Combination Cancer Chemotherapy
A Clinical Trial on Outpatients

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CHEMOTHERAPEUTIC AGENTS administered intermittently have been used effectively and with reduced toxicity in the palliative treatment of advanced malignancy. The response rate may be further enhanced without increased toxicity by suitable combinations of drugs (Hurley et al, 1960; Horton et al, 1967; Reitemeier et al, 1967; Israel et al, 1971). In this preliminary report we analyse our experience with a new regime using a combination of 5-Fluorouracil, Cyclophosphamide and Methotrexate administered intermittently to outpatients with a variety of advanced solid tumours.

Materials and Methods

During the twelve-month period from May, 1972 to April, 1973, 51 patients with advanced (massive, recurrent and residual) cancer, proven histologically, were treated in an outpatient Chemotherapy Clinic (Table I). Eleven of these patients had previous irradiation or chemotherapy.

The patients were advised to attend weekly whenever possible, but because of distance and socio-economic problems, many patients could only attend fortnightly. At each visit, the total white cell and the platelet count were done and if the readings exceeded 3,000 per c. mm and 100,000 per c. mm respectively, the patient received an intravenous injection of a combination of 5-Fluorouracil 12 mg per Kg., Cyclophosphamide 12 mg per Kg., and Methotrexate 0.5 mg per Kg. body weight. The injection was deferred if the patient complained of severe or prolonged nausea and vomiting after the previous injection.

Of the 51 patients admitted into the study, 45 patients received an adequate course of therapy (defined as at least three doses) and of these 34 had measurable lesions (Table I). A minimum of six doses was given whenever possible and only discontinued if tumour progression was evident. When response occurred, therapy was continued indefinitely until relapse occurred.

Of the 34 patients with measurable lesions, 16 had the minimum of three doses given weekly. The other 18 patients were considered to be on the fortnightly schedule and included those with less than three initial doses weekly (Table II).

Results

1. *Toxicity*

Of the 45 patients who received an adequate course of therapy, transitory leucopenia and/or thrombocytopenia occurred in 24 patients. Treatment was omitted on one or more occasions in eight patients with more marked bone marrow depression (white cell count $< 3{,}000$ per c. mm., and/or platelets $< 100{,}000$ per c. mm.). Interruption of treatment always resulted in bone marrow recovery. Nausea and vomiting was mild or moderate in 18 patients. In seven other patients it was severe and the drugs were omitted on one or more occasions. Alopecia occurred in 16 patients but was mild except in one patient. Other evidence of toxicity included chills and fever (4), diarrhoea (5), stomatitis (1) and sore throat (1).

Table I

Incidence of Tumour Regression in Relation to Tumour Type

Tumour Type	Adequate Therapy			No. of Patients with Non-measurable lesions	No. of Patients with Inadequate Therapy	Total No. of Patients
	Measurable lesions					
	No. of Patients	Objective Improvemnet	Subjective Improvement			
Carcinoma Stomach	11	1	1	3	3	17
Carcinoma Colo-rectum	4	1	1	5	2	11
Introral Carcinoma	7	2	2	3	—	10
Breast Carcinoma	4	2	—	—	—	4
Hepatoma	1	—	—	—	—	1
Hepatic Mesenchymal Sarcoma	1	1	—	—	—	1
Carcinoma Oesphagus	1	—	1	—	1	2
Carcinoma Anus	1	—	—	—	—	1
Bronchogenic Carcinoma	3	—	2	—	—	3
Lymphoma	1	1	—	—	—	1
Total	34	8	7	11	6	51

Table II

Drug Schedule for 34 Patients with Measurable Lesions

Tumours Type	Weekly Regime*		Fortnightly Regime†		Total	
	No.	Response	No.	Response	No.	Response
Carcinoma Stomach	3	1 (1)	8	0 (0)	11	1 (1)
Carcinoma Colo-rectum	1	1 (0)	3	0 (1)	4	1 (1)
Intraoral Carcinoma	4	1 (2)	3	1 (0)	7	2 (2)
Breast Carcinoma	4	2 (0)		—	4	2 (0)
Hepatoma	—	—	1	0 (0)	1	0 (0)
Hepatic Mescenchymal Sarcoma	1	1	—	—	1	1
Carcinoma Oesphagus	—	—	1	0 (1)	1	0 (1)
Carcinoma Anus	—	—	1	0	1	0 (0)
Bronchogenic Carcinoma	3	0 (2)	—	—	3	0 (2)
Lymphoma	—	—	1	1	1	1
Total	16	6 (5)	18	2 (2)	34	8 (7)

