PAPERS AND ORIGINALS

Study of Cytotoxic Chemotherapy as an Adjuvant to Surgery in Carcinoma of the Bronchus

REPORT BY A MEDICAL RESEARCH COUNCIL WORKING PARTY

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Summary

This report gives the findings after two years of a study of long-term oral cytotoxic chemotherapy with busulphan or cyclophosphamide in carcinoma of the bronchus compared with two placebos, identical in appearance to the drug-containing tablets. A total of 753 patients who had had a total resection of the tumour, who had no detectable extrathoracic metastasis, and who were able to attend chest clinics monthly were admitted to the study from January 1965 to January 1968. Twenty-seven patients were excluded from all the analyses.

The 217 patients admitted up to December 1965 form the "early" intake, the remaining 509 the "late" intake. There were no significant differences between the series in either intake period in a number of pretreatment factors studied. At 24 months 46% of the busulphan, 44% of the cyclophosphamide, and 49% of the placebo series were alive in the early intake, as were 49%, 50%, and 50% respectively in the late intake. There were no important differences between the series in survival related to pretreatment condition, cause of death, time of detection of metastases, and condition of the survivors at 24 months. Maintenance chemotherapy was interrupted to a greater extent in the busulphan than in the cyclophosphamide series and least in the placebo series.

In both intakes clinical toxicity was more frequent in the cyclophosphamide series and similar in frequency in the busulphan and placebo series. Haematological toxicity was particularly frequent and severe in the busulphan series, especially in the early intake, platelet depression being the predominant manifestation.

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Report to the Medical Research Council by the Working Party on the Evaluation of Different Methods of Therapy in Carcinoma of the Bronchus.

During the conduct of this study the membership of the Working Party was: Professor J. G. Scadding (chairman), Dr. J. R. Bignall (secretary until April 1970), Dr. L. G. Blair, Mr. W. P. Cleland, Professor A. L. d'Abreu, Dr. Wallace Fox, Dr. D. A. G. Galton, Professor J. Gough, Professor Sir Alexander Haddow, F.R.S., Dr. J. F. Heffernan, Sir Austin Bradford Hill, F.R.S., Dr. K. E. Halnan, Dr. K. F. W. Hinson, Dr. G. S. Kilpatrick, Dr. A. M. Jelliffe, Dr. J. R. Lauckner, Dr. A. B. Miller (secretary from April 1970), Dr. I. Sutherland, Sir Brian Windeyer, and Sir Michael Woodruff, F.R.S.

It is concluded that there is no evidence that either of the two cytotoxic drugs in the dosage prescribed improved survival for the two-year period of observation, though a final evaluation of the adjuvant chemotherapy as studied in this investigation will have to await the results at five years.

Introduction

Many deaths after potentially curative resection for carcinoma of the bronchus are due to distant metastases. These must either have been present at the time of operation or have arisen from carcinoma cells circulating in the blood or from inapparent carcinoma tissue left in the thorax. It is possible that cytotoxic chemotherapy begun shortly after operation could keep metastases in check and prolong survival time.

Nitrogen mustard given in high dosage at the time of surgery, however, increased postoperative mortality in the first 30 days (Veterans Administration Adjuvant Cancer Chemotherapy Cooperative Group, 1961; Higgins *et al.*, 1962), while in lower dosage, though not increasing early postoperative mortality, it did not improve long-term survival (Hughes and Higgins, 1962). Nevertheless, as some investigators had reported favourably on long-term adjuvant chemotherapy with cyclophosphamide (Denk and Karrer, 1961; Poulsen, 1962, 1963) it was decided in 1964 to study *long-term* cytotoxic chemotherapy with cyclophosphamide, chosen in view of the above favourable reports, and with busulphan, chosen because of its activity in inoperable bronchial carcinoma (Sullivan, 1958) and its relative freedom from side effects (Galton, 1953).

This report gives the results up to two years; those up to five years will be reported later.

The study was organized by the Medical Research Council Tuberculosis and Chest Diseases Unit and was co-ordinated by Dr. A. B. Miller. The results were analysed and the report was prepared by Dr. Miller, Dr. Wallace Fox, Mr. P. R. Somasundaram, and Miss Ruth Tall. The slides of the operation specimens were assessed and the histological appearances of the tumours classified by Dr. K. F. W. Hinson, who acted as the reference pathologist.

Plan and Conduct of Study

Patients were admitted to the study from 23 centres throughout

Great Britain. These were centres in which the chest physicians in the area and the thoracic surgeon to whom they normally referred patients agreed to co-operate and where patients could be transferred from the care of the surgeon after discharge from hospital to that of the chest physician for the study follow-up.

