A TRIAL OF MITHRAMYCIN IN THE TREATMENT OF ADVANCED MALIGNANT DISEASE

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PREVIOUS clinical studies of Mithramycin have been conducted in the United States of America. Human pharmacological studies were reported by Curreri and Ansfield (1960); clinical assessment to determine the spectrum of activity by Parker, Wiltsie and Jackson (1960), Kofman and Ream (1963) and Spear (1963). The earlier papers suggested that this drug had only limited activity with early onset of dangerous toxic side effects. However, Kofman (1963) suggested that careful monitoring during treatment would reveal a wider range of activity with reduction in toxic side effects, and this was borne out in a careful survey by Kofman, Medrek and Alexander (1964).

With this information in mind, we have conducted a clinical trial of Mithramycin on a small group (26) of patients with advanced malignant disease. Our dosage regime was based on the most recent reports on the use of the drug (Brown and Kennedy, 1965). The results recorded are those of the first clinical trial of the drug in the United Kingdom.

Mithramycin

United States Cancer Chemotherapy National Service Center No. 24559.
Synonyms: PA–144. A–2371 (John L. Smith Memorial Foundation).

The spacial molecular structure of this drug is so far unknown, but it has been credited with a molecular formula (empirical) of $C_{44}H_{70}O_{22}$, with a molecular weight of 950 ± 50. It is a yellow crystalline compound, weakly acid, and is soluble in water (15 mg. per ml.), ethyl alcohol and acetone. However, it is stable in solution only at low temperatures and in darkness.

The compound is derived from an actinomycete of the Streptomyces genus. It is remarkable amongst cytotoxic agents for the absence of nitrogen from its structure. The drug is supplied in vials containing 2·5 mg. of the pure crystalline material, and to reduce decomposition to the minimum, these vials must be kept in cold storage and darkness at $-10°$ C. until immediately before use.

Selection of patients

The first trial of Mithramycin in the United Kingdom has been devoted to a wide range of cases of advanced malignancy, the majority of which had had previous therapy. The range of tumour types studied is shown in Table I, the age range in Table II and in the histogram in Fig. 1, and the extent of previous therapy amongst the patients in the series in Table III.

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TABLE I.—*Sites of Primary Lesions and their Cell Types of Patients with Advanced Malignant Disease Treated with Mithramycin*

Site of primary lesion	Histological diagnosis (Cell type)	Number of cases
Breast	Adenocarcinoma	1 (7)
	Anaplastic invasive carcinoma	1
	Malignant melanoma	1
	Not determined	4
Testis	Seminoma	2 (3)
	Adenocarcinoma	1
Stomach	Anaplastic invasive carcinoma	3
Ovary	Poorly differentiated adenocarcinoma	2
Pancreas	Adenocarcinoma	2
Caecum	Adenocarcinoma	1
Colon	Mucus gland carcinoma	1
Rectum	Adenocarcinoma	1
Parotid gland	Salivary adenocarcinoma	1
Thyroid gland	Anaplastic carcinoma	1
Ileum	Leiomyosarcoma	1
Femur	Sarcoma—alveolar celled	1
Choroid	Malignant melanoma	1
Unknown (? ovary)	Poorly differentiated adenocarcinoma	1
Total number of different primary sites = 13 definite 1 unknown	No. of Distinct cell types = 8	Total number of patients = 26

TABLE II.—*Age Range of Patients Treated with Mithramycin*

Age group	Individual ages	Numbers
30–39	35–35–37–38–38–39	6
40–49	41–45–48–48	4
50–59	51–53–54–56–56–57	6
60–69	63–63–64–65–67	5
70–79	72–74–77–78	4
80–89	81	1
		26

Average age = 56 years, approximately.

