INOPERABLE BRONCHIAL CANCER TREATED BY COMBINED TELECOBALT AND NATULAN THERAPY

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The treatment of inoperable bronchial carcinoma remains unsatisfactory. In 1962 one of us (T.F.)[1] reported on the value of telecobalt therapy alone in the treatment of 77 patients suffering from inoperable bronchial cancer, and in 1965 Brulé, Schulemleger and Griscelli[2] reported therapeutic response in bronchogenic carcinoma treated with Natulan (N-Iso-propyl-alpha-[2-methylhydrazino]-p-toluamide hydrochloride; N.S.C. 77213; Ro 46467 Ibenzmethazine).

We have observed objective improvement following the use of combined Natulan and telecobalt therapy in the treatment of malignant mesothelioma[3,4] and of inoperable malignant melanoma.[5] It therefore appeared logical to us to treat inoperable bronchial carcinoma with combined telecobalt and Natulan therapy.

MATERIALS AND METHODS

A total of 21 patients suffering from inoperable bronchial cancer were treated with combined telecobalt and Natulan therapy.

These patients presented with either one or other of the following objective criteria of malignancy: (*a*) Radiographic evidence of a measurable tumour mass in the chest and/or (*b*) clinical evidence of a measurable tumour mass involving regional lymph nodes or skin.

In 19 of the 21 patients the diagnosis was confirmed histologically: 7 were squamous cell carcinoma, 5 were undifferentiated, 6 were oat cell, 1 was an adenocarcinoma and 2 were histologically unknown. These 2 cases, however, had the clinical criteria and the support of special investigations to establish the diagnosis of bronchial carcinoma, but unfortunately bronchoscopic biopsy was not possible. These two cases have been included in this assessment of results.

The patients' ages varied from 41 to 81 years with an average age of 60·2 years. There were 17 males and 4 females in the series. No patient who had a serious infection, was actively bleeding, or who had an associated severe systemic disease was entered on the clinical trial. At the commencement of treatment all these patients had an estimated expectation of life of more than 3 weeks. All the patients had a total white cell count of more than 4,500 cells/cu.mm. and a blood urea of less than 40 mg./100 ml. Only one patient (no. 10) had received prior cancer chemotherapy with cyclophosphamide, otherwise none of these patients received a concomitant drug which might have had an effect on the malignancy.

SPECIAL INVESTIGATIONS

The following special investigations were performed on patients entering this clinical trial: (*a*) Full blood count, (*b*) urinalysis, (*c*) serum alkaline phosphatase, (*d*) serum bilirubin, (*e*) serum albumin-globulin determination, (*f*) blood urea and uric acid, and (*g*) X-ray examination of the chest.

Blood counts were repeated biweekly during periods of active treatment and X-rays of the chest were taken frequently during periods of active treatment.

At the commencement of treatment all patients were classified according to the stage of the disease and according to their performance status.

CLINICAL STAGING

As there is no satisfactory method of clinical staging of bronchial cancer acceptable to all and agreed to internationally, we have introduced our own criteria for clinical staging which are tabulated in Table I:

TABLE I. CLINICAL STAGING OF BRONCHIAL CANCER DETERMINED RADIOGRAPHICALLY

Stage I	T1	A radiographic tumour mass in the chest of less than 2·0 cm. in diameter and situated either in the hilar region (central) or in the parenchyma (peripheral)
	NO	No hilar lymph node involvement
Stage II	T2	A radiographic tumour mass in the chest of between 2·0 and 5·0 cm. in diameter causing occlusion of a segmental or lobar bronchus with or without segmental or lobar atelectasis/consolidation
	NO	No hilar lymph node involvement

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TABLE I (CONT'D.)

Stage III	T3	A radiographic tumour mass in the chest of more than 5·0 cm. in diameter causing occlusion of the main bronchus with or without atelectasis/consolidation, or
	N1	Hilar lymph node involvement
Stage IV	T4	Radiographic evidence of a pleural effusion associated with either T.1, T.2 or T.3 or rib erosion as in a Pancoast (superior sulcus) tumour with
	N1	Hilar lymph node involvement, or
	M1	Supraclavicular or axillary node metastases, or
	M2	Distant metastases to lung, liver, brain, bone, skin, etc.

This system of clinical staging is open to criticism. We are well aware of its many defects. The chief difficulty lies in determining whether the hilar lymph nodes are involved or not, because this finding is responsible for placing the case either in stage II or stage III. All 21 patients in this series were classified either as stage III or stage IV. Of the 21 cases, 12 were classified as stage III and 9 as stage IV. We have found this method of clinical staging simple and satisfactory.

