Phase I Study of Capecitabine, Carboplatin and Intensity-modulated Radiation Therapy for Head and Neck Cancer

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Abstract. Background: To determine the maximally tolerated dose (MTD) of capecitabine when given concomitantly with carboplatin and intensity-modulated radiation therapy (IMRT) for treatment of localized stage III/IV squamous cell carcinomas of the head and neck (HNSCC). Patients and Methods: After six weeks of induction chemotherapy with capecitabine and carboplatin, patients received a second course with concomitant IMRT. The MTD for capecitabine during chemoradiation was determined by a standard phase I trial design. Results: Nine out of the eleven patients qualified for chemoradiation. With weekly carboplatin AUC=1.5 and IMRT, the MTD of capecitabine was 850 mg/m²/day when given in divided doses on days 1-14 and 22-35. The dose-limiting toxicity was myelosuppression and other adverse effects were modest. Eight patients experienced complete response after chemoradiation and seven remain relapse-free after 34 months. Conclusion: Capecitabine, carboplatin, and IMRT given as described were well tolerated by HNSCC patients and in this pilot study produced a promising rate of disease control.

Randomized clinical trials have shown that the addition of platinum-based chemotherapy to radiotherapy improves disease control rates for patients with locally advanced stage III and IV squamous cell carcinomas of the head and neck (HNSCC) (1). Induction or neo-adjuvant chemotherapy given prior to definitive radiation may also be helpful (2, 3). However, the optimal chemotherapy program, radiation technique, and schedules for these modalities have not been defined. In general, the more intense therapies appear to be more effective but at the expense of increased short and/or long-term complications (1, 2, 4). Thus, there is a need to identify treatment programs that provide satisfactory tumor control but limit toxicities.

We postulated that a combination of carboplatin and capecitabine given prior to and during intensity-modulated radiotherapy (IMRT) would reduce toxicity but retain the anti-tumor activity of more aggressive treatment programs. Carboplatin has less non-hematological toxicity than cisplatin and is also active against HNSCC, particularly when combined with infusional 5-fluorouracil (5-FU), paclitaxel, and/or radiation (1, 3, 5). Capecitabine is an oral fluoropyrimidine that is metabolized in vivo to its active metabolite 5-FU by the enzyme thymidine phosphorylase, which in some cases is overexpressed in the tumor cells (6). Not surprisingly, the clinical activity and toxicities of capecitabine resemble those of infusional 5-FU, including the ability to act in combination with cisplatin to induce tumor regression in the majority of patients with advanced HNSCC (7, 8). A practical advantage of capecitabine is that unlike 5-FU, it does not require a central venous catheter and thereby avoids the thrombotic and infectious complications associated with these devices. The use of IMRT may also lessen toxicity as compared to conventional radiotherapy by allowing more conformal treatment of the tumor volume which, in turn, reduces the dose delivered to uninvolved tissues (9, 10).

As a first step to test the feasibility of combining capecitabine with carboplatin and IMRT for treatment of HNSCC, we conducted a phase I study to determine the maximum tolerated dose (MTD) for capecitabine during chemoradiation following a six-week course of induction chemotherapy.

Patients and Methods

Patient eligibility. The study was open to non-pregnant patients over 17 years of age with previously untreated and measurable locally advanced stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx (T2-4, N0-3, M0), ECOG performance status ≤2, no significant co-morbidities, and a signed study-specific written informed consent approved by the University of Virginia Protocol Review and Human Investigation Committees.
Chemotherapy and treatment program. Induction chemotherapy included six weekly doses of carboplatin area under the concentration-time curve=2 mg/ml/min (AUC=2) and capecitabine up to 1,750 mg/m² given orally or per gastric tube in divided doses on days 1-14 and 22-36. After a one-week break and in the absence of progression, the patients received a second six-week cycle of chemotherapy and concomitant IMRT (see below). The drugs were given on the same schedule but the carboplatin dose was reduced to AUC=1.5 with a starting dose of capecitabine of 1,000 mg/m²/day (dose level=0), rounded to the closest amount for a combination of 500 and 150 mg tablets. The carboplatin dose was adjusted weekly using a modified Calvert formula in which the estimated creatinine clearance was determined by the standard Cockcroft-Gault equation. The minimal value for the serum creatinine in the formula was set at 0.8 mg/dl to account for non-renal reduction in creatinine related to reduced muscle mass and nutritional intake. The use of anti-emetics such as ondansetron or prochlorperazine was permitted throughout therapy.