TABLE III.—*Extent of Previous Therapy Given to Patients Presenting for Treatment with Mithramycin*

Type of treatment	Numbers
Surgery + radiotherapy + cytotoxic agents	6
Surgery + radiotherapy	4
Surgery + cytotoxic agents	2
Radiotherapy + cytotoxic agents	2
Surgery alone	9
Radiotherapy alone	1
Cytotoxic agents alone	1
No previous treatment	1

Different types and combinations of treatment = 7
Number of patients = 26

Thirteen confirmed and separate primary sites and an unknown primary site were selected, from all of which a definitely invasive malignant spread had occurred. The histopathological features in these cases were varied enough to ensure a broad survey for therapeutic activity of the drug.

The youngest patient in the series was 35 years of age and the oldest was 81 years, but inspection of Table II and the histogram in Fig. 1 reveals that the majority (16) were under 60 years, and there is also a large proportion under the age of 50 years (10 cases).

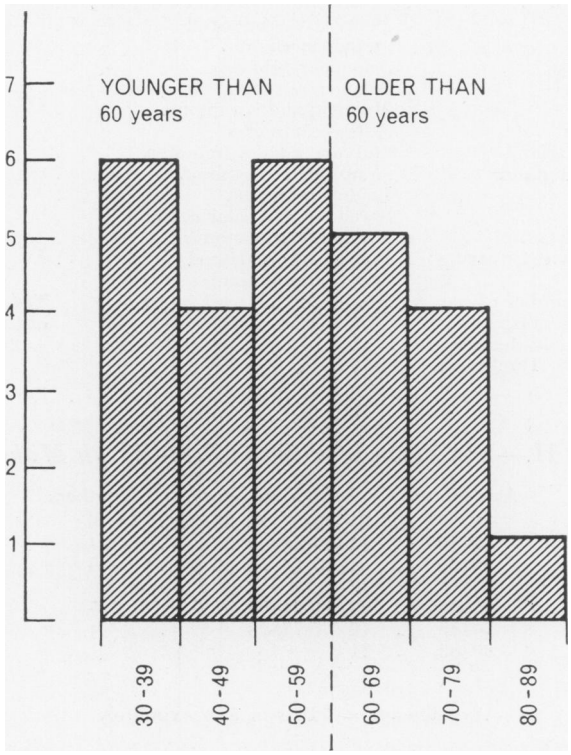

FIG. 1.—Age range and distribution of patients undergoing treatment with Mithramycin; the majority are under 60 years of age, and there is a high proportion under 50.

Dosage

The drug was given at the rate of 25 micrograms per kilogram of body weight per 24 hours in every case. Bearing in mind the warnings of Kofman and others regarding the narrow margin between chemotherapeutic effect and toxicity, no attempt was made to increase the daily dose to an individual maximum toleration. At the dose-level used, side effects were few, and in most cases easily controlled.

Therapeutic regime

Immediately before administration, the vial containing the drug was taken from cold storage at $-10°$ C. and allowed to thaw gently. 10 ml. of sterile

glucose-saline of pH 3·6–3·9 was used to mix and dissolve the drug. The resulting solution contained 0·25 mg. per ml. The calculated 24 hour alliquot for the patient was withdrawn and mixed with 500 ml. of sterile glucose-saline solution at the same pH as for the original mixing and dissolving procedure. The resultant dilute solution of Mithramycin was then given intravenously : patients in Westminster Hospital and the Gordon Hospital were given the drug over a period of 12 hours, but those in Queen Alexandria's Military Hospital and in Queen Elizabeth II Hospital, Welwyn Garden City, were given the drng over 24 hours. With 2 exceptions, all the 26 patients reported here had 8 or 10 alliquots on a 24 hour basis, but the overall period of time for which the drug was administered varied from 8 to 14 days because administration of the drug was always stopped at the onset of troublesome side effects.

Side effects

Side effects were few and consisted most frequently of nausea, occasional vomiting and headache. Nausea and vomiting were controlled by phenothiazone compounds in the majority of cases, but in more resistant cases, intramuscular Droperidol was found effective, although the doses required caused drowsiness.

