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A PRELIMINARY CLINICAL STUDY IN THE USE OF MISONIDAZOLE IN CANCER OF THE HEAD AND NECK

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Summary.—The value of misonidazole in advanced head and neck cancer was examined in 3 ways and the preliminary results are reported in a randomized study with large fractions of irradiation, when misonidazole appeared to confer no advantage; whereas in previously (partially) treated patients misonidazole was possibly useful. The combination of hyperbaric oxygen and misonidazole did not appear to be toxic.

THE PROGNOSIS of advanced head and neck cancer is poor, with about 15% of patients surviving for one year. Since most of these patients die from the effects of local disease, it was considered worthwhile to explore misonidazole in this disease.

MATERIALS AND METHODS

This study comprises 38 patients with histologically-confirmed cancer of the head and neck, 37 with squamous carcinoma and 1 with malignant melanoma. Of these patients, 23 received misonidazole and 15 control patients did not. Of those patients who received misonidazole, 13 were part of a randomized study (compared with the 15 controls), 7 received misonidazole with radiation after previous treatment, and 3 with radiation in hyperbaric oxygen.

Patients selected for this study all had locally advanced disease, that is, Cape Town t.3/t.4 or n.3 disease. The primary growths, therefore, measured at least 4 cm in diameter and were often massive, or the smaller lesions were accompanied by fixed nodes in the neck.

Radiation treatment was given on a cobalt unit with fields large enough to encompass the lesion with a 1–2 cm margin. Midline lesions were treated with 2 opposing fields, whereas those more laterally placed were treated with individually drawn planned fields using beam direction shells and tissue compensators. The tumour dose was 3600 rad in 6 fractions in 17 days overall time, that is, a T.D.F. of 93.

The dose of misonidazole was standardized at 2 g/m^2 of body surface given orally 4 h before treatment.

The age of the patients randomized to receive, or not to receive, misonidazole ranged on the one hand from 33–71 years, and on the other, from 30–71 years. The mean ages for the 2 groups was 57 and 58 years respectively.

A comparison of the stages of the lesions in the 2 groups shows that the mean t. weighting in the misonidazole group was 3·1 and in the control group, 3·2. Likewise, the mean node weighting in the misonidazole group was 0·9 and in the control group, 1·2. (This is calculated by summating the products of the number of subjects in each stage with the stage number and dividing by the number of the total subjects in each group.)

Both groups showed a predominance of well-differentiated to moderately differentiated squamous carcinoma, although the proportion of non-keratinizing tumours (5/12 and 4/15) was slightly higher in the misonidazole group and the proportion of poorly differentiated and anaplastic tumours was slightly higher in the control group (1/12 and 4/15). There was a similar preponderance of lesions of the tongue, floor of mouth and lower jaw in each group (10/13 and 12/15 respectively).

RESULTS

In the Misonidazole group there were 18 lesions where the tumour volume could be assessed. The total tumour volume of all these lesions was 1789 cm^3 with a mean of 99 cm^3 per lesion. However, 2 of these

patients only recently completed treatment and if these 2 patients are excluded, the mean tumour volume of the remaining 16 lesions is 107 cm³. One lesion, a mass of glands of the neck, had an initially computed volume of 840 cm³, and if this is also excluded, the total volume of the remaining fifteen lesions is 872 and the mean 58. After completion of treatment, when the reaction had settled, the minimum individual tumour volume was again assessed. The total residual volume of tumour in the remaining 16 lesions was estimated to be 181 cm³ with a mean of 11 cm³. If, once again, the very large lesion of 840 cm³ is excluded from these calculations, the total tumour volume in the fifteen remaining lesions was estimated to be 91 cm³ with a mean of 6 cm³.

In the control group where no misonidazole was given, there were 23 lesions where the tumour volume could be assessed, the total being 1091 cm³ with a mean of 47 cm³. However, 8 of these are in patients who are on treatment at the present time or who still have reaction following treatment. If these 8 are excluded, the total tumour volume in the remaining 15 lesions is 928 cm³ with a mean of 62. After treatment, the total residual volume of these tumours was measured as 111 cm³ with a mean of 7·4.

The total residual volume, therefore, in those patients who received misonidazole after treatment, is 10% of the volumes measured before treatment, compared with 12% in those patients who did not receive the drug.

At the present time, 4 of 13 patients who received misonidazole are clear of disease, 3 are indeterminate where an ulcer or a mass remains or reaction is still present, and 6 have suffered a recurrence of their tumours. In those 15 patients who did not receive the drug, 3 are clear of disease at the present time, 7 are indeterminate where an ulcer or a mass remains or still have a radiation reaction, and 5 have suffered a recurrence of their tumours.

