High-Dose Intra-arterial Cisplatin Therapy Followed by Radiation Therapy for Advanced Squamous Cell Carcinoma of the Head and Neck

Objective: To assess the effectiveness of a protocol consisting of 4 cycles of high-dose intra-arterial cisplatin infusions followed by radiation therapy for improving chemotherapy response rates, organ preservation, and survival in patients with advanced-stage untreated and previously treated squamous cell carcinoma of the head and neck.

Design and Setting: A prospective study of sequentially enrolled patients treated in an academic medical center. The Kaplan-Meier method was used for survival analysis.

Patients: Fifty-eight nonpregnant adults, 18 years of age or older, with measurable untreated or recurrent advanced biopsy-proven squamous cell carcinoma of the head and neck.

Main Outcome Measures: Response rate to targeted intra-arterial cisplatin infusions, organ preservation, and survival.

Results: Fifty-eight patients (44 men and 14 women) were followed up for at least 2 years (median duration of follow-up, 27 months). Twenty-nine (67%) of the 43 previously untreated patients had a complete response to intra-arterial cisplatin therapy. Of the untreated patients, 28 are alive and disease free after a median follow-up time of 30 months. Five of the patients with recurrent disease had a complete response to intra-arterial cisplatin therapy. There were 4 survivors after a median follow-up time of 17.5 months. Of note, there were no deaths or serious complications related to the treatment in either group.

Conclusions: High-dose intra-arterial cisplatin therapy provides a high complete and partial response rate (91%). The combination of high-dose intra-arterial cisplatin and radiation therapy is effective in improving survival and organ preservation rates in patients with previously untreated, advanced squamous cell carcinoma of the head and neck. This treatment protocol is much less effective for recurrent disease.


TREATMENT OF head and neck cancer has evolved considerably over the past 20 years. Surgeons have made remarkable improvements in the ability to resect advanced tumors and to reconstruct the resulting defects. Despite these advances, it is acknowledged that preservation of the vital structures of the head and neck, if accomplished without added mortality, provides the best physiological and cosmetic results. Radiation therapy has long served as both a primary and an adjunctive treatment method directed to this goal. Hyperfractionated radiation techniques have increased the likelihood of locoregional tumor control by reducing affected tumor cell recovery. Chemotherapeutic agents with demonstrated efficacy against squamous cell carcinomas (SCCs) now appear to have improved both survival and organ integrity when used in anticipation of or in conjunction with radiation therapy.1,2

In 1994, our group began a study to assess the efficacy of intra-arterial cisplatin therapy in reducing the tumor cell mass present at the primary site prior to the initiation of radiation therapy. Our protocol, based on the method pioneered by Robbins et al,3 used selective intra-arterial infusions of cisplatin to achieve a high-dose intensity directed into the tumor bed, with the simultaneous intravenous infusion of the rescuing agent sodium thiosulfate. Our goals were to look at the survival benefits and preservation of vital organs in patients with previously untreated and recurrent advanced SCC of the head and neck.

RESULTS

Between August 1994 and July 1998, a total of 58 patients were entered in the...
PATIENTS AND METHODS

PATIENT SELECTION

This study was approved by the institutional review board of the George Washington University Medical Center, Washington, DC. Patients gave informed consent prior to participation in the study. All patients had biopsy-proven advanced SCC of the head and neck (ie, tumors located between the skull base and clavicles), and all were examined and staged by the head and neck tumor board team consisting of head and neck surgeons, medical oncologists, radiation oncologists, and neuroradiologists. The tumors were staged according to the criteria set forth by the American Joint Committee on Cancer Staging. Determinations were made by physical examination, computed tomography, or magnetic resonance imaging.

Patients were admitted to the study whether or not their tumors had been previously treated. Among the patients with recurrent and stage IV disease, almost all the tumors were resectable. Computed tomographic scans of the chest, as well as bone scans when there was a suspicion of bone involvement or metastases to bone, were obtained in all cases. The entry criteria were biopsy-proven, measurable, advanced SCC; nonpregnant adults 18 years of age and older with no upper age limit; and cardiac function sufficient to withstand the fluid loading associated with high-dose intra-arterial chemotherapy. The exclusion criteria included a creatinine clearance of less than 60 mL/min, a Karnofsky performance status of greater than 60%, or an Eastern Cooperative Oncology Group performance status of less than 2. The patients were then scheduled to begin 2 phases of treatment: the first included 4 weekly cycles of intra-arterial cisplatin infusions, followed by the second, radiation therapy.