We have found it profitable to assess the patient's performance status at the beginning of treatment. The patient is placed into one of 4 categories defined as follows (Table II):

TABLE II. CATEGORIES OF PERFORMANCE STATUS (PS)

A	Normal activity
B	Unable to work Living at home Caring for personal needs
C	Unable to care for personal needs Living at home Needing help
D	Very ill Bed-ridden Needing hospitalization

The categories of response, as proposed by Karnofsky,[6] have been used, which are summarized in Table III.

TABLE III. CATEGORIES OF RESPONSE TO TREATMENT

Category 0:	No clinically useful effect on the course of the disease
0-0	Disease progresses. No subjective benefit
0-A	Disease progresses. Subjective benefit without favourable objective changes
0-B	Favourable objective changes without subjective benefit
0-C	Subjective benefit and favourable objective changes in measurable criteria, but of less than one month's duration, then the disease progresses
Category 1:	Clinical benefit with favourable objective changes in all measurable criteria of disease
1-A	Distinct subjective benefit with favourable objective changes in all measurable criteria for one month or more
1-B	Objective regression of all palpable or measurable neoplastic disease for one month or more in a relatively asymptomatic patient who is able to carry on his usual activities without undue difficulty. The observed tumour regression should be unequivocal and, as a suggestion, all lesions should be reduced by at least 50%. This category applies as long as the regression persists and ends if any lesion, old or new, recurs
1-C	Complete relief of symptoms, if any, and regression of all manifestations resulting from active disease for one year or more. The relation to the frequency of therapy is not relevant if the disease does not recur between courses of therapy

Note: Categories apply as long as improvement from baseline persists.
Superscriptions above 0, A, B and C represent the time in months of the duration of the response

The stage of the disease and performance status (PS) of each patient is shown in Table IV.

TABLE IV. AN ANALYSIS OF 21 PATIENTS TREATED WITH RADIOTHERAPY AND NATULAN

No.	*Age*	*Sex*	*Presenting symptoms*	*Surgery*	*Pathology*	*Site*	*PS*	*Stage*	*Radiotherapy* *Co–60: 3,000 Curie source H.V.L. 10·4 mm. Pb. D.X.T. 220 K.V. H.V.L. 1·8 mm. Cu. Tumour dose in rads*	*Chemotherapy* *Natulan dosage in mg. in number of days and lowest white cell count*	*Response*
1	56	F^A	Cough, haemoptysis, dyspnoea, pain. Duration: 3 mths.	Br. scopy	Squamous cell	R. lower lobe	B	III	*Co–60*: (1) 2500r in 15 days – 3 fields (9/7/65) (2) 2,000r in 10 days – 3 fields (3/9/65) (3) 1,000r in 5 days – 3 fields (8/11/65) (4) 994r in 5 days – 3 fields (24/12/65)	19,800 mg. in 216 days. Lowest WBC 4,000	$I–A^7$ Alive and in remission
2	50	M^A	Dyspnoea. Duration: 4 mths.	Lobectomy	Squamous cell	L. upper lobe	B	III	*Co–60*: 1,000r in 5 days – 2 fields (11/1/65)	27,050 mg. in 394 days. Lowest WBC 2,600	$I–A^{12}$ Alive and in remission
3	68	M^D	Cough, haemoptysis. Duration: 3 mths.	Br. scopy	Squamous cell	L. upper lobe	B	III	*Co–60*: 1,801r in 9 days – 3 fields (18/5/65)	1,250 mg. in 5 days. Lowest WBC 5,100	$0–0^1$
4	61	M^D	Cough, infection. Duration: 3 mths.	Br. scopy	Squamous cell	R. lower lobe	B	III	*Co–60*: (1) 2,000r in 12 days – 3 fields (6/5/65) (2) 1,000r in 5 days – 3 fields (28/6/65) (3) 1,000r in 5 days – 3 fields (16/8/65) (4) 1,000r in 5 days – 3 fields (18/10/65)	4,750 mg. in 171 days. Lowest WBC 3,100	$I–A^7$ Died of coronary thrombosis
5	81	M^D	Cough, pain. Duration: 4 mths.	Br. scopy	Undiffer.	R. lower lobe	C	IV	*Co–60*: 1,013r in 5 days – 3 fields (18/10/65)	1,250 mg. in 5 days. Lowest WBC 2,300	0–0
6	61	M^D	Cough, pain. Duration: 6 mths.	Thorac.	Undiffer.	R. upper lobe	D	IV	*Co–60*: 667r in 5 days – 1 field (3/5/65)	1,250 mg. in 5 days. Lowest WBC 17,000	0–0

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TABLE IV. (CONT'D.)