Mucosal reactions were assessed during the treatment and scored as minimal or none, patchy membrane or confluent/thick membrane. Numerical values of 1–3 were assigned to these reactions. The mean reaction in 12 patients who received the drug was 2·8 compared with a mean value of 2·4 in 14 patients who did not receive the drug. In 3 of the 12 patients who received the drug, the reaction was sufficiently intense to compel suspension of treatment until it had subsided; whereas,

TABLE I.—*Comparison of 2 Groups in Randomized Trial*

		Misonidazole		None	
Age		N = 13		N = 15	
Range		33–71		30–71	
Mean		57		58	
Staging		N = 14	Stage × N	N = 15	Stage × N
Primary growths	t. 1	1	1	0	0
	2	0	0	0	0
	3	9	27	12	36
	4	4	16	3	12
Mean			3·1		3·2
Nodes	n. 0	7	0	7	0
	1	4	4	2	2
	2	1	2	2	4
	3	2	6	4	12
Mean			0·9		1·2
Histology			N = 12		N = 15
Keratinizing			7		11
Non-keratinizing			5		4
Well/Moderately Diff.			11		11
Poorly Diff./Anaplastic			1		4
Site					
Tongue/F.O.M./Jaw			10		12
Pharynx			3		3

TABLE II.—*Comparison of Results in Randomized Trial*

	Misonidazole	None
Tumour volumes	N = 15	N = 15
Total pre-treatment	877 (1717)	928
Mean	58	62
Total post treatment	91 (181)	111
Mean	6	7·4
Residual % volume	10	12
Present clinical state	N = 13	N = 15
Clear	4	3
Recurrence	6	5
Indeterminate	3	7
Mucosal reactions	N = 12	N = 14
Mean score	2·8	2·4
Treatment interrupted	3	3

in 3 of 14 patients who did not receive the drug was this necessary.

Seven patients who had had previous treatment were also treated with misonidazole and radiation in the same dose; however, 6 treatments were given to 2 patients, 5 to 2 patients and 4 to 3 patients. The previous treatment varied from 2000 rad in 5 fractions to 6000 rad in 44 fractions. The age range of patients was 44 to 79 years with a mean of 63; the mean t. weighting was 2·8 and the mean node weighting 1·1. The total tumour volume before treatment in 8 lesions was 652 cm^3 with a mean of 82. In 7 lesions after treatment, the total residual tumour volume was 108 cm^3 with a mean of 15. The residual percentage of tumour volume was therefore 16%, a figure similar to that seen in the other patients. In these 7 patients, the mean mucosal reaction was assessed at 2·1 as compared with 2·8 in those patients receiving the drug who had had no previous treatment. None of the 7 patients required to be rested from treatment and at the present time, 4 of the 7 are locally free of disease.

Three patients were treated with Misonidazole and irradiation in the same scheme, but in hyperbaric oxygen. One patient had a malignant melanoma of the palate measuring 7 cm long with multiple glands in the neck. A further patient had a very large squamous carcinoma of the tongue and a further patient had a very large carcinoma of the pharynx. The last 2 patients had received methotrexate treatment previously. The patient with malignant melanoma had complete healing of the primary tumour, as did the patient with the carcinoma of the tongue. Both these, however, experienced metastatic disease outside the irradiated volume. No added neurotoxicity was noted in these 3 patients with the combination of the hyperbaric oxygen and the misonidazole, and it would appear, therefore, to be a practical and possible avenue of treatment.

Toxicity

During the course of the study, complications due to misonidazole were diligently sought. Repeated enquiries were made for evidence of neurological toxicity, the blood count, blood pressure, urine and serum chemistry were examined before, during and after treatment. Of the 23 patients who received misonidazole, 9 experienced sensory neuropathy. In all cases this was mild and only incapacitating in one patient who had pre-existing rheumatoid arthritis. One patient experienced transient ataxia and a further vertical nystagmus. Both were somewhat dehydrated and the symptoms cleared rapidly with intravenous fluids. Two patients experienced constipation with the clinical picture being reminiscent of that sometimes seen after the administration of vincristine. Minimal and transient findings included albuminuria in 2 patients, glycosuria in one patient, a rise in the serum alkaline phosphatase in one patient and the L.D.H. in one patient. One patient died with a severe local reaction of pneumonia and electrolyte imbalance. He had initially refused hospital admission.

In the control group, one patient experienced a depression in the platelet count to 42,000

DISCUSSION

The failure to show clinical advantage with misonidazole in the randomized study, is disappointing. However, this may be a similar situation to that seen in the treatment of tumours with hyperbaric oxygen, where an advantage was found for smaller tumours and not for larger tumours. Under ordinary circumstances, the patients treated in this study would have been given palliative treatment only. On the other hand, the results obtained in patients who had had previous treatment were unexpected and gratifying.

The reactions seen were judged to be at the limit of clinical tolerance. It is felt that these could be reduced by careful treatment planning to reduce the areas of high dose only to that volume occupied by the tumour and to have a tumour surrounding normal tissue ratio of about 5:4.

Another approach to the use of this drug might be to treat large lesions with split course therapy. An initial course of 2000 rad in 5 fractions in 5 days followed by a month's rest and then 4 twice-weekly fractions of 600 rad with Misonidazole would appear to be practical.

The levels of toxicity noted are acceptable and the significant ones appear to be those of the mucosa and nervous system. It would seem to be important to ensure that the patient has a large fluid intake after each dose of Misonidazole and if 6 fractions are to be used, hospitalization may be necessary.

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