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TOPICAL TREATMENT OF ULCERATIVE MAMMARY CARCINOMA BY THIOTEPA COMPRESSES

by

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The alkylating cytostatic thiotepa (N, N', N''-triethylene thiophosphoramide) has been used since 1953 for the palliative treatment of a large number of malignant diseases. It has usually been administered parenterally but topical application has also been tried successfully in certain benign and malignant conditions. The intrapleural and intraperitoneal instillation of thiotepa, performed once to several times in single doses of 10 to 65 mg, has proved effective in the treatment of recurrent malignant effusions. BATEMAN et coll. (1955), for instance, reported good effects in eleven out of sixteen patients with pleural effusion and in five out of eight patients with peritoneal effusion. GROESBECK & CUDMORE (1962) found the same favourable effect in thirteen out of fifteen patients with pleural effusion and in seven out of twelve with peritoneal effusion.

A number of widespread, benign and malignant, bladder papillomas have been sucessfully treated by intravesical instillations of thiotepa. The doses have generally been 30 to 60 mg, repeated four to six times at intervals of 2 to 7 days. The effect has been most marked upon superficial papillomatous tumours, while infiltrating tumours have failed to respond. JONES (1963), for

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Table

Results of treatment with thiotepa in 11 patients with ulcerating breast cancer during the period October 1964 to August 1966

Case	Age	Lesion	Applications/ days	Total dose thiotepa, mg	Additional treatment
1	64	Adenocarcinoma	25/33	375 mg	Prednisone
2	63	Carcinoma	15/?	225 mg	Stilboestrol + prednisone
3	56	Sol. scirrh. carcinoma	23/23	345 mg	Hypophysectomy 9 months/earlier
4	72	Sol. carcinoma	28/28	420 mg	None
5	47	Intracanal. carcinoma	19/19	285 mg	Prednisone
6	59	Scirrh. carcinoma	13/13	185 mg	Testosterone
7	75	Sol. scirrh. carcinoma	21/21	945 mg	Prednisone
8	56	Carcinoma	22/40	330 mg	Prednisone
9	64	Scirrh. carcinoma	12/19	180 mg	Prednisone
10	61	Carcinoma	82/122	1 230 mg	Stilboestrol
11	51	Sol. scirrh. carcinoma	14/16	210 mg	Prednisone

* Symbols: — no effect, + sporadic epithelialization, ++ < 50 pct epithelialization, +++ total epithelialization.

instance, reported total or almost total disappearance of multiple papillomatous tumours in seventeen out of twenty-four patients. ESQUIVEL et coll. (1965) recorded complete tumour destruction in three, and partial destruction in two out of eight patients with benign papillomatosis. Two of a group of twelve patients with carcinomatous lesions responded only slightly; the tumours were quite superficial (stage A) in both. In all the other patients with more deeply infiltrating tumours the treatment was ineffective.

CHENG & VEENEMA (1965) applied thiotepa topically in six patients with

Table *(cont.)*

Min. values/μl: Leucocytes (L) Platelets (P)	Effect*	Survival after treatment, months	Comments
No depression	+++	6	(See Fig. 1)
No haematologic control	+++	13	(See Fig. 2)
No depression	++	9	Recurrent ulceration 6 months later; New topical thiotepa without effect
No depression	++	4	
L: 2100 P: no depression	++	$1^1/_2$	Additional intrapleural thiotepa (45 mg)
No depression	++	2	
L: 100 P: 10.000	+		(See Fig. 3)
No depression	+	14	
No depression	—	8	
L: 1100 P: 12.000	++	8	Ulcerating primary tumour
No depression	+	5	Pyocyaneus infection during thiotepa treatment

penile tumours. In dealing with tumours of the urethra they used suppositories of 15 mg, applied once daily for 2 hours, while tumours affecting the glans penis were bathed in a solution of 60 mg thiotepa in 60 ml distilled water once or twice daily for 2 hours at a time. Out of four patients with condylomata acuminata they obtained complete disappearacne of the lesion in one patient, in whom the lesion affected the urethra, and partial disappearance in three patients, in whom the lesions affected the glans. Superficial regression of the tumours was achieved in only two patients with squamous cell carcinoma.

