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CLINICAL TRIAL OF RADIOSENSITIZERS, INCLUDING SYNKAVIT AND OXYGEN INHALED AT ATMOSPHERIC PRESSURE

by

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This is an account of a clinical trial of radiosensitizers, which was started in February 1958. It was organized to try to reach a decision concerning the value of intravenous Synkavit, of oxygen inhaled at atmospheric pressure and of the combined use of intravenous Synkavit and oxygen inhaled at atmospheric pressure as radiosensitizers in the radiotherapy of patients with inoperable carcinoma of the bronchus. Synkavit (Roche Products) is chemically 2-methyl-1,4-naphthaquinol bis(disodium phosphate). In addition, a closely related compound, 2,3-dimethyl-1,4-naphthaquinol bis(disodium phosphate), described here as compound-28, was included in this trial, because animal experiments with the Walker rat carcinoma 256 and preliminary clinical studies suggested that it might be a radiosensitizer (MITCHELL 1960).

Laboratory studies, and clinical trials of Synkavit and related compounds as chemical radiosensitizers, have been in progress in Cambridge since 1946. Detailed accounts of this work have been published (MITCHELL 1953, 1960, MARRIAN, MARSHALL & MITCHELL 1961) and provide the evidence upon which the present trial was based. The results of an early trial of intravenous

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Synkavit as a radiosensitizer in the radiotherapy of inoperable carcinoma of the bronchus, with random allocation of patients, suggested that this compound has 'a small and sometimes useful effect'. However, this trial was open to criticism and it was considered that 'it is nevertheless wise to use the experience gained and carry out another trial' (MITCHELL 1960, p. 160). After a number of other clinical studies and trials, including a randomized 'pilot trial' of the effects of oxygen inhaled at atmospheric pressure, the results of which were suggestive but not conclusive, it was finally decided to set up the trial which is now described.

Meanwhile, two independent accounts of the study of intravenous Synkavit as a radiosensitizer in the radiotherapy of inoperable cases of carcinoma of the bronchus were published (DEELEY 1962, KONEČNY & MECHL 1962). The latter authors summarized their findings as follows: 'Though a small group of patients was treated, a positive effect could be proved on the tumourous focus, manifested also by a longer average survival time. More severe postradiation changes were, however, also observed, particularly the pulmonary fibrosis'. For cancer at other sites, it is relevant to mention that, in a randomized trial of cases of cancer of the cheek, which were regarded as usually radioresistant, SHANTA & KRISHNAMURTHI (1964) considered that intravenous Synkavit improved the results of radical radiotherapy.

It is clear that further evidence is needed. From a practical point of view it is almost essential to investigate common types of malignant disease, with a short natural history, in order to obtain a statistically significant result within a period of about 6 to 10 years. Inoperable carcinoma of the bronchus is an obvious choice for investigation. It is an extremely common type of malignant disease with a short average survival, from the beginning of treatment of about 4 months in representative series of patients receiving radiotherapy at palliative levels of dose (MITCHELL 1960, p. 145); however, the variability of the course of the disease in individual patients must be emphasized. Despite advances, only a relatively small proportion of all cases of carcinoma of the bronchus are curable by surgery. Untreated patients are often very miserable. The results of treatment of inoperable cases by present methods, including radical radiotherapy, are in general poor. Nevertheless, radiotherapy often has sufficient palliative value, apart from prolongation of life per se, to justify attempts to improve this method of treatment.

General aspects of the trial

The principles of the design and conduct of clinical trials of radiosensitizers have been discussed in some detail (MITCHELL 1960, pp 136—166; MARRIAN, MARSHALL & MITCHELL 1961, pp 254—263).

We felt that we had evidence that Synkavit was a radiosensitizer, and that oxygen inhaled at atmospheric pressure and Compound-28 might also be radiosensitizers. Accordingly, we did not feel justified in treating a group of patients with roentgen radiation only without the possible benefit of a radiosensitizer. The choice of our groups was designed to (1) re-assess the effect of Synkavit, (2) assess the effect of oxygen inhaled at atmospheric pressure, and (3) assess the effect of Compound-28.

