PHASE II CLINICAL TRIAL OF PARENTERAL HYDROXYUREA AND HYPERFRACTIONATED, ACCELERATED EXTERNAL BEAM RADIATION THERAPY IN PATIENTS WITH ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: TOXICITY AND EFFICACY WITH CONTINUOUS RIBONUCLEOSIDE REDUCTASE INHIBITION

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Abstract: Background. Almost all concurrent chemoradiation regimens for head and neck are platinum based; however, cisplatin is associated with severe renal, oto-, and neurotoxicity. Hydroxyurea (HU) has been associated with fewer irreversible toxicities. We obtained HU in parenteral form to be administered continually during the radiation treatment. Intravenous HU promised better pharmacokinetics and cell cycle blockade.

Methods. Participants had biopsy-proven, untreated squamous cell carcinoma of the oral cavity, oropharynx (stage IV) and hypopharynx (stages II–IV). Radiation therapy consisted initially of 74.4 Gy administered in twice daily 1.2-Gy fractions. After 20 patients, the radiation dose was reduced to 60.0 Gy, and another 16 patients were enrolled.

Results. Patients received HU by Continuous Ambulatory Drug Delivery (CADD) pump on a daily \( \times 5 \) schedule during radiation therapy. Because of persistent long-term dysphagia, after 20 patients, the dose of external beam radiation therapy was reduced from 74 to 60 Gy, and the duration of concurrent HU was correspondingly reduced. The new regimen was much better tolerated. The median survival for the group as a whole was 30 months. Within this small study, there were no significant differences in survival, regional control, or local control between the 2 groups.
Squamous cell carcinoma of the head and neck is a tobacco- and alcohol-related illness of the upper aerodigestive tract. Once the tumor is locally advanced, 5-year survival is relatively poor, approximately 40% for stage III and 30% for stage IV disease. Various factors complicate the issue of poor survival. Patients generally have poor respiratory function after years of smoking, as well as other alcohol-related morbidities. Efforts to cure these tumors surgically can be disfiguring and functionally unacceptable. Weight loss due to preexisting malnutrition, and treatment-related mucositis and dysphagia are common, and better therapies are needed.

For patients with locally advanced disease of the oral cavity, oropharynx, and hypopharynx, initial therapy is often dependent on local practice. The most common initial choice is between surgical and nonsurgical management. Among nonsurgical treatments, single modality external beam radiation therapy should probably be reserved for those patients who are unlikely to tolerate chemotherapy. For those who can tolerate combined modality treatment, concurrent cisplatin and 5-fluorouracil (5-FU) and external beam radiation therapy is likely the treatment of choice, possibly with the addition of cetuximab. Induction therapy, while producing objective responses in about 70% of patients, has not been shown to improve survival and should probably not be used routinely, except at specialized centers.

Although cisplatin and cisplatin-based chemoradiation therapies have become the standard of care, they can be toxic. Almost all patients develop subclinical renal dysfunction following treatment with cisplatin, including electrolyte leaks, renal tubular acidosis, and mild azotemia. Some patients develop frank renal failure. Less commonly, some patients develop a sensory neuropathy, which can be problematic. Administration of cisplatin requires substantial hydration and antiemetic therapy, which can increase the costs of drug administration and take up valuable time in the clinic.

Hydroxyurea (HU) is an inhibitor of the small subunit of ribonucleoside reductase, which is necessary to convert ribonucleoside diphosphates to deoxyribonucleoside diphosphates in the process of DNA production. HU has been shown to have clinical activity against hematologic malignancies, without much activity against refractory solid tumors. Extensive laboratory investigations have shown that HU potentiates radiation, giving rise to clinical trials in cancers of the cervix as well as head and neck using oral HU. In 1991, parenteral HU became available from the Cancer Treatment Evaluation Program (CTEP) at the National Cancer Institute. Based on detailed laboratory data, which demonstrated that prolonged exposure of human cancer cell lines to HU was more efficacious than shorter exposures, and because HU caused a cell cycle blockade in the radiosensitive G1-S phase interface, we hypothesized that prolonged infusions of HU in combination with external beam radiation therapy might be more effective than intermittent oral dosing.

