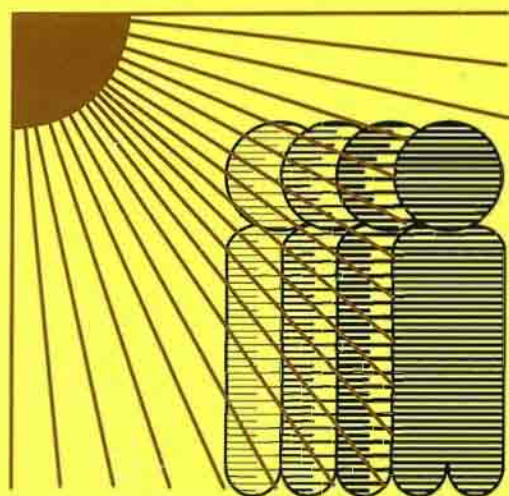
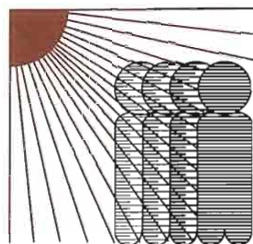


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F. Menezes Brandão, M.D

A Brief Note on the Author of this Special Issue

I first met Dr. Almeida Gonçalves in 1967 when, still in my fifth year of medical school, I attended a lecture he gave on Hansen's disease at the invitation of Professor Juvenal Esteves. Since then, I have followed his scientific activity with interest, namely during our encounters at dermatological meetings and through his publications and presentations at medical congresses and symposia.

Over time, our mutual professional respect evolved into a personal friendship and I learned to see in him a special, somewhat unconventional personality, often politically incorrect, a restless spirit, an innovative clinician and a dermatologic surgeon who has contributed greatly to our Specialty.

In 1974, he was invited to work in the Department of Dermatology at the Portuguese Institute of Oncology, in Lisbon. He accepted the invitation and enthusiastically embraced the study of cutaneous oncology and its therapeutic options. Still in 1974, he started using cryosurgery for the treatment of small tumours. As he acquired experience, he went on to treat larger lesions, ultimately establishing the respective treatment protocols. Interestingly, at the time, several cryosurgeons worldwide maintained that it was impossible to freeze tumours larger than 3 cm. Dr. Almeida Gonçalves devised original protocols that permitted the successful freezing of much larger tumoural masses at cancericidal temperatures, thus conferring a new dimension to cryosurgery.

Touched by the suffering of patients with inoperable external cancers, in the course of his 25 years at the Oncology Institute, he devised several important cryosurgical and chemosurgical techniques, with which he has treated large and invasive cancers of the face and trunk, and advanced, inoperable (by conventional surgery) carcinomas of the extremities, breast and vulva. The results that he presented and published were remarkable. Many of those patients -namely those with advanced breast and vulvar cancers- who were condemned to a short existence of excruciating pain and suffering were clinically cured and

survived for several years with good or acceptable quality of life.

He also created cryosurgical protocols for invasive basal-cell carcinomas of the eyelids and periorbital region. This fractional cryosurgery method again attests to Dr. Almeida Gonçalves' practical and inventive character: for relatively large tumours that present risk of post-cryosurgery retractile scars, he performs successive cryosurgical procedures that gradually reduce the size of the tumour, until the last intervention leaves an almost imperceptible scar.

His intensive work in the field of cryosurgery has been widely recognised and would culminate with his election, in 2001, for President of the International Society of Cryosurgery. He was also invited to contribute with the chapter "Cryosurgery of Advanced Skin Cancer" in the book "Basics of Cryosurgery" edited by Nikolai Korpan, in 2001, in Vienna, Austria.

In the early seventies, due to a mental disorder in a member of his family, he studied several mental syndromes and ended up founding the Portuguese Association for the Protection of Autistic Children, which was the first institution of its kind in the Iberian Peninsula.

Dr. Almeida Gonçalves is well respected by those who have worked close to him. However, his intellectual curiosity, rigorous inquisitiveness, honesty, professional courage and even his sense of humour are not always quite understood by those around him, and he has often had to battle bureaucracy and ignore envy. He is also a man of culture with a great love for music, as well as for the arts in general and history. He studied music and composition, and he still enjoys playing his piano after a day's work.

In what concerns his "Chemosurgery without Systematised Microscopic Control", the work presented in this Special Issue of SKIN CANCER is self-evident. Dr. Almeida Gonçalves' decision to republish an important part of his life's work, obviously now seen with different clinical and scientific perspectives than those at the dates of their original publication, is a deserved tribute to his professional achievements and to the passion that always motivated him.

Francisco Menezes Brandão, M.D.

Simplified Chemosurgery Revisited

I was pleased to be invited to guest edit this Special Issue of Skin Cancer. It is an excellent opportunity to review my research on the "chemosurgery without systematised microscopic control" for malignant skin tumours, also called "simplified chemosurgery", which I have been publishing in this Journal since its very inception, in 1986. The technique was then considered as a curiosity, but subsequent data proved its unique positive and intense immunologic activity, so I believe its re-publication has merit and, perhaps, specialists in this area will want to continue the research.



J. C. Almeida Gonçalves, M.D.

In 1975, I was working at the Portuguese Institute of Oncology, in Lisbon, Portugal, and visited the clinic of Dr. Frederick Mohs, in Wisconsin, U.S.A. I was fascinated with his work and delighted with his warm personality and simplicity, associated with the highest competence. He was extremely organized and his patients accompanied only by another physician, a nurse and a laboratory technician. He had four or five rooms where his patients, seating on dentist-type chairs, were examined and treated by him, as he went from one room to the other. The nurse's duty was to receive the patients and write their histories. Dr. Mohs read them and corrected some details onto a Dictaphone, and she modified them accordingly. Subsequently, he went to each room and, with scalpel, removed a layer from each tumour and handed it to the laboratory technician. When the respective histological slides were ready, he was called, studied them and recorded the data, which the nurse would transcribe into the patient's chart. Afterwards he would return to each patient and proceeded with treatment. With this method he serenely and efficiently treated 30 patients every day.

I greatly admired his work and technique, and wished to learn it, but soon found that it was not possible for, even if I would obtain a Portuguese grant (which were usually modest) I could not maintain my family at home and me in the U.S., during the training period.

Upon my return to Portugal, I began devising a simplified chemosurgical protocol in the hope of obtaining a new and efficient method. The paste then used by Dr. Mohs was only available to those who practiced the Mohs' technique, and those physicians acted almost as members of a closed Club. So, with the help of an American chemist who requested anonymity, a formula was prepared with the same percentage of zinc chloride (ZnCl) as the Mohs' paste, but with a different excipient that also keeps the ZnCl in suspension as is the case of Mohs' preparation. (A Portuguese chemosurgeon who once, was short of the Mohs' paste, used mine and told me that their pharmacologic activities were quite similar).

I performed a pilot trial and treated 13 small basal-cell carcinomas with only one application of the paste that was kept in place for 24 hours. Within 7-10 days, the fixed tissue sloughed off spontaneously or was easily removed with forceps. The entire tumour "seemed"

to come out completely. Alas, it was not always so. Six were not cured and persisted. Discussing the results with my collaborator, Dr. Cabral de Ascensão, he suggested applying the ZnCl paste three times, successively, but I opted for removing as much tissue and safety margin as we do with any other surgical method. Subsequently, we initiated the treatment of non-melanoma skin malignancies. We devised this treatment and, later on, I also prepared different protocols for other malignancies. With one exception, all my findings were published in this Journal. In this Special Issue of SKIN CANCER, I propose to republish all papers on the Simplified Chemosurgery, followed by a comment about each one.

Over a period of 12 years (1974 to 1986) I devised the Simplified Chemosurgery project and also a Cryosurgery programme for skin malignancies, particularly advanced cancers, with enormous personal effort because the working conditions at the Portuguese Institute of Oncology were far from ideal: All three dermatologists had two small rooms, one for consultation and another, slightly larger, for treatments and minor surgeries with only one nurse. Later on, I lost two collaborators -one died and the other pursued his academic carrier (Dr. Cabral de Ascensão). I then asked the Institute's administration for three new dermatologists and free access to the operating room to perform cryosurgery of extensive cancers, namely of the breast and vulva. I was given one dermatologist (a good one, indeed), but the difficulties in the access to the operating room were maintained. After 25 years of dedicated service, I decided to move to another hospital where I could continue my clinical research with better conditions and without the permanent stress, which I did two years later, when I opened the Department of Dermatology of the District Hospital, in Santarém.

There is still a lot of work to be done and my utter disappointment is that the support I needed was denied me in my own country.

As a curiosity, I will mention the reactions of my Colleagues at the Portuguese Institute of Oncology to my treatments with the ZnCl fixative paste. The more competent, clever and bright physicians actively collaborated with me, sending me patients and following my work with interest, while the mediocre ones ostensibly despised my research. Those who did not produce an iota of research and had low professional level were particularly ferocious towards me. Some interpreted this as jealousy, but I believe it was sheer pettiness. Jealousy would be more "natural" and, in a certain way, more excusable.

Fortunately, at present the number of advanced cancers is much smaller due to better medical assistance and increased knowledge of patients who seek help at earlier stages of the disease. Although some neglected cases still present at hospital Departments of Dermatology, these could benefit either from simplified chemosurgery or from cryosurgery.

Malignant melanoma, on the other hand, is an increasingly serious oncologic problem. It is irrational not to investigate new therapeutic possibilities. The immunological activity that has been strongly suggested by my work and supported by laboratory findings should inspire further study.

J. C. Almeida Gonçalves, M.D.

Chemosurgery Without Systematised Microscopic Control for Malignant Skin Tumours — A New Simplified Technique

J. C. Almeida Gonçalves, A. Cabral de Ascensão

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Key Words. Chemosurgery. Simplified chemosurgical technique. Basal-cell carcinoma. Squamous-cell carcinoma.

Abstract. A simplified chemosurgical technique for the treatment of malignant skin tumours has been devised.

Although chemosurgery with microscopic control is recognised worldwide as the most efficient technique for the treatment of external tumours, the number of chemosurgery centres around world, using it, is scarce, probably due to the fact that the method is too sophisticated and, technically, very elaborate.

The simplified method herein discussed was used to treat 179 basal-cell carcinomas, and 33 squamous-cell carcinomas. The follow-up on these patients ranges from 5 to 10 years, and no recurrences have been observed.

