

## REPORT ON TWENTY PATIENTS WITH MALIGNANT DISEASE TREATED WITH CYTOTOXIC AGENTS

S. V. HUMPHRIES, M.A., M.R.C.S., L.R.C.P., F.I.C.S., Formerly at Lilongwe Hospital, Nyasaland

Cytotoxic agents are valuable weapons in relieving the pain and distress of malignant disease, especially in that large part of the world's population to whom radiotherapy is not available. Their effects are palliative and symptomatic. They reduce the size of tumours, lessen pain, increase appetite and strength and consequently relieve mental depression. Sometimes they prolong life, but by their toxicity they may shorten it. It cannot be fairly held that they lengthen the patient's distress by prolonging life.

The patients here reviewed were all suffering from advanced malignant disease. They were treated with nitrogen mustard or cyclophosphamide ('endoxan'), or with both these agents. The agent administered could not usually be selected for the patient since supplies of both drugs were limited. The agent was usually given after making a diagnosis clinically and taking a specimen for biopsy, without waiting for confirmation from the laboratory, because the disease was advanced. Whenever possible a section was sent to the pathologist, Dr. S. T. H. H. Pilbeam, in Blantyre. A clinical diagnosis alone was made in 8 cases, and confirmation or correction obtained in 12. In some cases, e.g. carcinoma of the oesophagus, the tumour was too inaccessible to obtain a specimen; in others removal of the growth would have caused excessive haemorrhage or unnecessary suffering, or the patient was expected to die before a report could be received.

The usual adult course of nitrogen mustard consisted of 4 daily doses, each of 10 mg. given in 1 litre of dextrose in water or normal saline as an intravenous drip. If the leukocyte count was not reduced below 3,000 per c.mm. a second course was started after a few days. Subsequent courses were administered according to the leukocyte response provided that haemoglobin index was 60% or could be raised to near this level. Blood transfusions were given as indicated whenever possible. The use of these agents lowers the haemoglobin index, and blood transfusions therefore constitute an important part of the treatment. The availability of blood was often the deciding factor determining whether this kind of treatment could be carried out. Some benefit may be expected to result from the administration of iron, and vitamin B<sub>12</sub> is also recommended. Both 'imferon' and vitamin B<sub>12</sub> were used in this series. Promethazine chlorotheophyllinate ('avomine'), 25 mg., or chlorpromazine, 25 mg., given before starting the infusion, were useful in reducing nausea and vomiting.

'Endoxan', which is less toxic but more expensive than nitrogen mustard, was administered in courses of 5 injections, increasing daily from 100 to 500 mg. Subsequent courses were controlled by the blood picture as above.

It is not necessary to mention the indications for cytotoxic agents, since these are well known and available from the extensive literature on these drugs. My object is to show that benefit was obtained by 18 adult African patients out of 20, many of whom were suffering from types of cancer for which cytotoxic agents are not usually recommended.

### CASE REPORTS

#### *Case 1, Hodgkin's Disease (Proved Microscopically)*

M.J., male, aged 40, was admitted on 20 May 1962 with ulcerating glands of the left groin which had been present for a few months. Endoxan, 500 mg., and nitrogen mustard, 50 mg., reduced the leukocyte count from 10,800 to 3,650 per c.mm. He was discharged healed on 19 July. He returned in October with recurrence of the same complaint and treated with 5,000 mg. of endoxan, after which he was discharged healed in November. He returned on 12 February 1963 with a large growth in the left groin and 5 deposits in the chest, seen on the radiogram. Nitrogen mustard, 80 mg., followed by endoxan 2,500 mg. caused regression, but the growth later increased. It was evident that these agents were no longer effective. Later, the patient complained of pain in the left groin which became increasingly severe. On 25 June a right dorsal chordotomy was performed with complete relief. The patient is still in hospital.

