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INTRACAVITARY THIOTEPA IN MALIGNANT PLEURAL AND PERITONEAL EFFUSIONS

by

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A number of methods for controlling the exudation in serous cavities, in the palliative treatment of cases of effusions of malignant origin, have been introduced during the past two decades. Resort had previously to be made to frequent paracenteses, sometimes supplemented by roentgen irradiation to large thoracic or abdominal fields. Radiotherapy frequently caused severe side reactions, and its effect was often poor. Hormonal therapy was only occasionally beneficial.

Intracavitary application of radioactive isotopes was introduced in 1945 by MÜLLER who used ^{63}Zn and later (1950) ^{198}Au. Numerous reports have since been published, inter alios, by DENNIS et coll. (1956), HANSEN & HAUG (1960), and LAMBRETHSEN & SELL (1961) on favourable results with ^{198}Au, the exudation ceasing or being reduced in 50 to 70 per cent of the cases. However, this treatment has the drawback of requiring specially trained staff which will be exposed to a certain amount of radiation even with the best apparatus. Furthermore, it is rather costly and not suited for ambulatory use.

CLADIO & PERCESEPE (1958) employed prednisolone intrapleurally in a

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Table 1

Therapeutic results of intrapleural and intraperitoneal instillation of various cytostatics

Authors	Agent	Number of cases	Favourable effect	Side effects
BATEMAN et coll.	Thiotepa	24	16/24 : 66.7 %	
GROESBECK & CUDMORE	Thiotepa	27	20/27 : 74.1 %	Bone marrow depression
GOODMAN et coll.	KC-33	60	33/60 : 55.0 %	
WEISBERGER et coll.	HN2	41	26/41 : 63.4 %	Bone marrow depression, local pain
REEVE & MYHILL	HN2	13	11/13 : 84.6 %	Nausea
SUHRLAND & WEISBERGER	5-fluorouracil	52	29/52 : 55.8 %	Bone marrow depression
GELLHORN et coll.	Quinacrine	31	14/31 : 45.2 %	Fever, local pain

Table 2

Distribution by primary tumour, sex, and site of effusion

Primary tumour	Number of cases			Number of treated effusions		
	Males	Females	Total	Pleural cavity	Peritoneal cavity	Total
Breast cancer	0	16	16	14	2	16
Ovarian cancer	0	35	35	5	34	39
Genital cancers (ovarian cancer excl.)	3	6	9	3	6	9
Gastro-intestinal cancer	2	1	3	1	2	3
Cancer of the lung	3	5	8	8	0	8
Malignant lymphomas	3	3	6	8	0	8
Other cancers	6	3	9	3	6	9
Total	17	69	86	42	50	92

group of 20 cases with malignant pleural effusions. The treatment caused no complications and produced a positive result in 70 per cent of the cases.

Obliteration of the pleural cavity has also been employed in the treatment of malignant pleural effusions. HAUPT et coll. (1960) and STARKEY (1964), for instance, used intrapleural talc poudrage, while JENSIK et coll. (1963) performed pleurectomy. The results of these therapeutic methods appear to have been extremely satisfactory although it must have been unfortunate that such pa-

Table 3

Effect of intracavitary thiotepa in relation to primary tumour in the various groups

Primary tumour	Symbols for groups used in the assessement, see pp 372—373					
	++ & +		(++) & (+)	0	?	Total
Breast cancer	1	26 (47.2 %)	8	4	3	16
Ovarian cancer	6		11	12	10	39
Cancer of the lung	1		1	0	6	8
Malignant lymphomas	2		1	2	3	8
Other cancers	2		1	7	11	21
Total	12		22	25	33	92
		34 (37.0 %)				

tients, often in a poor general condition, had to be exposed to an operative procedure.

KARNOFSKY et coll. (1948) reported that they had obtained regression of recurrent pleural effusion following the intracavitary instillation of nitrogen mustard (HN2) in a case of bronchogenic carcinoma. Since then, other alkylating cytostatics have been tried, and have included in addition to HN2, KC-33 (N-hexamethylene-N′,N″-diethylene thiophosphoramide) and thiotepa (N,N′, N″-triethylene thiophosphoramide). Other agents have also been administered e.g. the pyramidine analogue 5-fluorouracil (SUHRLAND & WEISBERGER 1965) and the antimalarial quinacrine (GELLHORN et coll. 1961).