INTRODUCTION

One of the oldest methods for the treatment of cutaneous tumours is the use of cauterising substances which composition, for the most part, we are totally ignorant of. However, the use of topical agents containing arsenic is described among the Egyptians, for this therapeutic purpose¹. Also, in the last years of the nineteenth century, the use of a “caustic cosmetic paste” which composition included the ingredients mercury sulfide and arsenic², was recommended by *Hebra* for the treatment of these tumours. *Stelwagon*³ and *Darier*⁴ also mention the use of topical agents containing the latter substance.

But it was *Canquoin and Bougard* who, more than a century ago, observed the caustic properties of zinc chloride for the first time and successfully used it in the treatment of cutaneous neoplasms⁵. *Stelwagon*³ in 1900, described in detail its effect and the excellent results that he obtained using the product in the treatment of this type of tumours. *Landolfi*, who *Burg and Robins*⁶ cite as having been the person who introduced zinc chloride for this therapeutic purpose, was only resuming the studies of those investigators during the nineteenth-twenties.

It was in the early 1930's that *Mohs*⁷⁻⁹ devised and began to practice a method of extirpating cutaneous malignancies

by using a zinc chloride paste in serial applications monitored by histologic examinations of each layer of tissue removed. *Mohs'* method now comprises two techniques, namely, one in which layers of tissue are fixed by a paste of zinc chloride^{3,7} and another in which layers of unfixed tissue are successively excised⁸ until, in either case, histologic examination proves a base free of malignant process. The method is almost perfect, but is complicated in that it requires advanced surgical experience and highly trained personnel to process and read each layer of tissue removed, in both the "fixed" or "fresh" techniques.

Nowadays, there are several centres in the United States that practice *Mohs'* methods routinely and teach them. A few physicians from European countries have been trained in these techniques but there are still few places in Europe where the methods are practiced.

Schreus, in 1951, created a simple chemosurgical technique in which basal-cell carcinomas were removed by curettage and, then, cauterised with a 50% zinc chloride solution².

The purpose of our work was to create a simplified chemosurgical method, without sistematised microscopic control, adequate for most skin tumours, and to compare our results with those obtained by the conventional therapeutic methods. A pilot trial conducted on 43 patients with both basal-cell and squamous-cell carcinomas resulted in the protocol which was followed in the treatment of the cases herein reported.

Although we realise that, for the more invasive and larger tumours¹⁰, our method cannot compete with *Mohs'* statistical results, we believe that is a positive step forward in chemosurgery.

MATERIAL AND METHOD

1. Patients Data

Our experience is based on the treatment of 212 patients, 179 suffering from basal-cell carcinoma and 33 from squamous-cell carcinoma. All patients had one single lesion each.

a) Basal-cell carcinoma

Of the 179 mentioned patients, 86 were male and 93 female. Their ages ranged between 34 (1 patient) and 82 (1 patient), the average being 65.33.

Excepting 7 cases, all lesions were on the head and neck (Table I).

Only 6 patients had previously been submitted to surgery with subsequent recurrences. The remaining ones had not received any previous specific treatment.

One hundred and seven tumours were of the nodulo-ulcerative type, 36 were nodular, 25 pigmented, 6 superficial, 3 plano cicatricial and 2 of the morphea-like type.

TABLE I
Basal-cell Carcinomas: Localization of the Lesions

Localization	No. of Patients
Cheeks	73
Nose	34
Lower eyelids	15
Forehead	20
Temporal regions	14
Upper lip	6
Chin	5
Upper eyelids	4
Dorsal region	3
Lumbar region	3
Neck	1
Lower limbs	1
Total	179

The size of the lesions ranged from 0.3 to 3.5 cm.

The histological classification of the tumours was: 142 solid, 28 adenoid and 9 keratotic.

b) Squamous-cell carcinoma

Of the 33 treated patients, 15 were male and 18 female. The youngest patient was 51 and the eldest was 83, the average being 70.63.

All lesions were on the head and neck (Table II).

Five patients suffered from Bowen's disease, 6 from nodular type and 22 from nodulo-ulcerative type of tumour.

The size of the lesions varied from 0.7 to 4.5 cm.

The histological classification of the tumours was: 5 intra-epithelial, 11 grade I and 17 grade II.

TABLE II

Squamous-cell Carcinomas: Localization of the Lesions

Localization	No. of Patients
Cheeks	17
Chin	3
Forehead	5
Nose	2
Neck	2
Upper lip	2
Lower lip	1
Temporal region	1
Total	33

2. Chemosurgical Procedure

Our simplified method consists in the application of a paste (kindly supplied by Orewa Pharmaceuticals, Inc.) containing 45% zinc chloride in a special vehi-

cle* that slowly releases the salt for about 24 hours.

Prior to the beginning of treatment, a history is taken, photographs are made and all tumours are biopsied. (Since the paste fixes the tumour, or, at least, its superficial layer "in vivo", the fragment required for the histological examination can be removed with a scalpel the day after the first application, with no pain or haemorrhage, local anaesthesia and haemostasis being, therefore avoided).

The paste is applied, with a wooden spatula, to the clinically judged area of malignant involvement, plus a margin of normal looking tissue of 5 to 10 mm, in a layer of not less than one mm thick. Surrounding skin beyond this margin is protected by flexible collodium (Fig. 1). A non-occlusive dressing is applied for 24 hours. Analgesia by common drugs (such as Glafenin) is prescribed routinely.

The paste is permitted to act for 24 hours in order to achieve tissue fixation. The area of the lesion becomes grey and necrotic with inflammatory signs around it (Fig. 2). A definite demarcation appears between the lesion and the normal looking skin, with a groove isolating the fixed tissue (Fig. 3). By five to ten days, the lesion sloughs off spontaneously or is easily removed with forceps (Fig. 4). A clean base of granulation tissue is thus achieved (Fig. 5), which heals by second intention with good or acceptable cosmetic results (Fig. 6).

* Formula

Zinc chloride	45 g
<i>Sanguinaria canadensis</i>	10.8 g
<i>Alpinia officinarum</i>	7.2 g
Deionised water	q.s. 100 g
(European Patent n.º 0025649)	



Fig. 1 - Application of zinc chloride paste and flexible collodium.



Fig. 2 - Necrosis of the lesion 1 day after application of the zinc chloride paste.

The measurements and depth of the resulting ulceration are appreciated and, if they are not satisfactory in terms of the established "safety margin" in depth and/or periphery, a second or third (rarely more) application of the paste is made (Fig. 7).

If there is clinical suspicion of persistence of neoplastic tissue, biopsies are made and, if necessary, other applications are made.

After the cure, a final biopsy is taken. All patients are observed at 3 month intervals for the first year following treatment and, thereafter, at 6 month intervals for, at least, 5 years.

RESULTS

a) Basal-cell carcinoma

In 111 cases (62.01%), one single application was sufficient to obtain clinical cure. In 64 cases (35.76%) 3 applications were necessary, and only in 4 patients (2.23%) 2 applications were made, the average of applications being 1.40.

The time for healing after the last application was 9 days in one patient and 53 days in another-average of 22.26 days.

The total time of treatment was of 13 days in 4 patients and 70 days in one patient-average of 30.45 days.

From the cosmetic point of view, 79.21% of the patients had good or acceptable results (Figs. 8-13).

In all cases, the histological examination carried out a few days after any application of the paste showed a marked necrosis of the tumour with a demarcating inflammation rich in polymorphonuclear cells, plasmocytes and lymphocytes around it. Biopsies made later on the surface of the ulcerations, showed granulation tissue rich in connective fibres.

Pain was either non-existent, slight or moderate in 86.04% of the patients and intense in 13.96%. When present, in most cases it started either immediately or within 4 hours of treatment, and persisted between 1 hour and around 24 hours.

Erythema and dermatitis of the surrounding skin were either non-existent, slight or moderate in 94.5% of the patients.

Oedema was intense in 10 patients, but in the remaining 169 (94.41%) it was either slight or non-existent.

Necrosis of the normal skin around the lesion and haemorrhage was present



Fig. 3 - Demarcation between necrotic tissue and normal skin.

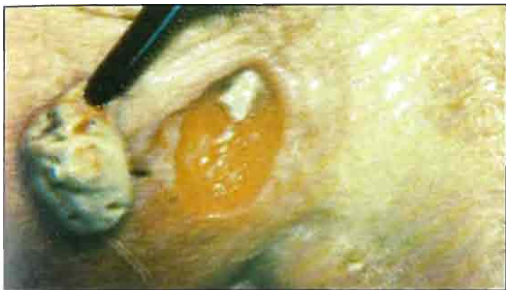


Fig. 4 - Removal of the necrotic tumour.



Fig. 5 - Clean and granulating wound, 4 days after removal of the tumour.



Fig. 6 - Clinically cured, 18 days after tumour removal.

in 7.3% of the patients only and was either superficial or slight.

The time of follow-up was: 5 years (112 patients); 6 years (53 patients); 7 years (4 patients); 8 years (2 patients); 9 years (2 patients); and 10 years (6 patients). So far no recurrences have been observed.

b) Squamous-cell carcinoma

The number of applications varied between 1 (15 patients) and 4 (3 patients), the average being 1.81.

The time for healing after the last application was 13 days in one patient and 35 in another, the average being 22.75 days.

The treatment lasted for 19 days (1 patient) and 58 days (1 patient) — average, 33.77 days.

In what concerns the cosmetic results,

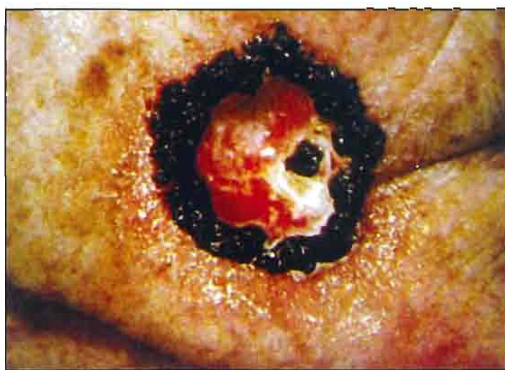


Fig. 7 - Second application, on the border of the ulceration and on a suspicious site.

87.75% of the patients had slight or moderate scars (Figs. 14-16).

The histological features — tumour necrosis, type of infiltration and scar tissue — were similar to those observed in the basal-cell carcinomas.



Fig. 8 - Necrotic basal-cell carcinoma 1 day after application of the paste.



Fig. 11 - Pigmented basal-cell carcinoma, before treatment.



Fig. 9 - 7 days after application.



Fig. 12 - Immediately after tumour removal.



Fig. 10 - Aspect of the scar.



Fig. 13 - Aspect of the scar.

Pain was either non-existent, slight or moderate in 77.73% of the patients. When present, it started immediately in almost all patients and persisted between 1 hour and 24 hours.

Erythema and dermatitis of the surrounding skin were non-existent to moderate in 91.67% of the patients.