PATIENTS ELIGIBLE FOR THE STUDY

Men of any age and women aged 45 or over were eligible for the study provided that: (a) the surgeon had just completed a total resection of the tumour, all visible intrathoracic growth having been removed; (b) there was a firm diagnosis of bronchial carcinoma (a few patients in whom the diagnosis was not confirmed histologically after operation were subsequently excluded); (c) there were no detectable extrathoracic metastases; (d) the patient had not had radiotherapy or treatment with a cytotoxic drug before operation; (e) it was not planned to give a postoperative course of radiotherapy; (f) the chest physician had indicated that it would be possible for the patient to attend the chest clinic monthly for the control of chemotherapy; and (g) there were no known contraindications to the use of either cytotoxic drug under study.

CHEMOTHERAPY

Patients were allocated at random to receive busulphan, cyclophosphamide, or a placebo for two years, all given by mouth. The first patient was allocated on 7 January 1965 and the last on 31 January 1968. Busulphan was given as tablets each containing 0.5 mg. Cyclophosphamide was given as tablets each containing 25 mg. Two suitable inactive preparations were used as placebos—one was bland and similar in taste to busulphan, and the other was bitter, containing 1 mg of quinine, similar in taste to cyclophosphamide.

All the tablets were identical in appearance, being specially made for the study. Each consisted of a core containing the active drug (or placebo) in its commercial formulation inside a compressed lactose coat. The tablets were supplied to the centres already labelled with a serial number for each patient in quantities sufficient for a six-month supply in the "early intake" and 12 months in the "late intake" (see below).

ALLOCATION TO CHEMOTHERAPY

Each centre was provided with a patient register with serial numbers already entered, corresponding to the supplies of tablets. Allocation to chemotherapy was made after operation by writing the patient's name in the next available line in the register, thus providing the patient's serial number. Chemotherapy was started as soon as possible after allocation, usually within a few days of operation.

INITIAL CHEMOTHERAPY DOSAGE

Throughout the study all patients received as initial therapy eight tablets in one dose daily for 10 days. The dosages of the active agents were therefore: busulphan 4 mg daily, cyclophosphamide 200 mg daily.

MAINTENANCE CHEMOTHERAPY DOSAGE

Maintenance therapy began on the 11th day. Though the dosage of the drugs was decided on the basis of information available when the study was planned, an unexpectedly high incidence of toxicity to the drugs occurred among the early patients. Because of this, in December 1965 the maintenance

dosage of both cytotoxic drugs was reduced, leaving the initial dosage the same. As a result there were two maintenance dosage levels, one given during the "early intake" period up to December 1965 and the other during the "late intake" period.

Maintenance Dosage in the Early Intake.—All patients were prescribed six tablets in one dose daily. The dosages of the active agents were therefore: busulphan 3 mg daily, cyclophosphamide 150 mg daily.

Maintenance dosage in the late intake.—All patients were prescribed three tablets in one dose daily. The dosages of the active agents were therefore: busulphan 1.5 mg daily, cyclophosphamide 75 mg daily.

The maintenance dosage was controlled by the physician at monthly visits of the patient to the clinic. The dosage was reduced if toxicity occurred. In particular, it was recommended that chemotherapy should be interrupted if the total white cell count fell rapidly below $2,000/\text{mm}^3$ or slowly below $1,000/\text{mm}^3$ or if the platelet count fell below $100,000/\text{mm}^3$.

The study was conducted "double blind" throughout the two-year period of treatment and the subsequent three-year follow-up. Thus neither the patient, nor the surgeon, nor the physician knew whether the patient was receiving busulphan, cyclophosphamide, or a placebo, though every patient was managed as if receiving a cytotoxic drug. The indications for reduction of dosage or for interruptions of chemotherapy were therefore those which apply to the use of cytotoxic drugs and were the same for every patient in the study.

If circumstances arose which made it necessary for the surgeon or chest physician to know the exact nature of the tablets the patient was receiving, the information could be obtained from the unit staff. Such circumstances arose for only three patients, one in each series.

PRETREATMENT OBSERVATIONS AND INVESTIGATIONS

Reports were completed by the surgeon on the patient's mode of presentation, the date of the first symptom, the preoperative general condition, weight, degree of dyspnoea, blood picture (including haemoglobin level, total and differential white cell count, and platelet count), and the operative findings. A pre-operative chest radiograph was also sent to the unit.

A report was completed by the pathologist on the histological examination of the operation specimen, and slides of the primary tumour, of any involved intrathoracic lymph nodes, and of any preoperative bronchial biopsy specimen were sent to the reference pathologist.

FOLLOW-UP ASSESSMENTS

From the date of operation monthly follow-up reports were sent by the physician (or the surgeon if the patient was still in hospital) on the patient's general condition, weight, degree of physical activity, degree of dyspnoea, results of examination for metastases, the haemoglobin estimation, total white cell and platelet counts, and details of the chemotherapy received in the previous month and prescribed for the next month.

Wherever possible a home visit was made during each month by a health visitor in order to assess the regularity of self-administration of the drug by a count of the patient's stock of tablets.