IMRT commenced on day 1 of the second cycle of chemotherapy. All patients underwent computed tomography (CT) planning in a Picker CT scanner (Picker, Cleveland, OH, USA) with 3-mm slice thickness. The gross target volume (GTV) was contoured and this volume was expanded by 1-2 cm to create the clinical target volume (CTV). The latter covered all volumes at risk for microscopic spread of disease around the primary lesion and included the bilateral clinically uninvolved cervical lymphatics. The CTV was expanded by 3 mm to allow for daily setup variability and patient movement to create the planning target volume (PTV). The IMRT dosimetry was planned with inverse planning software inverse treatment planning system (CORVUS, Nomos Corporation, Sewickly, PA, USA) to meet specified target homogeneity and conformity constraints and organ at risk dose limitations. The prescribed dose to the primary site and involved lymph node groups was 50 Gy and 45-50 Gy for uninvolved cervical lymph nodes depending on the relative risk of microscopic tumor burden. PTV containing gross disease was then boosted to 70 Gy by 3D conformal radiation techniques. With this design, the dose per fraction was 1.8 to 2.0 Gy for all target volumes and all radiation treatments were completed in 35 fractions over 7 weeks.

Patients with N2 or N3 nodal involvement or residual N1 disease were eligible for neck dissection four weeks after chemoradiation. The protocol also allowed for early salvage surgery, if feasible, in those that had inadequate tumor responses after 50 Gy.

Study design, endpoints, and adverse event assessment. The primary objective was to determine the maximally tolerated dose (MTD) of capecitabine given with a fixed-dose weekly carboplatin of AUC=1.5 and concomitant IMRT. The secondary goals were to define the dose-limiting toxicities (DLTs) and estimate tumor response rates. The MTD was determined using the standard ‘3 + 3’ phase I dose escalation design as described by the NCI (http://ctep.cancer.gov/protocolDevelopment/templates_application s.htm). The increments between dose levels 1 to 5 were 100, 150, or 250 mg/m². The MTD was defined as the maximum dose that produced DLT in fewer than 33% of patients with a minimum of 6 patients treated at that dose. The DLTs were defined as grade 3 or 4 non-hematological toxicities (NCI Common Toxicity Criteria 2.0), ≥grade 3 thrombocytopenia, grade 4 anemia, or absolute neutrophil count of <750 (ANC=750-999 was considered tolerable grade 4 neutropenia). However, clinically tolerable grade 3 radiation-related mucositis, dysphagia, pain, fatigue and/or dermatitis were excluded.

Primary and nodal tumor responses were determined by RECIST criteria from CT and/or magnetic resonance imaging (MRI) scans performed within 4 weeks of study entry and after completion of induction chemotherapy and chemoradiation. Partial radiographic responses were reclassified as pathological complete responses if there was no microscopic evidence of viable tumor in the neck dissection and/or resected tissues.

Results

Patients and toxicity. The characteristics of the eleven patients entered on study are listed in Table 1. Two patients had stage III and nine had stage IVA disease, all potentially resectable. Ten had primary tumors of the oropharynx, including one woman with two primary tumors. Induction chemotherapy was well tolerated and only one patient experienced greater than grade 2 adverse effects (grade 3 diarrhea and dehydration). Nine patients qualified for chemoradiation and received IMRT, weekly carboplatin AUC=1.5 on days 1, 8, 15, 22, 29, and 35, and capecitabine given in split doses on days 1-14 and 22-35 of a six-week cycle. At the starting dose of capecitabine (1,000 mg/m²/day), two of the first three patients developed DLTs with grade 3 thrombocytopenia; one also had grade 4 neutropenia that qualified as a DLT. The six subsequent patients were treated at a reduced dose (level 1) and none exhibited DLTs. This established the MTD for capecitabine at 850 mg/m²/day. Other higher grade adverse effects were restricted to those associated with local radiation effects which did not meet DLT parameters; grade 3 mucositis and dysphagia (4 patients), local pain (3 patients), radiation dermatitis (2 patients), and fatigue (3 patients). As per protocol, a value of 0.8 mg/dl was used in place of the actual serum creatinine to calculate creatinine clearance in three patients. This led to a reduction in the carboplatin dose of approximately 10% on thirteen occasions but all patients achieved a complete tumor response without DLTs.