In the present trial, which was started on 11 February 1958 and finished on 31 March 1963, there was random allocation of the patients, with proper safeguards, to one of the following four groups: (a) Synkavit, oxygen and roentgen therapy (abbreviated as S + O_2 + X) 61 cases; (b) Synkavit and roentgen therapy (S + X) 75 cases; (c) oxygen and roentgen therapy (O_2 + X) 51 cases; (d) Compound-28 and roentgen therapy (28 + X) 53 cases.

The details of the intravenous administration of the compounds, of the oxygen inhaled at atmospheric pressure, and of the radiotherapy, were substantially the same as in the previous trials and will be described below. It is to be noted that the standard radiotherapy was an 8-day course of roentgen irradiation at the medium palliative level of dose.

It was intended that comparison of group (a) with group (c) would give a measure of the effect of Synkavit, while comparison of group (a) with group (b), would give a measure of the effect of oxygen. Comparison of groups (b) and (d) would give a measure of the relative effects of Synkavit and Compound-28 as radiosensitizers. Accordingly, every patient in the trial received treatment which was expected to produce results which would be at least as good as those of conventional radiotherapy and probably would be appreciably better.

It was planned to continue this trial to include at least 200 patients. Only the male patients in this trial are considered. The trial was stopped after the treatment of 240 patients as soon as the results of a survey of the first 200, treated up to 1 June 1962 and assessed at 30 November 1962, became available. Among many other results, it was found that, when all patients in each group were considered, the 12-month survival rate, calculated by the actuarial method, was significantly greater with group (a) than with group (c) the difference being $= 0.168 \pm 0.077$; $P = 0.034$. It appeared that the survival in group (c) was less than in the other three groups.

Although the difficulties of stopping the trial, when a certain level of statistical significance had been reached, were fully appreciated (see ARMITAGE 1958), it was felt that the advantages of the combined treatment (Synkavit plus oxygen inhalation plus roentgen irradiation) were 'fairly certain' and that the trial must be stopped, and whenever possible, the patients should be given intravenous Synkavit and oxygen inhaled at atmospheric pressure as radio-

sensitizers. This problem is a further example of the necessity of planning to depart from what may be termed the ideal form of clinical trial, with deliberate sacrifice of some information in the interest of the patients.

In assessing the results of the different types of treatment, it was decided that the only criterion applicable as a reliable quantitative measure was the time of survival after the first radiation treatment. It must be emphasised that survival per se is not always the most important factor to be considered. The benefits of palliative radiotherapy in the relief of haemoptysis and of the symptoms of superior mediastinal obstruction are to a large extent not reflected by the survival times. In the earlier clinical trial of Synkavit (MITCHELL 1960, pp 139—140, and 154—157), the use of the 'performance status' (KARNOFSKY et coll. 1951) was studied with a view to estimate the prolongation of useful life attributable to the treatment. There appeared to be a general parallelism between increased survival and prolongation of useful life, and there were very few patients with long survivals at a miserable level of existence. It was concluded that there can be little doubt, from observation of the patients, that in many cases without evidence of extrathoracic spread, treatment with roentgen therapy combined with intravenous Synkavit has been amply justified.

Details of trial. The trial was organized according to the following rules. In all cases of inoperable carcinoma of the bronchus — with the exception of cases after thoracotomy or any other form of surgery other than biopsy — as soon as the provisional diagnosis was made, the case was registered with the trial and allocated to one of the four forms of treatment, using two tables of random numbers:

Table 1	*Table 2*	*Treatment*
Even	Even	Roentgen therapy and oxygen
Even	Odd	Roentgen therapy and oxygen and intravenous Synkavit
Odd	Even	Roentgen therapy and intravenous Synkavit
Odd	Odd	Roentgen therapy and intravenous Compound-28

The oxygen was administered by inhalation at atmospheric pressure by means of either a B. L. B. mask or plastic Polymask (British Oxygen Company, No. 330 216) at the rate of 8 l/min starting 20 min before and continuing throughout the whole of the irradiation on each day of treatment.

The intravenous injections of Synkavit and Compound-28 were started as soon as possible after allocation of the type of treatment, and every endeavour was made to reach as high a dose of the compound as possible or as tolerated. If there was an undesirable reaction to the intravenous injections, the dose was reduced temporarily and then increased slowly.