Oedema was intense in 5 patients. In the remaining ones it was non-existent to moderate.

Necrosis of the normal skin around the lesion, dermatitis and haemorrhage were non-existent in all patients.

One patient felt slight nausea, vomiting and dizziness a few hours after treatment. All remaining patients had no general symptoms or signs.

The time of follow-up was: 5 years (20 patients); 6 years (2 patients); and 7 years (1 patient). So far, no recurrences have been observed.



Fig. 14 - Ulcerated squamous-cell carcinoma, before treatment.



Fig. 15 - Immediately after removal of the tumour.



Fig. 16 - Aspect of the scar.

COMMENT

The changes observed in the tumour cells are the result of the fixative action of zinc chloride. Along with fixation, it solubilises some cell components which may be important to the triggering of a systemic reaction which is suggested by the histology of the demarcating inflammation referred to above. Bearing in mind the strong caustic effect of zinc chloride, patients complaints of intense pain would seem natural. However,

reports on discomfort varied greatly and a significant number of patients did not even feel the need for the prescribed medication. Zinc chloride appears to have also a speeding action in the wound's healing process^{2,11}.

The small number of applications required (an average of less than 2 applications was sufficient), the simplicity of the technique, its efficiency (the cure rate is higher than that obtained by conventional surgery¹², radiation therapy¹³ and cryosurgery¹⁴ at the same time of follow-up), and the good cosmetic results are, in our opinion, the main advantages of our method.

Excluding some special cases (for which Mohs' technique seems preferable), such as: a) certain uncommon types — grade IV squamous-cell carcinoma, morphea-like and *ulcus rodens* types of basal-cell carcinoma; b) very invasive tumours conclusively proved either by their architecture or by the invasion of neighbouring tissues; c) persistently recurring tumours, particularly those previously treated by radiation — our simplified chemosurgical technique^{15,16} appears to be indicated to handle the great majority of skin epithelial malignancies.

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COMMENT

Four hundred and five skin cancers were treated by simplified chemosurgery, with the same protocol, but, at the date of the first publication (1986), only 212 had been followed for at least 5 years. So, only these were reported. This paper is now reprinted without alterations.

When I left the Portuguese Institute of Oncology, I had 193 other patients treated with the same method, but all of them had less than 5 years of follow-up. All were clinically cured except one whose cancer, on the external ear, persisted and was re-treated by conventional surgery. I was absolutely astonished with this cure rate, because it is not normally obtained with any method. Theoretically, I supposed that the 24-hour action of the paste could produce some immunological activity that could explain such a surprisingly high cure rate. When I started treating larger and advanced cancers, I verified the limitations of the method, as will be shown. One incon-

venience of the simplified chemosurgery was pain. It was intense in 13.96% and non-existent or moderate in the remaining patients, in whom it was managed with common analgesic drugs. I tried to improve the paste by adding powdered analgesics to it, without success. Only several years later, already working in Santarém, did I find two efficient solutions.

I would like to emphasise that this work was not, in any way, done against the genial Dr. Frederic Mohs, whom I consider a Master and whose work I profoundly admire. I have studied his book¹ with great interest, particularly in what concerned the thickness of paste that should be applied to fix an intended depth in millimetres of tissue. I adopted his recommendations and criteria, which correctness I was able to confirm.

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Chemosurgery without Systematised Microscopic Control of Advanced Cutaneous Cancer: I-Report of 9 Cases of Squamous-Cell Carcinoma

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Key Words. Chemosurgery. Simplified chemosurgical technique. Skin cancer. Squamous-cell carcinoma.

Abstract. Nine advanced cutaneous squamous-cell carcinomas were treated by the new method "Chemosurgery without Systematised Microscopic Control", which consists in the easy removal (with scalpel and/or scissors) of the necrotic masses resulting from the topical application of a zinc chloride paste.

Clinical cure, histologically confirmed, was obtained in all patients.

Introduction

Having established, in 1975 — with the co-operation of *Ascensão* — a chemosurgical protocol for the treatment of cutaneous tumours, and encouraged by the good results obtained¹⁻⁴, I started using the technique in varied neoplasms, particularly in cases for which the conventional therapeutic methods were inadequate. Accordingly, I modified the protocol to suit the various types of tumours.

The present report illustrates the efficacy of this chemosurgical technique in the treatment of advanced squamous-cell carcinomas of the skin.

Nine patients suffering from advanced skin cancer were treated. Only one patient had undergone previous treatment.

The tumours were measured and their thicknesses were clinically evaluated. At the time of examination, no adenopathies were palpable in any of the patients.

Method

A paste, containing 45% zinc chloride in a special vehicle* that slowly releases the salt for about 24 hours, was applied over the surface of the tumours. The thickness of the layer of paste varied according to the degree of penetration desired — the criterion was based on Mohs' indications in his authoritative book⁵. In order to prevent displacement of the paste, a plastic spray dressing was routinely applied over it, followed by a non-occlusive dressing.

Common analgesics were prescribed to be taken during the 24 hours following application of the paste.

After the paste was permitted to act for 20/24 hours, tissue fixation was achieved and the surface of the tumour became necrotic. Removal of the necro-

* Formula

Zinc chloride	45 g
<i>Sanguinaria canadensis</i>	10.8 g
<i>Alpinia officinarum</i>	7.2 g
Deionised water	q.s. 100 g
(European Patent n.º 0025649)	

tic tissues was easily carried out, with scalpel and/or scissors, 1 to 3 days after application of the paste. When all the necrotic mass was removed, another application was made and all steps were repeated until there were no clinical nor histological signs of persistence of neoplastic tissue. (Suspicious sites were always biopsied and, if cancer cells were present, another application of the paste would be made). At this stage, an ulceration with a clean base of granulation tissue was achieved. Its measurements were compared with those of the initial tumour, allowing for the required "safety margin" around and under it, as practiced with the conventional methods. Enlargement of the ulceration, if necessary, was achieved by applying further amounts of the paste where needed.

The entire procedure described does not require anaesthesia nor the use of an operating theatre.

The ulcerations healed by second intention between 3 and 6 weeks with good or acceptable cosmetic results.

Case Reports

Case 1—A 60-year-old caucasian man.

History: He had burned his right forearm as a child aged 10. Two years before examination, a moderate traumatic accident caused a small erosion of the burn scar, resulting in a fast growing tumour.

Examination: Protuberant, ulcerated and fungating tumour, measuring 50 × 40 × 17 mm, sur-

rounded by a burn scar (Fig. 1).

Histological examination: Grade II squamous-cell carcinoma.

Treatment and evolution: Three applications of the paste were made, over a period of 30 days. The final ulceration (Fig. 2) was entirely removed in order that a thorough histological examination be carried out — no neoplastic cells were present.

The patient died of an unrelated cause, 3 years after the chemosurgical treatment, without recurrence of the tumour.

Case 2—A 67-year-old caucasian woman.

History: She was epileptic and had suffered severe burning of the whole right side of the torso, during an attack, 30 years ago. She was mentally deficient and was unable to provide a history.

The tumour was unsuitable for conventional surgery due to its extension, the severe infection present and the restricted abduction of the arm.

Examination: Very thick, fungating and fetid tumour, measuring 150 × 70 mm, with an irregular and ulcerated surface, occupying the right axillary region and deeply infiltrating the surrounding tissues (Fig. 3). Abduction of the right arm was restricted due to retractile burn scar.

Histological examination: Grade II squamous-cell carcinoma.

Treatment and evolution: Seven applications of the paste were made over a period of 3 months. Six months after treatment, there were no signs of local recurrence (Fig. 4) but an axillary ganglion was detected. The patient was submitted to lymphadenectomy and, in order to permit abduction of the arm, plastic surgery was also performed and I requested excision of the chemosurgical scar for histological examination, which showed absence of cancer cells. The ganglion, however, revealed lymphatic metastases of squamous-cell carcinoma.



Fig. 1 - Before treatment (Case 1).



Fig. 2 - After eradication of the carcinoma.

The patient was followed up for 2 years, without recurrence, when she died during an epilepsy attack (drowned).

Case 3—A 65-year-old caucasian man.

History: He had suffered, for 3 years, from a varicose ulcer of the left leg. Five months prior to the examination, a nodule appeared in the ulcer; this was soon followed by many other nodules which spread over the internal aspect of the lower left leg.

The Department of Surgery of this Institute proposed amputation of the leg. The patient was referred to me and I decided to attempt and prevent mutilation.

Examination: Ulcerated tumour, with an irregular and whitish surface, measuring 190×150 mm (Fig. 5).

Histological examination: Grade II squamous-cell carcinoma.

Treatment and evolution: Seven applications of the paste were made over a period of 9 months. Clinical cure was achieved and amputation was avoided (Fig. 6).

The patient died, of a cerebrovascular disease, 10 months after the chemosurgical treatment, without recurrence of the tumour.

Case 4—A 78-year-old caucasian woman

History: She had had a tumour of the nose for 2 years. It started as a small ulceration which grew quickly during the year preceding examination.

Examination: Tumour with an ulcerated, red, shiny surface, measuring $45 \times 40 \times 23$ mm. There was perforation of the right ala (Fig. 7).

Conventional surgery would be very mutilating.

Histological examination: Grade III squamous-cell carcinoma.

Treatment and evolution: Two applications of the paste were made, with 2 days interval. Clinical cure was achieved with a moderate deformity (Fig. 8).

The patient was followed up regularly for 5 years without recurrence.

Case 5—A 77-year-old caucasian woman.

History: Four years previously, a nodule appeared, on the extremity of the nose, which quickly increased in size and developed a central ulceration. The patient was submitted to 3 cryosurgery treatments, over a period of 9 months, without success in eradicating the carcinoma. The last cryosurgery was followed by an explosive and very invasive growth of the tumour.

Examination (5 weeks after 3rd cryosurgery): The extremity of the nose had been destroyed. On what was left of the nasal septum, there was a fungating tumour measuring 40×30 mm, with an irregular surface, expanding to the lateral sides of the nose, with a deep infiltration — regrettably, the photograph taken before chemosurgery was damaged in processing (Fig. 9).

Histological examination: Grade III squamous-cell carcinoma.

Treatment and evolution: A thick layer of the paste was applied. Four days later, the fixed tissue was removed and a new application of the paste was made. The same procedure was carried out the following day. Five days later a 4th application was made and the remaining fixed masses were removed the following day. The tumour was entirely removed in 10 days. Fig. 10 illustrates the resulting scar.

The patient was followed up for 15 months, after which period she died of heart disease without recurrence of the tumour.



Fig. 3 - Before treatment (Case 2).



Fig. 4 - Clinically cured.