#### *Case 2, Hodgkin's Disease (Proved Microscopically)*

A.N., male, aged 42, was sent here for splenectomy on 8 June 1962 with splenomegaly and anaemia. Splenectomy was performed. The spleen, which weighed 3½ lb., was infiltrated with white tumours. Nitrogen mustard, 70 mg., was administered. He was discharged asymptomatic on 26 September. He returned on 18 January 1963 with a mass of glands above the right clavicle. Endoxan, 3,000 units, caused no improvement. He was discharged on 16 February. He has not returned.

#### *Case 3, Hodgkin's Disease (Proved Microscopically)*

T.C., male, aged 30, was admitted on 5 September 1962 with a painful swelling on the right side of the neck of 1 year's duration, splenomegaly, and oedema and pitting of both legs. A mass of glands were removed and 40 mg. of nitrogen mustard administered. The condition was much improved and the patient was discharged on 17 October. He has not returned.

#### *Case 4, Kaposi's Sarcoma (Proved Microscopically)*

E.L., male, aged 25, was admitted on 26 November 1962 with tumours on the second left toe and two tumours on the foot. Pain had been felt in the toe for 10 years. The tumours were removed on 27 November, but the wounds became septic. Nitrogen mustard, 40 mg., was administered. The patient absconded on 27 December with the wounds healing well.

#### *Case 5, Kaposi's Sarcoma (Proved Microscopically)*

K.M., male, aged 25, was admitted on 29 January 1963 with nodules of the left upper eyelid, gums, tongue, palate, face, and scalp, which had started 2 months previously. Specimens were removed for microscopy and nitrogen mustard, 40 mg., administered. Some subjective and objective improvement followed, and the patient was discharged at his own request on 22 February.

#### *Case 6, Carcinoma of the Stomach (Found at Operation)*

K.A., male, aged 29, was admitted on 14 August 1962, extremely dehydrated and emaciated with a large palpable mass in the epigastrium. Pain and vomiting were complained of for 6 months. He vomited almost everything taken by mouth. An augmented histamine test showed 6.8 mEq. of free acid before histamine and 4.4 mEq. after histamine. A barium meal showed a large filling defect in the pyloric region. Much barium was retained in the stomach after 4 hours. Laparotomy on 30 August showed a large tumour on the lesser curvature near the pylorus. An anterior gastro-enterostomy was performed, after which he could take food and fluids. After a few days the wound broke down with the escape of gastric contents. Nitrogen mustard, 60 mg., and endoxan, 1,000 mg., were administered. This caused no vomiting, the wound healed,

and the patient was much happier up to the time of his death on 14 November.

*Case 7, Carcinoma of the Stomach (Found at Operation)*

A.E., female, aged 50, was admitted on 12 November 1962 with abdominal pain, vomiting, and abdominal swelling for 6 months. She vomited almost everything taken. A large tumour was palpable in the epigastrium, and numerous hard glands were palpable on the left side of the neck and in the left groin. Hb. 55%. At laparotomy the pyloric portion of the stomach was found to be extensively infiltrated with tumour. A posterior gastro-enterostomy was performed and 2 pints of blood given. Endoxan, 100 mg., was given daily for 10 days, which caused immediate subsidence of the glands in the neck and great improvement in the general condition, with no vomiting. A second course of endoxan was started on 6 December, but the patient absconded.

*Case 8, Carcinoma of the Cervix and Vagina (Diagnosed Clinically)*

M.S., aged 40, was admitted on 26 November 1962 with metrorrhagia for 4 months. Vaginal examination revealed an extensive tumour of the cervix and upper part of the vagina. Nitrogen mustard, 40 mg., was administered. The bleeding stopped, but there was still a watery vaginal discharge. The patient felt much better and asked to be discharged on 4 December. Next day she absconded.

*Case 9, Carcinoma of the Cervix (Diagnosed Clinically)*

V.E., aged 40, was admitted on 7 February 1962 with a large growth of the cervix. Laparotomy had been performed at another hospital in July 1962, when considerable haemorrhage had been encountered requiring the administration of 2 pints of blood. The growth was inoperable. She was treated with nitrogen mustard, 40 mg., after which she felt much better. She absconded on 22 February.

