a 10% ineligibility rate) were to be accrued to each of the two cohorts. Response rates of 40% and 20% were considered promising in groups A and B, respectively. If at least 4 responses were seen in in group A and at least 1 response in group B, accrual would continue to the second stage to accrue 18 additional patients in each group (i.e. the total accrual goal was 32 eligible patients for each group). OS was defined as the time from registration to the date of death or last follow-up. Progression-free survival (PFS) was defined as the time from registration to disease progression or death from any cause or last follow-up. Two-stage confidence intervals, two-stage power calculations, and the two-stage stopping rules were used to analyze the data in regards to the study's two-stage design [18]. Fisher's exact test [19] was used to analyze the contingency tables of response and to compare the distribution of categorical data between

groups. Cochran-Mantel-Haenszel test was used to assess the association between response and categories adjusting for the differences in prior treatment status. The Wilcoxon rank sum test [20] was used to compare the distribution of continuous data between the two groups. Kaplan-Meier curves were plotted for OS and PFS [21]. The log-rank test statistic was used to compare survival curves between categories and a stratified log-rank test was used to adjust for differences in prior treatment status. Moreover, logistic and Cox proportional hazards regression models [22] were respectively used to model objective response and survival data on covariates of interest while adjusting for prior treatment status. Mehta's exact test for ordered categorical data was used to test for associations between UGT1A1 genotype and toxicity severity [23]. Two-sided p-values are reported for all the statistical tests used in the analysis.

Correlative studies

Immunohistochemistry for COX-2 and VEGF—Immunohistochemistry for the determination of COX-2 and VEGF in archival formalin-fixed paraffin-embedded tumor tissue was performed using commercially available antibodies: a monoclonal mouse anti-human COX-2 (Cayman Chemical, Ann Arbor, MI), at 1:50 dilution, and a polyclonal rabbit anti-human VEGF(A-20) (Santa Cruz Biotechnology, Santa Cruz, CA), at 1:500 dilution. For VEGF cytoplasmic staining, tumors were assigned a score of either 0 (negative), 1+ (weak <1% of cells), 2+ (medium 1–10% of cells), or 3+ (strong >10% of the tumor cells); for COX-2 membrane staining, tumors were assigned a score of either 0 (negative, or faint in <10%), 1+ (faint >10% of cells), 2+ (moderate >10% of cells), or 3+ (strong, complete in >10% of the tumor cells). The median intensity of VEGF was used to classify the cases into low (<1.5) or high (>1.5) VEGF categories. A cutoff of 2+ COX-2 intensity was used to classify the cases into low (≤ 2) or high (>2) categories.

Serum VEGF—Quantitative determination of human VEGF concentrations in serum was performed by ELISA using either kit DY293B or DVE00 from R&D SYSTEMS (Minneapolis, MN). Samples were measured in duplicate, and VEGF standard was included with every group of sera tested. The coefficient of variation for VEGF standard was ± 10% (62.5 pg/ml–2000 pg/ml). The median serum VEGF score was used to classify the cases into low (≤394) or high (>394) serum VEGF categories.

UGT1A1 genotyping—Genomic DNA for UGT1A1 determination was prepared from whole blood (100–200 ml) using the QIAmp blood kit (Qiagen). A standard PCR was performed using UGT1A1 specific primers that flanked the TATA region with the forward primer biotinylated. TA repeat number was determined by pyrosequencing with a PSQ 96MA pyrosequencer and software (Biotage, Uppsala, Sweden) by standard methods [24,25]. Genotypes for the cell lines DU145 and MCF-7 were previously determined to be 6/7 and 7/7 respectively. DU145 (n=7) and MCF-7 (n=3) were assayed with 100% accuracy for each gene. One or both of these cell lines were included as a positive control along with patient samples in each pyrosequencing reaction.