Fig. 5 - Before treatment (Case 3).



Fig. 6 - After eradication of the tumour (Case 3).



Fig. 7 - Before treatment (Case 4).



Fig. 8 - Clinically cured (Case 4).



Fig. 9 - 5 weeks before treatment (immediately before the 3rd cryosurgery - case 5).



Fig. 10 - Clinically cured (Case 5).

Case 6—An 86-year-old caucasian woman.

History: An ulceration appeared on the right cheek but, for two and a half years, she did not notice a significant change. Six months prior to the examination, there was rapid growth and frequent bleeding.

The patient could not undergo conventional surgery due to her advanced age and poor general condition.

Examination: Protuberant, fungating and ulcerated tumour, measuring 45×35×25 mm, par-

tially covered by haemorrhagic crust (Fig. 11).

Histological examination: Grade IV squamous-cell carcinoma.

Treatment and evolution: Over the period of 8 days, 3 applications of the paste were made, the last of which only on the contour of the lesion. The ulceration healed with a surgical-like scar (Fig. 12).

The patient was examined 2 weeks ago (3 years after chemosurgery) and has no signs of recurrence. The scar is now moderate and very small.



Fig. 11 - Before treatment (Case 6).



Fig. 12 - Clinically cured.

Case 7—A 74-year-old caucasian man.

History: Thirteen years previously he had been examined at this Institute. He then had numerous solar keratoses on the face. He did not follow the suggested treatment and only came back 11 years later. On the right zygomatic region, he had an ulcerated tumour measuring 20 mm in diameter. He refused the proposed surgery and returned to the Institute 2 years later, when the tumour was no longer suitable for conventional surgery.

Examination: Ulcerated fungating tumour, with an irregular and whitish surface and a well defined contour. The lesion measured $90 \times 55 \times 25$ mm, and went from the right zygomatic region to the external ear and invaded the external auditory meatus (Fig. 13).

Histological examination: Grade IV squamous-cell carcinoma.

Treatment and evolution: Eleven applications of the paste were made, over a period of 7 months. The patient did not keep his appointments regularly; after removal of the superficial layers of the carcinoma, he interrupted the treatment for 2 months. When he returned, the

tumour had enlarged towards the cheek and completely obstructed the external auditory meatus (Fig. 14). Treatment was resumed but always on an irregular basis. The most difficult part of the treatment was the eradication of the tumour invading the external auditory meatus.

Paralysis of the lower branches of the facial nerve occurred after treatment. A tomographic study of the mandible and temporal bone articulation did not reveal any abnormality.

Clinical cure was achieved 7 months after beginning of the chemosurgical treatment (Fig. 15).

The patient has been followed up with surprising assiduity for 4 years, without signs of recurrence.

Case 8—An albino negro man, aged 30, who is mentally deficient and was unable to provide a history.

Examination: Ulcerated, fungating and fetid tumour of the left cheek, partially necrotic, with raised border and irregular surface. It measured $90 \times 60 \times 35$ mm and was unsuitable for conventional surgery (Fig. 16).

Histological examination: Grade IV squamous-cell carcinoma.

Treatment and evolution: The patient was hospitalised for the duration of the treatment. Six applications of the paste were made over a period of 2 months (Figs. 17 and 18). Due to the patient's extreme sensitivity, the analgesics administered after each application were stronger than those routinely prescribed.

The large ulceration healed by second intention (Fig. 19).

The patient has been closely followed up for 5 and a half years, without recurrence. Many actinic keratoses and small independent tumours, which keep appearing on his face and forearms, have been treated by cryosurgery.

Case 9—A 69-year-old caucasian woman.

History: Over the past 30 years, several epidermal cysts were present on the scalp and received no treatment. Two years prior to the examination, one of the cysts enlarged and ulcerated.

The patient was referred to me by the Department of Surgery of this Institute.

Examination: Very protuberant, ulcerated and fetid tumour, with an irregular whitish surface, measuring $120 \times 100 \times 75$ mm. A yellow liquid dripped from inside the carcinoma (Fig. 20).

Histological examination: Grade I invasive squamous-cell carcinoma.



Fig. 13 - Before treatment (Case 7).



Fig. 14 - During treatment.



Fig. 15 - Clinically cured.

Treatment and evolution: Over a period of 4 weeks (the first 2 under hospitalisation) 6 applications of the paste were made (Fig. 21). When removing fixed material, after the 3rd application, I opened a cystic cavity which walls were infiltrated by the squamous-cell carcinoma (confirmed by histological examination).

Clinical cure was achieved in February 1986 — a final photograph is not yet available.

Comment

Excepting case 1, all patients presented difficult therapeutic problems. That case was the first advanced squamous-cell carcinoma selected for treatment by the new chemosurgical technique without systematised microscopic control because, from my previous experience, I could anticipate that, after complete removal of the tumoural mass, the resulting ulceration could be entirely excised with scalped, for thorough histological examination. That operation was effected and the histological diagnosis confirmed the complete eradication of the carcinoma. This encouraged me to persevere in my attempts to treat advanced cutaneous cancer.

Also excepting case 1, none of the patients could have been treated by conventional surgery, nor, in my opinion, would radiation therapy have been helpful, for I have not seen good results with such large, thick and irregular tumours. Cryosurgery might have been useful in some cases, but hospitalisation and general anaesthesia would have been indispensable.

Due to the large number of patients treated at this Institute, there is a constant shortage of beds and hospitalisation is subject to a waiting list. Obviously, the patients in the present series could not afford to wait several weeks, and the fact that this chemosurgical technique can be performed on an out-patient basis was another important factor. Only one patient (Case 8) was hospitalised for the duration of his treatment, and another (Case 9) for the first 2 weeks.

Only one patient (Case 5) had received previous treatment. This patient presented a very serious and uncommon situation: a cancer which, following an

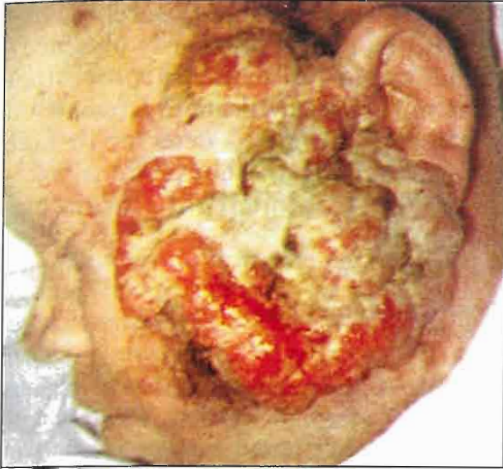


Fig. 16 - Before treatment (Case 8).



Fig. 18 - After complete removal of the cancer.



Fig. 17 - After partial removal of the tumour.



Fig. 19 - Clinically cured.

aggressive but ineffective cryosurgery, became acutely invasive. When this occurs, further conventional surgery is no longer appropriate, for it will hasten the terrible evolution of the disease which, almost inevitably, will cause death.

My aim was to perform the treatment within the shortest possible time, and I succeeded in eradicating the carcinoma in 10 days. I am convinced that, if total eradication had not been achieved, the

explosive development of this cancer, at such an aggressive phase, would have continued. The patient died 15 months after chemosurgery, of heart disease, without recurrence of the tumour.

All ulcerations resulting from the chemosurgical treatment healed by second intention and no plastic correction was carried out in any patient.

The results of treatment were excellent. Only Case 9, being very recent, lacks adequate follow up, but I trust it



Fig. 20 - Before treatment (Case 9).



Fig. 21 - During treatment (Case 9).

will confirm the clinical cure.

Of the 4 patients (Cases 1, 2, 3 and 5) who died of unrelated causes, Case 3 provided the shortest follow up — only 6 months — but, still, clinical cure was achieved and it was very gratifying to have prevented amputation of the patient's leg. None of the 4 patients had any signs of recurrence up to the time of their deaths (Case 5 — 15 months; Case 2 — 2 years; Case 1 — 3 years).

The remaining patients (Cases 4, 6, 7 and 8) have follow up ranging from 3 to 5 and a half years.

Cure of such advanced cancers corroborates the results previously obtained¹⁻⁴ and should, conclusively prove that "Chemosurgery without Systematised Microscopic Control" deserves to take its place among the conventional methods for treatment of cutaneous malignancies⁶.

Acknowledgments

I wish to express my thanks to Dr. Simões Raposo for reviewing histology slides, and to Miss L. D. Rebelo for her valuable assistance in the compilation of the case reports data and in considerably improving my English writing.

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COMMENT

After having established the technique for small tumours, I began treating larger ones and, soon after, advanced cases and even others that were considered unsuitable for treatment with the techniques then available.

I would like to draw the attention of my readers (if any...) to some particularly serious cases. The normal treatment of Case 3, a squamous cell carcinoma of the leg, measuring 190mmx150mm, would be amputation; simplified chemosurgery prevented that radical option. The follow-up was short because the patient died of cerebrovascular disease, 6 months after treatment, without recurrence of the tumour.

The patient described in Case 5 was a sweet 77-year-old lady. She came to the Institute irregularly for cryosurgery, during 9 months, and was submitted to three treatments, without success. The third procedure provoked a very invasive and expanding cancer, probably due to metaplastic transformation. Due to the urgency of the situation, a biopsy was not done and an aggressive treatment with the ZnCl paste was performed in five successive days. The carcinoma was completely removed. I'm sure that the result was superior to and shorter than radiotherapy.

Case 7 was a very serious challenge because the carcinoma invaded the external ear. I recall applying the paste inside

the ear canal, carefully removing the necrotic tissue and cautiously applying another layer of the paste. The patient was cured and followed for 15 years, without recurrence.

I accepted to treat Case 8 because there was no other available treatment for such an advanced cancer, where more than half of the left hemi-face was attained. Actually, I had limited hope of achieving a cure. During two months, I performed six successive treatments and went on destroying the thick carcinoma with heroic sufferance of the patient. The analgesic drugs, in this location, were of limited help. I was surprised by the unexpected cure. Fortunately there were no metastases. I followed him for 14 years, without recurrence, until he was murdered in some nightlife brawl. I don't know of any other existing treatment – then or now – that could cure such an advanced cancer.

Before treating Case 9, I asked the surgeons from the Head and Neck Department, who had referred the patient to me, if they could reduce the tumoural mass, which they refused to do. Clinical cure was achieved with 6 applications of the ZnCl paste. The patient refused to come for the regular follow-up visits, but, at my request, she sent me a Christmas card, every year and I could follow her, at a distance, for six years, without recurrence.

Chemosurgery without Systematised Microscopic Control of Advanced Cutaneous Cancer: II Report of 2 Cases of Invasive Squamous-cell Carcinoma of the Hand

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Key Words. Chemosurgery. Simplified chemosurgical technique. Invasive cancer of the hand. Squamous-cell carcinoma.

