

Neoadjuvant Therapy for Advanced Head and Neck Cancer With Allopurinol-Modulated High Dose 5-Fluorouracil and Cisplatin

A Phase I-II Study

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The combination of cisplatin (100 mg/m²) and 5-fluorouracil (5-FU) by continuous infusion (1 g/m²/day for 5 days) has been reported to produce a high response rate as neoadjuvant therapy for advanced squamous cell head and neck cancer. We sought to improve the response rate by increasing the dose of 5-FU to 1.5 g/m²/day and 2.0 g/m²/day with allopurinol modulation to reduce toxicity. The overall response rate in the 30 patients who received three courses of chemotherapy was 100% with a 50% complete response (CR) rate. A 50% CR rate was observed in patients with T3 (six of 12) and N3 (four of eight) disease. Six patients (four with CR) did not complete subsequent treatment as planned. Seven of 11 (63.6%) chemotherapy complete responders and three of 12 (25%) partial responders (one lost to follow-up) who received all planned treatment are free of disease. The major toxicity encountered was stomatitis (severe in 32%) followed by leukopenia. The maximum tolerated dose of 5-FU in this combination with allopurinol protection was 1.5 g/m²/day. Cisplatin plus high dose 5-FU does not appear to be associated with a higher CR rate than that reported with conventional doses of 5-FU and is more toxic.

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THE RESULTS OF THE STANDARD THERAPY of patients with stages III and IV head and neck cancer remain unsatisfactory. The use of chemotherapy before surgery or irradiation in these patients is being widely studied in hopes of improving survival by increasing the local control rate and eliminating possible distant micrometastases. In this setting, response rates in excess of 70% have frequently been observed with several regimens.¹⁻³ In general, there have been no significant problems with post-chemotherapy surgery and/or irradiation. The combination of cisplatin at a dose of 100 mg/m² and 5-fluorouracil (5-FU) at a dose of 1 g/m² for 5 days by continuous infusion is

now one of the most commonly used induction regimens in the US.⁴⁻⁷ It has been reported to produce a high overall response rate with a significant proportion of complete responses and is associated with acceptable toxicity.

When 5-FU is administered in conjunction with allopurinol, the daily continuous infusion dose can be increased to up to 2.5 g/m²/d for 5 days without marked increase in toxicity.^{8,9} The mode of action of allopurinol is through oxipurinol, the active *in vivo* metabolite of allopurinol, which inhibits orotate phosphoribosyl transferase and, in addition, is a weak inhibitor of thymidine phosphorylase. Both of these enzymes activate 5-FU. Unfortunately, in colorectal carcinoma no superiority for high dose 5-FU over standard doses has been demonstrated.⁹⁻¹¹ Allopurinol however, has been found to provide protection from marrow toxicity although stomatitis remains a dose limiting toxicity.⁸⁻¹¹

We have demonstrated *in vitro* that oxipurinol does not significantly inhibit the activity of 5-FU against several human tumor cell lines.¹² The objective of this study was to determine whether the use of an increased dose of 5-FU by continuous infusion combined with cisplatin would lead to improved efficacy in patients with advanced head

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TABLE 1. Patient Characteristics

No. of evaluable patients	33
Age (yr)	
Median	61
Range	(43-73)
Karnofsky performance score (%)	
Median	80
Range	60-100
Stage III	13
Stage IV	20
Primary sites	
Tongue	11
Tonsil	7
Retromolar trigone	5
Posterior pharynx	2
Floor of mouth	2
Nasopharynx	1
Alveolar ridge	1
Hypopharynx	1
Larynx	1
Soft palate	1
Unknown	1

and neck cancer. In this phase I-II study we increased the doses of 5-FU by 50% and 100%.

Materials and Methods

Eligibility was limited to patients with histologically proven stages III and IV squamous cell carcinoma of the head and neck region. They were required to have measurable local disease, no evidence of distant metastases, and no prior therapy for their malignancy. Pretreatment studies included a history and physical examination with a complete description of the extent of the primary and regional disease if present, triple endoscopy, routine studies of hematologic, renal and liver function, and a chest x-ray. Patients were required to have a Karnofsky performance score of no less than 50%, a serum creatinine of less than 1.5 mg/100 ml and/or a creatinine clearance of greater than 50 ml per minute, a leucocyte count greater than 4000/ μ l, and a platelet count greater than 150,000/ μ l.

