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Methotrexate and 5-fluorouracil in the treatment of squamous and other carcinomas of the head and neck

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Summary. Thirty-two patients with squamous cell carcinomas of the head and neck and three patients with parotid gland carcinomas were treated with methotrexate 40 mg/m^2 followed 1 h later by 5-fluorouracil 600 mg/m^2. Treatments were repeated on day 8, then every 2 weeks, toxicity permitting. Of 30 evaluable patients with squamous cell carcinomas, 9 (30%) achieved a partial (8) or complete (1) remission. Performance status and prior treatment history appeared to affect the probability of response. The original site of the primary had no apparent effect on response rate. Six patients having objective tumor regression but less than the amount required for classification as partial remission all had marked symptomatic relief and had "response" durations and survivals quite comparable to those in patients achieving partial remission. One patient with a parotid gland carcinoma attained a complete remission, one had a minor response, and one refused to return for follow-up. Myelosuppression and stomatitis were dose-limiting in some patients, although the regimen was generally well tolerated. Three patients (9%) developed cerebellar toxicity, suggesting that prior ethanol abuse could possibly predispose to this side effect.

Introduction

Methotrexate and 5-fluorouracil are both active chemotherapeutic agents in the treatment of squamous cell carcinomas of the head and neck [2, 12, 16]. There are limited data on the effectiveness of these and other agents in parotid and other types of head and neck carcinomas [7, 18, 21]. In recent years a great deal has been published on the theoretical advantages of biochemically sequencing methotrexate and 5-fluorouracil, such as giving methotrexate at least 1 h before the 5-fluorouracil [3, 4, 15]. Initial clinical studies in a variety of malignancies tended to support the concept of biochemical sequencing [6, 9, 13, 15, 17, 19, 24], although at least two later randomized studies have failed to demonstrate any superiority of this regimen over concurrent methotrexate-5-fluorouracil administration or administration of 5-fluorouracil before methotrexate [5, 22]. Nevertheless, the activity of the combination has been somewhat higher than anticipated.

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Preclinical data suggested that a methotrexate dose of at least 200 mg/m^2 was needed for biochemical sequencing to result in synergism [15]. and in most studies doses ranging from 200 to 1000 mg/m^2 have been used. One might speculate that the higher response rates than expected seen with the combination might be due to the methotrexate dose used rather than to sequencing; however, the combined costs of methotrexate and calcium leucovorum for such doses are high, and toxicity is occasionally severe. In November, 1980, we initiated a study of biochemically sequenced methotrexate and 5-fluorouracil in squamous and other carcinomas of the head and neck. Instead of using a methotrexate dose of 200 mg/m^2, we used standard-dose methotrexate (40 mg/m^2) because of the high cost and potential toxicity of a higher dose and because it had not been proven in humans that a higher dose was necessary. In this paper we report our results.

Method

Thirty-five consenting patients were entered on this study, including 32 with squamous cell carcinomas of the head and neck and 3 with carcinomas of the parotid gland. Among those with squamous cell carcinomas, 16 had had prior chemotherapy and radiotherapy (including 6 with prior exposure to methotrexate), 2 had had prior chemotherapy only, 13 had had prior radiotherapy only, and 1 had had no prior chemotherapy or radiotherapy. All 3 patients with parotid carcinomas had had prior chemotherapy (including 1 with prior 5-fluorouracil) and radiotherapy. The Zubrod performance status was 0 in 2 patients, 1 in 8 patients, 2 in 23 patients, 3 in 1 patient, and unspecified in 1 patient.

Patients received methotrexate 40 mg/m^2 by rapid IV infusion followed in 1 h by 5-fluorouracil 600 mg/m^2. Treatments were repeated 1 week after the first dose administration, then every 2 weeks thereafter, providing recovery from toxicity had occurred.

Leukocyte, granulocyte, and platelet counts were determined once a week, and hepatic and renal function tests were performed prior to each course of therapy. Chemotherapy doses were decreased by 20% if the granulocyte nadir was $< 500/\mu l$, if the platelet nadir was $< 50\,000/\mu l$, or if the patients developed moderately severe stomatitis. In some patients, doses were escalated by 20% if the patient had had no myelosuppression, stomatitis, or other dose-limiting toxicity. Methotrexate doses were decreased

by 50% in patients with a serum creatinine of 1.5–2.0 mg%, and patients with a serum creatinine >2.0 mg% were excluded from the protocol.