Abstract. Two advanced and very invasive squamous-cell carcinomas of the hand were treated by Chemosurgery without Systematised Microscopic Control. Both tumours deeply invaded the structures between the metacarpals and, in both cases, amputation by the forearm had been proposed.

Cure was achieved. In each case, 2 fingers were irrecoverable and their amputation was carried out by the same chemosurgical technique. The perserved fingers remained functional.

The Simplified Chemosurgical Technique recently published¹ has — after suitable modification of the protocol — been used to treat advanced cutaneous cancers with equally successful results².

Two advanced and very invasive squamous-cell carcinomas of the hand — in both cases, amputation by the forearm had been proposed — were treated by that simplified chemosurgical method and are, herein, reported.

Case Reports

Case 1 (Summarily described in a previous paper³).

A 74-year-old caucasian man.

When he was first examined, he had 2 fungating and ulcerated tumours on the dorsum of the left hand, with 6 months evolution. The smaller lesion, over the base of the first and second metacarpals, measured 33 mm in diameter and was not adherent to the underlying tissues. The larger one, over the heads of the second and third metacarpals, measured 46 mm in diameter and deeply invaded the underlying structures, causing considerable oedema of the second and third fingers (Fig. 1).

The histological diagnosis⁴ was Grade II squamous-cell carcinoma.

The Department of Surgery had proposed amputation by the forearm and the patient was referred to me, considering that I was gathering a series of patients for a programme on cryosurgery of advanced cancer of the extremities³.

I performed cryosurgery on both lesions, under general anaesthesia. The smaller one cured easily with one session, following the technique devised for that series³. The larger tumour underwent 3 cryosurgery treatments, at temperatures as low as $\approx 80^{\circ}\text{C}$, but the cancer kept recurring between the metacarpals.

The Surgeon who initially had recommended amputation, insisted that it be carried out.

At this stage, I decided to treat the persisting carcinoma by the Simplified Chemosurgical Technique², in a final attempt to save part of the patient's hand although it was obvious that the index and the middle fingers were invaded beyond recovery.

The zinc chloride paste* was applied on the cancer and at the base of the 2 fingers. In the

* Formula

Zinc chloride	45 g
<i>Sanguinaria canadensis</i>	10.8 g
<i>Alpina officinarum</i>	7.2 g
Deionised water q.s.	100 g

(European Patent n.º 0025649)

Kindly supplied by Orewa Pharmaceuticals, Inc.



Fig. 1 - Before treatment (Case 1).



Fig. 2 - Finger amputation, 12 days after beginning of treatment.

following days, the necrotic tissue was removed with scissors and/or scalpel until a raw surface was obtained. A layer of paste was applied to that surface. Inasmuch as the zinc chloride paste does not easily penetrate intact palmar skin, I carried out a superficial contact probe cryosurgery to provoke a bulla on that area. On the following day the epidermis over the bulla was removed and the zinc chloride paste was applied to the palmar aspect of both fingers and to their base. In this way, the carcinoma and invaded fingers were being fought from both aspects.

When complete necrosis of both fingers was achieved, they were removed with scissors, without any pain or need for anaesthesia or analgesia (Fig. 2). After elimination of all the necrotic masses, granulation tissue developed. Throughout the treatment, many biopsies were carried out on suspicious sites, but all the histological diagnoses were negative.

A total of 4 applications of the zinc chloride paste were made. Oral analgesics were prescribed to be taken during the 24 hours following each application. The patient endured the treatment with the utmost courage and interest.

The ulceration healed by second intention 20



Fig. 3 - Two and a half months after cure.



Fig. 4 - Same day, holding a sheet of paper.

days after removal of the 2 fingers.

In the meantime, an axillary metastasis had developed and was surgically excised 2 weeks after healing of the hand. The patient was, also, submitted to physiotherapy.

The remaining fingers maintained their mobility and function (Figs. 3 and 4).

The patient died 17 months later, of an unrelated cause, without recurrence of the tumour.

Case 2

An 81-year-old caucasian woman.

The patient could not provide a reliable history and was inconsistent even as to the probable time of evolution of the tumour. She had not received any previous treatment.

On examination, she had an enormous tumour — 115×72 mm — on the dorsum of the right hand spreading over the first and part of the second phalanges of the middle finger and over the base of the index. The cancer deeply invaded the underlying structures around the third and fourth metacarpals. The surface was irregular, well-defined, bright red and granuloma-like, but



Fig. 5 - Before treatment (Case 2).



Fig. 6 - Palmer aspect of the hand, 10 days after beginning of treatment.

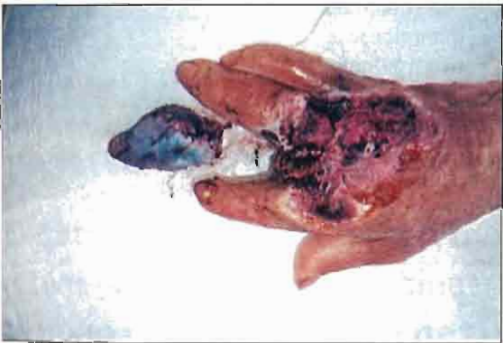


Fig. 7 - Same day, after amputation (Case 2).

not regenerating (Fig. 5).

The histological diagnosis⁴ was Grade IV squamous-cell carcinoma.

The patient was referred to me when the Department of Surgery proposed amputation by the forearm. Due to the deepness of the invasion, I did not think that Cryosurgery was indicated in

this case, and decided to attempt saving, at least, part of the hand by the same Simplified Chemosurgical Technique².

The zinc chloride paste was applied following a similar procedure to that in Case 1, including the superficial contact probe cryosurgery to facilitate the action of the paste in the palmar aspect of the hand.

When necrosis of the middle finger was achieved (Fig. 6), it was removed with scissors without any pain or need for anaesthesia or analgesia (Fig. 7).

More zinc chloride paste was applied until the third and fourth metacarpals could be removed as, inevitably, was the ring finger.

All the biopsies carried out after removal of the tumoural masses confirmed the absence of neoplastic cells.

A total of 7 applications of the paste were made. Oral analgesics were prescribed to be taken during the 24 hours following each application.

Healing by second intention took longer in this case — 5 weeks after removal of the fingers.

The patient underwent physiotherapy and recovered mobility and function of the remaining fingers (Figs. 8 and 9).

She was treated in December 1985 and, to date, has had no recurrence of the tumour.

Comment

The 2 cases herein reported do not, in my opinion, require a lengthy discussion.

To have been able to actually prevent severe mutilation in these 2 patients, even at the cost of 2 fingers, was a most rewarding experience. The fact that it was achieved with a technique which does not require costly or sophisticated equipment nor highly trained medical staff, but, in reality, can be carried out in any modest hospital in any remote part of the globe, seems to make it a particularly advantageous method.

Acknowledgments

I would like to thank Ms. Lila Rebelo



Fig. 8 and 9 - Cured (Case 2).

for her continual and valuable assistance, especially in reviewing my manuscripts and their English versions.

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COMMENT

This paper shows the chemosurgical treatment of two advanced cancers of two hands for which amputation was (apparently) the

only therapeutic option. In both cases, the hands were partially preserved, with amputation of only two fingers each.

Chemomastectomy for Advanced Cancer

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Key Words. Chemomastectomy. Simplified chemosurgical technique. Breast cancer.

Abstract. Fifteen women suffering from advanced breast cancer were treated by Chemomastectomy.

All tumours were inoperable by conventional surgery and could not be treated by the usual therapeutic methods.

The chemosurgical technique is described.

Clinical cure was obtained in one third of the patients and local eradication of the carcinoma was achieved in a total of 12 patients.

Advanced cancer of the breast is extremely distressing, mostly due to the realisation of the irreversible deterioration and, not seldom, of the proximity of the terminal phase of the disease. Added to the terrible discomfort and suffering is the fact that the patient feels inexorably impaired in her femininity and, often, even in her human condition as can be the case when, necrosis having occurred, the resulting nauseating stench becomes unendurable to relatives and friends.

Advanced breast cancer patients fall into two categories: those who sought medical attention, at some stage of their disease, but whose treatments were not successful, and those who, for various reasons, refuse to undergo any treatment until their condition has deteriorated to the extreme. The main causes for the odd behaviour of the latter group appear to derive from ignorance. Frequently, the patient does not realise the true nature of her disease and seeks medical advice only when it is already too late. Also, a common concept among people of a lower cultural stan-

dard is that "cancer gets worse once it starts being handled"; these people tend to infer their reasoning from the exception rather than from the rule — the rare cases of tumours that grow worse with the beginning of treatment are the impressive examples which will influence those particular people and, when faced with the fact that they have cancer, they refuse to be treated at an early stage of their disease when cure might still be feasible.

Generally, when a carcinoma of the breast is too advanced for conventional surgery, the treatments administered are radiation, hormonotherapy and chemotherapy, although they seldom can control the evolution of the tumour.

The treatment of extensive and advanced external tumours has, for many years, played a predominant part in my work¹⁻⁵. In 1975, I devised a cryosurgical technique to treat advanced breast cancer⁶. Four years later, a 67-year-old patient was referred to me with a recurrent adenocarcinoma (Fig. 1). She had undergone radical mastectomy by conventional surgery 23 years pre-

viously. Three years after that, the tumour recurred and radiation was administered. The cancer persisted and, over the subsequent years, the patient was submitted to further radiation treatments, as well as to hormonotherapy and chemotherapy. Eventually, she no longer responded to the two latter types of treatment and could tolerate no more radiation. At this stage, I was asked to perform cryosurgery. However, since there was invasion of the thoracic wall, I decided to attempt treatment with the simplified chemosurgical technique (chemosurgery without systematised microscopic control)⁷⁻⁹. The results, which were surprisingly good, encouraged me to develop a protocol suitable for very advanced carcinomas of the breast. This was satisfactorily achieved 2 years later when I performed the first Chemomastectomy (Figs. 1-4).

The present paper refers my experience with the first 15 cases.

Material and Method

Fifteen women suffering from advanced breast cancer were submitted to Chemomastectomy or treated by the simplified chemosurgical technique, as was the case with the recurrences post-mastectomy by conventional surgery.



Fig. 1 - Recurrence of invasive ductal carcinoma, before chemosurgery.



Fig. 2 - Application of the zinc chloride paste.



Fig. 3 - After removal of the fixed tissue.



Fig. 4 - After healing (this was the first patient of the present series).