*Case 10, Squamous-cell Carcinoma of the Penis (Proved Microscopically)*

L.A., aged 62, was admitted on 19 June 1962 with an extensive growth of the penis and a large mass of glands in the right groin, stated to be of 4 months' duration. Complete removal of the penis was performed on 11 July, but the glands were found to have broken down and were extending backwards deeply into the pelvis. As much as possible was removed and drains were inserted. Nitrogen mustard, 120 mg., and endoxan, 1,000 mg., caused a reduction of the leukocyte count from 21,600 to 3,600 per c.mm. By September the wound in the right groin was much reduced in size and the patient was considerably more comfortable than on admission. He died on 6 November of anaemia and weakness.

*Case 11, Secondary Squamous-cell Carcinoma of Glands of the Right Side of the Neck (Proved Microscopically)*

W.I., male, aged 30, was admitted on 24 September 1962 with a stony hard mass of glands on the right side of the neck of 2 years' duration. A considerable portion of the tumour was removed 3 days later with a segment of the internal jugular vein. No primary tumour could be found. Endoxan, 1,500 mg., was administered, and he was discharged on 19 October with the wound healed and the remaining glands decreased in size.

*Case 12, Lymphatic Leukaemia (Diagnosed by the Leukocyte Count)*

N.D., male, aged 60, was admitted on 30 August 1962 with a spleen which almost completely filled the abdomen. Pain and swelling of the abdomen had been noticed for 1 year. The leukocyte count was 74,000 per c.mm., polymorphs 8%, lymphocytes 90%. Endoxan, 2,000 mg., was administered. Though the leukocyte count increased to 118,500 per c.mm. the patient felt much better within less than a month, and was discharged.

*Case 13, Lymphoma (Diagnosed Clinically)*

K.B., female, aged 40, was admitted on 30 August 1962 with a swelling of the right side of the face for 4 months. The

appearance of the tumour with displacement and loosening of the teeth and the absence of glandular enlargement were strongly suggestive of malignant lymphoma, in spite of the patient's age. Small fragments of tumour taken from inside the mouth and examined microscopically, showed only non-specific inflammatory change and many plasma cells. An attempt was made to find the external carotid artery to perfuse it by means of a cannula inserted into one of its branches, but the common carotid artery was followed up to the level of the mastoid process, and no branches were given off. Endoxan, 7,500 mg., was administered intravenously. This caused reduction in the size of the tumour and considerable subjective improvement. The patient was discharged on 3 October.

*Case 14, Mycosis Fungoides (Proved Microscopically)*

H.L., male, aged 42, was admitted on 27 October 1962 from Kochira Leprosarium. Dr. Gordon Currie, to whom the patient had been sent for suspected leprosy, had excluded the possibility of this disease and had confirmed his diagnosis of mycosis fungoides by biopsy. The disease had started with itching in 1959. There were numerous white patches on the skin all over the body, scattered abscesses, tumour-like nodules on the back, and a chronic penile ulcer which had caused an indurated fibrosis. The Kahn test was negative. Circumcision was performed. Endoxan, 1,500 mg., and nitrogen mustard 60 mg. were administered. The patient was discharged on 6 December with considerable improvement of all his lesions.

*Case 15, Reticulosarcoma of Chest (Proved Microscopically)*

C.N., male, aged 50, was admitted on 19 November 1962 with a tumour on the left side of the chest anchored to the ribs, of 2 months' duration, and a large mass of glands in the axilla. The glands were removed next day. Nitrogen mustard, 80 mg., and endoxan, 2,400 mg., were administered. The tumour of the chest disappeared and the axillary scar was completely healed when the patient absconded on 18 December.