Results

From October 2002 until August 2004, a total of 54 patients were enrolled, 18 in group A and 36 in group B. Two patients in group B never started treatment; one patient who withdrew consent and another who signed consent but died before starting treatment. Four patients were reclassified with respect to their prior chemotherapy, 1 from group A to B and 3 from group B to A. As a result, there were 52 analyzable patients; 20 in group A, and 32 in group B. Although 4 objective responses were observed in group A, one was not confirmed by repeat imaging, and accrual did not proceed to the second stage for that group. Patient

characteristics and prior treatments are shown in Table 1 and Table 2. Patients received a median of 3 cycles of irinotecan and docetaxel (range, 1–10 cycles).

Response

In group A, there were 3 partial responses for a response rate of 15% (90% confidence interval, 4.2% – 34.4%) and in group B, there was 1 partial response for a response rate of 3.1% (90% confidence interval 0.004% – 19.6%). There was an additional unconfirmed partial response in each group (Table 3). Of the 52 patients, 13 were unevaluable as no post-treatment measurements were taken: 4 patients had symptomatic deterioration, 1 patient died prior to first follow-up assessment, 4 patients withdrew from study after only one cycle of treatment due to toxicity, 3 patients had not inadequate data or were lost to follow-up, and 1 patient did not have a consistent method of evaluation.

Overall and progression-free survival

At the time of this analysis, all patients but one have progressed or died. For patients in group A, the median OS was 8.2 months and for patients in group B, the median OS was 5.0 months (Table 3 and Figure 1). In group A, the median PFS was 3.3 months and in group B, the median PFS was 1.9 months. No baseline characteristic was found to be statistically significant in predicting survival, but the study was not powered to identify such factors.

Toxicity (Table 4)

Three deaths, all in group B, were deemed possibly related to study treatment. Two were due to sepsis, in one case associated with neutropenia, diarrhea and dehydration. The third patient presented after 2 weeks of treatment on cycle 1 with fever, chills and dyspnea, refused treatment and died at home 2 days later from presumed pneumonia. Two other patients, one in each group, died from grade 5 carotid hemorrhage without thrombocytopenia, which was attributed to disease progression. The most common grade 3 or 4 events in the 2 groups combined were diarrhea (grade 3, 21%; grade 4, 4%), fatigue (grade 3, 17%), anorexia (grade 3, 8%; grade 4, 4%), and neutropenia (grade 3, 8%; grade 4, 13%). Only 1 patient (2%) had febrile neutropenia.

COX-2 and VEGF

Forty-one patients consented for the use of their samples for correlative studies. COX-2 and VEGF tumor expression data were available for 31 and 29 cases, respectively. We did not detect any significant differences in overall survival or progression-free survival between groups on the basis of COX-2 or VEGF expression presumably because of smallsample sizes (Table 5). Baseline serum VEGF data were available for 18 patients. The association between serum VEGF at baseline and median PFS is shown in Table 5. Patients with high baseline VEGF levels had a median PFS of 2.84 months versus 1.73 months for patients with low VEGF (p=0.085, using stratified log-rank test).

UGT1A1

We explored the association between polymorphisms in the UGT1A1 gene and race, neutropenia, diarrhea, and any toxicity among 35 patients with available data. There were no statistically significant differences in the pattern of worst degree toxicity, or in the grade intensity of neutropenia, or diarrhea by TA repeat category (data not shown).

Discussion

We evaluated the combination of docetaxel and irinotecan, a novel non-platinum-containing regimen, in the first- or second-line treatment of patients with recurrent or metastatic