Although HU has excellent oral bioavailability, our opinion that continuous-infusion HU might be advantageous was reinforced by pharmacokinetic studies reported by Belt et al. The plasma half-life of oral HU was 3.5 to 5 hours, and so Belt et al chose to study q 4 hour dosing. If we believe cell cycling to be a key mechanism for HU, then nadir plasma concentrations become critical. Comparing mean nadir concentrations after 6 q 4 hour doses with mean nadir levels after 12 q 4 hour doses, the mean plasma levels were 37% higher at 500 mg/m² after 12 doses, which suggests that, at best, a steady state takes at least 2 days to achieve. For the 800 mg/m² dose level, the mean nadir plasma concentration fell 25% when plasma concentrations after 12 doses were compared with 6 doses, which suggests increased clearance after 2 days makes a steady nadir level difficult to achieve (Figure 1). Continuous infusion for 5 days has produced steady plasma concentrations of HU. In our head and neck patients, q 4 hour oral dosing compliance over many weeks of therapy would have been unrealistic. Most clinical trials for both cervical and head and neck cancers used oral HU twice weekly.

Of great importance is that the toxicities of HU are reversible and not nearly as severe as the worst toxicities associated with cisplatin. Therefore, the phase I–II study was undertaken to determine the maximum tolerated dose and dose-limiting toxicities of parenteral HU in combination with radiation therapy. HU was administered as a continuous infusion on days patients were receiving radiation therapy; in the phase I portion of the study, the drug was escalated between patient cohorts.
PATIENTS AND METHODS

Administrative. This was a single-institution trial conducted at the Montefiore Medical Center and Albert Einstein College of Medicine beginning November 3, 1995. The aims of the phase I trial were to determine the maximum tolerated dose and dose-limiting toxicities of parenteral HU administered with hyperfractionated, accelerated external beam radiation therapy in patients with locally advanced squamous cell carcinoma of the head and neck.23 The phase II portion sought to define the clinical efficacy of this regimen assessed by objective response, time to relapse, and overall survival. We will only be reporting on the results of the phase II trial in this report. The study was approved and supervised by the Protocol Review Committee of the Albert Einstein Comprehensive Cancer Center and by the Institutional Review Board (IRB) for the Montefiore Medical Center.

Eligibility. All patients had biopsy-proven, non-metastatic, untreated American Joint Committee on Cancer (AJCC) stage IV squamous cell carcinomas of the oral cavity or oropharynx or stage II–IV squamous cell carcinoma of the hypopharynx. All patients had a Karnofsky performance status of >60, hemoglobin >10.0, serum creatinine <1.5 mg/dL, leukocytes >1500 mm\(^{-3}\), platelets >100,000 mm\(^{-3}\), serum bilirubin and AST <3× the upper limit of normal, and were >17 years of age. Feeding tubes were inserted liberally, patients underwent twice a day spraying with aerosolized saline to improve oral hygiene, and for both logistical and medical reasons, almost all patients received inpatient care. All patients had pretreatment endoscopic staging. Patients with prior malignancies, prior radiation therapy or surgery to the primary tumor or draining lymphatics, prior chemotherapy or uncontrolled substance abuse or comorbid disease were excluded. All patients gave written informed consent.

Treatment. Radiation therapy consisted initially of 74.4 Gy administered in 1.2-Gy fractions twice daily with at least 6 hours between treatments, Monday through Friday. The plan was to administer 62 fractions. After 20 patients were enrolled, with IRB approval, the radiation dose was reduced to 60.0 Gy, as discussed later and as detailed in prior publications.24,25 Patients were treated with a monoisocentric technique with appropriate blocks. The fields were reduced off the spinal cord after 45.6 Gy. The dose level of parenteral HU was 0.313 mg/m\(^2\)/min, and was derived from the phase I portion of the study. All parenteral HU was administered as a continuous infusion by Continuous Ambulatory Drug Delivery (CADD) pump on a daily \(\times 5\) schedule during radiation therapy. Parenteral HU was supplied by CTEP. The dose of HU was modified for leukopenia (leukocytes <1000 mm\(^{-3}\)), thrombocytopenia (platelets <50,000 mm\(^{-3}\)), severe mucositis (defined as deep ulceration precluding further radiation treatment), or grade 3–4 diarrhea. The study specified that patients with >N1 disease underwent a neck dissection >6 weeks after completing radiation therapy.