RESULTS

An analysis of the clinical material used to assess Mithramycin in this trial, together with a broad classification of the results of treatment, is given in Table IV.

Of the 26 patients who were treated with Mithramycin, the majority (16 cases) showed no improvement either immediately or during the follow-up period of the survivors. In this group, the tumours remained unaltered in size or increased, fresh metastases were discovered, there was failure to gain weight or there was no improvement in the performance status (Karnofsky *et al.*, 1951). Six patients benefited by a temporary arrest of their disease, but there was recurrence of the disease in all cases in under 1 month following cessation of therapy. However, at the time of writing (January, 1966), 4 of the 26 patients undergoing trial have shown a definite quantitative remission.

Within 1 month of commencing treatment, 7 patients had died of their disease, 1 patient died during the course of treatment but from causes other than could be ascribed to drug toxicity, and 1 patient died of congestive cardiac failure although in at least temporary remission following treatment with Mithramycin.

Of the patients considered to have a temporary remission of their disease, all were given a specified maximum total dose of 2·0 mg. per kilogram body weight. All had extensive metastases and had not responded to previous surgery, radiotherapy or cytotoxic agents. These cases included primary malignant changes in the colon, pancreas, testis, ovary and included adenocarcinoma, anaplastic carcinoma, seminoma and leiomyosarcoma cell types.

Definite quantitative remission occurred in 4 of the 26 patients in the trial. One had an anaplastic invasive carcinoma of the breast, the second an adenocarcinoma of the rectum, the third a poorly differentiated cystadenocarcinoma of the ovary and the last had extensive metastases from a malignant melanoma originating in the choroid. However, it must be specifically emphasised that our period of follow-up of these patients is necessarily short and it is, of course,

TABLE IV.—*Summary of Primary Sites of Tumours, Histological Confirmation of Cell of Administration of Mithramycin, Side Effects and*

	Site of primary tumour	Histopathology (Cell Type)	Spread
Group I : No influence on the progress of the disease			
1	Left breast	Malignant melanoma	Surrounding tissues, skin, bone
2	Left breast	Not determined	Lymph nodes, lung, liver, bone
3	Left breast	Not determined	Lymph nodes, lung, bone
4	Both breasts	Not determined	Skin, lymph nodes, lung, liver
5	Left breast	Adenocarcinoma	Surrounding tissues, liver, bone
6	Left breast	Not determined	Skin (with fungation), lymph nodes
7	Stomach	Anaplastic invasive carcinoma	Lymph nodes, liver
8	Stomach	Anaplastic invasive carcinoma	Lymph nodes, lung and liver
9	Stomach	Anaplastic invasive carcinoma	Soft tissues, lymph nodes, liver, brain
10	Carcum	Mucus-secreting adenocarcinoma	Lymph nodes
11	Pancreas	Adenocarcinoma	Lymph nodes, liver
12	Right parotid gland	Salivary mucous gland carcinoma	Lymph nodes, lung
13	Thyroid gland	Anaplastic carcinoma	Soft tissues, lymph nodes
14	Right testis	Seminoma	Lymph nodes, lung, brain
15	Left Femur	Alveolar cell sarcoma	Soft tissues, lung, bone
16	Not determined (possibly ovary)	Poorly differentiated adenocarcinoma	Skin, lymph nodes, liver
Group II : Temporary arrest of the disease			
17	Colon	Mucous gland carcinoma	Skin, lymph nodes, liver
18	Pancreas	Anaplastic adenocarcinoma	Soft tissues, omentum, liver
19	Left testis	Seminoma	Soft tissues, lymph nodes, lung, bone, brain
20	Left testis	Adenocarcinoma	Lymph nodes, lung
21	Right ovary	Poorly differentiated adenocarcinoma	Lymph nodes, transverse colon, pancreas
22	Ileum	Leiomyosarcoma	Breast, skin, skeletal muscle, liver, thyroid, vaginal wall
Group III : Measurable quantitative remission (up to 3 months after treatment)			
23	Left breast	Anaplastic invasive carcinoma	Lymph nodes, bone
24	Rectum	Adenocarcinoma	Lymph nodes, bone
25	Right ovary	Poorly differentiated cystadenocarcinoma	Peritoneum (ascites)
26	Left choroid	Malignant melanoma (amolanotic)	Skin (27 countable lesions), lymph nodes, liver, lung