REPORTS ON DEATH OF PATIENTS

When a patient died a report was obtained on the terminal illness, together with the findings of the final medical examination before death. If necropsy was performed a report of the findings was also obtained.

Results. (1) Patients and Condition on Admission**PATIENTS ADMITTED TO THE STUDY**

A total of 753 patients were allocated to treatment, 251 to the busulphan (B) series, 241 to the cyclophosphamide (C) series, and 261 to the placebo (P) series.

Twenty-seven (8 B, 7 C, 12 P) patients have been excluded from all analyses—13 (4 B, 2 C, 7 P) had no evidence of carcinoma on histological examination of the resected specimen, 6 (2 B, 2 C, 2 P) died before chemotherapy could be started, 2 (1 B, 1 P) had an incomplete resection of the tumour, 2 (1 C, 1 P) had postoperative radiotherapy, for 2 (1 B, 1 C) supervision was not possible at a chest clinic, 1 (P) refused chemotherapy, and 1 (C) was a woman aged less than 45 years. After these exclusions 726 (243 B, 234 C, 249 P) patients remain in the analysis, 217 (76 B, 68 C, 73 P) in the early intake and 509 (167 B, 166 C, 176 P) in the late intake.

CONDITION ON ADMISSION TO THE STUDY

In both intakes the condition on admission and the clinical course of the patients who received the placebo resembling busulphan in taste and those who received the placebo resembling cyclophosphamide were very similar in all respects (data not tabulated here). Throughout the report, therefore, the two groups are amalgamated to form the single placebo (P) series.

The distributions were also similar for the three series for both intake periods. The condition on admission to the study for the patients in the three series is therefore set out in Table I for the early and late intakes combined. Nearly all the patients were male: 82% of the B, 74% of the C, and 71% of the P group were aged 55 or more ($P = 0.02$, 2 D.F.); about half had a pneumonectomy; just over half had squamous tumours; and just under half had one or more nodes involved on histological examination of the resected specimen.

TABLE I—Condition on Admission to the Study for the Combined Early and Late Intakes

Factor	Treatment Series					
	Busulphan		Cyclophosphamide		Placebo	
	No.	%	No.	%	No.	%
Sex:						
Male	225	93	214	91	231	93
Female	18	7	20	9	18	7
Age (years):						
Less than 45	8	3	8	3	10	4
45-54	36	15	52	22	61	24
55-64	132	54	130	56	130	52
65 or more	67	28	44	19	48	19
Operation:						
Segmental resection	6	2	4	2	2	1
Lobectomy	112	46	115	49	112	45
Pneumonectomy	125	51	115	49	135	54
Site of tumour:						
Right {						
Main bronchus	4	2	4	2	10	4
Upper lobe	56	23	49	21	46	18
Middle lobe	8	3	11	5	8	3
Lower lobe	40	16	50	21	50	20
Left {						
Main bronchus	15	6	9	4	11	4
Upper lobe	71	29	79	34	79	32
Lower lobe	49	20	32	14	45	18
Histology of tumour:						
Squamous	137	56	138	59	131	53
Undifferentiated squamous	17	7	21	9	20	8
Adenocarcinoma	21	9	20	9	27	11
Undifferentiated adenocarcinoma	15	6	12	5	18	7
Oat cell	14	6	9	4	16	6
Undifferentiated	34	14	32	14	35	14
Other	5	2	2	1	2	1
Resected intrathoracic nodes:						
Involved histologically	117	48	100	43	119	48
Total patients	243	100	234	100	249	100

(2) Clinical Course of Patients in Two-year Follow-up Period**POSTOPERATIVE COMPLICATIONS**

Bronchopleural fistulae or empyemata occurred in 5 (7%) of the B, 9 (13%) of the C, and 3 (4%) of the P patients in the early intake and in 10 (6%) of the B, 9 (5%) of the C, and 4 (2%) of the P patients in the late intake (none of the differences were statistically significant).

FIG. 1—Survival up to 24 months.

SURVIVAL UP TO 24 MONTHS

Survival was very similar in the three series (Table II and Fig. 1). At 24 months 46% of the B, 44% of the C, and 49% of the P patients were alive in the early intake as were 49%, 50%, and 50% respectively in the late intake. There were no statistically significant differences between the series in either intake at any month.

SURVIVAL AT 24 MONTHS RELATED TO PRETREATMENT CONDITION

As detailed analyses showed no differences between the early and late intake in survival at 24 months related to the pre-treatment condition, the patients in the two intakes have been amalgamated in Table III. The survival in the three series was similar for most of the factors considered. Many of the differences are based on small numbers and none is statistically significant.

CAUSE OF DEATH

Most patients who died were certified as dying of carcinoma of the bronchus—namely, 105 (83%) of 127 B, 98 (81%) of 121 C, and 107 (86%) of 125 P patients; 22 of the 105 B, 22 of the 98 C, and 21 of the 107 P patients had terminal broncho-pneumonia, while 2 B, 1 C, and 1 P patients also had an empyema.