The results of treatment with the mentioned substances in a varying series of malignant effusions, are presented in Table 1. The results appear to be similar to those obtained with ^{198}Au. Direct comparison of the various substances and series is however hardly possible since the assessment criteria often differ and the number of unassessable cases varies.

Treatment with cytostatic agents has considerable advantages over the other therapeutic methods mentioned. Cytostatics are easy to administer; they are also relatively cheap, and require no special apparatus or specially trained staff. The side effects are generally mild and usually restricted to bone marrow depression. However, HN2 may produce local pain and nausea, and quinacrine may also induce fever. These two substances should therefore be given only to in-patients while the others are well suited for the out-patients clinics.

Material and therapeutic procedure. The material comprises 86 cases treated during the period 1956—1967 and was made up of sixty-eight from the Radium

Table 4

Effect of intracavitary thiotepa in relation to site of effusion

Effect*	Pleural effusions	Peritoneal effusions	Total
++	2	4	6
	5	7	12
+	3	3	6
	18 (42.9 %)	16 (32.0 %)	34 (37.0 %)
(++)	8	5	13
	13	9	22
(+)	5	4	9
0	8	17	25
?	16	17	33
Total	42	50	92

* For explanation of symbols, see pp 372—373.

Centre in Aarhus and eighteen from the Radium Centre in Odense. The distribution, by primary tumour, sex, and site of effusion, is indicated in Table 2. The group of 35 cases with ovarian carcinoma includes eleven cases in which only the ascitic fluid had been examined histologically, but the clinical course had been typical of ovarian carcinoma. The number of treated effusions amounts to 92 since a few patients had effusions in two or three sites. Seventy-seven of the patients were in the age group 40 to 70 years, six being older and three younger. At the time when the analysis was closed (June 1st, 1967) seventy-three patients had died, while thirteen were alive and attending ambulatory control. No patient had been lost to follow-up.

The therapeutic procedure was as follows. After adquate paracentesis, 45 mg thiotepa dissolved in 10 ml water were instilled direct through the same needle. The dose was however sometimes 30 mg into the pleural and 60 mg into the peritoneal cavity. Two children received a small dose adapted to body weight.

Assessing the results, the following symbols were used:

++ No paracentesis for more than 4 months (regardless of subsequent intractable recurrence).

+ No paracentesis for from 2 to 4 months, or a double interval between the punctures.

(Within groups ++ and + any simultaneous treatment was started more than 2 months before the thiotepa therapy, and the frequency of punctures prior to this treatment had been less than 2 months.)

(++) & (+) Same criteria as above but other simultaneous treatment had

Table 5

Other simultaneous treatments in groups (++) and (+)

	Group (++)	Group (+)	Total
Relevant roentgen therapy	3		3
Hormone and/or castration therapy	4	3	7
Instillation of ^{198}Au		2	2
Systemic cytotoxic therapy	4	2	6
Intracavitary thiotepa at first paracentesis	2	2	4
Total	13	9	22

been instituted less than 2 months prior to the thiotepa therapy, or else thiotepa was administered at the very first paracentesis.

0 indicates an unchanged frequency of punctures and/or fluid production.

? indicates unassessable cases due to (1) death within 2 months of the first administration of thiotepa, (2) prophylactic treatment, and (3) deficient data.

Other simultaneous treatments consisted in (A) relevant radiotherapy, (B) hormone therapy with or without castration, and (C) systemic cytotoxic treatment.

Results

The results of the treatment in relation to the primary tumour are given in Table 3. The majority of the cases of mammary carcinoma, pulmonary carcinoma and malignant lymphoma had pleural effusions while the others had mostly peritoneal effusions (cf. Table 2).

In Table 4, the relationship between the therapeutic effect and the site of effusion is illustrated. The thirty-three unassessable cases were almost without exception in a wretched state and survived for less than two months after thiotepa therapy. Twenty-two received some other simultaneous treatment or else intracavitary thiothepa at the very first paracentesis. They have therefore been classified as (++) or (+). The numerical distribution of these groups is listed in Table 5.