No.	Age	Sex	Presenting symptoms	Surgery	Pathology	Site	PS	Stage	Radiotherapy Co-60: 3,000 Curie source H.V.L. 10·4 mm. Pb. D.X.T. 220 K.V. H.V.L. 1·8 mm. Cu. Tumour dose in rads	Chemotherapy Natulan dosage in mg. in number of days and lowest white cell count	Response
7	49	M^A	No symptoms. Duration: 1 mth.	Biopsy and br. scopy	Undiffer.	R. upper lobe	A	IV	*Co-60*: (1) 2,000r in 12 days – 3 fields (5/7/65) (2) 1,200r in 5 days – 3 fields (7/9/65) (3) 1,200r in 5 days – 3 fields (1/11/65) *D.X.T.*: (4) 1,500r in 5 days – 1 field (1/11/65 – supraclavicular) (5) 1,625r in 5 days – 1 field (3/1/66 – supraclavicular) *Co-60*: (6) 1,200r in 5 days – 3 fields (3/1/66)	16,450 mg. in 269 days. Lowest WBC 5,100	I–B[8] Alive and in remission
8	70	M^D	Cough, haemoptysis, infection. Duration: 6 mths.	Br. scopy	Undiffer.	R. upper lobe	B	III	*Co-60*: (1) 5,390r in 20 days – 3 fields (22/9/64) (2) 1,000r in 5 days – 2 fields (9/4/65)	24,500 mg. in 350 days. Lowest WBC 1,700	I–A[11] Died of pneumonia
9	73	M^A	Cough, haemoptysis, dyspnoea. Duration: 3 mths.	Br. scopy	Oat cell	L. lower lobe	B	III	*Co-60*: (1) 1,947r in 12 days – 3 fields (15/10/65) (2) 1,002r in 5 days – 3 fields (10/12/65) (3) 1,000r in 5 days – 3 fields (31/1/66)	5,000 mg. in 111 days. Lowest WBC 7,100	I–A[4] Alive and in remission
10	41	M^A	Cough, haemoptysis, dyspnoea, pain. Previously Endoxan 4,000 mg. in 14 days, 10 days earlier. Duration: 3 mths.	Br. scopy Thorac.	Oat cell (scalp metastases anaplast. Ca.)	R. upper lobe	B	III	*Co-60*: (1) 1,995r in 12 days – 3 fields (30/4/65) (2) 1,199r in 5 days – 3 fields (4/8/65) (3) 4,500r in 15 days – 1 field (8/11/65)	29,850 mg. in 312 days. Lowest WBC 2,000	I–A[3] Alive, but now scalp metastases
11	59	M^D	Cough, dysphagia. Duration: 2 mths.	Br. scopy	Oat cell	R. main lobe	B	III	*Co-60*: (1) 1,600r in 6 days – 3 fields (7/12/64) (2) 1,200r in 5 days – 3 fields (15/2/65)	1,940 mg. in 112 days. Lowest WBC 1,300	I–A[6]
12	61	M^D	Cough, pain, glands. Duration: 3 mths.	Br. scopy	Oat cell	R. upper lobe	B	IV	*Co-60*: 1,000r in 5 days – 3 fields (Dec. 1964)	9,500 mg. in 50 days. Lowest WBC 900	0–0
13	51	M^D	Infection, paralysis, brain metas. Duration: 2 mths.	Biopsy	Oat cell	R. upper lobe	D	IV	*Co-60*: 1,502r in 7 days – 3 fields (22/12/65)	2,000 mg. in 8 days. Lowest WBC 5,000	0–0
14	66	M^A	Cough, haemoptysis, dyspnoea, sup. vena cava. Duration: 11 mths.	Br. scopy	Unknown	R. middle lobe	B	IV	*Co-60*: (1) 1,996r in 12 days – 3 fields (12/8/65) (2) 1,196r in 5 days – 3 fields (18/10/65) (3) 1,184r in 5 days – 3 fields (13/12/65)	4,000 mg. in 127 days. Lowest WBC 3,900	I–A[8] Alive and in remission
15	73	M^D	Cough, dyspnoea. Duration: 5 mths.	Br. scopy	Well dif. mucus sec. adeno Ca.	R. upper lobe	C	III	*Co-60*: (1) 2,698r in 12 days – 3 fields (5/4/65) (2) 2,402r in 8 days – 3 fields (24/5/65)	3,000 mg. in 56 days. Lowest WBC 5,800	O–A[3]
16	73	F^A	Dyspnoea, pain, haemoptysis. Duration: 3 mths.	Thorac.	Necrotic mass/ pleural cavity	L. lower lobe	C	IV	*Co-60*: (1) 1,995r in 12 days – 3 fields (6/12/65) (2) 998r in 5 days – 3 fields (14/2/66)	3,750 mg. in 73 days. Lowest WBC 4,300	I–A[2] Alive and in remission
17	55	F^A	Cough, pain, glands. Duration: 6 mths.	Br. scopy	Oat cell	R. upper lobe	B	IV	*Co-60*: (1) 3,000r in 12 days – 3 fields (15/11/65) (2) 1,500r in 5 days – 3 fields (31/1/66)	9,150 mg. in 83 days. Lowest WBC 1,900	I–A[3] Alive and in remission
18	52	F^A	Haemoptysis, sup. vena cava. Duration: 6 mths.	Br. scopy Thorac.	Squamous cell	R. lower and middle lobe	C	III	*Co-60*: (1) 2,000r in 12 days – 2 fields (13/12/65) (2) 1,059r in 5 days – 2 fields (21/2/66)	3,500 mg. in 75 days. Lowest WBC 8,800	I–A[1] Alive and in remission
19	49	M^A	Dyspnoea, cough. Duration: 6 mths.	Thorac.	Anaplast. Ca.	R. lower lobe	A	IV	*Co-60*: (1) 2,000r in 12 days – 2 fields (22/11/65) (2) 1,000r in 5 days – 2 fields (2/2/66)	11,650 mg. in 87 days. Lowest WBC 5,500	I–A[3] Alive and in remission
20	51	M^A	Haemoptysis, loss of weight. Duration: 5 mths.	Br. scopy Mediastinoscopy Thorac.	Squamous cell	R. main lobe	B	III	*Co-60*: (1) 2,000r in 12 days – 2 fields (17/9/65) (2) 1,000r in 5 days – 2 fields (Nov. 1965) (3) 1,000r in 5 days – 3 fields (Jan. 1966)	5,000 mg. in 119 days. Lowest WBC 4,300	I–A[2] Alive and in remission
21	65	M^A	Cough, pain. Duration: 12 mths.	Br. scopy	Unknown	R. upper lobe	B	III	*Co-60*: (1) 1,900r in 12 days – 3 fields (8/9/65) (2) 999r in 5 days – 3 fields (15/11/65) (3) 999r in 5 days – 3 fields (10/1/66)	5,000 mg. in 132 days. Lowest WBC 4,400	I–A[3] Alive and in remission