TREATMENT PROTOCOL

Intra-arterial Cisplatin

The first treatment phase consisted of 4 weekly cycles of intra-arterial cisplatin infusions. The patients were admitted to the arteriography suite and underwent intravenous line placement and urinary tract catheterization to allow sufficient hydration to promote a brisk urinary output. Arterial catheters were placed in the femoral artery and passed up to the region of the tumor, and an initial arteriogram was obtained outlining the vasculature of the tumor to serve as a guide for the planned arterial infusions. Subsequently, 25 g of sodium thiosulfate was infused intravenously and immediately followed by the directed intra-arterial infusion of cisplatin (150 mg/m²) to the tumor bed. Amifostine (740 mg/m²) was administered intravenously to the patients if in the course of therapy their creatinine clearance was reduced to less than 60 mL/min. The patients were observed overnight and discharged the following morning. The serum creatinine levels and complete blood cell counts were carefully monitored throughout the study.

Radiation Therapy

We used a modified version of the University of Texas M. D. Anderson Cancer Center accelerated fractionation scheme using a concomitant boost schedule so that the

<table>
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<th>Primary Location</th>
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<th>Survival Status</th>
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<tr>
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*Skull based, skin, deeply invasive.
†Human immunodeficiency virus positive.

George Washington University Medical Center protocol, treated, and followed up for a minimum of 24 months (median duration of follow-up, 27 months). Survival was analyzed using the Kaplan-Meier survival method. There were 44 men and 14 women (age range, 29 to 85 years; median age, 59.5 years). Forty-three patients presented with untreated primary tumors (Table). The tumors were staged according to the TNM system as follows: stage II (n = 1), stage III (n = 3), and stage IV (n = 39). Twenty-nine of the 43 patients had a complete response (no tumor identified on physical examination or magnetic resonance imaging scans) to the 4 courses of intra-arterial cisplatin, 10 had a partial response, and 4 had no response, for a response rate of 91%. Twenty-eight patients (65%) remained disease free after a median follow-up of 30 months (Figure 1). Only 1 surviving patient has undergone the loss of a vital organ, the larynx.

Of the 15 patients that presented with recurrent disease, 4 remained alive and disease free (27%), after a median follow-up of 17.5 months. Five patients had a complete response to the intra-arterial therapy, 6 a partial response, and 4 no response. Of these 15 patients with
twice-daily fractions were given during the last 2.5 weeks of the radiation therapy course. For the twice-daily fractions, however, we selected the 160-rad (1.6-Gy) fraction size that was established by Wang et al. Therefore, radiation therapy to a dose of 6800 rad (68 Gy) was given in 2 phases. The first phase consisted of 20 daily fractions of 180 rad (1.8 Gy), delivering 3600 rad (36 GY) over a 4-week period, and continued without planned break into the second phase, also consisting of 20 fractions delivering 3200 rad (32 GY). In this second phase, however, an accelerated fractionation scheme consisting of 2 daily fractions of 160 rad (1.6 GY) given 6 hours apart was used. With this twice-daily fractionation, 3200 rad (32 GY) was administered within 2 weeks, while the overall course of 6800 rad (68 GY) was completed by 6 weeks.

Opposed lateral fields were used most often for the primary site and the upper neck area. The lower neck area and the supraclavicular fossa were treated with an anteroposterior field to a dose of 3140 rad (31.4 Gy). Larger nodes that were not located within the primary site fields were boosted further with photon and/or electron beams to a dose of 6000 rad (60 Gy). After the first 3600 rad (36 Gy), the spinal cord was excluded from the fields, and therapy to the posterior neck area was completed with electron beams to a dose of 3000 to 3500 rad (30-55 Gy).

The energies selected were 6 or 4 MV for the photon beams and 6 to 12 MeV for the electron beams. All beams were shaped with custom blocks or a multileaf collimator. Shields were reshaped, typically after a dose of 5420 rad (54.2 Gy) and again after 6480 rad (64.8 Gy), to tighten the margins around tumors as the radiation progressed.