The therapeutic results for the entire material, as well as for pleural and peritoneal effusions separately, are set out in Table 6 in relation to other materials treated with intracavitary application of alkylating agents. In these other materials, unassessable cases do not appear to have been excluded, and only GROESBECK & CUDMORE (1962) give any detailed account of other concomitant treatment. If unassessable cases are excluded, a favourable effect

Table 6

Effect of intracavitary thiotepa compared with other materials treated with alkylating agents

Site of effusion	Effect**	Incl. unassessable	Excl. unassessable	Average of other materials treated with alkylating agents
Pleural + peritoneal	++ & +		12/37 (32.4 %)*	
	++ & + and (++) & (+)	34/92 (37.0 %)	34/59 (57.6 %)	106/165 (64.2 %) Ref. 1, 6, 7, 15 and 19
Pleural	++ & +		5/13 (38.5 %)*	
	++ & + and (++) & (+)	18/42 (42.9 %)	18/26 (69.2 %)	42/61 (68.9 %) Ref. 1, 7 and 19
Peritoneal	++ & +		7/24 (29.2 %)*	
	++ & + and (++) & (+)	16/50 (32.0 %)	16/33 (48.5 %)	20/31 (64.0 %) Ref. 1, 7 and 19

* Group (++) & (+) also excluded

** For explanation of symbols, see pp 372—373.

of the treatment was obtained in 57.6 % of the present cases. This corresponds to an average of 64.2 % in other materials. But if the unassessable cases are included, a favourable result was obtained in 37.0 % of the present cases. Furthermore, if the therapeutic results are accepted as definitely positive only in cases that received no other simultaneous treatment, there is a favourable result in only 32.4 % of the cases after exclusion of the unassessable cases and the cases receiving other simultaneous treatment. The corresponding values for pleural and peritoneal effusions respectively are evident from Table 6.

Table 7 indicates the relationship between the nature of the effusion and the therapeutic result. An equally large number of cases (21/21) with serous effusions responded favourably or not at all. It will be seen that with haemorrhagic effusions a favourable response was obtained in 13 out of 17 cases. These values indicate the possibility of a better therapeutic result in this condition.

We also investigated the relationship between the therapeutic result and the number of instillations. Twenty-three of the thirty-four cases that responded well to the treatment needed only one instillation of thiotepa, while seven

Table 7

Effect of intracavitary thiotepa in relation to nature of effusion

Effect*	Haemorrhagic effusions	Serous effusions	Chylous effusions	Unknown	Total
++ & + (++) & (+)	13	21			34
0	4	21			25
?	13	18	1	1	33
Total	30	60	1	1	92

* For explanation of symbols, see pp 372—373.

cases received two instillations. Only four cases had from 3 to 11 instillations, but all responded to the first or second treatment, later instillations being given for recurrences, generally with good effect. Eleven of the twenty-five cases that failed to respond received from 3 to 6 instillations. A favourable effect, if any, may thus be expected at least after the second instillation. If a case has shown no response at that time, the chances of a response to thiotepa are slight.

Fifty-seven of the eighty-six cases exhibited adequate haematologic control during the treatment. Thirty-five developed mild to moderate leukopenia and/or thrombocytopenia of a transient nature, but none had signs of serious bone marrow depression. No relationship was found between a positive response and signs of bone marrow depression, which thus does not appear to be essential for a favourable therapeutic result.

As already mentioned, seventy-seven of the subjects were in the 40 to 70 year age group; no definite difference was observed in the therapeutic results in those who were in their forties, fifties, or sixties.

Among the unassessable cases, thirty of which survived for less than two months after the thiotepa therapy, there was a preponderance of histories of less than two months duration, while among those with a favourable response to the treatment the majority of histories exceeded a year. Most of the unassessable cases were not, however, at the time of the treatment in such a poor general condition that a rapidly fatal course could have been predicted. It was a characteristic finding that while only about a quarter of the cases in the groups of breast and ovarian carcinoma were unassessable, about half the number of those with growths in other sites were unassessable.