Complete remission was defined as disappearance of all tumor and resolution of all symptoms for >4 weeks. Partial remission was defined as a 50% or greater reduction in the sum of the products of perpendicular diameters of all measurable lesions or an estimated 50% or greater reduction in size of evaluable lesions for >4 weeks. The category stable disease included patients with <50% reduction in tumor size and <25% increase in tumor size, maintained for a minimum of 8 weeks. Treatment failures included patients who died too early to be evaluated fully.

Results

Of the patients with squamous cell carcinomas, 2 refused to return for follow-up. Overall, 9 of 30 evaluable patients (30%) with squamous cell carcinomas responded to treatment, and 14 patients (47%) were classified as having stable disease, including 6 patients (20%) with subjective improvement and objective tumor regression but by <50% ("minor responses"). The one complete remission lasted 40 weeks. The median duration of partial remissions was 21 weeks (range, 7+ to 32 weeks). The median duration of stability was 14 weeks (range, 8–25 weeks). If patients with minor responses are separated out from others classified as having stable disease, then median duration of minor response is 20 weeks (range, 11–21 weeks), while the remainder of the stable disease group had stable disease for a median of 11 weeks (range, 8–19 weeks). The patient achieving a complete remission survived 53 weeks. The median survival for patients achieving partial remission was 29 weeks (range, 7+ to 45+ weeks, with 2 patients still alive). Patients classified as having stable disease also had a median survival of 29 weeks (range, 8+ to 143 weeks, with 1 patient still alive). The subcategory of patients with stable disease consisting of those with minor responses, had a median survival of 32 weeks (range, 23–83 weeks), while the combined other patients from the stable disease category had a median survival of 21 weeks (range, 8+ to 143 weeks). Treatment failures had a median survival of 4 weeks (range, 2–14 weeks).

We examined the effect of various prognostic factors on the response rate (Table 1). The response rate in performance status 0 and 1 patients was 63% (5 of 8), compared with 19% (4 of 21) for evaluable patients with performance status 2 or 3.

All 3 patients without prior radiation responded, as opposed to 6 of 30 patients (20%) with prior radiation exposure. The single patient with prior methotrexate exposure who responded to the methotrexate-5-fluorouracil combination had not been demonstrated to be methotrexate-resistant. Overall, 6 of 18 patients (33%) with any prior chemotherapy responded, as against 3 of 12 (25%) without prior chemotherapy exposure.

Table 1. Response of squamous cell carcinoma of the head and neck to methotrexate – 5-fluorouracil by various prognostic factors

Patient Characteristics[a]	No. (%) evaluable	No. (%) CR or PR[b]	No. (%) stable	No. (%) failing
Prior treatment				
None	1	1 (100)		
XRT only	11	2 (18)	8 (73)	1 (9)
Chemotherapy only[c]	2	2 (100)	0	0
XRT + MTX (± other chemotherapy)	6	1 (17)	3 (50)	2 (33)
XRT + other chemotherapy	10	3 (30)	3 (30)	4 (40)
Performance status				
0	1	0	1 (100)	0
1	7	5 (71)	2 (29)	0
2	20	3 (15)	10 (50)	7 (35)
3	1	1 (100)	0	0
Unknown	1	0	1 (100)	0
Tumor site				
Hypopharynx	6	2 (23)	2 (33)	2 (33)
Tongue	5	2 (40)	2 (40)	1 (20)
Larynx	4	2 (50)	1 (25)	1 (25)
Mouth floor	3	1 (33)	2 (67)	0
Tonsil	3	1 (33)	1 (33)	1 (33)
Alveola	3	0	2 (67)	1 (33)
Epiglottis	2	0	1 (50)	1 (50)
Soft palate	1	0	0	1 (100)
Sinus	1	0	1 (100)	0
Skin	1	1 (100)	0	0
Unspecified	1	0	1 (50)	0

[a] XRT, radiotherapy; MTX, methotrexate
[b] CR, complete remission; PR, partial remission
[c] Neither of these 2 patients had previously received methotrexate

Table 2. Toxicity of biochemically sequenced methotrexate and 5-fluorouracil

Toxicity	% Courses with toxicity[a]
Granulocyte nadir:	
>1000/μl	86
500–1000/μl	12
<500/μl	2
Infections	1
Platelet nadir:	
>100 000/μl	97
50 000–100 000/μl	3
<50 000/μl	0
Bleeding	0
Stomatitis	
None	65
Mild	27
Moderate	6
Severe	2
Nausea, vomiting	
None	77
Mild	14
Moderate	6
Severe	3
Conjunctivitis	2
Diarrhea	2
Facial swelling	1
Postural hypotension	1
Central nervous system	2

[a] 133 courses evaluable

One patient with a parotid gland carcinoma experienced a complete remission lasting 62 weeks. Her condition deteriorated rapidly following development of meningeal carcinomatosis, and she died 2 weeks later. An additional patient with parotid carcinoma experienced a minor response, and the third patient refused to return for follow-up.