A few patients with mycosis fungoides have been treated by thiotepa 0.2 % in a lanolin-petroleum jelly base and were much improved (GRUPPER & SIRKIS 1965, MICHEL et coll. 1965).

The recurrence rate of pterygium, reported to be 20 % to 30 % after surgery alone, may be greatly reduced by the postoperative instillation into the conjunctiva of thiotepa 0.05 % in Ringer's solution every third hour for 6 to 8 weeks. This treatment is said to produce no local irritation. CASSADY (1966) has reported the results of treating 78 patients, among whom there were six recurrences; out of this series, however, forty-six had been treated for more than 2 months and in these there were no recurrences.

VOUTILAINEN & SALMI (1965) have published two cases of ulcerating cutaneous metastases from mammary carcinoma treated with compresses soaked in thiotepa solution. In one of these cases they used a solution of 15 mg thiotepa applied once daily, with a total of 20 applications in the course of 36 days. Colimycin compresses were used in the intervals between the applications. Three months after the discontinuation of the treatment the ulceration had undergone epithelialization. In the other case, they employed a solution of 30 mg thiotepa, applied 8 times in the course of 21 days. One month after the treatment had been discontinued the ulceration had diminished but thereafter it again progressed.

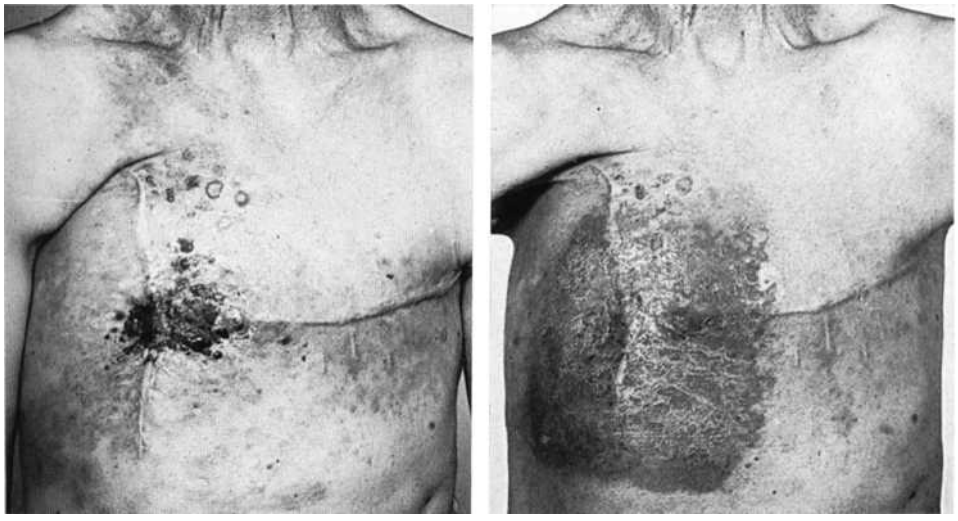
We have tested the last mentioned method, which is easy to administer and has produced good palliation in several cases.

Method. An amount of 15 mg thiotepa is dissolved in 20 to 30 ml sterile water. A compress of the same size as the ulceration is soaked in the solution, applied to the ulcerated site, covered with gutta percha, and held by an ordinary dressing. The compresses are changed daily. While the treatment is continued, white cell and platelet counts are made 2 to 3 times weekly. Should signs of bone marrow depression appear, the applications should be interrupted immediately and not be resumed until the marrow has been restored to normal.

Results

We have treated 11 patients with ulcerating breast cancer by the above procedure during the period October 1964 to August 1966. The results are given in the Table.