In regard to late toxicities, all patients that completed protocol therapy had grade 2 or less xerostomia, fibrosis, or dysphagia, and are feeding tube-independent. However, one patient developed focal grade 4 osteoradionecrosis of the mandible after 15 months. On review, this complication appeared to be unrelated to an IMRT-generated ‘hot spot’ which can receive up to 15% more than the prescribed dose. Osteoradionecrosis is a known complication of conventional radiation but is also seen with IMRT (10).

Tumor response and efficacy of treatment. Of the eleven patients that received induction chemotherapy, the primary site responded in eight and nodal disease in six. One had a complete response, one had stable disease, and two progressed and were taken off study. Eight out of the nine patients that finished the protocol chemoradiotherapy achieved a complete response. In four of these, partial responses based on imaging criteria were reclassified as
complete responders because of negative histopathology of subsequent neck dissection specimens or repeat biopsies. In one case of partial response, residual nodal disease was confirmed by pathology.

Seven out of the eight complete responders are free of recurrence after an average follow-up 34 months. The patient that relapsed underwent resection of two pulmonary metastases and has been free of disease for 31 months. The individual with a partial response to chemoradiation developed local recurrence and died of disease. One out of two patients that progressed during induction chemotherapy also died but the other was salvaged by non-protocol chemoradiation (Table I).

Discussion

Consistent with our hypothesis, the combination of capecitabine and carboplatin was well tolerated when given as induction chemotherapy or as concomitant chemotherapy with IMRT. During chemoradiation in which the patients also received weekly carboplatin AUC=1.5, the MTD for capecitabine on the described schedule was 850 mg/m²/day. The DLTs were thrombocytopenia and a qualifying neutropenia. Otherwise, the higher grade short- and long-term toxicities were limited to those expected in patients treated with curative doses of radiation. The exception was one patient that developed a focal grade 4 osteoradionecrosis of the mandible. Overall, the low frequency of serious adverse effects compares favorably with those associated with cisplatin-based chemoradiotherapy programs (1).

Based on previous reports of other chemoradiation trials, the MTD for capecitabine observed in this study was lower than expected (Table II). The estimated dose-intensity for capecitabine (average weekly dose) at the MTD described here was 4,000 mg/m²/week. This compares to 6,300 and 7,000 mg in HNSCC patents that were treated with single-agent capecitabine and radiation, and 4,500 and 7,700 mg in those that also received concurrent cisplatin (11-14). In another trial, patients with esophageal cancer were treated with the capecitabine, carboplatin, paclitaxel, and concomitant radiation (15). Although the dose and schedule of carboplatin (AUC=1.5/week) were the same as used in the