SCCHN. Both drugs were given on a weekly schedule of administration based on prior phase I experience [13]. Phase II trials of docetaxel and irinotecan, using weekly or every 3 weeks schedules of administration, have been conducted in many other solid tumors [26–33]. To the best of our knowledge, this is the only phase II study of docetaxel and irinotecan in recurrent or metastatic SCCHN. Although objective responses were observed, the pre-specified criteria for efficacy were not met. In the first-line setting (group A), 4 objective responses were observed as required per study design but one was unconfirmed which did not allow the study to accrue beyond the first stage of a two stage Simon design. The statistical design assumed a target response rate of 40% in group A which in retrospect was rather high for the cooperative group setting and with the application of RECIST. Other cooperative group studies in comparable patient populations, such as E5397 and E1595, showed that single-agent chemotherapy with cisplatin achieves an objective response rate of 10% and median survival of 8 months (E5397) [34] and that cisplatin doublets (cisplatin/5-FU or cisplatin/paclitaxel) result in objective response rates of 26–27% and median survival of 8.1–8.7 months (E1395) [3]. In the current study, docetaxel and irinotecan produced a response rate of 17% (22% counting an unconfirmed response), median PFS of 3.3 months and median of OS 8.2 months. Therefore, survival results with docetaxel and irinotecan may be comparable to platinum-based combinations.

The group of patients treated in the second-line setting (group B) is one of the largest that have been studied so far and it was characterized by a high representation of patients with distant metastasis (78%) and previous treatment with paclitaxel (81%). In these patients, the efficacy of docetaxel and irinotecan with a response rate of 3% (6% counting an unconfirmed response), median PFS of 1.9 months and median OS of 5.0 months cannot be considered satisfactory. As single agent, irinotecan may be inactive in previously treated recurrent or metastatic SCCHN [11], whereas data with single-agent docetaxel is limited in a similar setting but activity has been reported [35].

The docetaxel and irinotecan regimen we used in our study was associated with expected toxicities which were predominantly non-hematologic, including diarrhea, anorexia, and fatigue. Although most of the patients had received paclitaxel in the past, grade 3 or 4 neuropathy was not seen. Grade 4 toxicity was observed in 30% of chemotherapy naive patients in this study versus 42% and 50% with cisplatin/paclitaxel and cisplatin/5-FU, respectively, in E1395, whereas there was no treatment-related death versus 5% and 7% with cisplatin/paclitaxel and cisplatin/5-FU, respectively [3]. However, there were some differences in the toxicity criteria used between these ECOG studies so the rates of grade 3 and 4 toxicities may not be directly comparable. Polymorphisms in the UGT1A1 gene have demonstrated racial variability and have been shown to be associated with differences in observed toxicities among patients treated with irinotecan. We could not demonstrate any correlation of toxicities with UGT1A1 genotypes, possibly because of the small sample size, or the low dose of irinotecan used in this study [40].

COX-2 and VEGF are overexpressed in SCCHN and have been suggested as potential predictors of outcome [14–16] [36]. Moreover, COX-2 expression has been reported to correlate with the expression of VEGF in SCCHN. Based on preclinical observations it has been proposed that docetaxel may have an antiangiogenesis effect [37]. We elected to assess VEGF as well as COX-2 on baseline tumor tissue and attempted to associate its expression with outcome. However, in the clinical setting examined we could not demonstrate that expression of either COX-2 or VEGF correlated with worse survival possibly because of insufficient sample size [38]. Patients with high serum VEGF levels had a trend towards improved PFS with docetaxel and irinotecan versus patients with low levels at baseline, an observation that may require further evaluation in subsequent studies.

The docetaxel and irinotecan regimen we used was feasible and was associated with a toxicity profile potentially favorable to cisplatin-based combinations. However, its antitumor activity is unlikely to be superior to platinum-based combinations in the first-line treatment of recurrent or metastatic SCCHN, whereas its antitumor activity in the second-line setting was rather disappointing. It has been reported that selected patients, such as those with tumors with high levels of excision repair cross complementation group 1 (ERCC1), may benefit less from platinum-based chemotherapy [39]. Whether docetaxel and irinotecan, a non-platinum doublet, will be beneficial in selected patients, such as those with tumors with high ERCC1, is a worthwhile hypothesis to be evaluated in future clinical trials in patients with SCCHN.