* At least 3 doses of drugs at weekly intervals initially
† Include those with less than 3 initial doses of drugs at weekly intervals
() Numbers in parenthesis indicates patients with subjective improvement

2 *Anti-tumour Response*

(a) Objective response (tumour shrinkage of 50% for at least 2 months) occurred in eight of the 34 patients (23.5%) with measurable components of their disease (Table I). Tumour response usually occurred in the first month of treatment and continued for several months (Table III). Seven other patients, (20.5%) had subjective improvement.

(b) The anti-tumour response in relation to the weekly and fortnightly regime is analysed in Table II. Sixteen patients had three to fourteen weekly doses, before subsequently changing to fortnightly injections. Of these, six had objective response, 37.5% and another five had subjective response.

Table III

Case Histories of 8 patients with Objective Response to Chemotherapy

No.	Initial	Age	Sex	Race	Primary	Secondaries	Surgery	Previous Chemo-therapy	Previous Radio-therapy	Duration of Response (months)	Survival (months)
1.	Y	61	F	Ch.	Ca Stomach	Liver, gall bladder, pancreas	Gastro-jejunostomy for gastric-outlet Obstruction 4 months before	F F.U.	—	4	6
2.	T	55	F	Ch.	Ca Sigmoid Colon	Colo-vesical fistula	Colostomy	—	—	4	7
3.	C	64	F	Ch.	—	Liver, spine, metastasis from Ca breast	Rt. radical mastectomy 2 yrs. before	5 F.U.	—	9 (to date)	Alive and well to date
4.	S	45	F	M	—	Rt. Supra-clavicular node 8cm x 6cm metastasis from breast	Rt. radical mastectomy 6/12 before	Testoster-rone oopho-rectomy	—	6 (to date)	Alive and well to date
5.	M	67	M	I	Recurrent Ca Cheek	—	Rt. Com-mando operation 3 years before	—	Yes	6	Lost to Follow up
6.	R	52	F	I	Ca Rt. Cheek	Cervical nodes mandible	—	—	—	3 (Rt. Com-mando Opn.)	Alive and well to date
7.	K	13	M	M		Peritoneal metastasis ascites	Rt. Hepatec-tomy for mesenchy-mal sarcoma 1 yrs. before	—	—	3	7
8.	L	53	F	Ch.	Reticulum cell sarcoma cervical nodes	Colerectum	—	—	—	2	Second remission to vincris-tine and predniso-lone Loss to Follow Up sub-sequently

In contrast, in 18 patients on fortnightly regime, there was an objective response in only two patients (11.1%) and subjective improvement in another two.

(c) The case histories of the eight patients who had objective response are summarised in Table III.

Patient C presented with hepatomegaly, the left lobe of the liver extending to the level of the umbilicus due to metastatic breast cancer. She failed to respond to stilboesterol, but the liver shrunk dramatically on the weekly regime. She has been in good health for the past 10 months and the left lobe of the liver has remained inpalpable. Patient S had a rapidly growing right supraclavicular node from a metastatic breast cancer, causing dysphagia (Figure 1). The lesion shrunk after the first dose, disappeared within 2 months and has been in remission for the past seven months (Figure 2).