One patient (Case 10) had an ulcerating primary tumour, while the others had cutaneous metastases that had ulcerated. The material was not selected, except for the fact that only patients in an acceptable general condition were included. In two patients, the treatment resulted in total epithelialization of the



a b

Fig. 1. Case 1. a) Ulceration in the metastatic scar. b) Total epithelialization 33 days later after 25 applications of thiotepa.

ulcerated area, while in five patients the epithelialization covered more than 50 % of the area. Three patients had scattered epithelialization, while the treatment failed in one patient, who will be discussed later.

Illustrative cases

Case 1. Woman, aged 64, underwent right-side mastectomy with axillary dissection in March 1961. The microscopic examination disclosed adenocarcinoma. Postoperative irradiation by the McWirther field technique was given.

Progressive cutaneous metastases around the mastectomy scar were present in November 1963. In March 1964 there were diffuse neoplastic infiltrations in the entire left breast and left-side axillary metastases; simple palliative left mastectomy was then performed, and in April treatment with androgenic hormones was started. The skin metastases regressed slightly. In September 1964, carcinosis of the right pleural cavity was treated by pleural puncture and instillation of ^{198}Au.

Progression of the cutaneous metastases was noted in February 1965, and an area of ulceration, 5 cm × 7 cm, appeared in the right mastectomy scar (Fig. 1a). The androgenic therapy was discontinued and prednisone was instituted. At the same time the ulceration was treated with thiotepa compresses (25 applications/33 days with a total of 375 mg thiotepa). This resulted in total epithelialization of the area (Fig. 1b), while other, non-ulcerating cutaneous lesions progressed.

In September 1965, there were signs of hepatic metastases, and death occurred at the end of the month.

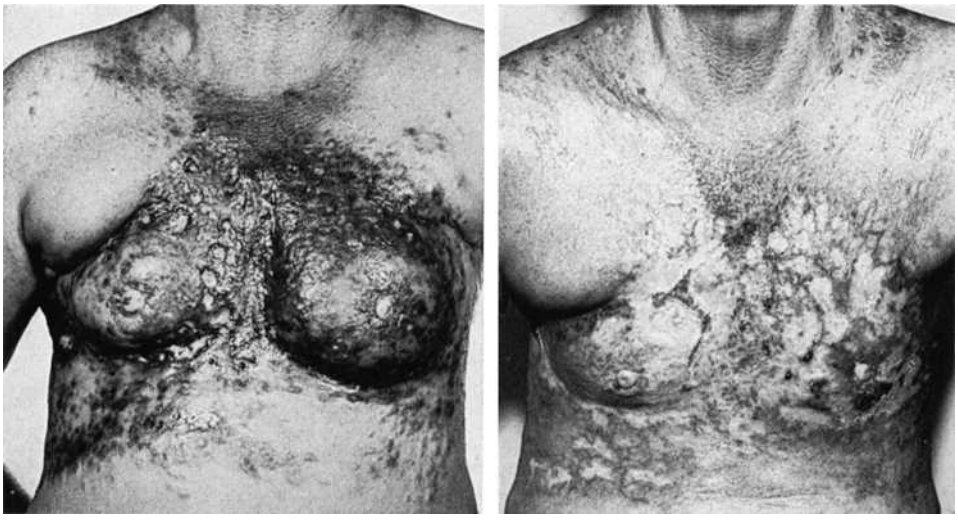


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Fig. 2. Case 2. a) Ulceration of widespread cutaneous metastases. b) Total epithelialization after 15 applications of thiotepa.

Case 7. Woman, aged 75, had right-side mastectomy in March 1963. Microscopy showed scirrhous carcinoma. No postoperative radiotherapy.

In September 1964, increasing number of cutaneous metastases in the right chest and right upper arm; prednisone medication was ineffective.