Allopurinol was administered at a dose of 900 mg per day orally beginning 1 week before the initiation of chemotherapy and continued for 1 week after the termination of the 5-FU infusion. Patients were hydrated with 1 l of normal saline with 10 mEq of KCL infused over 1 to 2 hours; 100 mg/m² of cisplatin plus 50 g of mannitol in 1 l of normal saline were infused at a rate of 1 mg of cisplatin per minute. Following the cisplatin infusion, patients received 5-FU at a dose of either 1.5 g/m²/d or 2 g/m²/d for 5 consecutive days as a continuous infusion in 2 l of 5% dextrose in 0.5 normal saline per day. Antiemetics in combination were administered to control nausea and vomiting.

If there was no evidence of progression a second course of chemotherapy was administered 3 weeks after the start of the first course providing side effects from chemotherapy had satisfactorily resolved. If the second course of chemotherapy had to be postponed because of leukopenia (leucocyte < 3500/ μ l) or severe stomatitis, then the duration of the 5-FU infusion was reduced to 4 days. A third and final course of chemotherapy was administered three weeks after the second providing there were no persistent side effects or evidence of progression.

A three-stage study was employed. Ten patients were to be entered in Stage I and receive 1.5 g/m² of 5-FU. This number was considered sufficient to conclude that the rate of life-threatening toxicity was less than 20%. In Stage II ten additional patients were to be entered at a 2 g/m² dose of 5-FU. This number would be sufficient to conclude that the incidence of life-threatening toxicity was less than 20%. An additional 15 patients were to be entered in the third stage of the study, sufficient to estimate all median duration to failure with a coefficient of variation of less than or equal to 0.20 in all response rates with a standard error of less than or equal to 0.10.

Three weeks after the conclusion of the chemotherapy administration, patients were referred for definitive surgery and/or radiation therapy at a combined modality conference. A biopsy of the primary site was recommended for patients who were to receive radiation therapy following a complete clinical response to chemotherapy.

A complete response (CR) was defined as a complete disappearance of all evidence of tumor for more than 1 month. A partial response (PR) was defined as greater than a 50% reduction of the product of the longest perpendicular diameter of all measurable tumor for 1 month or more in the absence of any new lesions.

Results

Thirty-seven patients were entered onto this study between December, 1982 and November, 1985. Two were ineligible because of nonsquamous histology, and one because of the presence of metastatic disease. One patient died of aspiration pneumonia several hours following the start of chemotherapy. The remaining 33 patients who received at least one course of chemotherapy are evaluable for response and toxicity. Patient characteristics are shown in Table 1. The most frequent primary site was tongue followed by tonsil and retromolar trigone. In Table 2 the T and N stages are shown. Nearly all patients had either T3 or T4 disease. The commonest nodal status was N1 followed by N3.

Responses

Thirty patients received all three courses of chemotherapy. One patient had a cerebral vascular accident after

two courses and was taken off the study. Two patients received only a single course of chemotherapy, one refused further chemotherapy, and the other died of complications of chemotherapy. The responses observed are shown in Table 3. For all evaluable patients, the complete response rate was 45% and the partial response rate 55% yielding a 100% total response rate. For patients who received the prescribed three courses of chemotherapy, the complete and partial response rates were each 50%. There was very little difference in the complete and partial response rate between patients with Stage III or Stage IV. The response rates by T stage are given in Table 4. There was no significant difference in the complete response rates between T2, T3, or T4. The same was true for the response rates by N stage (Table 5). Of note, is the 50% complete response rate in patients with N3 disease which included four patients with N3a and four with N3b. The complete response rate for N3a was 25%, and 75% for N3b. In the latter group were three patients with at least one node > 6 cm and all three achieved a complete response.

There appeared to be a correlation between the percent of 5-FU administered and the complete response rate. As shown in Table 6, eight of the 12 patients who received 100% of their calculated 5-FU dose achieved a complete response in comparison to three of eight who received 87% of their 5-FU dose, and only one of four who received 80% of their 5-FU dose. A logistic regression analysis¹³ was performed to examine the relationship between 5-FU dose and complete response. The test resulted in a *P*-value of 0.099 suggesting marginal significance. Thus, despite the small sample size, there was some indication of a dose response effect.