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References

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. CA Cancer J Clin. 2008
2. Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol. 2006; 24:2644–2652. [PubMed: 16763278]
3. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2005; 23:3562–3567. [PubMed: 15908667]
4. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol. 2007; 25:2171–2177. [PubMed: 17538161]
5. Bria E, Cuppone F, Ciccarese M, et al. Weekly docetaxel as second line chemotherapy for advanced non-small-cell lung cancer: meta-analysis of randomized trials. Cancer Treat Rev. 2006; 32:583–587. [PubMed: 16919884]
6. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000; 18:2354–2362. [PubMed: 10856094]
7. Hitt R, Amador ML, Quintela-Fandino M, et al. Weekly docetaxel in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Cancer. 2006; 106:106–111. [PubMed: 16329139]
8. Guardiola E, Peyrade F, Chaigneau L, et al. Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. Eur J Cancer. 2004; 40:2071–2076. [PubMed: 15341981]
9. Cote JF, Kirzin S, Kramar A, et al. UGT1A1 polymorphism can predict hematologic toxicity in patients treated with irinotecan. Clin Cancer Res. 2007; 13:3269–3275. [PubMed: 17510208]
10. Lankisch TO, Schulz C, Zwingers T, et al. Gilbert's Syndrome and Irinotecan Toxicity: Combination with UDP-Glucuronosyltransferase 1A7 Variants Increases Risk. Cancer Epidemiol Biomarkers Prev. 2008; 17:695–701. [PubMed: 18349289]
11. Murphy BA. Topoisomerases in the treatment of metastatic or recurrent squamous carcinoma of the head and neck. Expert Opin Pharmacother. 2005; 6:85–92. [PubMed: 15709886]
12. Murren JR, Davies M. Irinotecan and taxane combinations for non small-cell lung cancer. Clin Lung Cancer. 2001; 2 Suppl 2:S20–S25. [PubMed: 14725726]
13. Bleickardt E, Argiris A, Rich R, et al. Phase I dose escalation trial of weekly docetaxel plus irinotecan in patients with advanced cancer. Cancer Biol Ther. 2002; 1:646–651. [PubMed: 12642688]