Data Collection. All patients underwent a history and physical examination, routine laboratory values, and a chest imaging prior to initiation of therapy. All patients had a CT scan or MRI of the head and neck. All patients underwent endoscopic staging prior to the initiation of therapy. Patients were restaged posttherapy with a CT or MRI and

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**Table 1. Demographic characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
</tr>
<tr>
<td>Pyriform sinus</td>
<td>11</td>
</tr>
<tr>
<td>Tongue (1 oral, 12 base of tongue)</td>
<td>13</td>
</tr>
<tr>
<td>Tonsil</td>
<td>4</td>
</tr>
<tr>
<td>Soft palate</td>
<td>2</td>
</tr>
<tr>
<td>Posterior pharyngeal wall</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>66 years</td>
</tr>
<tr>
<td>Range</td>
<td>57–77 years</td>
</tr>
<tr>
<td>Male:female</td>
<td>33 M:3 F</td>
</tr>
<tr>
<td>PS 0:1:2</td>
<td>7:24:5</td>
</tr>
</tbody>
</table>

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FIGURE 1. Mean nadir concentrations of q 4 hour oral HU. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
endoscopically. Follow-up was every 3 months for the first year, every 4 months for the second year, every 6 months for the third year, then annually.

**Statistical Considerations.** Response rates were estimated using observed proportion and 95% confidence intervals were calculated assuming binomial distribution. The survival curves were estimated using Kaplan–Meier analysis and 95% confidence intervals were estimated using the Greenwood formula. Survival was calculated from the first day of treatment, and survival curves were compared using the permuted log-rank test.

**RESULTS**

**Demographics.** As shown in Table 1, 36 patients were enrolled in this phase II trial; two thirds had either pyriform sinus ($n = 11$) or base of tongue ($n = 12$) primary tumors. The clinicopathologic staging is shown in Table 2.

**Toxicities.** The most severe acute toxicity of the study was mucositis, often associated with fever or positive blood cultures. Even in patients without frank mucositis, detailed radiographic studies demonstrated swallowing dysfunction. Midway through the phase II portion of the study, because of pharyngeal dysfunction, the dose of external beam radiation therapy was reduced from 74 to 60 Gy, which meant that the duration of the concurrent parenteral HU was decreased by 6 days. The new regimen was much better tolerated, without any apparent loss of efficacy. Better long-term tolerance included a decrease in odynophagia from 13 patients to 2 patients (64% vs. 11%, $p = .002$), decreased aspiration from 12 patients to 2 patients (60% vs. 11%; $p < .05$), and decreased requirement for a gastrostomy tube 16 patients to 3 patients (78% vs. 18%; $p = .002$). Other toxicities are shown in Table 3. There were no grade 4–5 toxicities.

**Response Rates.** As shown in Table 4, 21/36 (58%) patients were complete responders. One patient who never returned for follow-up was inevaluable. There was no difference between the high- and low-dose groups in terms of response rates.

**Survival, Local, and Regional Control.** Overall survival for the entire group is shown in Figure 2. With a mean follow-up of 35.1 months for the high-dose group and 25.5 months for the low-dose group, overall survivals were not significantly different (permuted log-rank test, $p = .42$) between the low- and high-dose groups, data not shown. Likewise, if we compare local (see Figure 3) and regional control (see Figure 4), there were no significant differences between the groups. It should be noted that the study was not originally designed to make those comparisons.

**DISCUSSION**

The aims of the current study were to combine the best available external beam radiation therapy with HU, a well-known radiation sensitizer delivered in a novel way in patients with unresectable squamous cell carcinoma of the oral cavity, oropharynx, and hypopharynx. Cisplatin ± 5-FU has become the standard of care for these patients;

### Table 2. Clinicopathologic staging.

<table>
<thead>
<tr>
<th>T classification</th>
<th>N0</th>
<th>N1</th>
<th>N2A</th>
<th>N2B</th>
<th>N2C</th>
<th>N3</th>
<th>Total no. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>T3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>T4</td>
<td>11</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>36</td>
</tr>
</tbody>
</table>

### Table 3. Acute toxicities.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>NCI CTCAE v2 grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>14</td>
</tr>
<tr>
<td>Infection</td>
<td>10</td>
</tr>
<tr>
<td>Fever</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>10</td>
</tr>
<tr>
<td>Neurologic</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>2</td>
</tr>
<tr>
<td>Liver</td>
<td>0</td>
</tr>
</tbody>
</table>

Other toxicities: pulmonary/pneumonia, 11; cardiac, 2; dysphagia, 4; thrush, 4.
however, therapy with cisplatin in combination therapy with external beam radiation is toxic. In 1 study, cisplatin-associated grade 3 or 4 hypomagnesemia or hypocalcemia occurred in 13 (30%) patients, hearing loss in 2 (5%), grade 3 or 4 neutropenia in 41 (95%), febrile neutropenia in 8 (19%), and serious infection in 1 patient (2%).