Type, Extent of Spread, Previous Treatment, Age, Body Weight, Dosage and Time Period Fate of 26 Patients Participating in the Clinical Trial

Previous treatment	Age	Body weight (kg.)	Total dose (mg.)	Length of treatment (days)	Side effects	Fate
Radical mastectomy : radiotherapy	51	58	12·5	10	Intermittent hyperpyrexia	Many new lesions
Bilateral radical mastectomy : adrenalectomy : oophorectomy : radiotherapy	56	66	13·2	14	Nausea, vomiting—disrupting treatment	General deterioration
Adrenalectomy : radiotherapy : Durabolin : Thiotepa	64	52	10·4	10	—None	General deterioration
Prednisone	65	57	11·3	8	Nausea	General deterioration
Radical mastectomy : radiotherapy : steroids	72	64	1·6	1	Nausea, vomiting, headache	Patient refused further treatment
Radiotherapy : Velbee	48	53	10·0	8	Nausea	Gained weight during course—rapid loss after cessation
Gastro-enterostomy	63	65	12·8	8	Nausea : abdominal distension	Slow deterioration
Total gastrectomy	63	54	10·4	8	Nausea	Rapid deterioration
Gastro-enterostomy	78	50	10·0	8	Anorexia : epileptic fits	Died 3 days after treatment ceased
Caecal resection	81	50	10·0	8	Anorexia : oedema : nausea	
Laparotomy (inoperable)	45	65	12·8	8	Nausea, vomiting : headache	Progressive deterioration
Parotidectomy & bloc, dissection : radiotherapy	38	46	9·2	8	Headache : leucopenia	——
Radiotherapy	74	46	5·8	5	Laryngeal obstruction	Died during treatment
Orchidectomy : radiotherapy : Velbee	38	64	16·0	10	Nausea	Died 6 weeks after treatment ceased
Radiotherapy : Velbee : Leukeran	35	40	8·0	10	Nausea, vomiting	Died 5 weeks after treatment ceased
Laparotomy : radiotherapy : Thiotepa	57	46	12·8	8	Nausea, vomiting	Died 3 months after treatment ceased
Hemicolectomy	53	55	12·4	9	Thrombocytopenia	Temporary remission of skin lesions
Partial pancreatectomy	67	54	10·4	8	Nausea	
Orchidectomy : radiotherapy : Melphalan	37	45	11·2	10	Anorexia : nausea	Died 6 weeks after treatment ceased
Orchidectomy : radiotherapy : prednisone	35	63	12·6	9	—None	Gained weight after treatment ceased
Oophorectomy : local resection of transverse colon	41	58	14·4	10	Nausea	Regression of mass in neck, but general deterioration began within 1 month
Radical mastectomy : ileal resections : local excisions : radiotherapy : Leukeran	48	60	15·0	10	—None	New nodules within 5 weeks of end of treatment
Radical mastectomy : oophorectomy : testosterone	39	60	9·6	8	Nausea : headache	Complete remission of pain and paraplegia
Abdomino-perineal excision of rectum	77	64	12·8	8	Anorexia : nausea	Remission of paraplegia : died of congestive cardiac failure 4 weeks after treatment ceased
Oophorectomy	56	47	9·4	8	Nausea : headache	Disappearance of ascites
Enucleation of globe : local excisions : Endoxana	54	53	10·4	8	—None	Excellent symptomatic improvement : disappearance of 7 skin lesions

impossible to forecast for how long the remission in this last group of patients will be maintained.