In February 1965 there was also widespread ulceration in the metastatic areas on the anterior aspect of the right chest and right upper arm (Fig. 3). Treatment with thiotepa compresses was instituted (21 applications/21 days with a total of 945 mg thiotepa). Epithelialization began to appear along the margins, and central islets of epithelium were observed, but at the same time the absorption of thiotepa from the ulcerated surfaces severely depressed the bone marrow. There was a fall in the white blood count to 100/μl and of the platelets to 10 000 μl. In spite of prednisone in large doses, the bone marrow could not be restored and the patient died of profuse rectal bleeding due to severe thrombocytopenia a month later.

Case 9. Woman, aged 64, who in February 1962 had ulcerating carcinoma of the left breast. Preoperative radiotherapy was followed by right mastectomy in April 1962. Microscopy showed diffuse scirrhous carcinoma. Postoperative irradiation of the regional lymph nodes and roentgen castration.

In November 1964, there were cutaneous metastases on the anterior surface of the right chest, with ulceration 2 cm $\times$ 2 cm in size which yielded to local irradiation.

In August 1965, further progression of lesion with ulceration despite prednisone therapy. The lesion measured 12 cm $\times$ 18 cm in February 1966; there was a 7 cm $\times$ 7 cm large central area of ulceration and marked necrosis. Treatment with thiotepa compresses was started (12 applications/19 days with a total of 180 mg thiotepa). The treatment had no effect, either upon the ulcerations or upon the necrosis. Prolonged energetic antiseptic therapy topically was

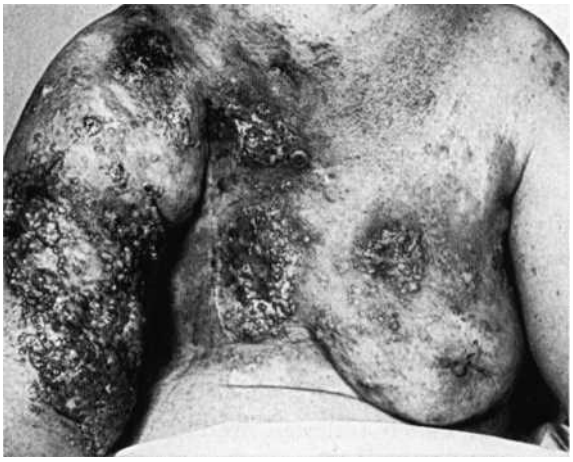

Fig. 3. Case 7. Widespread ulceration of the metastatic areas on the anterior aspect of the right chest and right upper arm.

given, but again had no effect upon the necrosis. Electron therapy (10 MeV, 3 150 rad/31 days) also seemed ineffective. Distant metastases gradually appeared, and the patient died in November 1966.

Discussion

Alkylating agents are chemically very active substances whose cytotoxic effect presumably consists mainly in an inhibition of the DNA synthesis. Morphologically, the effect is apparent as an inhibition of mitotic activity with characteristic chromosomal breakages. The cytotoxic action is not selective, and therefore the concentration in the tumour should preferably be higher than in the surrounding tissue. This is obtained by topical application of the agent.

The treatment with thiotepa compresses failed entirely in one of the patients in the present series (Case 9). The characteristics of this case was ulceration covered with thick encrustations, which is possibly the explanation of the absence of any effect from the thiotepa.

Ten of the eleven patients received hormone medication at the same time as the thiotepa application. The cases were analysed with a view to assessing to what extent the hormone may have contributed to the effect. In two instances (Cases 1 and 10) the hormone medication was started almost simultaneously with the thiotepa applications, which makes the evaluation difficult, but in these two cases other metastatic lesions progressed in spite of

the hormone. In the other eight patients the medication had been instituted several months before the thiotepa treatment without having favourably affected the ulcerating area, so that it is not likely that the hormone had any share in the effect.