The injections of Synkavit were given 30 min before starting the roentgen irradiation on each day of treatment and, where possible, injections were started 3 to 5 days before treatment.

For Compound-28, tetra-sodium 2 : 3-dimethyl-1 : 4-naphthahydroquinone diphosphate, the aim was to give the intravenous injection within 5 min before starting treatment on each day.

If there were medical contra-indications to intravenous Synkavit or Compound-28 (for example, cerebral metastases, severe myocardial degeneration, more than minimal superior mediastinal obstruction, laryngeal obstruction or impossible veins), or to the administration of oxygen, the case was classified according to the treatment corresponding to the random numbers, even though it may have been decided that some alternative form of treatment should be given.

If, for any reason, it was considered that an alternative form of treatment was desirable, this was used and noted, but the form of treatment from the point of view of assessment remained as allocated.

For the intravenous injections of Synkavit, the dosage was started usually with 75 mg and increased daily in steps of 25 mg. If any undesirable reaction such as excessive coughing, nausea, faintness or discomfort, or pain in the chest, was observed after the intravenous injection, the dose was reduced to a level at which there was no such reaction and then cautiously increased again on the following days, usually by steps of 25 mg but sometimes by steps of 10 mg. For most patients, the best maximum daily dose appears to be 100 mg; many tolerate 150 mg and a few will tolerate 200 mg or even 250 mg. With regard to the timing (which appears to be rather critical) in this trial, the injections have been given as closely as possible to 30 min before starting the roentgen irradiation on each day; the rule has been interpreted as meaning 30 ± 5 min and the exact times have been noted.

With Compound-28, although the timing was different, the dosage scheme was the same as that with Synkavit, although the upper limit reached with Compound-28 appears to have been 150 mg on any one day.

It must be emphasized that careful arrangements were made to prevent the doctor in charge of the patient from knowing the type of radiosensitization allocated.

In this trial, every endeavour was made to employ the normal methods of

Table 1

Mean values of the central tumour dose and overall time of roentgen therapy in all the histologically verified cases in the four treatment groups

(Numbers in brackets and the corresponding values of the mean central tumour dose refer to the groups, after exclusion of cases with incomplete treatment, i. e. after exclusion of cases receiving a central tumour dose less than 1 500 R and/or less than a total amount of 200 mg of Synkavit or Compound-28 and/or oxygen on less than two treatment days.)

Group	Treatment	Number of cases	Mean central tumour dose (R)	Mean overall time (days)
a	S + O_2 + X	42 (40)	1 780 (1 810)	9.48
b	S + X	47 (38)	1 720 (1 840)	9.29
c	O_2 + X	34 (28)	1 640 (1 780)	9.64
d	28 + X	32 (26)	1 720 (1 850)	9.40

roentgen therapy in use in the Radiotherapeutic Centre, Addenbrooke's Hospital, Cambridge and to avoid any modification of the techniques as a result of the use of the radiosensitizers. The radiotherapy has been of conventional type, using filtered 220 or 250 kV roentgen radiation, HVL 1.5 mm copper, usually with 50 cm FSD and in most cases with radiographic checking of the field positions. In all cases, only palliative roentgen therapy was considered justifiable, and the level of dosage corresponded to 'medium palliation' with the minimum tumour dose between one-third and two-thirds of the level of radical dose appropriate to the overall time of the fractionated treatment (see MITCHELL 1960, pp 149, 151).

The *standard technique* recommended in this trial was with two 15 × 15 cm fields, anterior and posterior thoracic, with a calculated central tumour dose of 1 750 R, given in seven treatments in an overall time of 8 days. In calculating the central tumour doses by means of depth dose tables, no air or bone corrections were made.

It was inevitable that the radiotherapy given should for individual patients to some extent depart from the standard technique, not only because of the differences in dimension of the patients and differences in the spread of tumour but also on account of great differences in the general medical condition of the patients. Within the agreed framework of trial, it was necessary to allow some degree of clinical flexibility to the doctor in planning the radiotherapy.