14. Kyzas PA, Cunha IW, Ioannidis JP. Prognostic significance of vascular endothelial growth factor immunohistochemical expression in head and neck squamous cell carcinoma: a meta-analysis. Clin Cancer Res. 2005; 11:1434–1440. [PubMed: 15746043]
15. Smith BD, Smith GL, Carter D, et al. Prognostic significance of vascular endothelial growth factor protein levels in oral and oropharyngeal squamous cell carcinoma. J Clin Oncol. 2000; 18:2046–2052. [PubMed: 10811669]
16. Gallo O, Masini E, Bianchi B, et al. Prognostic significance of cyclooxygenase-2 pathway and angiogenesis in head and neck squamous cell carcinoma. Hum Pathol. 2002; 33:708–714. [PubMed: 12196922]
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92:205–216. [PubMed: 10655437]
18. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989; 10:1–10. [PubMed: 2702835]
19. Agresti ACDA. Edition. New York: Wiley; 1990.
20. Wilcoxon F. Individual comparisons by ranking methods. Biometrics. 1945; 1:80–83.
21. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Statis Assoc. 1958; 53:457–481.
22. Cox DR. Regression models and life tables. Journal of the Royal Statistical Society, Series B. 1972; 23:187–202.
23. Mehta CR, Patel NR, Tsiatis AA. Exact significance testing to establish treatment equivalence with ordered categorical data. Biometrics. 1984; 40:819–825. [PubMed: 6518249]
24. Carlini LE, Meropol NJ, Bever J, et al. UGT1A7 and UGT1A9 polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/irinotecan. Clin Cancer Res. 2005; 11:1226–1236. [PubMed: 15709193]
25. Mercke Odeberg J, Andrade J, Holmberg K, et al. UGT1A polymorphisms in a Swedish cohort and a human diversity panel, and the relation to bilirubin plasma levels in males and females. Eur J Clin Pharmacol. 2006; 62:829–837. [PubMed: 16909274]
26. Burtness B, Thomas L, Sipples R, et al. Phase II trial of weekly docetaxel/irinotecan combination in advanced pancreatic cancer. Cancer J. 2007; 13:257–262. [PubMed: 17762761]
27. Polyzos A, Kosmas C, Toufexi H, et al. Docetaxel in combination with irinotecan (CPT-11) in platinum-resistant paclitaxel-pretreated ovarian cancer. Anticancer Res. 2005; 25:3559–3564. [PubMed: 16101180]
28. Stathopoulos GP, Tsavdaridis D, Malamos NA, et al. Irinotecan combined with docetaxel in pre-treated metastatic breast cancer patients: a phase II study. Cancer Chemother Pharmacol. 2005; 56:487–491. [PubMed: 15868147]
29. Sym SJ, Chang HM, Kang HJ, et al. A phase II study of irinotecan and docetaxel combination chemotherapy for patients with previously treated metastatic or recurrent advanced gastric cancer. Cancer Chemother Pharmacol. 2008
30. Wachters FM, Groen HJ, Biesma B, et al. A randomised phase II trial of docetaxel vs docetaxel and irinotecan in patients with stage IIIb-IV non-small-cell lung cancer who failed first-line treatment. Br J Cancer. 2005; 92:15–20. [PubMed: 15597104]
31. Yamamoto N, Fukuoka M, Negoro SI, et al. Randomised phase II study of docetaxel/cisplatin vs docetaxel/irinotecan in advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group Study (WJTOG9803). Br J Cancer. 2004; 90:87–92. [PubMed: 14710212]
32. Lordick F, von Schilling C, Bernhard H, et al. Phase II trial of irinotecan plus docetaxel in cisplatin-pretreated relapsed or refractory oesophageal cancer. Br J Cancer. 2003; 89:630–633. [PubMed: 12915869]
33. Kurtz JE, Negrier S, Husseini F, et al. A phase II study of docetaxel-irinotecan combination in advanced pancreatic cancer. Hepatogastroenterology. 2003; 50:567–570. [PubMed: 12749274]
34. Burtness B, Goldwasser MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol. 2005; 23:8646–8654. [PubMed: 16314626]

35. Numico G, Merlano M. Second-line treatment with docetaxel after failure of a platinum-based chemotherapy in squamous-cell head and neck cancer. Ann Oncol. 2002; 13:331–333. [PubMed: 11886014]

36. Lim SC, Park SY, Do NY. Correlation of cyclooxygenase-2 pathway and VEGF expression in head and neck squamous cell carcinoma. Oncol Rep. 2003; 10:1073–1079. [PubMed: 12883661]

37. Sweeney CJ, Miller KD, Sissons SE, et al. The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. Cancer Res. 2001; 61:3369–3372. [PubMed: 11309294]

38. Hoskins JM, Goldberg RM, Qu P, et al. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst. 2007; 99:1290–1295. [PubMed: 17728214]

39. Handra-Luca A, Hernandez J, Mountzios G, et al. Excision repair cross complementation group 1 immunohistochemical expression predicts objective response and cancer-specific survival in patients treated by Cisplatin-based induction chemotherapy for locally advanced head and neck squamous cell carcinoma. Clin Cancer Res. 2007; 13:3855–3859. [PubMed: 17606717]

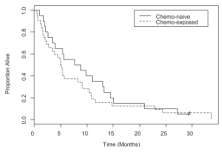

Figure 1. Overall survival by previous chemotherapy status

Kaplan-Meier estimation of overall survival by patient group: chemotherapy naive, group A (n=20), had a median survival of 8.2 months; previously treated, group B (n=32), had a median survival of 5 months.