Toxicities

As expected, the most frequent and clinically significant toxicity observed was stomatitis since allopurinol only provides partial protection from this toxicity when administered with high dose continuous infusion 5-FU.⁸⁻¹¹ The other three toxicities observed were leukopenia, nausea and vomiting, and diarrhea. Their incidence is shown in Table 7. Fifty-eight percent of the patients exhibited either moderate or severe stomatitis and 30% moderate or severe leukopenia. The incidence of life-threatening leukopenia was 6%. The majority of the patients (64%), however, had either no or mild leukopenia. For most patients (70%) nausea and vomiting were well controlled with antiemetics. No significant renal toxicity was observed. Two patients died secondary to leukopenia. One had the lowest Karnofsky performance score of the patients entered (60%) and the other refused appropriate medical management when he developed leukopenia and sepsis.

TABLE 2. T and N Stages

	N0	N1	N2	N3	Total
TX	—	—	—	1	1
T1	—	—	—	—	—
T2	—	—	1	1	2
T3	5	7	3	3	18
T4	2	5	2	3	12
Total	7	12	6	8	33

Two patients were escalated to the 2 g/m² dose level of 5-FU as planned. One developed moderate stomatitis and severe leukopenia and the other severe stomatitis, moderate leukopenia, and thrombocytopenia. Both had much less toxicity with a subsequent course at the 1.5 g/m² dose level. Because of the increased toxicity observed at the 2 g/m² dose level and the substantial toxicity already found at 1.5 g/m², the dose escalation was abandoned and all subsequent patients received 1.5 g/m²/d of 5-FU.

Subsequent Treatment

Twenty-five of the 30 patients who completed three courses of chemotherapy (12 complete responders and 13 partial responders) received a full course of radiation therapy. One of these complete responders relapsed during an inadvertent 3-week delay in starting radiation therapy and in another there was a long break during radiation therapy because of noncompliance. The doses to the primary ranged from 5040 rad to 7500 rad (median, 6660 rad). Ports were drawn to cover the primary tumor and draining regional lymph nodes. Neither doses nor ports were changed because of the preceding chemotherapy. The radiation therapy was well tolerated with no increase in side effects.

Five of the 30 patients who completed three courses of chemotherapy did not receive a full course of radiation therapy. Two died shortly after the conclusion of chemotherapy (one complete and one partial responder). One chemotherapy complete responder died of postoperative hemorrhage before starting radiation therapy and in another only surgery was recommended. The fifth patient (a partial responder) discontinued his radiation therapy after only a few treatments.

TABLE 3. Response to Chemotherapy

	% CR	% PR
Evaluable patients (33)*	45	55
Patients receiving three courses of chemotherapy (30)	50	50
Stage III (10)	60	40
Stage IV (20)	45	55

CR: complete response; PR: partial response.

* Number of patients.

TABLE 4. Response Rates by T Stage*

Response	Tx	T2	T3	T4
CR	1	1	7	6
PR	0	1	8	6
CR/Total %	1/1 100%	1/2 50%	7/15 47%	6/12 50%

CR: complete response; PR: partial response.

* Includes only patients who received three courses of chemotherapy.

The addition of surgery to chemotherapy and radiation therapy did not affect the relapse rate or improve overall survival compared with radiation therapy alone. This was not unexpected due to the predominance of chemotherapy partial responders who were selected to undergo surgery in addition to a full course of radiation therapy. In this group of 11 patients three are alive free of disease, one is alive with disease, six have died, and one is lost to follow-up (was free of disease at 19 months). The median survival for this group is 14 months. In comparison, the median survival for the group of 14 patients who received only radiation therapy to complete their planned treatment was 25 months. Six are alive free of disease, two alive with disease, and six have died. The only patient to develop distant metastases (skin) received all three treatment modalities.

The outcome of the complete and partial responders to chemotherapy is shown in Tables 8 and 9. The complete responders were analyzed separately as to whether or not they obtained a pathological complete response following chemotherapy, had residual carcinoma or carcinoma *in situ*, and those in whom no postchemotherapy biopsy or surgery was performed. A total of seven of the 15 complete responders are now free of disease from 18 to 45 months since the start of their treatment. Two of the pathologic complete responders have relapsed, one at 25 months who died, and the other at 11 months who had two subsequent surgical procedures and is now free of disease for 5 months.