TABLE II—Survival over 24 Months

Intake	Treatment Series	Total Patients	Patients Alive at (Months):													
			1		3		6		9		12		18		24	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Early	 { Busulphan Cyclophosphamide Placebo	76	76	100	73	96	62	82	54	71	45	59	42	55	35	46
		68	66	97	60	88	53	78	47	69	42	62	38	56	30	44
		73	68	93	65	89	61	84	57	78	48	66	41	56	36	49
Late	 { Busulphan Cyclophosphamide Placebo	167	160	96	155	93	139	83	122	73	112	67	93	56	81	49
		166	157	95	145	87	134	81	126	76	113	68	94	57	83	50
		176	170	97	162	92	147	84	129	73	115	65	93	53	88	50

Among deaths *not* certified as due to carcinoma of the bronchus the cause was aplastic anaemia in 2 B patients (both early intake), postoperative complications in 10 B, 16 C, and 13 P patients, bronchopneumonia in 5 B, 3 C, and 4 P patients, an empyema or bronchopleural fistula in 3 B, 3 C, and 1 P patients, a ruptured abdominal aneurysm in 1 B patient, and a myocardial infarct in 1 B and 1 C patient.

TABLE III—Survival at 24 Months Related to Pretreatment Factors for the Combined Early and Late Intakes

Factor	Treatment Series					
	Busulphan		Cyclophosphamide		Placebo	
	Total Patients	% Alive at 24 Months	Total Patients	% Alive at 24 Months	Total Patients	% Alive at 24 Months
Sex:						
Male	225	48	214	48	231	50
Female	18	(44)	20	(50)	18	(44)
Age (years):						
Less than 45	8	(50)	8	(38)	10	(50)
45-54	36	39	52	46	61	46
55-64	132	52	130	52	130	50
65 or more	67	43	44	43	48	54
Operation:						
Segmental resection	6	(67)	4	(75)	2	(50)
Lobectomy	112	61	115	52	112	59
Pneumonectomy	125	35	115	43	135	42
Histology of tumour:						
Squamous	137	53	138	55	131	62
Undifferentiated squamous	17	(59)	21	(38)	20	(70)
Adenocarcinoma	21	(43)	20	(50)	27	30
Undifferentiated adenocarcinoma	15	(27)	12	(33)	18	(44)
Oat cell	14	(21)	9	(0)	16	(12)
Undifferentiated	34	44	32	41	35	26
Other	5	(60)	2	(100)	2	(100)
Resected intrathoracic nodes:						
Involved histologically	117	36	100	38	119	38
Not involved	126	59	134	56	130	61
Total patients	243	48	234	48	249	50

Percentages in parentheses are based on fewer than 25 observations.

Metastases were reported as definitely present at the last examination before death in 67% of the B, 62% of the C, and 67% of the P patients who died of carcinoma of the bronchus, and were suspected in another 29% B, 28% C,

TABLE IV—Condition at 24 Months of the Survivors in the Combined Early and Late Intakes

Assessment	Treatment Series					
	Busulphan		Cyclophosphamide		Placebo	
	No.	%	No.	%	No.	%
General condition:						
Good	77	66	86	76	88	71
Fair	31	27	22	19	30	24
Poor	8	7	5	4	6	5
Activity:						
At work	46	40	54	48	44	35
Full activity but not at work	30	26	26	23	46	37
Out and about but activity restricted	33	28	24	21	26	21
Confined to home or hospital	7	6	8	7	6	5
Bedridden	0	0	1	1	2	2
Respiratory assessment:						
Climbs hills and stairs without dyspnoea	32	28	30	27	34	27
Walks any distance at normal pace on the flat without dyspnoea	38	33	57	50	57	46
Walks more than 100 yards (91 metres) at own speed without dyspnoea	27	23	10	9	22	18
Dyspnoea on walking 100 yards (91 metres)	15	13	9	8	7	6
Dyspnoea on mild exertion	4	3	6	5	4	3
Not assessed	0	0	1	1	0	0
Metastases:						
Absent	101	87	99	88	109	88
Suspected	8	7	7	6	5	4
Definitely present	7	6	7	6	10	8
Total patients alive at 24 months	116	100	113	100	124	100

and 26% P. patients. In contrast, in none of the patients whose death was certified as due to causes other than carcinoma was a definite metastasis reported.

Necropsies were carried out in 129 (35%) of the 373 patients who died. The necropsy findings closely paralleled the clinical findings. Thus of 54 patients with metastases reported as definitely present 53 (98%) had metastases at necropsy; of 30 patients with suspected metastases 22 (73%) had metastases at necropsy, while of 45 patients with metastases reported as absent only 12 (27%) had metastases at necropsy.