Out of the remaining cases twelve patients survived for from 2 to 4 months,

eight for from 4 to 6 months, eighteen for from 6 to 12 months, while three survived for more than a year. Thirteen patients were still alive at the time when analysis was closed.

Fifteen cases received intracavitary treatment with ^{90}Y or ^{198}Au before or after intracavitary thiotepa therapy. A favourable effect of isotope therapy after thiotepa was noted in six out of eleven cases and in three out of four cases a similar effect of isotope therapy prior to thiotepa was observed. All the four cases that received thiotepa after isotope therapy belonged to the group of unassessable cases.

Discussion

Intracavitary application of cytostatics makes it possible to obtain direct contact with malignant cells and thus to obtain a higher concentration than in systemic treatment. THOM (1964) found for instance that in malignant effusions treated with intracavitary thiotepa increasing oedema of the tumour cells occurred within in a few hours. After 24 hours, there were signs of necrobiotic changes, with loss of nucleoli, in most of the tumour cells.

Our results with thiotepa do not appear to be as satisfactory as those obtained by other workers with alkylating agents (Table 6). However, if the unassessable cases are excluded, and the influence of other simultaneous treatments is disregarded, they are on a level with previous results, although the authors cited do not seem to have excluded their unassessable cases. It is possible that our criteria of a positive therapeutic result have been stricter, since the data of assessment are not always accurately defined in other materials. It could also be that in the present series the doses of thiotepa were too low, or that too few instillations were employed. However, the doses were of such a magnitude that in 61 per cent of the controlled cases they induced mild bone marrow depression. A favourable response, if any, appears moreover to be obtained after at the most two instillations. As compared with other materials, the series also does not seem to contain a preponderance of cases with carcinoma in sites that usually fail to respond favourably to intracavitary cytotoxic therapy. In other words, the results suggest that the effect of intracavitary thiotepa in malignant effusions is not as good as previously assumed.

It is always difficult to evaluate the effect of other treatments given at the same time, but assuming they be of less importance compared with intracavitary thiotepa treatment, the results indicate the greatest effect in the groups of mammary and ovarian carcinoma (Table 3). This is in accordance with the findings of WEISBERGER et coll. (1955) using HN2, GOODMAN et coll. (1965) with KC-33, and BONTE et coll. (1956) with ^{198}Au.

Similarly, the results appear to be better in the treatment of pleural than of peritoneal effusions. This has already been pointed out by BATEMAN et coll. (1955), GROESBECK & CUDMORE (1962), and SUHRLAND & WEISBERGER (1965).

Conclusion

Treatment of malignant effusions with intracavitary thiotepa is of indubitable value in quite a large proportion of cases. It is devoid of risk to the patients as well as to the staff and entails so little discomfort and so few side effects that its selection for the first therapeutic attempt appears reasonable. The treatment seems to be most effective in mammary or ovarian carcinoma of long duration, and in cases of haemorrhagic effusions. Pleural effusions appear to react better than peritoneal effusions. If the case does not respond by a reduction in the effusion after two instillations of thiotepa, other methods should be tried.

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SUMMARY

Thiotepa injections into the pleural and peritoneal cavities were given in a series of 86 cases. The treatment had a favourable effect in 37 per cent, and, if unassessable cases are excluded, in 57.6 per cent of the cases. The greatest chance of response had cases with mammary or ovarian carcinoma of long duration and cases with haemorrhagic effusions.

ZUSAMMENFASSUNG

Thiotepa-Injektionen in die Pleurahöhle und die Peritonäalhöhle wurden in 86 Fällen durchgeführt. Eine günstige Wirkung der Behandlung wurde in 37 Prozent der Fälle erzielt, und wenn man zweifelhafte Fälle ausschliesst in 57,6 Prozent. Die beste Voraussetzung für einen guten Erfolg erboten Fälle von andauernden Brust- und Ovarial-Karzinomen und Fälle mit hämorrhagischen Ergüssen.

RÉSUMÉ

Une série de 86 malades ont été traités par injection de thiotepa dans les cavités pleurale et peritonéale. Ce traitement a eu un effet favorable dans 37 pour cent de l'ensemble des cas et si on élimine les cas impossibles à juger, il a eu un effet favorable dans 57,6 pour cent des cas. Les meilleures chances d'effet favorable se trouvent dans les cancers du sein ou de l'ovaire de longue durée et dans les cas d'épanchement hémorragique.