Seven of the 15 patients who obtained a partial response to chemotherapy were converted to a complete response following all planned treatment. Of these seven, three remain free of disease from 17 to 42 months from the start of treatment. One was lost to follow-up at 19 months

TABLE 5. Response Rates by N Stage*

Response	N0	N1	N2	N3
CR	3	5	3	4
PR	3	6	2	4
CR/Total %	3/6 50%	5/11 45%	3/5 60%	4/8 50%

CR: complete response; PR: partial response.

* Includes only patients who received three courses of chemotherapy.

TABLE 6. Percent 5-FU Administered and Response*

% 5-FU	No. of patients	No. achieving CR
100	12	8
93	6	3
87	8	3
80	4	1

5-FU: 5-fluorouracil; CR: complete response.

* Includes only patients who received three courses of chemotherapy

when he was free of disease. Three of the seven have relapsed and two have died.

The median survival time for all 33 patients entered onto this study was 21 months and the proportion surviving 1 year 73%. For patients who achieved a complete response to chemotherapy the 1 year survival was 87% compared with 67% for the partial responders who received three courses of chemotherapy. The median survival time for the chemotherapy complete responders was in excess of 25 months compared with 14 months for the partial responders. A log-rank test¹⁴ was used to compare overall survival between complete and partial responders. No significant differences were detected ($P = 0.18$).

Of the 30 patients who received three courses of chemotherapy only 24 received all planned treatment as scheduled. Currently ten are free of disease from 10 to 38 months from the start of treatment. Seven of the 11 complete responders to chemotherapy who received all planned treatment are free of disease (63.6%) compared with three of 12 partial responders (25%). One partial responder is lost to follow-up.

Discussion

In an attempt to improve the cure rate and take advantage of the higher response rate to chemotherapy observed in previously untreated patients,¹⁵⁻¹⁷ interest has been focused on the role of chemotherapy administered before surgery or radiation therapy in patients with advanced head and neck cancer. This approach, which is called neoadjuvant or induction chemotherapy, frequently produces dramatic tumor shrinkage in the majority of patients. Unfortunately, many patients eventually relapse and the impact of neoadjuvant therapy on overall survival has not been adequately established in properly conducted randomized studies.⁷

One of the most popular neoadjuvant regimens in this country is the combination of cisplatin plus 5-FU by continuous infusion originally described by the investigators at Wayne State University.⁴⁻⁷ They have reported that three courses of this regimen results in a 93% overall response rate and most importantly, a 54% complete response rate. Chemotherapy responders were observed to have improved survival compared with non-responders

TABLE 7. Toxicity (%) Grade*

Type	Absent	Mild	Moderate	Severe	Life-threatening
Stomatitis	26	16	26	32	0
Leukopenia	40	24	15	15	6
Nausea/ vomiting	41	29	27	3	0
Diarrhea	70	6	18	6	0

* Southwest Oncology Group criteria.

regardless of subsequent therapeutic modalities used. In addition, this regimen was associated with very acceptable toxicity and did not interfere with subsequent radiation therapy and/or surgery.⁷

We sought to improve the results of the cisplatin plus 5-FU regimen, especially as regards complete response rate by increasing the dose of 5-FU. Allopurinol was employed to modulate the toxicity of the high dose of 5-FU. Though increasing the dose of 5-FU did not improve the response rate in colorectal carcinoma,⁹⁻¹¹ a tumor notoriously refractory to chemotherapy, we thought that the higher dose of 5-FU might improve the response rate in squamous cell head and neck carcinoma, a tumor more sensitive to chemotherapy. We did not alter any of the other features of the Wayne State regimen, *i.e.*, the dose of cisplatin, the number of days of 5-FU infusion, the number of cycles, or the interval between courses.

Though no patient achieved less than a partial response, we were disappointed in the complete response rate which was no different from that reported by the Wayne State investigators.⁴⁻⁷ With the exception of preliminary results from pilot studies,¹⁸ however, their 54% complete response rate represents the highest reported to date for neoadjuvant therapy of head and neck cancer. Unfortunately, other investigators have reported a lower complete response rate (range, 17%–37%) for the cisplatin plus 5-FU combination.¹⁹⁻²²

It is possible that our regimen is superior in patients with the greatest nodal involvement (N3). We observed a 50% complete response rate (four of eight patients) in this category compared with the 25% complete response rate reported by Wayne State in patients with T4N3 disease.⁷ Unfortunately, these numbers are too small to allow an accurate comparison between the two regimens for this nodal stage.