TIME OF DETECTION OF METASTASES

In both the early and the late intake the distribution of the time of detection of metastases after operation was similar in all series. Thus within the first six months 38% of the 76 B,

TABLE V—Patients Not Receiving Tablets for the Stated Month

Intake	Treatment Series	1st Month		2nd Month		3rd Month		6th Month		12th Month		18th Month		24th Month	
		Patients		Patients		Patients		Patients		Patients		Patients		Patients	
		Total*	%†	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Early	Busulphan	76	0	76	5	74	5	64	33	47	66	44	84	35	89
	Cyclophosphamide	68	0	66	5	64	12	56	21	43	16	38	24	31	19
	Placebo	73	0	68	3	66	3	62	5	50	6	42	10	37	8
Late	Busulphan	167	1	160	4	157	8	147	16	118	45	93	61	84	70
	Cyclophosphamide	166	0	157	4	152	8	136	12	119	21	96	21	83	24
	Placebo	176	1	170	5	165	5	150	5	120	8	97	9	88	10

*"Total" includes all patients who were alive at the beginning of the month.
†% = Percentage not receiving any tablets.

35% of the 68 C, and 26% of the 73 P patients admitted to the early intake and 23% of the 167 B, 19% of the 166 C, and 22% of the 176 P patients in the late intake had had suspected or definite metastases reported (data not tabulated here). By 12 months the proportions were 51%, 50%, and 42% respectively in the early intake, and 41%, 43%, and 41% respectively in the late intake. Over the whole 24-month period the proportions were 62%, 56%, and 51%, and 51%, 57%, and 50% respectively.

The proportions are also similar if only definite metastases are considered. Thus at six months they were 8%, 7%, and 5% respectively in the early intake and 8%, 4%, and 7% in the late intake, at 12 months 16%, 15%, and 18% and 19%, 13%, and 20% respectively, at 24 months 29%, 24%, and 25% and 24%, 21%, and 28% respectively.

CONDITION OF THE SURVIVORS AT 24 MONTHS

The general condition was reported as good for the majority of the patients alive at 24 months (Table IV). Most were at work or on full activity but not at work (many were beyond retiring age), and many were able at least to walk any distance at normal pace on the flat without dyspnoea. Metastases were infrequent, being reported as definitely present in only 6% of the B, 6% of the C, and 8% of the P patients.

(3) Chemotherapy Received During the Two-year Period

START OF CHEMOTHERAPY

In all series the administration of the study tablets started shortly after operation. The intervals were, on average, 4.0 days for the B, 4.1 days for the C, and 4.0 days for the P patients. Further, nearly all the patients received eight tablets daily for 10 days as prescribed—namely, 92% of the 243 B, 94% of the 234 C, and 94% of the 249 P patients.

MAINTENANCE CHEMOTHERAPY

There were considerable differences between the series in the extent to which tablets were interrupted because of possible or definite toxicity. In each of the first three months few patients did not receive any tablets throughout the month (Table V). In the early intake in the sixth month, however, 33% of the B, 21% of the C, and 5% of the P patients did not receive any tablets. Thereafter the proportions increased markedly in the busulphan series, becoming 89%, 19%, and 8% respectively, in the 24th month. In the late intake 16% of the B, 12% of the C, and 5% of the P patients did not receive any tablets in the sixth month. Thereafter the proportion increased substantially in the busulphan series, becoming 70%, 24%, and 10% respectively in the 24th month. The proportion of patients receiving full dosage during the month in question is set out for the early and late intakes in Fig. 2.

(4) Incidence of Toxicity

DEATHS ATTRIBUTABLE TO CHEMOTHERAPY

There were four busulphan (early intake) patients in whom there was evidence that the chemotherapy materially contributed to death. In two the death was certified as due to aplastic anaemia and in two to carcinoma of the bronchus. No patient died of toxicity in the other two series in the early intake or in any series in the late intake.

Case 1.—A man of 71, after eight months on six tablets daily, had a haemoglobin level of 7.0 g/100 ml, a white cell count of 1,100/mm³, and no platelets. He had repeated transfusions but deteriorated and died after three weeks from aplastic anaemia. At necropsy the marrow of the humerus was greatly reduced. No metastases were found.

Case 2.—A man of 58 received six tablets daily for three and a half months and then three tablets daily. At six months the platelet count had fallen to 73,000/mm³ but the tablets were not stopped as indicated in the protocol. At seven months the platelet count was 120,000 but at eight months it had fallen to 2,500, the haemoglobin level being 11.5/100 ml and the white cell count 4,500/mm³. The tablets were then stopped, but in spite of the administration of corticosteroids and antibiotics the patient deteriorated and died of staphylococcal septicaemia in the 11th month. Necropsy showed no residual carcinoma or metastases.

FIG. 2—Percentage of patients receiving full dosage.