All the patients were referred to me by this Institute's Department of Surgery, after having been considered unsuitable either for conventional surgery or for any of the usual therapeutic methods. In all cases, the prognosis was extremely unfavourable and the treatment was attempted palliatively.

The age of the patients ranged between 38 and 71 (median age of 57.4 — Table I).

The duration of the disease varied from 1 year (2 patients) to 23 years (1 patient — Table II).

The histological classification of the tumours was: 8 invasive ductal carcinomas; 1 medullary carcinoma; 1 mixoid liposarcoma; 1 malignant cystosarcoma phyllodes; 1 squamous-cell carcinoma; 3 non-specified carcinomas.

Five tumours were primary; 5 were recurrent after mastectomy by conventional surgery; and 5 had persisted after the administered treatments. Table III indicates the treatments the patients underwent prior to the Chemomastectomy.

The primary cancers invaded the entire breast and were massive and fungating or with large ulcerations (Figs. 5 and 6); the recurrent tumours post-mastectomy by conventio-

nal surgery were nodular and ulcerated (Figs. 1, 7 - 9) and measured from 5 cm to 13 cm in diameter; the persistent ones consisted of cirrhotic breasts with ulcerations measuring over 10 cm in diame-

TABLE II

Duration of Disease	
Duration of disease (years)	No. of patients
1	2
2	4
3	2
4	3
5	2
12	1
23	1
Total	15

TABLE III

Previous Treatments	
Treatment	No. of patients
None	5
Mastectomy by conventional surgery	1
Mastectomy by conventional surgery + Radiations + Chemotherapy + Hormonotherapy	1
Mastectomy by conventional surgery + Radiations + Surgical excision of recurrence (twice) + Chemotherapy	1
Mastectomy by conventional surgery + Radiations + Surgical excision of recurrence (twice) + Axillary lymphadenectomy	1
Mastectomy by conventional surgery + Radiations + Ovariectomy + Chemotherapy	1
Radiations	3
Radiations + Chemotherapy + Hormonotherapy	1
Radiations + Radiogenic castration + Chemotherapy	1
Total	15

TABLE I

Age of Patients	
Age (years)	No. of patients
30-39	1
40-49	2
50-59	6
60-69	4
70-79	2
Total	15

38 — 1 patient

71 — 1 patient

\bar{x} = 57.4



Fig. 5 - Primary invasive ductal carcinoma, with 3 years evolution, before chemomastectomy. Small cutaneous metastases are noticeable.



Fig. 6 - Primary squamous-cell carcinoma, with one year evolution, before chemomastectomy.

ter, with one exception — 4 cm — (Figs. 10-12).

In 10 patients, there was involvement of other structures, as follows:

Invasion of the thoracic wall	3 patients
Invasion of the thoracic wall and generalised bone metastases	1 patient
Axillary metastases	1 patient
Axillary and bone metastases	1 patient
Axillary, lung and bone metastases	1 patient
Lung and bone metastases	1 patient
Generalised bone metastases	2 patients

A paste containing 45% zinc chloride — in a special vehicle* that slowly releases the salt for about 20 hours — is

* Formula

Zinc chloride	45 g
<i>Sanguinaria canadensis</i>	10.8 g
<i>Alpina officinarum</i>	7.2 g
Deionised water	q.s. 100 g
(European Patent n.º 0025649)	

Kindly supplied by Orewa Pharmaceuticals, Inc

applied to the tumour, in thick layers, preferably over ulcerated areas, followed by non-occlusive dressing.

No anaesthesia is required, but analgesics are prescribed to be taken during the 24 hours following each application of the paste.

On the subsequent days, the fixed tissue is removed with scalpel and/or scissors — also with no need for anaesthesia — until neoplastic tissue is, repeated as many times as necessary until complete excision of the tumour is achieved. Since the paste is an excellent fixative, any material removed can be immediately processed histologically without further fixation.

When nearing the thoracic wall, the paste must be applied in very thin layers and the utmost care must be taken in removing the necrotic material.

When all the macroscopic tumour is removed, multiple biopsies are carried out in the resulting ulceration and, if cancer cells are found, another application of the paste must be made on that site. Subsequently, if there should be a recurrence or appearance of cutaneous metastases, the treatment should be repeated, whenever feasible.



Fig. 7 - Recurrent invasive ductal carcinoma, before chemosurgery.



Fig. 10 - Persistent invasive ductal carcinoma, before chemomastectomy.



Fig. 8 - During treatment.



Fig. 11 - Persistent invasive ductal carcinoma, before chemomastectomy.



Fig. 9 - After healing.



Fig. 12 - Persistent non-specified carcinoma, before chemomastectomy.

The entire procedure described does not require the use of an operating theatre. The patient, however, should be hospitalised.

In order to perform a complete Chemomastectomy, 10 applications of the zinc chloride paste, on average, are necessary, over a period of 4 to 8 weeks — depending on the dimensions, architecture and histologic characteristics of the tumour.

The penetration of the paste is more difficult in fibrous tumours and in those which have fibrosis due to radiation treatments.

After tumour eradication, healing by second intention occurs between 5 and 15 weeks, depending on the extension of



Fig. 13 - Primary myxoid liposarcoma, with 4 years evolution, before chemomastectomy. The patient had severe anaemia



Fig. 14 - Five days after the first application of the zinc chloride paste.



Fig. 15 - Fixed tissue.



Fig. 16 - Clean ulceration after completion of chemomastectomy.



Fig. 17 - Two years after chemomastectomy.



Fig. 18 - Primary cystosarcoma phyllodes, with 12 years evolution, before chemomastectomy. The patient was severely anaemic due to daily haemorrhages.



Fig. 21 -Easy removal of the last layer of necrotic tissue.



Fig. 19 - The zinc chloride paste was predominantly applied on the base of the tumour.



Fig. 22 -An almost clean ulceration.



Fig. 20 - Cutting the peduncle of the tumour completely fixed by the zinc chloride paste.



Fig. 23 - Clinically cured, 3 months after chemomastectomy.

TABLE IV
Treatments Subsequent to Chemomastectomy and Evolution

Type of treatment	No. of patients	Alive with no evidence of disease	Alive with control of disease	Alive with generalised metastases but no local recurrence	Deceased of unrelated causes without local recurrence	Deceased due to metastatic condition, without local recurrence	Deceased, no eradication of tumour
None	5:	1 (3 yrs)	—	—	—	1 (10 mo) 1 (17 mo)	1 (4 mo) 1 (13 mo)
Free skin graft	1	1 (3 yrs)	—	—	—	—	—
Surgical removal of part of the tumour from under the pectoralis major	1	1 (5 yrs)	—	—	—	—	—
Simplified chemosurgery on local recurrences	1	—	1 (7 yrs)	—	—	—	—
Hormonotherapy	2:	—	—	—	—	1 (9 mo) 1 (3 yrs)	—
Chemotherapy	4:	1 (2 yrs)	—	1 (1 yr) 1 (2 yrs)	—	—	1 (6 mo)
Radiation	1:	—	—	—	1 (3 yrs)	—	—
TOTAL	15	4	1	2	1	4	3

the tumour and on the previous treatments — radiations, for instance, considerably delay healing.

Results

Excepting one case, all ulcerations healed by second intention. The exception was one patient whose tumour had persisted post radiation and, after Chemomastectomy, a free skin graft was performed to facilitate healing.

Table IV indicates the treatments subsequent to Chemomastectomy and the evolution of the patients.

Only in 3 patients did the treatment fail to achieve local eradication of the cancer — their survival times were 4, 6 and 13 months.

Four patients died as a result of their metastatic condition, without local recurrence of the tumours, with survivals ranging from 9 months to 3 years.

Two patients (both recurrences post mastectomy by conventional surgery) are at present — 1 and 2 years after treatment, respectively — in poor health, due to their metastatic condition, but they do not have local recurrence.

One patient died of unrelated causes, 3 years after Chemomastectomy, without recurrence or evidence of the disease.

In one patient (the first of the present series — Figs. 1-4), the consecutive recurrences — one every year, on average — have been treated with topical applications of the zinc chloride paste. This simplified chemosurgical technique has provided control of the disease over the period of 7 years — since the first treatment — during which the patient has led a normal life, carrying out her regular chores and daily activities.

One other patient (Figs. 13-17), had a

recurrence which was also partly treated with the zinc chloride paste; part of the tumour, which spread under the pectoralis major, was surgically removed. Her follow-up was 5 years.

The remaining 3 patients have follow-ups of 2 years (1 patient) and 3 years (2 patients). They have been examined recently and have no recurrence nor evidence of the disease.

Comment

All the carcinomas in the present series were inoperable by conventional surgery, and the currently used treatment methods could not provide control of the disease.

In view of the far advanced stage of the cancers, unless control of the malignancy was achieved and an attempt at drastically reducing the chance of disseminating malignant emboli was made, the life expectancy of these patients was very short and, assuredly, of great sufferance.

The presence of inoperable metastases in 9 patients rendered their biological cure impossible.

Inasmuch as Chemomastectomy was devised as a palliative treatment for very advanced, inoperable cancer, the results far exceeded my expectations. Even the 3 patients in whom the tumours persisted, benefited considerably from the treatment, insofar as they felt they were being looked after, they experienced relief and considerable improvement in their condition after removal of the tumoural mass, and they did not lose hope.

But the most gratifying surprise of this study was having achieved clinical cure in one third of the cases (one patient died, of unrelated causes, with 3 years' survival; 4 patients are alive with



Fig. 24 - Primary medullary carcinoma, with 2 years evolution, before chemomastectomy.



Fig. 25 - Removal of necrotic tissue after the 4th application of the zinc chloride paste.



Fig. 26 - Clean ulceration.



Fig. 27 - Two months after chemomastectomy, surgical-like scar by second intention.

follow-ups between 2 and 5 years). Although in these 5 patients distant metastases were not detected, the macroscopic (Figs. 5, 7, 12, 13 and 24) and histologic features of their tumours could not let me expect such excellent results.

In a previous report⁶, I described another technique devised for advanced breast cancer — Cryomastectomy — with which 10 patients were treated. It would be interesting to compare the relative values of both techniques. However, the number of patients treated in both these series is, for the time being, not statistically significant.

The current criteria for selecting either method are based on:

- tumour's histologic type (very fibrous lesions are unsuitable for Cryomastectomy, due to their resistance to freezing);
- patient's age and general condition (Chemomastectomy, not requiring general anaesthesia, is performable even in ladies of very advanced age or poor general health);
- access to hospitalisation and/or operating theatre (12 out of the 15 patients in the present series, for instance, were able to start treatment on an out-patient basis while

awaiting a vacancy for admittance to the Institute).