REFERENCES

1. BATEMAN J. C., MOULTON B. and LARSEN N. J.: Control of neoplastic effusion by phosphoramide chemotherapy. Arch. intern. Med. 95 (1955), 713.
2. BONTE F. J., STORAASLI J. P. and WEISBERGER A. S.: Comparative evaluation of radioactive colloidal gold and nitrogen mustard in the treatment of serous effusions of neoplastic origin. Radiology 67 (1956), 63.
3. CLAUDIO F. and PERCESEPE E.: Trattamento dei versamenti pleurici da neoplasie polmonari e pleuro-polmonari con prednisolone per uso topico. Rif. med. 72 (1958), 1095.
4. DENNIS J. M., WORKMAN J. B. and BAUER R. E.: Radioactive colloidal gold in the control of malignant effusions. Amer. J. Roentgenol. 75 (1956), 1124.
5. GELLHORN A., ZAIDENWEBER J., ULTMANN J. and HIRSCHBERG E.: The use of atabrine (quinacrine) in the control of recurrent neoplastic effusions. Dis. Chest 39 (1961), 165.
6. GOODMAN L. E., BAKAL D., TSOU K.-C. et coll.: Clinical experience with N-hexamethylene N'N''-diethylene thiophosphoramide (KC-33), a new agent for breast and ovarian carcinoma. Cancer (Philad.) 18 (1965), 307.
7. GROESBECK H. P. and CUDMORE J. T. P.: Intracavitary Thio-TEPA for malignant effusions. Amer. Surg. 28 (1962), 90.
8. HANSEN P. B. and HAUG A.: Treatment of pleural and peritoneal carcinomatous effusions with radioactive gold (1956—1959). Acta radiol. 53 (1960), 321.
9. HAUPT G. J., CAMISHION R. C., TEMPLETON J. Y. and GIBBON J. H.: Treatment of malignant pleural effusions by talc poudrage. J. Amer. med. Ass. 172 (1960), 918.
10. JENSIK R., CAGLE J. E., MILLOY F. et coll.: Pleurectomy in the treatment of pleural effusion due to metastatic malignancy. J. thorac. cardiovasc. Surg. 46 (1963), 322.
11. KARNOFSKY D. A., ABELMANN W. H., CRAVER L. F. and BURCHENAL J. H.: The use of the nitrogen mustards in the palliative treatment of carcinoma. Cancer (Philad.) 1 (1948), 634.
12. LAMBRETHSEN E. and SELL A.: Palliative treatment of carcinomatous effusions in the pleural and peritoneal cavities with radioactive gold. Acta radiol. 56 (1961), 33.
13. MÜLLER J. H.: Über die Verwendung von künstlichen radioaktiven Isotopen zur Erzielung von lokalisierten biologischen Strahlenwirkungen. Experientia 1 (1945), 199.
14. — Weitere Entwicklung der Therapie von Peritonealcarcinosen bei Ovariecarcinom mit künstlicher Radioaktivität (Au^{198}). Gynaecologia 129 (1950), 289.
15. REEVE T. S. and MYHILL J.: The role of radioactive isotopes and alkylating agents in the treatment of malignant effusions. Med. J. Aust. 2 (1962), 245.
16. STARKEY G. W. B.: Recurrent malignant pleural effusions. New Engl. J. Med. 270 (1964), 436.
17. SUHRLAND L. G. and WEISBERGER A. S.: Intracavitary 5-fluorouracil in malignant effusions. Arch. intern. Med. 116 (1965), 431.
18. THOM R.: Wirkungsunterschiede verschiedener Cytostatica bei serösen Ergüssen. *In:* H. P. Kuemmerle und P. Preziosi: Third International Congress of Chemotherapy. Vol II, p. 1220. Georg Thieme Verlag, Stuttgart 1964.
19. WEISBERGER A. S., LEVINE B. and STORAASLI J. P.: Use of nitrogen mustard in treatment of serous effusions of neoplastic origin. J. Amer. med. Ass. 159 (1955), 1704.