M^A = Male alive. M^D = Male dead. F^A = Female alive. F^D = Female dead. PS. = Performance status

The performance status at start of treatment was A in 2, B in 13, C in 4 and D in 2 patients.

TREATMENT

Treatment was administered as follows: A Siemens 3,000 Curie telecobalt unit was used. Using 3 fields, anterior, lateral and posterior, a tumour dose of 2,000r in 10 treatments over 2 weeks was administered in the first course of treatment. Variations on this dosage scheme may be seen in Table IV. At 8 weekly intervals thereafter a tumour dose of 1,000 - 1,200r was administered in 5 days. Natulan was given by intravenous injections, 250 mg. from 5 to 15 minutes before irradiation on each treatment day in 12 of the 21 patients. In the remaining patients, oral Natulan was administered.

Details of the radiotherapy and Natulan doses for each individual patient are shown in Tables III and IV.

The total dose of Natulan administered varied from 1,250 mg. in 5 days (patient no. 3) to 29,850 mg. in 312 days (patient no. 10). The minimum treatment administered to a patient for trial to be considered adequate was a tumour dose of 500 rads and a Natulan dose of 1,250 mg.

RESULTS

Therapeutic results for each patient are shown in Table IV. Fifteen of the 21 patients showed objective improvement following this treatment. Of the 21 patients, 12 are still alive and of these 11 are still in remission.

Of the 12 patients with stage III bronchogenic carcinoma, 10 showed both objective and subjective improvement of more than one month's duration and one showed subjective improvement only. Of the 9 patients with stage IV bronchogenic cancer, 5 showed objective and subjective improvement of more than one month's duration. Two of the 2 patients with performance status A, 11 of the 13 patients with performance status B, and 2 of the 4 patients with performance status C, responded objectively to treatment, but neither of the 2 with performance status D.

TOXICITY

The lowest white cell count recorded for each patient is shown in Table IV. Leucopenia below 3,000 cells/cu.mm. was recorded in 6 patients. Thrombocytopenia of clinical importance was not observed among the patients. Although nausea was observed in all patients this was never severe enough to preclude further treatment. Neurological effects were not observed among the patients.

CONCLUSIONS

The response to treatment with combined telecobalt and Natulan therapy is encouraging, but no cure can be claimed in the treatment of advanced inoperable bronchial cancer by this means. At most the period of extended life is made more bearable.

In the group of 21 patients with advanced bronchogenic cancer, better response was seen in those with stage III (10 out of 12) than those in stage IV (5 out of 9).

As might be expected, there is a direct relationship between the patient's performance status at the start of treatment and his response to treatment.

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