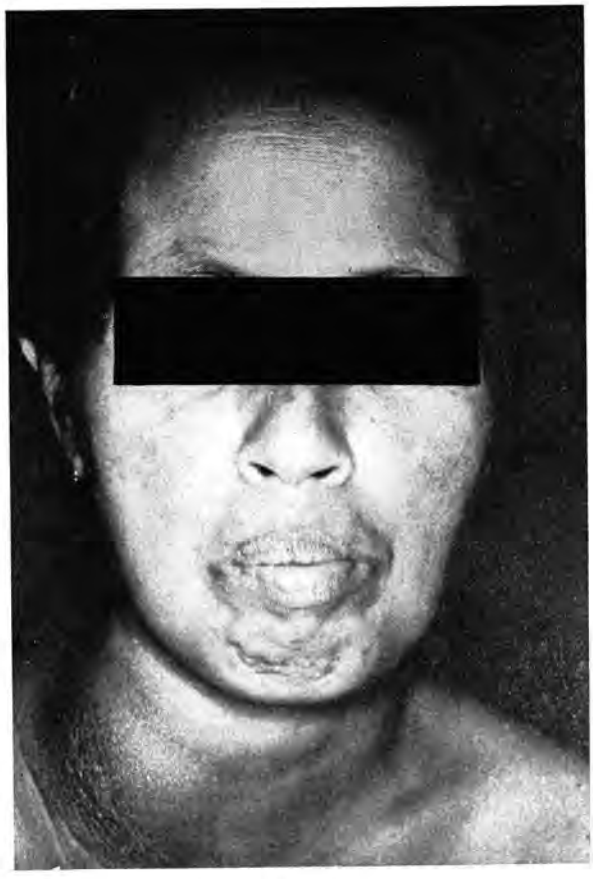

Fig. 1
Patient S. Metastatic breast cancer in right supraclavicular node.

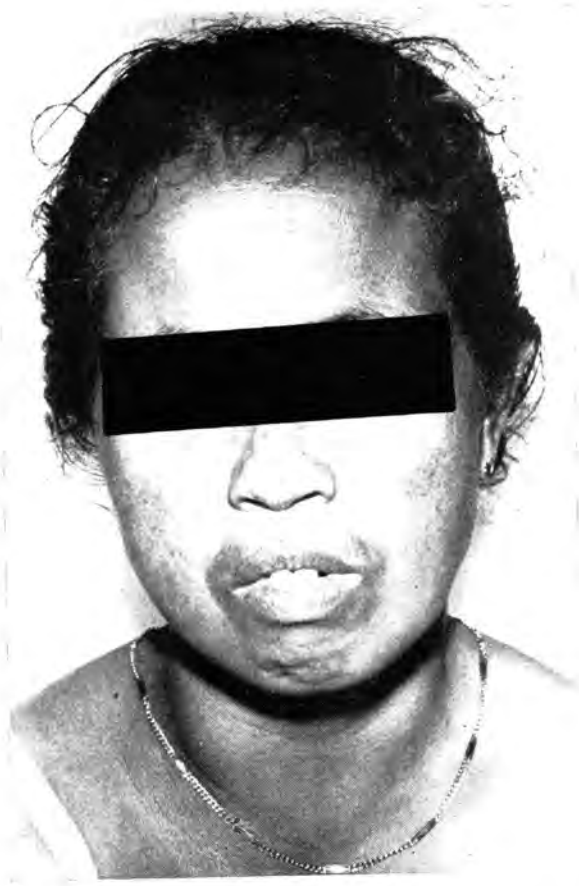

Fig. 2
Patient S. Note disappearance of right supraclavicular node after chemotherapy.

Two patients with advanced cheek cancer had good response. Patient R presented with a lesion on the right cheek involving the lower alveolus and mandible and encroaching the upper alveolus and the anterior faucial pillar so that she was inoperable when first seen (Figure 3). After three months of treatment the lesion had receded from the upper alveolus and the anterior faucial pillar permitting a sufficient margin for a radical excision (Figure 4). Postoperative wound healing was good.

Patient L (Figure 5) had subacute intestinal obstruction from colorectal reticulum cell sarcoma with cervical lymphadenopathy. She had a two-month remission (Figure 6).