Comments have already been made on side effects in connection with the plan and execution of therapy for this trial. Seventeen patients suffered from nausea, 12 of whom required therapeutic control, but only 5 progressed to troublesome vomiting necessitating more rigorous treatment than administration of phenothiazone compounds. An unexpected accompaniment of Mithramycin administration was dizziness and headache, which responded poorly to analgesics and antihistamines: one patient had several epileptic fits but was found at autopsy to have multiple cerebral metastases. In only 2 patients were side effects severe enough to demand temporary cessation of the trial. and only 1 patient did not complete the course of Mithramycin therapy from choice. Anorexia occurred in 4 patients, all of whom were cachectic before treatment was commenced. Apart from 1 instance of leucopenia and one of relative thrombocytopenia, there were no serious adverse effects on erythropoeiesis, leucopoeiesis or the coagulating factors, nor were adverse effects on liver function discovered.

DISCUSSION

The present position of cytotoxic agents in the treatment of malignant disease is controversial. Both clinicians and laboratory workers are more aware of the complexity of the problem and would appear to accept the fact that these agents are still in the experimental stage as regards the control of neoplastic changes in man. Particular aspects of this problem are fully discussed by Davis (1965). The closest co-operation between the laboratory and the ward cannot be too fully stressed, and this is particularly important when new agents which show promise from laboratory testing are investigated for their clinical effects. Carefully controlled animal experiments must be followed by equally carefully controlled clinical trials. In this respect, the phasing of clinical trials as discussed in the World Health Organization Technical Report No. 232 (1962) is logical in its concept and is reasonably practicable in its application.

The clinical pharmacology of Mithramycin was reported by Curreri and Ansfield (1960), but these authors did not discuss in detail some haematological factors of importance, although they did stress that thrombocytopenia occurred when not expected from the results of animal experiments. Later, clinical assessment for spectrum of activity by Parker, Wiltsie and Jackson (1960) suggested that the range of usefulness of Mithramycin was overshadowed by its toxicity. Such toxicity was most likely due to their method of administration in single calculated daily intravenous doses. Kofman (1963) points out that a reduction in dose rate and the use of continuous intravenous infusion mitigates toxicity, reduces side effects and broadens the spectrum of activity. Even so, careful assessment of the reports by Kofman and Ream (1963), Spear (1963), and Kofman, Medrek and Alexander (1964) shows that very few cell types and even fewer sites of primary growth are susceptible to cytotoxic activity when treated with Mithramycin. In fact, the only cases in which unequivocal remission has occurred are those of malignant disease of the testis and ovary, which is supported by the trials conducted by Brown and Kennedy (1965).

As outlined above, we have conducted a first trial in the United Kingdom of Mithramycin for its effect on advanced malignant disease. Our results from this trial show that the spectrum of activity of this drug is limited amongst the different

cell types studied and the primary sites represented in this series. Quantitative or even temporary remission was confined to a small proportion of the cases selected for study (up to the time of writing). These included cases of malignant changes in both the testis and the ovary and would certainly support the findings of Kofman, Medrek and Alexander (1964) and those of Brown and Kennedy (1965); our impression, therefore, is that Mithramycin may have some specific and beneficial effect on neoplastic changes arising in reproductive tissue. However, we are fully aware that all our patients were in an advanced stage of their disease; the fact that there had been little or no response to previous therapy was a fair indication that dramatic response to yet another cytotoxic agent was only a remote possibility.

The absence of overwhelming toxicity from the drug may indicate insufficient dosage, but the reports of others suggest that our daily dose was as high as possible, compatible with the very narrow effective therapeutic range of the drug. It has been suggested that final therapeutic effect may be delayed for many weeks and that remission can only be maintained by further courses of the drug. There is, therefore, the possibility that in some of the cases where temporary remission occurred, further courses of the drug may have had a more quantitative and lasting effect. Our preliminary investigations would indicate that further trials using more prolonged and repeated courses in patients showing response should be performed.

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