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PROLONGED METRONIDAZOLE ADMINISTRATION WITH PROTRACTED RADIOTHERAPY: A PILOT STUDY ON RESPONSE OF ADVANCED TUMOURS

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Summary.—In a pilot study, 2·5 g of metronidazole was administered in 3 divided daily doses for prolonged periods with protracted fractionated conventional radiotherapy. Total cumulative metronidazole dose was 94 g in 31 patients with head and neck carcinoma. In some others, lower dosage was used. Radiotherapy dose varied from 3000 rad in 5 patients to 7600 rad in 31 patients. Preliminary results with a minimum follow-up period of 6 months suggest enhanced tumour response without evident toxicity. The improved results, if sustained, may be speculatively explained by the combined or individual enhancement of effects due to the hypoxic radiosensitizer or by the high dose precision radiotherapy or by the specific elimination of the hypoxic tumour cells by the cytotoxic effect of prolonged metronidazole administration. Controlled trials are now needed.

A PILOT study was initiated in late 1974 to gain experience on the use of metronidazole as a radiosensitizer in some patients with advanced cancer. Only moderate dose of the drug was considered possible to be used in a normal conventional radiotherapy set-up, particularly in view of sufferings of the patients in older age groups. This paper reports the preliminary results at 2 sites; the head and neck tumours and the alimentary system carcinoma. The advanced tumours at the above 2 sites are known to be relatively radioresistant and in most situations high dose protracted radiotherapy is practised in many centres. Experience with prolonged metronidazole administration along with the usual daily fractionated radiotherapy is scarce in the literature and this paper is an attempt to fill up this gap.

MATERIALS AND METHODS

Thirty-six patients with advanced head and neck tumours and 12 with alimentary metastatic adenocarcinoma are eligible to be reported with a minimum follow-up period of 6 months. Two drop-outs due to excessive vomiting are not excluded while assessing the results.

Almost all the tumours at the head and neck site were classified as Stage III or Stage IV with T3 or T4 primary disease and N2 or N3 nodal metastasis. Two patients had non-classifiable advanced disease; 2 had laryngeal carcinoma (T1 N3, Stage IV; T1 N2b, Stage III); 2 patients had T2 pharyngeal carcinoma with multiple homolateral nodal masses (at least one measuring >3 cm). All the nasopharyngeal tumours of this series had extensions to or from the nose or at least one maxillary antrum.

Some tumours were visibly necrotic. All had high probability of hypoxic areas.

Metronidazole.—The purpose of the study was explained to all participants with an indication of probable toxicity of metronidazole. The daily dose of 2·5 g of metronidazole was administered in 3 doses with no restrictions on food-intake. A dose of 1 g was always taken 2 h before irradiation. Metronidazole was stopped from Friday afternoon to Sunday afternoon. The 5 patients with hepatic area irradiation received the minimum dose of 37·5 g of metronidazole, 10 patients received a minimum of 75 g and the remaining 31 patients received a minimum dose of 94 g of metronidazole.

Radiotherapy.—A 4 MeV Linear Accelerator has been used to treat all fields daily on 5 days a week basis, mostly with a tumour dose of 200 rad per day. A target volume beyond 400

cm^2 usually received 175 rad daily. Patients have received treatment through individually made shell-masks and iso-centric shrinking fields were used in most situations. Iso-dose distributions have been routinely chosen with the help of a dedicated planning computer and apart from use of a simulator, treatment verification films were routinely checked. Usually more than $\pm 5\%$ inhomogeneity in the area of maximum interest has been avoided.

The liver area was treated with up to 3000 rad in ~23 days (NSD ~1100 ret), other large abdominal areas received 5500 rad in ~40 days (NSD ~1650 ret) and most head and neck areas have been treated with 6500 to 7600 rad (NSD 1875 to 2050 ret) in ~50 days. For all patients treated for advanced disease primarily by radiotherapy a maximum dose of 7600 rad was attempted (2050 ret).