Therapeutics research is a school of humility: one is always preceded by somebody else. When nearing the conclusion of this article, I came across a case report of *Sonneland*¹⁰ concerning the successful treatment of one patient with breast carcinoma, also using a zinc chloride fixative with a procedure not unlike mine, but followed by a skin graft.

*Luca et al.*¹¹ treated a cystosarcoma phyllodes of the breast by conventional surgery. The cancer recurred 2 weeks later and "within a few more days the tumour attained the size previous to surgery. Four months later the patient died".

The general outcome of the present series — local eradication of the carcinoma in 12 out of 15 patients — proves that the described chemosurgical technique is not only executable in cases of far advanced breast cancer (primary or recurrent), but can produce very good results and even clinical cure. Moreover, by eliminating, or drastically reducing, the tumoural mass, this method widens the possibilities of adjuvant chemotherapy.

Figures 1 to 27 illustrate some cases of advanced cancer of the breast treated by Chemomastectomy.

Acknowledgment

I wish to express my gratitude to the Surgeons of the Portuguese Institute of Oncology who referred the patients in the present series to me; to Dr. Jorge Soares, Chief of Pathology of the same Institute, for reviewing histology slides; and to Ms. Lila Rebelo, for her dedication in com-

pling the patients' data and for her assistance in the preparation of the manuscript and its final English version.

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COMMENT

Fortunately, there are nowadays several good treatment modalities to deal with breast cancer, and locally advanced and uncontrollable cancer is an infrequent presentation. I saw many such cases that were neglected until they became inoperable and resistant to chemotherapy and radiotherapy. I developed a chemosurgical method and a personal protocol of cryosurgery to treat advanced breast cancer, and the selection criterion between the two was: patients who could stand general anaesthesia were treated by cryomastectomy, and those who could not underwent chemomastectomy.

The more difficult and dramatic case I treated was that of a patient with an enor-

mous myxoid liposarcoma. She was emaciated and severely anaemic; the tumour was continuously oozing haematic serum and her haemoglobin count was 4g/100ml. She was dying and obviously could not stand anaesthesia. I recall that the first applications were carried out on the isthmus of the tumour. Within a few days, the distal part of the tumoural mass fell down and the oozing and offensive smell were stopped. The patient was given blood transfusions and recovered fairly quickly. Some months after local cure was achieved, there was a recurrence under the pectoralis major that was surgically removed. She was alive and without signs or symptoms of recurrence 5 years after treatment.

Chemosurgery without Systematised Microscopic Control of Advanced Cutaneous Cancer: III — Report of a Case of Inguinal Metastasis of Malignant Melanoma

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Key Words. Chemosurgery. Simplified chemosurgical technique. Malignant melanoma.

Abstract. A case of Stage IV malignant melanoma is described.

The patient was treated by chemosurgery without systematised microscopic control followed by adjuvant chemotherapy. She has been regularly followed-up for 12 years, without signs of recurrence or other metastases.

The incidence of primary malignant melanoma of the skin has been increasing dramatically and so has its mortality rate¹⁻³. In some countries, the incidence has been reported to double about every decade^{2,4,5}. Moreover, there is a trend toward younger age incidence every year¹.

Although the relationship of malignant melanoma with actinic radiation is not clearly established, epidemiologic studies strongly suggest that prolonged sun exposure may be a determinant factor in this type of tumour⁵⁻⁷.

The prognosis of malignant melanoma is based mainly on the clinico-histological type, Clark's level, Breslow's thickness and mitotic activity of the primary tumour, characteristics of nodal involvement and distant metastases^{5,7-11}. The presence of metastatic lymph nodes considerably aggravates the prognosis — the 10-year survival rate of patients with histologically positive lymph nodes is one third to half of those with histologically negative nodes^{5,7-10}.

It has been reported that larger tumour volume is related to poorer prognosis^{8,10} and the existent therapeutic methods do not provide survival prospects for patients with fixed, metastatic melanoma measuring over 5 cm^{4,5,10,11}.

The purpose of the present paper is to report the successful treatment of one such case.

Case Report

A 42-year-old caucasian woman.

History: The patient had had, for some years, a "pigmented naevus", on the left leg, which increased in size, forming fissures. Four years prior to examination the lesion was excised — at a small country hospital — but not histologically examined. Two and a half years later, the patient noticed the appearance of a pigmented nodule, on the left inguinal region, with subsequent rapid growth.

The patient complained of intense pain and total incapacity for walking.

Examination: On the left inguinal region, there was a large, hemispheric, pigmented nodule (Fig. 1) with erythema, measuring 11 cm × 9 cm × 6 cm, adherent to the deep tissues, diagnosed as



Fig. 1 - Inguinal metastasis of malignant melanoma before treatment.

a Stage IV (TNM staging system) malignant melanoma).

There was no clinical evidence of the existence of other metastases.

Histological examination revealed metastasis of malignant melanoma.

Treatment and evolution: Due to the anatomic involvement and location of the lesion, the patient was referred to me with the request that I reduce the tumoural mass, in order that she may become somewhat more susceptible to respond to chemotherapy.

Treatment by chemosurgery without systematised microscopic control¹² began on the 5th August 1975. A total of 28 applications of the zinc chloride paste* were made: the first 4 at 24 hour intervals — a thick layer of the paste was applied on the tumour and, on the following day, the resulting necrotic material was removed with scissors; then, one application daily for 3 days, followed by 4 days rest and, again, one application daily for 3 days; thereafter, applications were made at intervals varying between 2 and 10 days — depending on the possibility to remove necrotic tissue — until the tumour was greatly reduced, in thickness and diameter (below the skin level and very close to the femoral artery — Figs. 2-4).

At this stage, the patient was submitted to 2 chemotherapy cycles (CCNU 200 mg; Procarbazine 150 mg; Vincristin 2 mg — POC regimen) (Figs. 5, 6).

* Formula

Zinc chloride	45 g
<i>Sanguinaria canadensis</i>	10.8 g
<i>Alpina officinarum</i>	7.2 g
Deionised water	q.s. 100 g
(European Patent n.º 0025649)	

When the patient was discharged, 6 months after the beginning of treatment, there was apparent local cure and a moderate scar (Fig. 7). Since then, the patient has been examined regularly — at 3-month intervals, for the first 18 months and, subsequently, every 6 months, without ever showing any signs of recurrence or of other metastases.

Twelve years after treatment — she was last examined in June 1987 (Fig. 8) — the patient enjoys a good general condition.

Comment

The staging of the present case (integrated classification scheme resultant from the agreement between the International Union Against Cancer and the American Joint Committee on Cancer, with a basis on the former's TNM system¹¹) was based on the clinical



Fig. 2 - Seventh application of the zinc chloride paste.



Fig. 3 - Six days after the 17th application.



Fig. 4 - Two-and-a-half months after beginning of treatment.



Fig. 5 - Three weeks after the last application of the paste.

appreciation of the lymph node metastasis. This inguinal metastasis was fixed, measured 11 cm × 9 cm × 6 cm and enclosed the femoral artery. It was, therefore, classified as Stage IV (T? N2 MO), which provided an extremely poor prognosis.

Chemosurgery without systematised microscopic control¹², which has proved to be an effective method, particularly



Fig. 6 - Twelve days later.

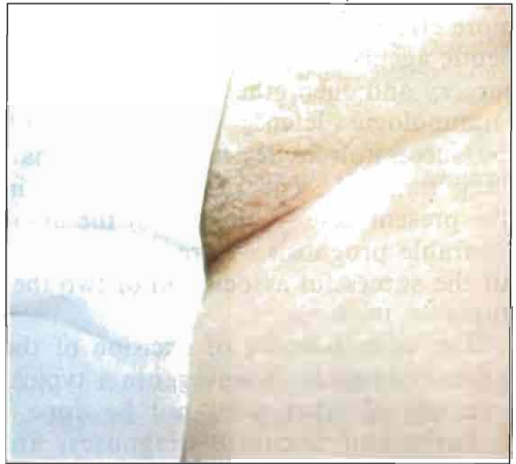


Fig. 7 - Local cure.



Fig. 8 - Twelve years after treatment.

for the treatment of advanced cancers¹³⁻¹⁵, was also successful in reducing the enormous mass in this melanoma. The remnant of the tumour, which was adherent to the femoral artery, was subsequently eliminated by the adjuvant chemotherapy (POC regimen^{16,17}) and the patient's immunologic defense system.

On the subject of "Chemotherapy", Kopf *et al.*¹⁸ stated that "In general, chemotherapeutic agents are more effective against small tumour burdens..." and "One purpose of surgery, then, is to reduce the tumour volume allowing for more effective action of the chemotherapeutic agents. It is hoped that, following surgery and chemotherapy, the patient's immunologic defense mechanisms will be successful in destroying the remaining tumour". The results obtained in the present case — in spite of the unfavourable prognosis — are paradigmatic of the successful association of two therapeutic methods.

The circumstances of excision of the primary tumour, however, are a typical example of what must not be done.

Early and accurate diagnoses, are important contributions toward improving prognosis and survival in malignant melanoma patients. Adequate campaigns for prevention and detection should be carried out internationally in an effort to reach both, the medical community — within the various specialties — and the public. Exemplary action has been taken by the American Academy of Dermatology who recently achieved formal declaration of "Melanoma/Skin Cancer Prevention and Detection Weeks" in the spring of each year¹⁹. In a pertinent Editorial entitled "No One Should Die of Malignant Melanoma", Ackerman²⁰ remarked upon the imperative need for an interna-

tional effort toward early detection and appropriate management of the disease. He concluded, on a expectant note: "With big enough hopes and serious enough convictions, no human being need die of malignant melanoma".

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I would like to thank Ms. Lila Rebelo for her assistance in the preparation of the manuscript and its final English version.

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COMMENT

The value of the treatment is evident, taking into account that this first patient treated

with a metastasis lived without recurrence for 12 years, which is quite remarkable.

Chemosurgery without Systematised Microscopic Control of Cutaneous Cancer: IV — Report of 8 Cases of Malignant Melanoma

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Key Words. Chemosurgery. Chemosurgical technique, simplified. Malignant melanoma.

Abstract. Eight patients suffering from malignant melanoma were treated by chemosurgery without systematised microscopic control. All tumours were primary and of the nodular type. The Clark level was V in 6 lesions, IV in another and unspecified in the remaining one.

Clinical cure was achieved in all cases. None of the patients underwent any other therapy post chemosurgery. Five patients died, of unrelated causes, without recurrence, with follow-ups ranging from 9 months to 5 years. The remaining patients are alive and with no signs of recurrence or metastases 4 years and 8 years (2 patients) after chemosurgery.