In some patients, the treatment could not be completed. With a considerable number of patients, it was considered wise to increase the overall time of the radiotherapy, and with some patients the central tumour dose as well as the overall time were increased to, e. g., a central tumour dose of 2 000 R delivered

in 8 fractions in an overall time of 11 days. In some patients with extrathoracic spread, it was necessary to treat additional extrathoracic areas; however, the doses delivered to these supplementary fields are not immediately relevant to the central tumour dose delivered by the anterior and posterior thoracic fields.

The mean values of the central tumour dose and the overall time of roentgen therapy, in all the histologically verified cases in the four treatment groups, are given in Table 1, together with the values, with exclusion of the cases with incomplete treatment (see below). The differences between the mean values of the central tumour dose for the four treatment groups must be regarded as within the range of the experimental error and not of statistical significance. It is interesting to note that the mean overall time is appreciably greater than the time of 8 days recommended for the standard technique, while the mean cental tumour dose for all groups is remarkably close to the recommended dose of 1 750 R.

The general organization and conduct of the trial presented considerable practical difficulties, which appear to be almost unavoidable in a busy radiotherapeutic centre. From experience of previous trials, it was decided that patients must be registered with the trial as soon as the provisional and plausible clinical diagnosis of inoperable carcinoma of the bronchus was reached after the first visit or admission of the patient to Cambridge. Many of the patients were referred from hospitals in the East Anglian Region. It was often necessary to start treatment before all the histologic evidence was available. A tremendous effort has been made as far as possible to establish a diagnosis with histologic verification. However, at the final assessment, only 155 cases out of the total number of 240, i. e. 64.6 %, were acceptable as cases of carcinoma of the bronchus with histologic verification.

We have followed the histologic criteria for classification of carcinoma of the lung and bronchus utilized by Dr G. A. Gresham, University Morbid Anatomist, Cambridge. This classification divides these carcinomas into the following groups: (1) squamous, (2) anaplastic, oat-celled or spheroidal-celled, (3) respiratory epithelial, (4) cubical- and columnar-celled, including adenocarcinoma, and (5) others.

However, the main problem is to obtain a definite diagnosis of carcinoma of the bronchus. In the earlier trial, MITCHELL (1960, pp. 152—153), it was found that among 157 male cases with a plausible original clinical diagnosis of inoperable carcinoma of the bronchus, not technically operable or treated surgically, the diagnosis must be regarded ultimately as unproved, unlikely or disproved in 22 cases, i. e. in 14.0 %. In the present trial, there were no cases that were regarded as technically operable, and a substantial proportion were

Table 2

All male patients in the trial — There are no significant differences in this table

Group	Treatment	Number of cases	Survival time (from the first roentgen treatment) Log mean value	Corresponding mean survival	Variance	S.E.
a	S + O_2 + X	61	0.6871	4.87 months	0.1835	0.0549
b	S + X	75	0.6721	4.70 »	0.1410	0.0433
d	28 + X	53	0.6486	4.45 »	0.0899	0.0410
c	O_2 + X	51	0.6260	4.28 »	0.1361	0.0517

in a poor general condition. A number of patients referred to us for the trial were so ill that radiotherapy was not justifiable; these patients were, of course, not registered with the trial. There was histologic evidence that two cases were carcinoma but not of the bronchus, and in a further case at autopsy, after death during the course of treatment, there was no evidence of carcinoma. Very few autopsies could be obtained, largely because most of the patients died at home. The low proportion of histologically verified cases almost certainly reflects the advanced stage of disease and the pathetic state of many of the patients.

It must be mentioned that throughout the whole of this trial and during the analysis of the results, careful arrangements were made to prevent the identification of the treatment groups by anyone involved in making clinical decisions.

Assessment of results

The criterion used for assessment of the results of the different forms of treatment is the time of survival in months from the first roentgen treatment; this is subsequently termed the survival time unless there is ambiguity. It is shown below that the length of history before treatment is not relevant.

Statistical treatment of the data is the basic necessity for assessment of the results but it is important to be cautious in making generalizations. In connection with the calculations, the following points should be noted:

1. The survival times are consistent with a log-normal distribution. Accordingly, all survival times in the calculations were rounded off to the nearest half month higher than the actual survival time. The minimum survival time was therefore half a month.