Table 1

Patient characteristics

	Group A N=20		Chemo-Exposed N=32	
	N	**%**	**N**	**%**
Age (years)				
Median	65		56	
Range	46–82		32–79	
Sex				
Male	15	75.0	26	81.3
Female	5	25.0	6	18.8
Race				
White	20	100.0	26	83.9
Black	0	0.0	5	16.1
Not Specified	0		1	
ECOG Performance Status				
0	8	40.0	7	21.9
1	12	60.0	25	78.1
Primary Tumor Site				
Oral Cavity	5	25.0	7	21.9
Oropharynx	5	25.0	8	25.0
Hypopharynx	1	5.0	3	9.4
Larynx	5	25.0	11	34.4
Salivary Gland – Parotid	0	0.0	1	3.1
Unknown Primary	1	5.0	1	3.1
Other	3	15.0	1	3.1
Cell Differentiation				
Well Differentiated	2	12.5	5	20.8
Moderately Differentiated	9	56.3	13	54.2
Poorly Differentiated	5	31.3	6	25.0
Unknown	4		8	
Weight Loss in Previous 6 Months				
< 5% of Body Weight	12	70.6	14	46.7
5 – <10% of Body Weight	3	17.6	5	16.7
10 – <20% of Body Weight	1	5.9	8	26.7
>= 20% of Body Weight	1	5.9	3	10.0
Unknown	3		2	
Smoking History				
Never Smoked	2	10.0	3	10.3
Pipe or Cigar Smoker Only	0	0.0	1	3.4
Cigarette Smoker <20 Pack-years	2	10.0	2	6.9
Cigarette Smoker 20–40 Pack-years	4	20.0	11	37.9
Cigarette Smoker >40 Pack-years	12	60.0	12	41.4

	Group A N=20		Chemo-Exposed N=32	
	N	%	N	%
Unknown	0		3	
Alcohol Consumption				
< 10 ounces of Whiskey/Week*	14	73.7	20	69.0
10–32 ounces of Whiskey/Week	3	15.8	4	13.8
> 32 ounces of Whiskey/Week	2	10.5	5	17.2
Unknown	1		3	
Metastatic Site Involvement				
Yes	13	65.0	25	78.1
No	7	35.0	7	21.9

* or equivalent

Table 2

Previous treatment

	Group A (N=20)		Group B (N=32)	
	N	**%**	**N**	**%**
Previous chemotherapy	6*	30.0	32	100.0
Received curative therapy only	6	100.0	20	62.5
Received palliative therapy only	-	-	7	21.9
Both palliative and curative	-	-	5	15.6
Prior paclitaxel	5	25.0	26	81.3
Prior biologic treatment	0	0.0	1	3.1
Prior surgery	17	85.0	22	68.8
Prior radiotherapy	18	90.0	29	90.6

*chemotherapy as part of potentially curative therapy > 6 months earlier

Table 3

Efficacy results: response rate, progression-free and overall survival

		Group A N=20	Group B N=32
Best confirmed response *			
Partial Response	No. (%)	3 (15.0%)	1 (3.1%)
Stable Disease	No. (%)	4 (20.0%)	9 (28.1%)
Progression	No. (%)	8 (40.0%)	14 (43.8%)
Unevaluable	No. (%)	5 (25.0%)	8 (25.0%)
Median progression-free survival	(Months)	3.3	1.9
	90% CI	2.0 – 6.7	1.8 – 2.7
1-year progression-free survival	(%)	10	6
	90% CI (%)	3 – 30	2 – 19
Overall survival	Median (Months)	8.2	5.0
	90% CI	3.9 – 13.2	3.4 – 9.1
1-year overall survival	(%)	35	16
	90% CI (%)	21 – 58	8 – 31

* 1 patient included in the stable disease group in each cohort had unconfirmed partial response