Toxicity is outlined in Table 2. Treatment was generally well tolerated. Stomatitis and myelosuppression were dose-limiting in some patients. There were no treatment-related deaths.

Discussion

Our regimen of methotrexate 40 mg/m^2 followed 1 h later by 5-fluorouracil 600 mg/m^2 provided palliation to a substantial proportion of our patients with squamous cell carcinoma of the head and neck, including 30% who achieved complete remission or partial remission and an additional 20% who experienced marked symptomatic relief concurrently with objective shrinkage of tumor by less than that required to qualify as a partial remission. While these results are no better than those previously reported for methotrexate alone [2, 8, 11, 12, 16], it is difficult to compare series because of differing patient characteristics. It is possible that use of a higher dose of methotrexate would have resulted in a higher response rate [15]. Some studies with higher doses of methotrexate than those used by ourselves have yielded higher response rates than we noted [5, 17, 19, 22], while others have reported comparable or lower response rates [10]. In our own experience (unpublished data), 10 patients treated with a comparable methotrexate-5-fluorouracil regimen except that the dose of methotrexate was higher (200 mg/m^2 with leucovorin rescue) had a lower response rate (10%) than that noted in this series. Theoretically, methotrexate doses of ≥ 200 mg/m^2 would be required for synergism with 5-fluorouracil [15], but this has never been directly tested in humans and some previous studies using methotrexate alone in head and neck cancers have not demonstrated a dose-response effect [8, 10, 11]. With high-dose methotrexate it is necessary to give folinic acid (citrovorum factor), and it is possible that the folinic acid could directly interfere with the synergism between methotrexate and 5-fluorouracil, although the folinic acid is not usually given until several hours after chemotherapy.

In any event, while our regimen was very well tolerated and very inexpensive, it is clear that it does not represent a major advance in the treatment of head and neck cancer.

The difficulties of assessing response of malignancies to chemotherapeutic agents have been well documented [23]. Generally, it appears that the smaller a lesion is, the greater the percentage change in tumor size that is needed to be certain that the change is real and not just due to observer error [23]. In addition, if a tumor is required to decrease in size by $>50\%$ before it is judged as having responded, the chance of a false-positive result is lower but the chance of a false-negative is higher than if only a 25% decrease in tumor size is required for a tumor to be judged as having responded to treatment [23]. It is of note that our patients with minor responses (i.e., definite objective tumor regression but by less than 50%) had "response" duration and survival quite comparable to those in patients with true partial remissions, and superior to those of other patients included in the stable disease category. While it is important that an attempt be made to observe rigid response criteria to facilitate comparisons between studies, it is also important to recognize that such minor responses often constitute a real biologic effect of treatment and frequently are associated with definite palliation of symptoms.

This treatment regimen was generally very well tolerated in our patients. Gastrointestinal toxicity was generally mild, and only one patient developed a potentially life-threatening complication (i.e., neutropenia-related pneumonia). It is of interest that 3 (9%) of our patients developed cerebellar toxicity. This complication has previously been reported to occur in up to 7% of patients receiving 5-fluorouracil [20], but it has been very uncommon in our experience of a large number of patients, including many with other malignancies that we have treated with various methotrexate-5-fluorouracil regimens. It is known that ethanol abuse is frequently an etiologic factor in head and neck cancers [14] and that ethanol abuse can also cause substantial damage to the cerebellum [1]. All 3 of our patients who developed cerebellar toxicity had a history of ethanol abuse, and it is quite possible that this predisposed our patients to 5-fluorouracil-induced cerebellar toxicity.

In summary, methotrexate 40 mg/m^2 followed 1 h later by 5-fluorouracil 600 mg/m^2 is an inexpensive, well-tolerated regimen capable of providing palliation to a substantial proportion of patients with advanced head and neck cancers. However, it cannot be determined from our data whether it is any better than methotrexate alone.

5-fluorouracil-induced cerebellar toxicity is not uncommon in this patient population.

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