The importance of achieving a pathologic complete response with neoadjuvant therapy has only recently been appreciated.⁷ In this group of patients prolonged survival has been reported by several investigators including studies in which only radiation therapy is used following neoadjuvant chemotherapy.^{20,23} The prognostic importance of a repeat biopsy of clinical complete responders was not appreciated when our trial began and, thus, nearly half

TABLE 8. Outcome of Complete Responders to Chemotherapy

Response after pathologic examination	No. of patients	Outcome
CR	5	1 discontinued XRT and relapsed.
CR	5	2 relapsed at 25* (died) and 11 mo (now NED).
CR	5	2 NED at 39 and 18 mo.
Carcinoma <i>in situ</i>	1	NED at 35 mo.
Residual carcinoma	2	1 died of postoperative hemorrhage. 1 NED at 45 mo.
Unknown	7	1 delay in starting XRT and relapsed.
Unknown	7	1 died of aspiration pneumonia.
Unknown	7	3 relapsed at 21, 15, and 10 mo.
Unknown	1	2 NED at 38 and 27 mo.

CR: complete response; XRT: radiation therapy; NED: no evidence of disease.

* Time from starting treatment.

of our complete responders (seven of 15) did not have a postchemotherapy biopsy or surgery. We were disappointed, however, to observe that two of the four patients who achieved a pathologic complete response and then received all planned therapy have relapsed, one as late as 25 months from the start of treatment.

We anticipated that even with protection from high dose allopurinol our toxicity would be greater than with

TABLE 9. Outcome of Partial Responders to Chemotherapy

Response after all treatment	No. of patients	Outcome
CR	7	2 relapsed and died at 14* and 13 mo.
CR	7	1 relapsed at 18 mos, alive at 29 mo.
CR	7	3 NED at 42, 26, and 17 mo.
CR	7	1 lost to FU (NED 19 mo).
PR	8	1 died shortly after chemotherapy
PR	8	1 discontinued XRT, alive with disease at 14 mo.
PR	8	6 died—21, 14, 10, 9, 8, and 6 mo.

CR: complete response; PR: partial response; FU: follow-up; NED: no evidence of disease; XRT: radiation therapy.

* Time from starting treatment.

conventional dose 5-FU, particularly in regards to stomatitis. Nearly one-third of our patients developed severe stomatitis in contrast to the 11% incidence of stomatitis (not graded) reported by the Wayne State investigators. Sixty percent of our patients developed leukopenia, not too dissimilar from the 41% incidence with conventional dose 5-FU. However, we had a 6% incidence of life-threatening leukopenia.

Other investigators have found the cisplatin plus conventional dose 5-FU regimen to be associated with significantly more toxicity. In fact, Amrein and Weitzman reduced the dose of 5-FU from 1 g/m²/day to 800 mg/m²/day in their trial because a few of their patients encountered severe leukopenia at the 1 g/m² dose level.²⁴ It is interesting to note that when 5-FU is administered as the only chemotherapeutic agent in colorectal carcinoma for a 120-hour infusion at a roughly equivalent dose level of 30 mg/kg/day there is a 37% incidence of severe stomatitis (three of eight patients).²⁵ This degree of severe stomatitis is even greater than we observed with the higher dose level of 5-FU.

Only two patients were escalated to the 2 g/m²/day dose level of 5-FU and both developed toxicity of such degree that on subsequent courses they could only receive a 1.5 g/m² dose level. Considering the toxicity we observed at the 1.5 g/m² dose level and the toxicity in these two patients who received 2 g/m²/day, we feel that the maximally tolerated daily dose of 5-FU by continuous infusion with allopurinol modulation is 1.5 g/m²/day when combined with cisplatin.

Though there are serious limitations in comparing two single institution clinical trials, the therapeutic results with our regimen appear roughly equivalent to the one initially reported by the Wayne State investigators using the 1 g/m² dose level of 5-FU. Support for a randomized trial comparing the 1 g/m² and the 1.5 g/m² dose levels of 5-FU with cisplatin will come if additional studies, including multi-institutional trials, demonstrate a significantly lower CR rate for cisplatin plus conventional dose 5-FU.

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