Case 3.—A man of 57 received six tablets daily for three months and then three daily for one month, when they were stopped on account of a fall in the haemoglobin to 7.4 g/100 ml and in the platelet count to 30,000/mm³. The haemoglobin continued to fall, reaching 4.7 g at six months, when the patient was transfused, and subsequently the platelets were reported to be less than 10,000. He died in the 10th month. Necropsy showed considerable hypoplasia of the bone marrow. There were metastases in the mediastinal nodes.

Case 4.—A man of 65 received six tablets daily for one month and then three tablets daily until five months, when the platelet count fell to 85,000/mm³. After an interruption of one month the count rose to 200,000 and two tablets daily were resumed. At 11 months the platelet count had fallen to 60,000 and the tablets were interrupted for two months. At 13 months the count was 125,000 and two tablets daily were resumed, but reduced to one daily at 14 months because of a fall in platelets to 100,000 and finally stopped at 15 months because of a fall to 45,000. At this time spinal metastases were suspected. He died in the 18th month, necropsy showing subdural haemorrhage but no intracranial metastases; many mediastinal nodes were involved by tumour.

INCIDENCE OF TOXICITY AND CLINICAL ACTION TAKEN

The placebo series is considered first in order to provide a baseline for the other two series.

Placebo Series

Toxicity was reported in 49% of the 73 P patients in the early intake (Table VI). Clinical toxicity occurred in 33%, the majority of symptoms being "gastric" (defined as nausea, abdominal discomfort, vomiting, and jaundice); haematological toxicity occurred in 18%, 14% having thrombocytopenia (defined as a fall in the platelets below 100,000/mm³). In the late intake 36% of the 176 P patients had toxicity. Clinical toxicity occurred in 15% and haematological in 20%.

In both early and late intakes clinical toxicity was reported most frequently in the first three months and haematological toxicity most frequently in the first six months.

Busulphan Series

Of the 76 B patients in the early intake 89% had toxicity (Table VI). Clinical toxicity occurred in 30% (some also had haematological toxicity at the time), virtually all the symptoms being "gastric." Haematological toxicity occurred in 83%. Anaemia (defined as a fall of haemoglobin below 9 g/100 ml) occurred in 24%, transfusions being given to 12 (16%) of the patients. Leucopenia (defined as a fall in total white cell count below 3,000/mm³) occurred in 29%. Thrombocytopenia occurred in 80% and tended to persist in spite of stopping the tablets. Thus 12 (36%) of 33 patients alive at 24 months who had had thrombocytopenia still had a platelet count below 100,000 at 24 months. Pancytopenia occurred in 11 (14%) patients. Of these, six died before 24 months, little or no improvement in the blood picture having occurred before death—three of carcinomatosis, one of bronchopneumonia, and two (cases 1 and 3 above) of aplastic anaemia. None of the five surviving patients who had had pancytopenia had a platelet count above 100,000 at 24 months.

In the late intake toxicity occurred in 80% of the 167 B patients. Clinical toxicity occurred in 17%, the majority of symptoms being "gastric." Haematological toxicity occurred in 69%; 10% had anaemia, transfusions being required in 7 (4%) patients, 14% had leucopenia, 66% thrombocytopenia, and 4% pancytopenia. As in the early intake thrombocytopenia was persistent in many patients. Thus 30 (42%) of the 71 patients who had had thrombocytopenia and were alive at 24 months still had a platelet count below 100,000. Of the six patients with pancytopenia three died before 24 months, all of carcinomatosis, though the blood picture did not become normal before death. Of the three survivors two had platelet counts below 100,000 at 24 months.

Most of the clinical toxicity occurred early—namely, 52% in the early intake and 55% in the late intake in the first three months. Haematological toxicity occurred later. Thus in the early intake 16% occurred between one and three months, 56% between four and six months, and 22% between 7 and 12 months, while in the late intake 30% occurred between one and six months and 53% between 7 and 12 months.

Cyclophosphamide Series

In the early intake 84% of the 68 C patients had toxicity (Table VI). Clinical toxicity occurred in 53%; 47% had "gastric" symptoms, 13% alopecia, and 6% cystitis. Haematological toxicity occurred in 54%; 7% had anaemia, a transfusion being given to one patient, 35% had leucopenia, and 21% thrombocytopenia. Pancytopenia occurred in only one patient, who had considerable recovery of the blood picture but died of carcinomatosis two months later. In the late intake toxicity occurred in 53% of the 166 C patients. Clinical toxicity occurred in 27%; 17% having "gastric" symptoms, 4% alopecia,