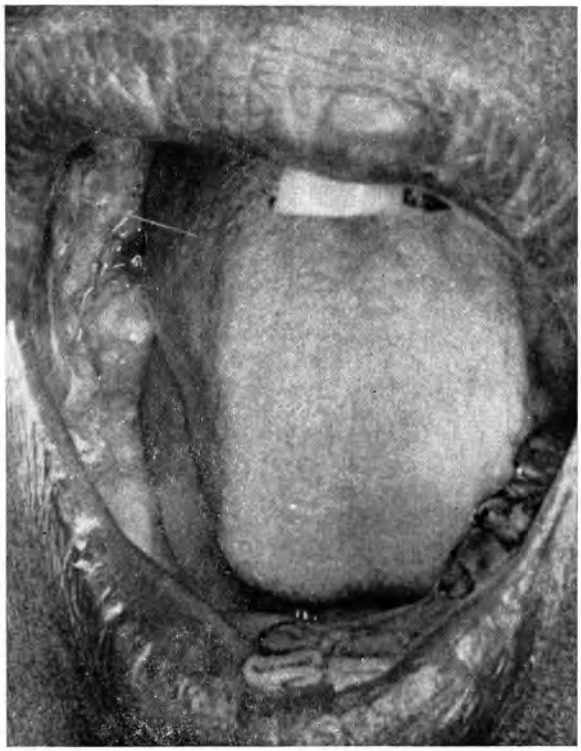

Fig. 3
Patient R. Cancer cheek involving anterior faucial pillar.

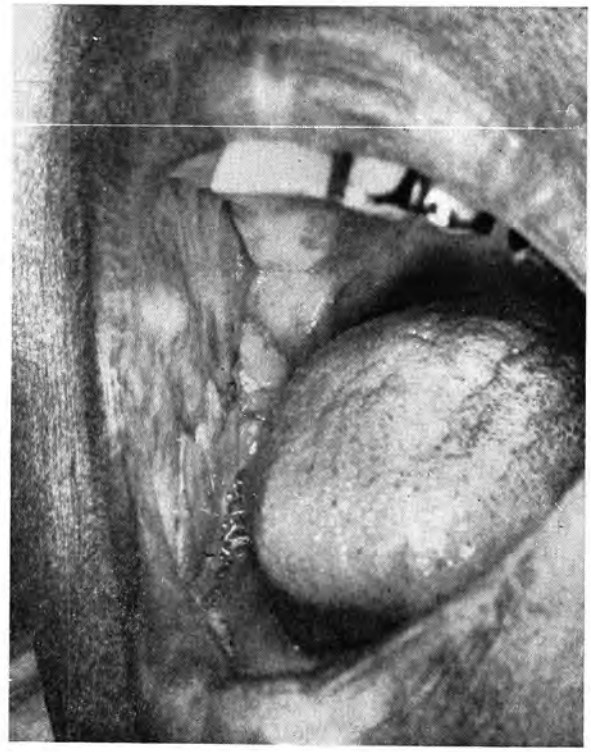

Fig. 4
Patient R. Note cancer cheek has receded from anterior faucial pillar after Chemotherapy.

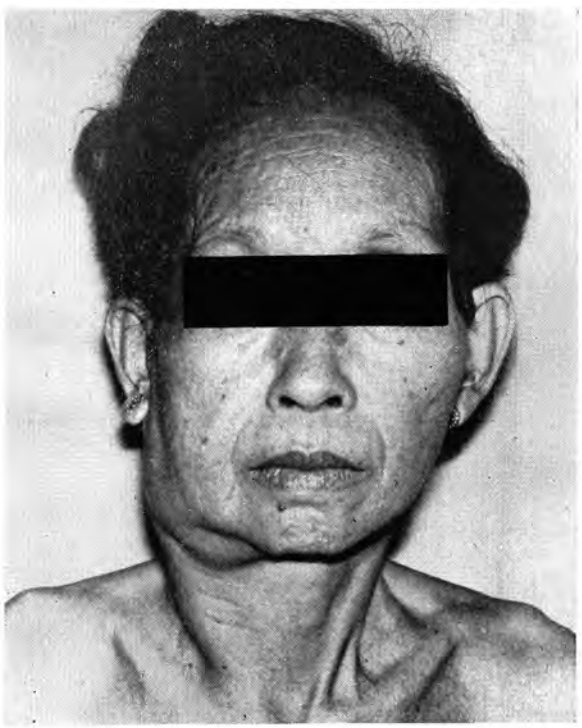

Fig. 5
Patient L. Reticulum cell sarcoma with cervical lymphadenopathy.