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**Table I. Summary of patients, treatment responses, toxicity and outcome.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Site</th>
<th>Stage</th>
<th>Induction chemotherapy: ( (Primary/\text{nodal}) )</th>
<th>Chemoradiation ( (mg/m²/day) )</th>
<th>Clinical response: ( (Primary/\text{nodal}) )</th>
<th>Surgical intervention</th>
<th>Clinical status (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tonsil</td>
<td>T2N2B</td>
<td>PR/PR</td>
<td>0=1,000</td>
<td>CR/CR</td>
<td>No</td>
<td>NED</td>
<td>Lung metastases, 27 months (resected)</td>
</tr>
<tr>
<td>2</td>
<td>BOT</td>
<td>T3N2C</td>
<td>CR/CR</td>
<td>0=1,000</td>
<td>CR/CR</td>
<td>No</td>
<td>NED</td>
<td>PR after RT; local failure</td>
</tr>
<tr>
<td>3</td>
<td>Tonsil</td>
<td>T3N2A</td>
<td>PD - 1 cycle</td>
<td>-</td>
<td>-</td>
<td>No</td>
<td>DOD</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>BOT</td>
<td>T2N2B</td>
<td>PR/SD</td>
<td>0=1,000</td>
<td>CR-PR*/pCR#</td>
<td>R-MND</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Tonsil</td>
<td>T3N1</td>
<td>PR/PR</td>
<td>-1=850</td>
<td>CR</td>
<td>No</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Piriform sinus</td>
<td>T2N1</td>
<td>PR/CR</td>
<td>-1=850</td>
<td>pCR#/CR</td>
<td>Bx only</td>
<td>NED</td>
<td>CR after RT + docetaxel (1 node + at surgery)</td>
</tr>
<tr>
<td>7</td>
<td>BOT</td>
<td>T3N2C</td>
<td>PD - 2 cycles</td>
<td>-</td>
<td>-</td>
<td>R&amp;R &amp; L MND</td>
<td>DOD</td>
<td>Local failure</td>
</tr>
<tr>
<td>8</td>
<td>Oroph</td>
<td>T4N2C</td>
<td>SD/SD</td>
<td>-1=850</td>
<td>CR/PR*</td>
<td>L-SND &amp; L-SoND</td>
<td>DOD</td>
<td>Late osteoradionecrosis mandible 8 months post-RT</td>
</tr>
<tr>
<td>9</td>
<td>BOT</td>
<td>T2N2B</td>
<td>PR/PR</td>
<td>-1=850</td>
<td>CR/pCR*</td>
<td></td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>BOT</td>
<td>T2N2C</td>
<td>PR/SD</td>
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</tr>
<tr>
<td>11</td>
<td>Oroph &amp; BOT</td>
<td>T4N1</td>
<td>CR/PR</td>
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<td>NED</td>
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<tr>
<td></td>
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<td>T2N1</td>
<td>CR/PR</td>
<td>-1=850</td>
<td>CR/CR</td>
<td></td>
<td>NED</td>
<td></td>
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</table>

BOT, Base of tongue; Oroph, oropharynx; CR, complete response; PR, partial response; CR-PR*, PR by imaging, CR by exam primary site, with negative neck dissection; pCR#, clinical partial response but pathological complete response; TP, thrombocytopenia; NP, qualifying neutropenia; NED, no evidence of disease; DOD, dead of disease; MND, modified radical neck dissection; SND, selective neck dissection; SoND, supraomohyoid neck dissection; R, right; L, left.
In our study, IMRT clearly exacerbated the hematologic toxicity of concomitant chemotherapy which limited the capecitabine dose. During induction chemotherapy and in the absence of radiation, the patients tolerated twice the amount of capecitabine (1,750 mg/m²/day) despite a 25% higher dose of concomitant carboplatin (AUC=2). We suspect that IMRT indirectly reduces tolerance to capecitabine by increasing carboplatin-induced myleosuppression. Presumably, radiation-induced mucositis and dysphagia lead to mild dehydration that reduces renal clearance of carboplatin without a significant alteration in the serum creatinine. Consistent with this proposition, both patients that developed DLTs were at increased risk for dehydration as one had the highest baseline serum creatinine and had declined placement of a gastric feeding tube prior to IMRT whereas the other suffered a gastric tube malfunction at the time of the DLT. Another possibility is that the induction chemotherapy reduced the bone marrow reserve in these two patients prior to the start of chemoradiation.

However, the effect was likely minor since the counts were normal before chemoradiation started and the DLTs occurred at the very end of treatment. Alternatively, IMRT coupled with chemotherapy may have impaired bone marrow function by damaging circulating hematopoietic stem cells.

Despite the relatively low dose of capecitabine given during IMRT, the rate of disease control in this small group of patients was excellent. The combination of capecitabine and carboplatin appears to be active against HNSCC since induction chemotherapy produced responses at the primary site in eight of the eleven patients. Thus, the response rate to this regimen may be similar to that reported for capecitabine and cisplatin (7, 8). Of the eleven patients entered into the study, nine patients completed protocol therapy and eight achieved a complete response; seven of these remained relapse-free after an average follow-up of 34 months. Although the small number of patients precludes firm conclusions, the disease control rate approximates those seen in other platinum-based chemoradiation programs (1). On the other hand, our results were likely influenced by the favorable prognostic features of the study population. That is, all of the patients had potentially resectable disease and, with one exception, the primary site was in the oropharynx.
Thus, additional studies will be required to determine if the described chemoradiation program for locally advanced HNSCC is less toxic and equally efficacious as the more aggressive cisplatin-based regimens or offers advantages over other non-cisplatin programs that include carboplatin, paclitaxel, and/or EGFR antibodies (1, 5, 17).

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References