TABLE VI—Incidence of Toxicity and Clinical Action Taken

Treatment Series and Total Patients	Toxicity	Early Intake				Late Intake			
		Patients with Toxicity							
		No.	% of Total Patients	Interruption of 30 Days or More (% of Total)	Treatment Not Resumed (% of Total)	No.	% of Total Patients	Interruption of 30 days or More (% of Total)	Treatment Not Resumed (% of Total)
Busulphan (76 patients in early intake; 167 patients in late intake)	All	68	89	5	75	134	80	14	54
	Clinical	23	30	1	17	29	17	4	4
	Gastric*	21	28	1	14	19	11	2	2
	Cutaneous	1	1	0	1	5	3	0	1
	Alopecia	1	1	0	1	1	1	1	0
	Cystitis	0	0	0	0	2	1	1	0
	Other	1	1	0	0	2	1	0	0
	Haematological	63	83	5	70	115	69	13	50
	Anaemia	18	24	0	22	17	10	1	9
	Leucopenia	22	29	1	25	24	14	4	5
	Thrombocytopenia	61	80	7	68	111	66	13	49
	Pancytopenia	11	14	0	14	6	4	0	4
Cyclophosphamide (68 patients in early intake; 166 patients in late intake)	All	57	84	29	21	88	53	8	17
	Clinical	36	53	10	15	44	27	4	8
	Gastric*	32	47	6	13	28	17	2	5
	Cutaneous	3	4	1	0	10	6	1	2
	Alopecia	9	13	4	0	7	4	0	1
	Cystitis	4	6	1	0	4	2	1	1
	Other	4	6	1	3	1	1	0	1
	Haematological	37	54	19	9	49	30	5	9
	Anaemia	5	7	0	3	10	6	0	2
	Leucopenia	24	35	9	6	14	8	1	2
	Thrombocytopenia	14	21	12	1	33	20	5	5
	Pancytopenia	1	1	0	1	0	0	0	0
Placebo (73 patients in early intake; 176 patients in late intake)	All	36	49	8	8	63	36	9	5
	Clinical	24	33	7	4	27	15	3	3
	Gastric*	18	25	4	4	21	12	2	2
	Cutaneous	4	5	1	0	6	3	2	0
	Alopecia	0	0	0	0	1	1	0	1
	Cystitis	0	0	0	0	2	1	1	0
	Other	6	8	3	0	2	1	0	0
	Haematological	13	18	1	4	36	20	5	2
	Anaemia	2	3	0	1	8	5	0	0
	Leucopenia	1	1	0	0	4	2	0	0
	Thrombocytopenia	10	14	1	1	27	15	5	2
	Pancytopenia	0	0	0	0	0	0	0	0

*Including jaundice (1B, 2C, 2P patients in the early intake and 2C, 3P patients in the late intake).

and 2% cystitis. Haematological toxicity occurred in 30%; 6% had anaemia, one patient had a transfusion, 8% had leucopenia, and 20% thrombocytopenia.

Clinical toxicity occurred in the first three months in 83% of the early intake and 53% of the late intake. Haematological toxicity occurred in 54% in the first three months, in 4% between four and six months, and in 19% between 7 and 12 months in the early intake, while in the late intake the corresponding proportions were 29%, 16%, and 32%.

Discussion

This study, which began in January 1965, was designed to test the hypothesis that long-term cytotoxic chemotherapy as an adjuvant to surgery for carcinoma of the bronchus would suppress the development of metastases and prolong survival. Oral chemotherapy, beginning as soon as possible after surgery, was chosen for several reasons. Firstly, nitrogen mustard had been found to be apt to increase early postoperative mortality without improving long-term survival (Hughes and Higgins, 1962). Secondly, daily oral therapy with cytotoxic drugs is a commonly used method of administration. Thirdly, this method was administratively suitable within the framework of chest clinic practice, because long-term chemotherapy for tuberculosis has been widely organized for many years. Finally, the control series, especially valuable in evaluating the clinical course and also minor side effects of the cytotoxic drugs, could receive an oral placebo preparation, and in consequence the study could be conducted double-blind.

The main early finding of this study was the unexpectedly high incidence of hazardous toxicity with busulphan. The dosage of busulphan had been selected on the basis of previous experience in chronic myeloid leukaemia, but even in this disease aplastic anaemia is a distinct risk (Weatherall *et al.*, 1969). There was also a high incidence of side effects in the cyclophosphamide series but these were less serious. As a result the maintenance dosage of both cytotoxic drugs was halved after the study had been in progress for 11 months. The data on toxicity illustrate the importance of keeping a close watch on the progress of individual patients as well as undertaking interim analyses in the course of a study. The lowering of the maintenance dosage resulted in two dosage groups, the high maintenance dosage "early intake" and the low maintenance dosage "late intake," which meant that the intake period had to be prolonged to admit a total of about 750 patients rather than 600 as originally planned. It also added to the complexity of the analysis and of the present report.

The therapeutic results at two years are disappointing, for there is no evidence that either of the two cytotoxic drugs in the dosage used improved survival, either in the early intake with the higher maintenance dosage or in the late intake with the lower maintenance dosage. Further, none of the subsidiary groups analysed, particularly with regard to age, sex, and histological type of tumour, showed meaningful differences between the series in survival. Thus, as used in this study, neither cytotoxic drug was beneficial.

