CHROMOMYCIN A 3 (TOYOMYCIN) AND RADIOTHERAPY IN THE TREATMENT OF ADVANCED MALIGNANCY

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Since early in 1962 Chromomycin A 3 (Toyomycin) has been used in clinical trials for patients with advanced cancer at the Pretoria General Hospital. The results of our first experience with this anti-tumour antibiotic were reported in 1964.[1] The present report deals with the results obtained in 123 patients treated with this agent.

Chromomycin A 3 is the most effective tumour-suppressing part of chromomycin, an antibiotic discovered in a culture of *Streptomyces griseus* Nr. 7 by the Takeda Research Laboratory in Japan.[2,3] Chromomycin A 3, Mithramycin and Olivomycin are three chemically related antibiotics. The latter two were discovered in the United States of America[4] and the Soviet Union[5] respectively. These substances are inactive against Gram-negative organisms, but inhibit the growth of Gram-positive organisms.

Chromomycin A 3 inhibits RNA synthesis by the RNA polymerase, but only when the DNA template contains guanine.[6] Goldberg,[7] of Harvard Medical School and Beth Israel Hospital, Boston, has done extensive studies on this and other actions of chromomycin, including those that show that Chromomycin A 3, Mithramycin and Olivomycin produce different spectra with DNA but only in the presence of a divalent cation. The magnitude of the change in the spectrum of chromomycin produced by DNA is a function of the Mg^{++} concentration.

MATERIALS AND METHODS

All patients had histologically confirmed inoperable malignant neoplasms. The patients treated by intravenous Chromomycin A 3 were as follows: Ovarian cancer 15, cancer of the cervix 7, cancer of the corpus 2, cancer of the stomach 10, cancer of the colon and rectum 11, cancer of the pancreas 3, cancer of the bronchus 21, cancer of the bladder 4, hypernephroma 3, seminoma 2, cancer of the prostate 2, malignant hepatoma 8, cancer of the pharynx 3, cancer of unknown origin 5, cancer of the penis 1, Hodgkin's disease 5, reticulum-cell sarcoma 4, glioblastoma multiforme 4, and 1 each of the following: mixed tumour of the broad ligament, fibrosarcoma, synoviosarcoma, spindle-cell sarcoma, neuroblastoma, Schwannoma, and lymphosarcoma.

Thirty-five patients received concomitant radiotherapy. In these patients the Chromomycin A 3 was usually given only on the days that radiotherapy was administered. Twenty of these patients had bronchogenic cancer.

A further 5 patients with squamous carcinoma of the head and neck were treated by continuous intra-arterial Chromomycin A 3. The intra-arterial chromomycin was administered by means of a pump connected to an intra-arterial catheter which was placed in the arterial supply to the tumour area under general anaesthesia. Visualization of the tumour blood supply was achieved by first injecting sulphan blue into the catheterized artery and by moving the catheter until an optimal position was achieved.

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RESULTS

Toxicity

Except for pain followed by induration if the drug was accidentally injected extravascularly, no side-effects were encountered. Although in some patients a mild leucopenia occurred, in several patients a rise in white blood cell count followed Chromomycin A 3 administration.

We have previously described skin changes ascribed to Chromomycin A 3, but these are seldom of clinical importance, although regularly discernible histologically when large total doses are employed.[8]

Therapeutic Response

The results of treatment are shown in Table I; 123 patients were treated:

49 showed neither subjective nor objective improvement (0 - 0 in Table).
18 showed subjective response only (0 - A in Table).
5 showed objective response without subjective benefit (0 - B in Table).
15 showed subjective and objective response of less than 1 month's duration (0 - C in Table).
36 showed distinctive subjective benefit with favourable objective changes in all measurable criteria for 1 month or more (1 - A in Table).

Of the 35 patients who received concomitant radiotherapy:

13 showed neither subjective nor objective improvement (0 - 0 in Table).
2 showed subjective response only (0 - A in Table).
0 showed objective response without subjective benefit (0 - B in Table).
4 showed subjective and objective improvement of less than 1 month's duration (0 - C in Table).
16 showed distinctive subjective benefit with favourable objective changes in all measurable criteria for 1 month or more (1 - A in Table).