RESULTS

The preliminary response of the tumours has been assessed with the awareness of the difficulties of the evaluation. The criteria of Total Local Clearance of palpable or visible tumour (TLC 100%), or more than 50% regression in the visible or palpable tumour mass (Partial Regression: PR > 50%) has been accepted only when both the responses were sustained at least for 2 months. The Table reveals the results. The follow-up period is short but the rate of total local clearance of 47% in advanced tumours at head and neck site without recurrence in 6 months appears to indicate an enhanced response in this series. A non-randomized, but stage matched series of patients with advanced head and neck tumours treated in a conventional way before 1974 in this hospital have revealed lower incidence of TLC (see the Table) at 6 months. Most failures at this site were evident as residual growth right from the end of irradiation or recurred within one year. Total local clearance of tumour at 3 months following initiation of radiotherapy has been found to be a reasonable predictor of local control at 2 years by Sobel *et al.* (1976).

Toxicity

Enhanced nausea and vomiting are noticed in all the patients receiving abdominal irradiation and 20 patients with irradiation at other sites. However, in most patients this was mild. In 5 patients, a moderate to severe degree of vomiting was noticed. However, 3 recovered and could continue with the schedule of radiotherapy and metronidazole with an interruption of less than 1 week. In 2 patients, metronidazole had to be discontinued. Routine weekly clinical examinations, blood counts, blood chemistry, including

TABLE.—*Results showing Sustained Response of Advanced Tumours Irradiated with Metronidazole Administration*

No. of patients	Site	Partial response 50%	Total local clearance 100%	Historical control	Remarks
14	Pharynx	5	6	30%	4/6 Oropharynx tumours totally cleared
12	Larynx	6	6	40%	of 6 PR, 2 are biopsy negative
8	Oral cavity and other sites	1	3	25%	
2	Acinic cell Ca. 1 Palate, 1 Cheek	0	2	Unknown	
36	Head & neck	12	17 (47%)*		
2	Hepatoma	0	0		
5	Colon-rectum	3	?		2 surviving usefully 6 months
3	Metastatic liver	1	0		9 months
2	Metastases in lung	1	0		15 months
12	Alimentary Adeno Ca.	5	0		4 useful survivors

urine examinations, were conducted. No enhanced abnormality could be detected. In some patients, urine tended to attain an increasing dark brown discolouration towards the week-end after about 4 weeks of drug administration but this became normal by the beginning of the following week.

Tiredness was complained of by some but none had drowsiness. No neurological abnormality was noted. Excessive radiation reactions in the skin or the mucosa were not observed.

DISCUSSION

The long metabolic half life with low toxicity and the capability of wide distribution in tissues are known characteristics of metronidazole although the radiosensitization enhancement ratio is only of moderate degree (1·1 to 1·3). In one controlled study using unconventional radiotherapy schedule and dose, a significant difference in survival has been demonstrated in favour of high dose pulsed metronidazole administration as a radiosensitizer (Urtasun *et al.*, 1976).

Most clinical radiosensitization studies have usually reported short periods of high dose of a nitroimidazole with relatively low cumulative total dose (Dische *et al.*, 1977). Experience with use of metronidazole in divided daily moderate dosage with a high total cumulative dose is, so far, rare to find. In this pilot study, 31 patients received 94 g of metronidazole over a period of 52 days in daily divided doses without evident toxicity and with apparently enhanced tumour response to radiotherapy. If this enhanced response is sustained in future, one may speculate that even the lowest sensitization enhancement ratio (1·1) might have delivered to the hypoxic areas the equivalent of a higher dose than the 7600 rad given. The relatively steep dose response curve in some advanced head and neck tumours is described (Karim *et al.*, 1978). The probability of local control in this series might have been enhanced due to the dose-response effect in the presence of a true radiosensitizer. Precision radiotherapy could also be playing a role, perhaps a minor one.

The other possible reason for enhanced response in this study is the specific elimination of hypoxic cells by the cytotoxic effect of metronidazole on prolonged contact inherent in the method of administration of the drug in this series. This has been indicated by studies of Foster *et al.* (1976). Repeated low dose metronidazole administration without altering established radiotherapy fractionation schedules may be helpful in eliminating hypoxic tumour components and thus enhancing effects of conventional radiotherapy. All these factors might have contributed in a combined way in this study.

In conclusion, the preliminary results of this pilot study appear to be encouraging with the finding of tolerable metronidazole dose schedules with a well-established radiation fractionation scheme. Controlled studies are now needed with such a method of drug administration.

NOTE ADDED IN PROOF

The author has so far come across in a series of 76 patients who underwent radiotherapy with metronidazole, only 2 patients with mild peripheral sensory neuropathy. The neuropathy was totally reversible within a period of 2 and 6 weeks.

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