Most of the patients in this study who died had evidence of recurrence of the disease, and there was no difference between the series in either the time of onset of metastases or the cause of death. Further, though postoperative infective complications were more frequent in the two cytotoxic drug series than the placebo series there was no evidence of an increased incidence of death due to infection in either the busulphan or the cyclophosphamide series.

Though in the past few years other investigators have reported benefit from the use of cyclophosphamide as an adjuvant to surgery for carcinoma of the bronchus (Karrer, 1965, 1967; Kutschera and Schnetzer, 1965; Poulsen, 1965; Pfeiffer *et al.*, 1966) only one studied concurrent randomly allocated controls. One study of 30 patients (Horwitz *et al.*, 1965) has also reported benefit from the use of chlorambucil as suppressive

chemotherapy in carcinoma of the bronchus after irradiation. Karrer (1970) reported observations suggesting that patients receiving daily cyclophosphamide do less well than patients receiving cyclophosphamide intermittently.

Karrer (1967) reported that patients with carcinoma of the bronchus who developed leucopenia after treatment with cyclophosphamide had a better prognosis than those who did not, though he did not present evidence that the two groups were similar in other respects. Bross *et al.* (1966a, 1966b) queried whether it is necessary to give toxic doses of cytotoxic drugs in order to ensure that a therapeutic effect is achieved. In the present study there was no direct evidence that patients who developed toxicity to either of the cytotoxic drugs did better than those who did not, though this will be examined in more detail, taking into consideration factors of possible prognostic importance. The detailed analysis will be reported, together with multiple regression analysis of these factors, when the five-year survival data are available.

The period of observation reported here is two years. All the surviving patients are, however, being followed up to five years, and none have so far been lost to observation. A final evaluation of the adjuvant chemotherapy as studied in this investigation will be made when the full five-year results are available.

The following surgeons, physicians, and pathologists co-operated in the study.

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Serum Transaminases during Salicylate Therapy

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Summary

In 8 out of 32 juvenile patients suffering from chronic polyarthritis and in one patient with dermatomyositis, raised transaminase levels were found; the salicylate level was above 35 mg/100 ml in all except one. Reduction in the salicylate level led to a prompt fall in the serum transaminases. Despite a rise in alkaline phosphatase in three cases there was no other evidence of liver dysfunction in the children. Only one of the adults showed a rise in transaminase levels, and she had mild cirrhosis.

Introduction

Our attention was drawn to the association of increased levels of serum transaminases with high serum salicylate levels in a girl with juvenile chronic polyarthritis admitted routinely for establishment on a salicylate regimen. She complained of feeling unwell and was found to have mild hepatomegaly and raised transaminase levels; at this time her serum salicylate level had risen to 45 mg/100 ml. On stopping aspirin therapy the transaminase levels rapidly returned to normal and the hepatomegaly disappeared. In view of this 50 further patients were studied.

Patients and Methods

Of the 50 patients 32 were children aged 2 to 15 years and 18 were adults aged 29 to 68. There were six males among the children and five among the adults. All were inpatients at the time, and apart from one child with dermatomyositis all had juvenile chronic polyarthritis or definite rheumatoid arthritis.

Salicylates were being administered as part of their therapeutic regimen either in the form of Enseal aspirin or Disprin. None of the patients were taking ibuprofen but some were receiving prednisone.

On the same sample of blood the salicylate levels were assayed by the method of Trinder (1954) and transaminase levels by that of Reitman and Frankel. The levels accepted here as normal are serum aspartate aminotransferase (SGOT) 8-40 units, serum alanine aminotransferase (SGPT) 5-35 units. The alkaline phosphatase was measured in King-Armstrong units, the normal range being 5-12 units in adults; however, a level of up to 20 units in a growing child was not considered necessarily abnormal.

Results

Raised transaminase levels were seen in nine children and one adult (Tables I and II). All but one of the children with

TABLE I—Results in 33 Children and 18 Adults

	Salicylate Level (mg/100 ml)	No. of Patients	No. with Raised Transaminase Level	No. with Raised Alkaline Phosphatase
Children	>35	14	8	2/6
	<35	19	1	*2/11
Adults	>35	3	1	1/1
	<35	15	0	0/8

*In one case associated with increased transaminase levels.

TABLE II—Maximum Levels of Transaminases Seen in the Nine Children and One Adult with Raised Levels

SGOT	SGPT	SGOT	SGPT	SGOT	SGPT
Children					
99	79	840	2,000	66	84
43	35	150	200	94	105
530	260	65	53	>150	>150*
Adult					
>150	>150				

*Patient referred to in the Chart.

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raised transaminase levels had a serum salicylate of over 35 mg/100 ml (equivalent to 2.5 mmol salicylates). None of the children had nausea, sweating, or hyperventilation to suggest salicylate toxicity. One child with a mildly raised