SUMMARY AND CONCLUSIONS

This drug was used in patients with advanced cancer, most of whom were already resistant to standard cytostatic drugs and many of whom had previously received radiotherapy. The drug was well tolerated by even moribund patients. In this group of 123 patients some response was observed in 76 patients, although significant objective response of more than 1 month's duration was only seen in 36 patients. Of the 36 patients who showed worth-while improvement, 16 received concomitant radiotherapy, and 9 of these had bronchus cancer and received radical doses of telecobalt. The most encouraging results with Chromomycin A 3 on its own have been in the treatment of stomach, colon and gynaecological malignancies.

It is concluded that the agent is worth while when other treatment cannot be administered because of leucopenia or the poor general condition of the patient, but

TABLE I. RESULTS OF TREATMENT

Tumour	*Treatment*	*Number of patients*	*Response*[9]				
			0–0	*0–A*	*0–B*	*0–C*	*1–A*
Ovary	CrA3	12	3	2	1	0	6
	CrA3 + RT	3	1	1	0	0	1
	Total	15	4	3	1	0	7
Cervix	CrA3	7	3	1	0	1	2
Corpus	CrA3	2	0	1	1	0	0
Stomach	CrA3	7	3	2	0	0	2
	CrA3 + RT	3	1	0	0	0	2
	Total	10	4	2	0	0	4
Colon	CrA3	7	3	1	0	1	2
Rectum	CrA3	1	1	0	0	0	0
	CrA3 + RT	3	0	1	0	0	2
	Total	4	1	1	0	0	2
Pancreas	CrA3	3	3	0	0	0	0
Bronchus	CrA3	1	1	0	0	0	0
	CrA3 + RT	20	9	0	0	2	9
	Total	21	10	0	0	2	9
Bladder	CrA3	4	2	0	0	1	1
Hypernephroma	CrA3	2	2	0	0	0	0
	CrA3 + RT	1	1	0	0	0	0
	Total	3	3	0	0	0	0
Seminoma	CrA3	2	1	0	0	1	0
Prostate	CrA3	2	0	2	0	0	0
Malignant hepatoma	CrA3	8	4	3	1	0	0
Pharynx	CrA3	3	0	1	0	1	1
Unknown origin	CrA3	5	3	0	0	2	0
Penis	CrA3	1	0	0	1	0	0
Hodgkin's disease	CrA3	4	0	1	0	2	1
	CrA3 + RT	1	1	0	0	0	0
	Total	5	1	1	0	2	1
Reticulum-cell sarcoma	CrA3	3	0	0	1	0	2
	CrA3 + RT	1	0	0	0	0	1
	Total	4	0	0	1	0	3
Glioblastoma multiforme	CrA3	3	1	1	0	0	1
	CrA3 + RT	1	0	0	0	0	1
	Total	4	1	1	0	0	2
Mixed tumour	CrA3 + RT	1	0	0	0	1	0
Mesothelioma	CrA3	1	0	0	0	1	0
Fibrosarcoma	CrA3	1	0	0	0	0	1
Synoviosarcoma	CrA3	1	0	1	0	0	0
Spindle-cell sarcoma	CrA3	1	0	0	0	1	0
Neuroblastoma	CrA3	1	1	0	0	0	0
Schwannoma	CrA3	1	1	0	0	0	0
Lymphosarcoma	CrA3	1	0	0	0	1	0
Head and neck	CrA3 intra-arterial	5	3	0	0	2	0

Abbreviations used: CrA3 = Chromomycin A 3.
RT = Radiotherapy.
Symbols used for response are those suggested by Karnofsky.[9]

that under these circumstances the drug is well worth considering.

This drug can be administered concomitantly with radical radiotherapy without adding to total patient toxicity and its further value may lie in this field.

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