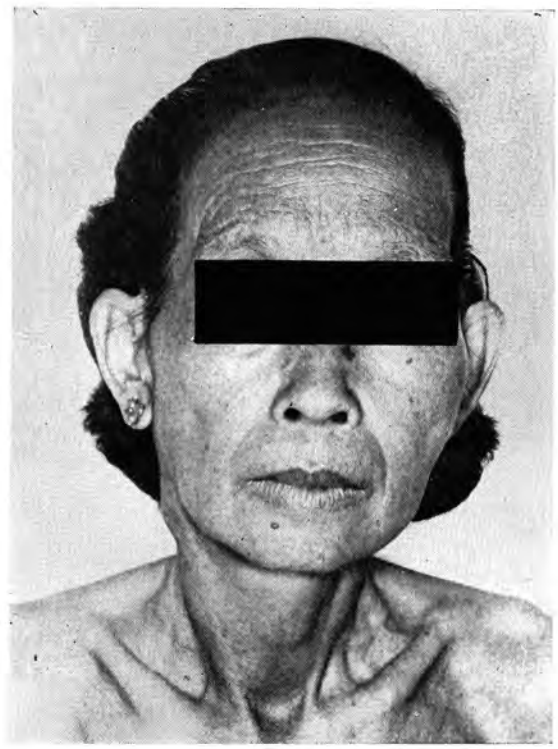

Fig. 6
Patient L. Note shrinkage of cervical nodes after Chemotherapy.

Discussion

An overall objective response rate of 23.5% for a mixed group of solid tumours appears to be acceptable. Although lack of randomisation makes comparison difficult, analysis of the results in Table II suggests that the schedule of weekly injections, particularly at the initial stages of treatment is superior to the fortnightly regime.

The excellent results obtained in the two patients with advanced lymphatic and hepatic metastatic breast cancer have been particularly gratifying. Encouraging results have also been obtained from the treatment of advanced intraoral carcinoma, an all too common problem in this country. The successful management of patient R suggests the possibility of the wider use of preoperative combination chemotherapy with our regime in patients with intraoral carcinoma too extensive for excision when first seen. This would overcome the problems associated with preoperative radiotherapy i.e. avascularity leading to a higher rate of wound infection and breakdown (Sivaloganathan, 1971).

The response rate in carcinoma of the large intestine appeared satisfactory. Carcinoma of the stomach responded poorly, the rapid downhill course of these patients progressing relentlessly.

Bone marrow depression has been mild. From the patient's point of view, a main source of dissatisfaction was nausea and vomiting (56%), but fortunately this usually lasted one to two days and was rarely severe and incapacitating.

The relatively low toxicity and acceptable effectiveness of our regimen allows treatment to be conducted on an outpatient basis. One of the reasons why patients with advanced cancer are often not offered the possible benefits of chemotherapy, especially in a developing country like Malaysia, is hospital bed shortage. Suitable regimens of intermittent chemotherapy on an outpatient basis would alleviate this problem.

Summary

A clinical trial using intermittent weekly and/or fortnightly intravenous injections of a combination of 5-Fluorouracil 12 mg/Kg., Cyclophosphamide 12 mg/Kg., and Methotraxate 0.5 mg/Kg. body weight has been carried out on 51 outpatients with advanced cancer over a one year period. Of 45 patients who received an adequate course of therapy, (defined as more than three doses), 34 had measurable lesions. Objective response (tumour shrinkage of 50% for 2 months) occurred in 8 of 34 cases, 23.5%. Seven other patients 20.5% had subjective improvement. Particularly encouraging results have been obtained in breast and intraoral cancer. This regime is well tolerated and can be safely administered on an outpatient basis.

References

1. Horton, J., Gehrt, P., Cunningham, J., and Sullivan, J., (1967). A Comparison of Combination and Single Drug Chemotherapy in Cancer of the Colon, Breast and Other Organs. Proc. Am. Assoc. Cancer Res., 8: 31.
2. Hurley, J. D., Ellison, E. H., Riesch, J., and Schulte, W. (1960) Chemotherapy of Solid Tumours. J. Am. Med. Assoc., 174: 1696-1701.
3. Israel, L., Depierre, A., and Chahinian, P., (1971). Combination Chemotherapy for 418 cases of Advanced Cancer. Cancer, 27, 1089-1093.
4. Reitemeier, R. J., Moertel, G. G., and Hahn, R. G., (1967). Comparative Evaluation of Palliation with Fluorometholone and 5-Fluorouracil. Cancer Chemotherapy Rept. 51, 77-80.
5. Sivaloganathan, V. (1971). Surgical Management of Patients with Advanced Buccal Ponch Cancer. The Med. J. of Malaya 26-119. 6, 11