Table 3

Male patients with diagnosis verified histologically

Group	Treatment	Number of cases	Survival time (from the first roentgen treatment)			
			Log mean value	Corresponding mean survival	Variance	S.E.
a	S + O_2 + X	42	0.7344	5.42 months*	0.1703	0.0637
d	28 + X	32	0.6783	4.77 »	0.1223	0.0619
b	S + X	47	0.6649	4.62 »	0.1475	0.0560
c	O_2 + X	34	0.5758	3.77 » *	0.1662	0.0700

* The increased mean survival of 1.65 months for group (a) in relation to group (c) is probably significant (74 d.f.; t = 1.676, P = 0.049).

Table 4

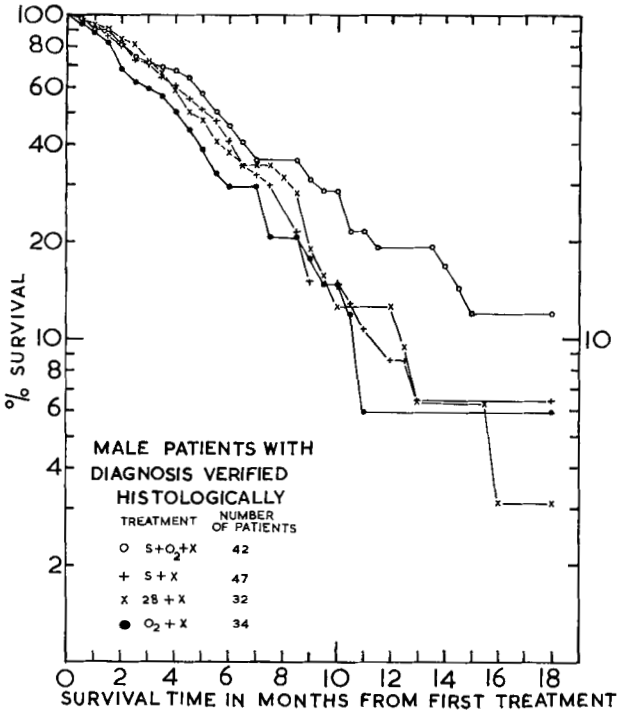
Male patients with diagnosis verified histologically and with no evidence of extra-thoracic spread and excluding those with incomplete treatment

Group	Treatment	Number of cases	Survival time (from the first roentgen treatment)			
			Log mean value	Corresponding mean survival	Variance	S.E.
b	S + X	20	0.7857	6.11 months*	0.1054	0.0725
a	S + O_2 + X	32	0.7844	6.09 » *	0.1498	0.0684
d	28 + X	19	0.7412	5.52 »	0.1048	0.0744
c	O_2 + X	22	0.6227	4.20 » *	0.1466	0.0817

* The increased mean survival time of 1.90 months for groups (a) and (b) combined in relation to group (c) is probably significant (72 d.f.; t = 1.693, P = 0.047).

2. Patients with 'incomplete treatment' are defined for this purpose as receiving a central tumour dose less than 1 500 R and/or less than a total amount of 200 mg of a radiosensitizing chemical (Synkavit or Compound-28) and/or oxygen on less that 2 treatment days.

3. All the tests of significance are one-sided. The question is asked whether the mean survival time observed with a particular radiosensitizer, e. g. S+ O_2 + X, exceeds the mean survival for the control group, O_2 + X, by an exceptional amount. A decision is required only about a positive difference (see e. g. PEARSON & HARTLEY 1954, pp 3, 21; VAN DER WAERDEN 1957, pp 29—30 and 339, and Table 7).



Results of the clinical trial of radiosensitizers in the treatment of inoperable carcinoma of the bronchus (February 1958—March 1963). Survival curves for the four treatment groups for all the male patients with the diagnosis verified histologically.

The most important results are summarised in Tables 2 to 4 and in the accompanying Diagram. In the tables, the four treatment groups are arranged in order of decreasing mean survival times; it is to be noted that group (c) in all the tables has the shortest mean survival time. For all the 240 male patients in the trial, it is clear from Table 2 that any advantages of groups (a) and (b) over (c) are very small; in fact, none of the differences are significant. However, the total of 240 patients consists of 155 with the diagnosis of carcinoma of the bronchus verified histologically, together with 85, with the diagnosis unconfirmed, of which in a few at least the diagnosis was proved not to be carcinoma of the bronchus.