PATIENT MONITORING

Follow-up Methods

All patients were carefully monitored for renal function status and changes in blood cell count. The patients were asked if any change in hearing was noted, and if affirmed, audiograms were obtained. Also, all patients were examined every 6 weeks by a head and neck surgeon for evidence of residual or recurrent tumor. Magnetic resonance imaging scans were obtained after the completion of the intraarterial infusions, 6 weeks after completion of the radiation therapy, and, subsequently, every 6 months to ensure that there were no deep nonpalpable recurrences and that there had been no unfavorable change in the residual scar at the tumor site.

Management of Residual Tumor

Magnetic resonance imaging scans were obtained after completion of both the 4 courses of intra-arterial therapy and the radiation therapy phase. The option of surgical intervention was open at both of these times. If the course of chemotherapy failed to result in significant reduction of primary or metastatic neck disease, the surgical intervention option could be exercised either before or after the radiation therapy phase. Remaining neck nodes larger than 2 cm were an indication for neck dissection. Since residual primary tumor is difficult to differentiate from posttherapy scarring, a biopsy was required prior to any major resection.

COMMENT

The objective of this study was to improve organ preservation and survival in patients with advanced untreated and/or recurrent SCC of the head and neck by the use of recurrent disease, 10 had undergone previous radiation therapy or radiation therapy with surgery or chemotherapy, 4 had undergone surgery alone, and 1 had undergone chemotherapy alone.

The cause of death of 26 (45%) of the 58 enrolled patients was evaluated. Most patients (n=13) died of distant disease. Seven patients died of locoregional disease; 3 died of unrelated disease; and 3 were unavailable for follow-up and were counted as deaths (Figure 2). Ten patients underwent resection of a residual mass in the primary tumor bed with neck dissection. No tumor was found in the specimens from 3 of the 10 patients. Another 24 patients had neck dissections for residual cervical adenopathy. Only 1 patient was unable to complete the protocol.

There were no deaths or serious complications that were attributable to the arteriography and no grade III/IV toxic reactions that were attributable to the chemotherapy.

Figure 1. Kaplan-Meier analysis of 58 patients with previously untreated (n=43) and recurrent (n=15) squamous cell carcinoma of the head neck between August 1994 and July 2000. Most deaths in the previously untreated group occurred within the first 20 months, although some patients died as late as 31 months.

Figure 2. Distant metastases represented the majority cause of death among 58 patients with squamous cell carcinoma of the head and neck, pointing up a weakness in the study protocol that has since been corrected by adding 2 cycles of intravenous chemotherapy.
intra-arterial infusions of cisplatin in high doses designed to enhance chemotherapy response rates in the primary and cervical metastatic tumor beds prior to the initiation of radiation therapy. The 2-year survival rate of 65% among these patients is greater than that in historical experience. The primary cause of death—distant spread of disease—represents a problem that could occur for several reasons. First, the locoregional control of the disease is effective, thereby allowing the patients to live sufficiently long for distant metastases to affect survival. Second, the focused arterial chemotherapy and radiation dose does not address the generalized microscopic spread of tumor cells. As a consequence, we have changed the comprehensive program for head and neck cancer to include 2 cycles of intravenous chemotherapy after completion of the intra-arterial chemotherapy phase and before the radiation therapy phase.

The results of intra-arterial chemotherapy and radiation therapy on recurrent squamous tumors were disappointing but not entirely surprising. Previous surgery and irradiation both have a detrimental effect on the arterial bed of the tumor site. Also, prior chemotherapy, especially with cisplatin, would have the tendency to select out resistant tumor cells. It is for these reasons that we think that intra-arterial infusion of cisplatin was of little benefit to these patients.

It is also important to note that none of the 58 patients suffered a grade III or IV toxic reaction, and there were no treatment-related deaths due to the neutralization of the toxic effects of cisplatin in the general circulation by the sodium thiosulfate. The adverse effects were limited to mild nausea, ipsilateral alopecia, mild unilateral hearing loss, and transient reduction of creatinine clearance. Nevertheless, a high response rate was achieved. Only 1 patient elected not to complete the full 4 cycles of intra-arterial cisplatin therapy.

CONCLUSIONS

The use of a targeted intra-arterial cisplatin protocol produces a high tumor response rate in previously untreated patients with advanced SCC of the head and neck. The combination of high-dose, intra-arterial cisplatin infusions and subsequent radiation therapy is effective in improving survival and organ preservation rates in previously untreated patients. This treatment method is of limited effectiveness for patients who have previously treated recurrent SCC.

Accepted for publication April 6, 2001.

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REFERENCES