*Case 16, Carcinoma of both breasts (Diagnosed Clinically)*

F.S., female, aged 40, was admitted on 30 January 1963 with typical scirrhous carcinoma of both breasts, fixed to the chest wall, with extensive involvement of the skin. She complained of severe pain in the skin nodules. Endoxan, 1,600 mg., and nitrogen mustard, 70 mg., caused considerable reduction of pain and great subjective improvement by 11 February, but by 18 February the leukocyte count had dropped to 2,500 per c.mm., and the next day she died suddenly.

*Case 17, Carcinoma of the oesophagus (Diagnosed by Barium Swallow)*

H.A., male, aged 70, was admitted on 18 January 1963, extremely wasted and hardly able to swallow anything. Resistance was felt in the epigastrium. A barium swallow showed a filling defect consistent with advanced carcinoma involving the lower half of the oesophagus. Endoxan, 3,000 mg., was administered, which caused a reduction in the leukocyte count from 5,000 to 2,400 per c.mm. Great improvement resulted in the patient's general condition, weight, and sense of well-being. He died suddenly on 13 February.

*Case 18, Pseudomucinous Cystomata of the Ovary (Diagnosed at Laparotomy)*

T.W., female, aged 36, was admitted on 13 August 1962 with severe abdominal discomfort for 4 months and loss of weight. A large hypogastric swelling was palpable which was proved at laparotomy to be caused by numerous cystic tumours in the pelvis, too numerous and fixed for removal, and a hydrosalpinx. Specimens were sent for microscopy, but the report mentioned only the hydrosalpinx. Nitrogen mustard, 80 mg., was administered, which caused considerable improvement, and she was discharged on 31 October. She returned on 6 May 1963 when two rounded tumours could still be felt in the lower abdomen, but the patient refused further treatment.

*Case 19, Neurofibroma (Diagnosed Microscopically)*

J.T., male, aged 45, was admitted on 26 July 1962 with a tumour of the right buttock about the size of a football, which

had been present for 2 years. The inguinal glands were enlarged and very hard. The haemoglobin was only 54%, but no blood could be obtained. Nitrogen mustard, 40 mg., was administered, and the tumour was then removed under local anaesthesia and part of the raw area skin grafted. By 22 August all the grafts had taken well, but on 26 August the patient complained of cough and sudden pain in the chest, and died. Section of the growth removed showed spindle cells and some hyaline change. It was thought to be a neurofibroma.

*Case 20, Chondrosarcoma (Diagnosed Microscopically)*

L.I., female, aged 23, was admitted on 23 November 1962 with a swelling about 6 inches in diameter in the left buttock for 6 months. The X-ray showed destruction of the left iliac bone with encroachment on to the sacrum. Small portions were removed for microscopy. It was a predominantly spindle-cell tumour with primitive cartilage formation and a few giant cells—probably a chondrosarcoma. Nitrogen mustard, 60 mg., was given, but no improvement resulted, and the patient absconded on 26 December.

COMMENT

Many of the patients described here could not be followed up since they did not return for further examination after

discharge (or absconding) from hospital. Though this renders the clinical pictures incomplete it does not detract from the fact that the treatment benefited most of the patients temporarily, which is all that can be legitimately claimed for cytotoxic agents in the treatment of malignant disease.

SUMMARY

1. Twenty patients with malignant disease are described, of which 8 were treated with nitrogen mustard, 5 with endoxan, and 7 with both these agents. Improvement was obtained in all but 2 (Cases 19 and 20).

2. The value of these agents is stressed, and the usefulness of the leukocyte count and haemoglobin index for the control of treatment is mentioned. The availability of blood for transfusion was often the main factor determining whether this form of treatment could be instituted and continued.

3. Nine patients were discharged, 6 absconded, 1 is still in hospital, and 4 died.

4. Of the deaths, 3 patients died of generalized weakness (Cases 6, 16, and 17). The remaining death (Case 19) would probably not have occurred if blood had been available.