The results for the 155 male patients with the diagnosis confirmed histologically are shown in the survival curves in the Diagram and summarised in Table 3. It is interesting that in the Diagram the survival curve for group (a) is at the highest level, with 19 % survival at 12 months. Table 3 shows that the

increase in mean survival to 5.42 months for group (a) from 3.77 months for group (c) is probably significant at the 5 % level. The additional mean survival of 1.65 months is small but corresponds to a 44 % increase. For the same group of 155 patients, it was found that the mean length of history, corresponding to the log-mean values, was as follows for the four treatment groups: (a) = 3.74 months, (b) = 3.07 months, (c) = 3.69 months, and (d) = 4.26 months. There are no significant differences between any of these values. There is no correlation between length of history and length of survival. The length of history is almost exactly the same for groups (a) and (c), which show the greatest difference in survival. Addition of the mean lengths of history to mean survivals does not change the order of the groups in Table 3.

Further evidence is presented in Table 4 which gives the mean survival times in four treatment groups for 93 male patients with the diagnosis verified histologically and with no evidence of extra-thoracic spread of the tumour, and excluding those with 'incomplete treatment'. The increased mean survival of 1.90 months, corresponding to 45 %, for the combined groups (a) and (b) in relation to groups (c), is probably significant at the 5 % level.

A number of negative results must be mentioned briefly. No significant differences were found between the four treatment groups for the following: all patients except those with 'incomplete treatment', all patients without extrathoracic spread, all patients with histology confirmed but excluding those with incomplete treatment or those without extra-thoracic spread, all patients with histology in groups (1) or groups (1), (2) and (3) combined. However, it is of interest that in almost all these tests the lowest value of the mean survival was in group (c).

Discussion

The results of this clinical trial of radiosensitizers in inoperable male cases of carcinoma of the bronchus show that in cases with the diagnosis verified histologically there is a small increase in mean survival, by about 44 % for the treatment group (a), S + O_2 + X, in relation to the treatment group (c), O_2 + X. This increased survival is regarded as 'probably significant' at the 5 % level.

This finding and the other results summarised in Tables 2 to 4 and the Diagram suggest that:

(1) the radiosensitizing action of intravenous Synkavit is confirmed;

(2) there is no convincing evidence that under the conditions of this trial oxygen alone at atmospheric pressure is effective as a radiosensitizer; and

(3) Compound-28 may have a small effect as a radiosensitizer but no

statistically significant advantage of treatment in group (d), 28 + X, over treatment in group (c), O_2 + X, has been demonstrated.

It is concluded that intravenous Synkavit has a, probably significant, small, and sometimes useful, effect as a radiosensitizer.

The organization of this trial has emphasized the many practical difficulties of clinical trials and the need to introduce some degree of flexibility as an integral part of the design and conduct of clinical trials of different forms of treatment of patients with advanced malignant disease.

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SUMMARY

Description of design and conduct of a clinical trial of the radiosensitizers Synkavit, oxygen inhaled at atmospheric pressure, and a compound closely related to Synkavit, in palliative radiotherapy of inoperable cases of carcinoma of the bronchus. The only conclusion which emerges from the statistical assessment of the results is that intravenous Synkavit has a small, probably significant, radiosensitizing effect.

ZUSAMMENFASSUNG

Es wird über die Planierung und Durchführung klinischer Versuche — in der palliativen Radiotherapie des inoperablen Bronchus-Karzinoms — mit Strahlensensibilisatoren, Synkavit und bei atmosphärischem Druck eingeatmeten Sauerstoff, sowie ein dem Synkavit ähnliches Präparat, berichtet. Statistisch konnte nur festgestellt werden, dass das intravenös injizierte Synkavit einen geringen, wahrscheinlich signifikanten, radiosensibilisierenden Effekt hat.

RÉSUMÉ

Description du plan et de l'exécution d'une expérimentation clinique de radiosensibilisateurs: Synkavit, oxygène inhalé à la pression atmosphérique, et un composé voisin du Synkavit, dans la radiothérapie palliative de cas inopérables de cancer bronchique. La seule conclusion qui ressorte de l'analyse statistique des résultats est que le Synkavit intraveineux a un petit effect radiosensibilisant, probablement significatif.

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