VOUTILAINEN & SALMI recommend the use of colimycin compresses during the intervals between the thiotepa applications in order to prevent the growth of microorganisms in the treated area. This or similar procedures were not used in the present series. One of the patients (Case 11) developed a pyocyaneus infection in the ulcerated area, while the others exhibited regression of superficial infectious lesions, in keeping with the fact that alkylating agents per se are bactericidal.

Three of the patients developed signs of bone-marrow depression in the course of the treatment. This manifested itself as a decrease in the white cell or platelet count. In one of these patients (Case 5), however, it was difficult to assess the share in these complications of the thiotepa compresses as, due to a pleural effusion, intrapleural thiotepa therapy (45 mg) was administered at the same time. Case 10 developed a depression of the bone marrow after prolonged treatment (1 230 mg thiotepa/122 days) in spite of a rather small area of ulceration (about 13 square cm); the signs consisted of decreased white cell and platelet counts and progressing anaemia. In the course of a month blood transfusions restored the haematologic condition to normal, however. Case 7 had very widespread ulcerating lesions and was given a daily dose of 45 mg thiotepa (the usual is 15 mg). In the course of three weeks there was a massive decrease in the haemoglobin level, white cell and platelet counts, and the patient died of haemorrhagic diathesis.

Thiotepa, whose molecular weight is 189, can be absorbed to a certain extent from the outer and inner surfaces of the body, especially if these have undergone pathologic changes. Indeed, others have also reported absorptive side effects with thiotepa. ESQUIVEL et coll., for instance, observed an action upon the bone marrow in five out of twenty patients treated by intravesical instillations of thiotepa; however, all rapidly improved. ORAVISTO (1965), treating six patients by intravesical thiotepa, found severe leukocyto- and thrombocytopenia after a total dose of 150 mg thiotepa in one patient while another patient died of massive hepatic necrosis 16 days after 120 mg thiotepa/7 days, after having had but a modest decrease in the white cell and platelet counts. EDGREN et coll. (1966) have also published a case of severe bone marrow depression after 360 mg thiotepa/8 days in the urinary bladder.

GROESBECK & CUDMORE found a slight haematologic depression in a few patients treated with thiotepa, administered intrapleurally and intraperiotoneally, although only in those who had already received radiotherapy, ^{198}Au

therapy, or who were simultaneously on parenteral chemotherapy. CHENG & VEENEMA observed a slight depression of the white blood count in the topical treatment of penile and urethral tumours with thiotepa. MICHEL et coll. have reported a case of leukocyte and platelet depression after the topical treatment of mycosis fungoides with a total dose of 1.4 g thiotepa/34 days. CASSADY noted no absorptive side effects in the treatment of pterygium and VOUTILAINEN & SALMI observed no such effects in their two patients treated for ulcerative mammary carcinoma. The present results indicate however that the blood picture should be carefully checked during the treatment, which should be interrupted immediately if signs of bone marrow depression appear. Furthermore, it seems inadvisable to administer more than 15 mg thiotepa daily, and particular caution should be observed with large areas of ulceration and prolonged treatment.

It does not seem reasonable to try this treatment unless the patients are in a fair general condition and are likely to survive for a certain length of time. Incidentally, the treatment is well-suited for out-patient use, provided that the haematologic condition can be followed.

SUMMARY

The results of the local application of thiotepa compresses to ulcerative mammary carcinoma in 11 patients are reported. The risk of haematologic complications is stressed. The literature on this topical treatment is reviewed.

ZUSAMMENFASSUNG

Es wird über die Resultate der Behandlung mit lokalen Kompressen von Thiotepa von 11 Patienten mit ulcerativen Mammakarzinomen berichtet. Das Risiko von hämatologischen Komplikationen wird betont. Die Literatur wird besprochen.

RÉSUMÉ

Les auteurs présentent les résultats de l'application locale de compresses imbibées de Thiotepa sur des cancers du sein ulcérés chez 11 malades. Ils insistent sur le danger des complications hématologiques. Ils donnent une revue de la littérature sur ce traitement local.

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