In a randomized trial of radiation therapy versus radiation therapy + cisplatin, grade 3 or worse toxicity occurred in 52% of patients enrolled in arm A, radiation therapy alone, compared with 89% enrolled in arm B, radiation therapy + cisplatin (p < .0001). In a randomized postoperative trial of radiation therapy alone versus radiation therapy + cisplatin, severe (grade 3 or higher) adverse effects were more frequent after combined therapy (41%) than after radiotherapy (21%, p = 0.001). Therefore, we undertook to study the role of HU as a potentially less toxic radiation sensitizer. The results from the phase I portion of the trial have been published.

HU is an inhibitor of the small subunit of ribonucleotide reductase, and its preclinical activity has been well described. In brief, HU inactivates the iron-free radical, and therefore the reduction step, in the synthesis of nucleoside diphosphates for DNA synthesis. Other investigators have employed oral HU, usually 2 to 3 times a week, as part of multimodality therapy for advanced disease. These regimens have generally been well tolerated.

In our study, parenteral HU was employed because of the ability to maintain a steady plasma concentration versus oral HU even when oral HU was administered every 4 hours in a monitored setting for a finite period of time. In contrast, 72 hours of parenteral HU resulted in essentially steady state plasma levels for 72 hours at 488, 460, 537, 760, and 1090 µM for doses of HU from 2 to 3 mg/m²/min (2.9–4.3 g/m²/day). The failure of earlier regimens employing oral HU administration in patients with solid tumors may have resulted from a suboptimal pharmacokinetic profile.

Chemoradiation can result in improved quality of life compared to surgery plus chemoradiation for locally advanced head and neck cancer. Often

### Table 4. Response rates.

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients (%)</th>
<th>N = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>21 (58)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Stable disease/minor response</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6 (16)</td>
<td></td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (5)</td>
<td></td>
</tr>
</tbody>
</table>

![FIGURE 2](https://www.interscience.wiley.com)

**FIGURE 2.** Overall survival for the entire group of patients (n = 36). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
this is because of the preservation of the larynx and the ability to speak. In Radiation Therapy Oncology Group (RTOG) trial 91-11, laryngectomy-free survival at 2 years for the patients treated with concomitant chemotherapy and radiotherapy was significantly better than for patients treated with radiotherapy alone \( (p = .018) \).\(^{43}\) Locoregional control at 2 years for patients in the concurrent treatment arm \((78\%)\) was significantly better than either radiation alone \((61\%)\) or induction therapy \((56\%)\) \( (p < .01) \).\(^{44}\) Overall survival was very similar for the patients in the 3 treatment arms (approximately 75\% at 2 years).

The external beam radiation therapy that was chosen for our study was considered at the time to be the most aggressive treatment for a group of patients with a uniformly poor prognosis. Preliminary results from RTOG 90-03\(^{45}\) suggested that hyperfractionated, accelerated radiation therapy resulted in better outcomes in patients with squamous cell carcinoma of the oropharynx, oral cavity, larynx, and hypopharynx, and was well tolerated.

At doses of 74 Gy, the toxicities of this regimen were formidable, with most patients requiring long-term alterations in diet, either tube feeding or liquid diet.\(^{24}\) The dysphagia toxicities were mirrored by centers using regimens containing oral twice daily HU,\(^{39,46,47}\) as well as in the University of Michigan study\(^{48–50}\) using gemcitabine, another ribonucleotide reductase inhibitor. Despite each center independently performing a phase I study, with longer follow-up, each of the other 2 groups also eventually chose dose reduction. After reducing both the dose of radiation, as well as the duration of HU, our regimen was also better tolerated.\(^{26}\)

With similar follow-up, the 2-year survival for the group receiving 60 Gy was slightly better than the 2-year survival noted in RTOG 9003,\(^{51}\) 65\% vs. 55\% in the arm employing hyperfractionated treatment. Such comparisons need to be made with extreme caution, and selection bias is a potential problem comparing disparate studies as is relatively small numbers. Because of the relatively small size of our study, equivalence would have to be confirmed by a randomized trial.

Projected survival in this group of patients is comparable to that achieved with platinum-based therapies. The dose reduction in both the HU and the radiation improved quality of life and maintained the clinical outcome. HU is off patent and so it is relatively inexpensive. Unfortunately, supply of intravenous HU is problematic. Nevertheless, given toxicities of standard platinum-based regimens, it would be worthwhile to compare par-
enteral HU-based therapy with platinum-based therapies in combination with external beam radiation therapy in patients with locally advanced squamous cell carcinoma of the head and neck.

REFERENCES

Parenteral Hydroxyurea and Radiotherapy