CI, confidence interval

Table 4

Grade 3–5 toxicities with irinotecan and docetaxel

	Group A (N=20)						Group B (N=32)					
	Grade 3		Grade 4		Grade 5		Grade 3		Grade 4		Grade 5	
Hemoglobin	-	-	-	-	-	-	1	3%	-	-	-	-
Leukocytes	4	20%	2	10%	-	-	5	16%	2	6%	-	-
Lymphopenia	-	-	-	-	-	-	1	3%	-	-	-	-
Neutrophils	2	10%	4	20%	-	-	2	6%	3	9%	-	-
Transfusion of packed red blood cells	1	5%	-	-	-	-	3	9%	-	-	-	-
Hypotension	-	-	-	-	-	-	-	-	2	6%	-	-
Thrombosis/embolism	-	-	-	-	-	-	1	3%	-	-	-	-
Cardiac-other	-	-	-	-	-	-	-	-	1	3%	-	-
Fatigue	2	10%	-	-	-	-	7	22%	-	-	-	-
Fever	-	-	-	-	-	-	1	3%	-	-	-	-
Prothrombin time	-	-	-	-	-	-	1	3%	-	-	-	-
Anorexia	1	5%	1	5%	-	-	3	9%	1	3%	-	-
Dehydration	6	30%	-	-	-	-	3	9%	-	-	1	3%
Gastritis	1	5%	-	-	-	-	-	-	-	-	-	-
Stomatitis	1	5%	-	-	-	-	-	-	-	-	-	-
Nausea	-	-	-	-	-	-	2	6%	-	-	-	-
Vomiting	1	5%	-	-	-	-	1	3%	1	3%	-	-
Diarrhea	8	40%	1	5%	-	-	3	9%	1	3%	-	-
Gastrointestinal bleeding	1	5%	-	-	-	-	-	-	-	-	-	-
Alkaline phosphatase	1	5%	-	-	-	-	-	-	-	-	-	-
Hypoalbuminemia	-	-	-	-	-	-	1	3%	-	-	-	-
Febrile neutropenia	1	5%	-	-	-	-	-	-	-	-	-	-
Infection with grade 3 –4 neutropenia	1	5%	1	5%	-	-	-	-	1	3%	1	3%
Infection with unknown neutrophil count	-	-	-	-	-	-	1	3%	-	-	-	-
Infection without neutropenia	-	-	-	-	-	-	-	-	2	6%	1	3%
Hypokalemia	1	5%	-	-	-	-	1	3%	-	-	-	-
Hyponatremia	7	35%	-	-	-	-	3	9%	-	-	-	-
Depressed level of consciousness	-	-	-	-	-	-	2	6%	-	-	-	-

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	Group A (N=20)					Group B (N=32)				
	Grade 3		Grade 4		Grade 5	Grade 3		Grade 4		Grade 5
Dizziness/lightheadedness	-	-	-	-	-	1	3%	-	-	-
Anxiety/agitation	1	5%	-	-	-	1	3%	-	-	-
Hypoxia	1	5%	-	-	-	-	-	-	-	-
Pleural effusion	1	5%	-	-	-	-	-	-	-	-
Pulmonary-other	-	-	1	5%	-	-	-	-	-	-
Syncope	-	-	-	-	-	1	3%	-	-	-
Abdominal pain	-	-	-	-	-	1	3%	-	-	-
ARDS	-	-	-	-	-	-	-	1	3%	-
Dyspnea	-	-	-	-	-	1	3%	1	3%	-
Creatinine	-	-	1	5%	-	1	3%	1	3%	-
WORST DEGREE	9	45%	6	30%	-	14	44%	5	16%	3	9%

Table 5

Progression-free survival by COX-2/VEGF expression

		Median (months)			P-value*
	Number of patients	All patients	Chemo-naïve (group A)	Chemo-exposed (group B)	
Tumor COX-2					0.4927
Low	20	2.00	2.89	1.86	
High	19	2.73	3.56	1.87	
Tumor VEGF					0.9739
Low	15	2.10	3.22	1.95	
High	24	2.35	3.68	1.87	
SerumVEGF					0.0853
Low	9	1.84	1.91	1.81	
High	9	2.73	7.2	2.73	

* stratified log-rank p-value (all patients)