Survival rates in patients suffering from malignant melanoma (MM) are inversely related to the level of cutaneous invasion of the malignant cells^{1,4}. Moreover, the nodular type of malignant melanoma (NMM) has been reported to have the worst prognosis of all the growth patterns^{1,3,4}.

Eight cases of MM were treated solely by chemosurgery without systematised microscopic control. All lesions were of the nodular type. In 6 tumours the Clark level was V, one was IV and the remaining tumour was unspecified.

The cases herein presented are the very first 8 MM treated by this simplified chemosurgical method.

Material and Methods

All patients in this series were unsuitable for conventional surgery due either to their general condition, the anatomic location of the tumour, or because they refused to submit to conventional surgery. They were treated in the Out-Patients Department of Dermatology of the Portuguese Institute of Oncology.

Of the 8 patients, 6 were females and 2 were males. With the exception of one patient, they were all in the seventh and eight decades of life, with a mean age at diagnosis of 73.38 years (Table. I).

All MM were of the nodular type, as indicated in Table II, which also refers

TABLE I
Age of Patients

Age (years)	No. of Patients
40 - 49	1
50 - 59	
60 - 69	
70 - 79	4
80 - 89	3
TOTAL	8

45 years - 1 patient

86 years - 1 patient

$\bar{X} = 73.38$

the anatomic distribution.

Histopathologic examination revealed that six tumours were of Clark level V and one was level IV. In one case, the biopsy material was damaged in processing and the level of invasion could not be ascertained.

All NMM located on the face (6) had developed on lentigo maligna. One lesion had appeared on a pigmented naevus, on a buttock, and the remaining tumour arose on a leg, with no precursor lesion. All MM were primary and none of the patients had received any previous treatment.

The patient whose MM was located on the buttock had several inguinal adenopathies, one of which was large and hard. No other patients had clinically detectable adenopathies.

Three patients could not provide reliable information as to the evolution of the disease but, whereas the duration of the precursor lesions was reported as ranging from 1 to 20 years, that of the NMM varied between 3 months and 6 years.

The diameters of the lentigo maligna (6 patients) ranged from 25 mm to 43 mm, whereas the MM nodules over those lesions measured between 8 mm and 35 mm. The two NMM of the leg and buttock measured 18 mm and 50 mm in diameter, respectively.

The method is based on the simplified chemosurgical technique devised, in 1975, with the co-operation of *Ascensão*, and consists in the application of a zinc chloride paste* — in layers of up to 5 mm, according to the degree of penetration desired — over the surface of the tumours, plus an adequate margin. The resection margin criterion was that used in conventional surgery. The surrounding skin, beyond that margin, was routinely protected with flexible collodium. In order to prevent displacement of the paste, a plastic-spray was applied over it, followed by a non-occlusive dressing.

*Formula

Zinc chloride	45 g
<i>Sanguinaria canadensis</i>	10.8 g
<i>Alpina officinarum</i>	7.2 g
Deionised water	q.s. 100 g
(European Patent n.º 0025649)	

TABLE II
Clinical Classification VS. Anatomic Distribution

Clinical Type	Anatomic Location	No. of Patients
NMM over lentigo maligna	Face	6
NMM	Leg/Buttock	2
Total		8

Common analgesics were prescribed, to be taken during the 24 hours following application of the paste.

The paste was permitted to act for 24 hours, during which tissue fixation is achieved. The surface of the tumour becomes necrotic with inflammatory signs around it. A definite demarcation occurs with a groove separating the fixed tissue from the normal looking skin (Figs. 1 and 2). Five to ten days after application, the tumour sloughs off spontaneously or can be easily removed with forceps. The measurements and depth of the resulting ulceration were appreciated and, if they did not comply with the intended resection margin, in depth and



Fig. 3 - Third (and last) application of the paste.



Fig. 1 - Malignant melanoma, before treatment.



Fig. 4 - Final ulceration.



Fig. 2 - One week after the first application of the zinc chloride paste.



Fig. 5 - Clinically cured (the healing occurred by second intention in all cases).

periphery, another application of the paste was made on the border of the ulceration or on any other suspicious site (Fig. 3).

All ulcerations healed by second intention, with slight or moderate scars (Figs. 4 and 5).

Results

The number of applications was of 2 in 3 patients, 3 in 3 patients and 6 in 2 patients.

Treatment — which was performed on an ambulatory basis — lasted between 3 and 8 weeks.

None of these patients underwent chemotherapy or any other treatment post chemosurgery.

The patient who had inguinal adenopathies was not submitted to regional lymph node dissection — he was 86 years old and very frail. However, the nodal situation remained stationary throughout the follow-up period. The patient died two and a half years after chemosurgery, of an unrelated cause, without recurrence or evidence of other metastases.

Clinical cure was achieved in all patients (Figs. 6-12).

All ulcerations healed by second intention, with excellent cosmetic results.

Of the total group, 5 patients died, of unrelated causes, without recurrence of the MM, with follow-ups of 9 months, 2 and a half years, 3 years (2 patients) and 5 years, respectively. The 3 remaining patients are alive and with no signs of recurrence or metastases, 4 years and 8 years (2 patients) after chemosurgery.

Comment

The standard treatment for MM is still surgical excision with adequate resection

margins. It permits the collection of relevant histologic data essential for prognosis evaluation.

Excepting the superficial spreading type, MM has such negative prognosis that researchers are not encouraged to develop alternative therapies. When per-



Fig. 6 - Malignant melanoma, before treatment.



Fig. 7 - Clean ulceration, 6 days after the 2nd (last) application.



Fig. 8 - Clinically cured.

forming conventional surgery, the therapist is never criticised — let alone accused of malpractice — for poor results obtained with MM. They simply are accepted as a normal outcome. However, a similar attitude cannot be expected if patients suitable for surgery are treated by an alternative method.

In 1978, *Frederic Mohs*⁶ reported having treated, with his fixed tissue technique, 103 MM with 5 years follow-up. He, then, stated that the unpredictable extensions of the cutaneous melanoma can be eradicated by chemosurgery with microscopic control, and yet, he achieved 50 % cures. He considered his results better than those obtained by radical surgery and he reminded his readers that “with chemosurgery there is no evidence from animal experience or from long clinical experience that chemical fixation *in situ* has any tendency to disseminate malignant cells”.

My own experience in treating many advanced external cancers⁷⁻⁹, including an inguinal MM metastasis¹⁰, by chemosurgery without systematised microscopic control firmly supports my belief that the method can be widely used in the treatment of MM. The intense inflammatory reaction that occurs after application of the paste plays an important role in hin-



Fig. 9 - 82-year-old patient, before treatment.



Fig. 10 - Three days after 2nd application of the paste.



Fig. 11 - Clean ulceration, 3 days after the last (6th) application.



Fig. 12 - Clinically cured.

dering possible peripheric extensions of the tumour, thus strongly contributing to the very low recurrence rate prevailing in the method.

As far back as 1900, *Stelwagon*¹¹, who used caustics in the treatment of skin cancer, stated that “the outlying pathological epithelial cells may often be found considerably beyond the apparent border of the disease and are, therefore, often missed by the surgeon’s knife. In the caustic method such cells are usually des-

troyed or weakened by the products of cauterization or by the marked inflammatory action resulting, and a reappearance of the growth is thereby rendered less probable. ... I believe that the caustic method properly followed out lessens the chances of recurrence".

For ethical reasons, I decided to use the simplified chemosurgical method to treat only MM patients unsuitable for conventional surgery and also those in such advanced stages that only palliative treatment can be attempted. This criterion results in a restriction of the number of MM patients treated, which, therefore, is not large enough for statistical analysis. Nevertheless, the excellent results obtained in the present series and with other cancers, over the past 14 years^{5, 7-10} — with cure rates higher than those provided by all conventional methods, equivalent only to those achieved by Mohs' chemosurgery — render chemosurgery without systematised microscopic control a therapeutic method indicated for most types of cutaneous tumours, particularly in advanced stages.

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COMMENT

The eight melanomas were treated by this method because the patients were either not eligible for conventional surgery or refused such treatment. All tumours were between 10mm and 20mm thick. It would be

logical to anticipate the development of metastases, which did not occur. Although eight patients is not a statistically significant number, the results obtained are highly suggestive of immunologic stimulation.

Chemosurgery without systematised microscopic control (Simplified chemosurgery) for advanced skin cancer

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Key Words. Chemosurgery without systematised microscopic control. Chemosurgery, simplified. Basal-cell carcinoma. Advanced skin cancer.

Abstract. A simplified chemosurgical method, effectively used in the treatment of skin malignancies for 20 years, was used in the management of advanced basal-cell carcinoma, achieving clinical cure, histologically confirmed. The data on the method is reviewed and discussed.

Introduction

The first description of a chemosurgical technique for the removal of skin cancers using a zinc chloride paste is ascribed to *Stelwagon*¹. In the 1930s, *Frederic Mohs* developed a highly sophisticated method² which consisted of chemical fixation of the tumours by means of serial applications of a zinc chloride paste followed by excision of layers of tissue under microscopic control, until a surface histologically free of malignancy was achieved. The method, which subsequently comprised two techniques —“fixed tissue”, as originally devised, and “fresh tissue”, wherein the removed tissue is not previously fixed^{2,4}— is excellent but too complicated, in its sophisticated complexity, to be available worldwide, even more than five decades after its conception.

An interesting aspect is that the term “Mohs’ chemosurgery” is often used to

describe microscopically controlled surgery⁴ —or the fresh tissue technique, currently designated as “Mohs’ micrographic surgery”⁵— which is not preceded by the use of zinc chloride or any other chemical agent, thus, rendering the word “chemosurgery” inaccurate to characterize the method⁶.

With the co-operation of *Ascensão*, in 1975, *Gonçalves* developed a chemosurgical method for the treatment of cutaneous tumours, using a zinc chloride paste. The results obtained were very good and were presented at various scientific meetings and first published in 1981⁷. Five years later, *Gonçalves and Ascensão*⁸ reported the treatment of 212 patients —179 basal-cell carcinomas with diameters ranging from 3mm to 35mm and 33 squamous-cell carcinomas with diameters from 7mm to 45mm — followed up between 5 and 10 years. Clinical cure was achieved in all patients with very good cosmetic results.

As *Gonçalves* kept treating more and more skin malignancies and ascertaining the effectiveness of his simplified chemosurgical method, he started modifying the protocol to suit other types of skin malig-

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nancies, particularly those for which the conventional therapeutic modalities were inadequate, namely for advanced squamous-cell carcinoma^{9,10}, invasive squamous-cell carcinoma of the hand (2 cases proposed for amputation in which he prevented such mutilation)¹¹, malignant melanoma^{12,13}, and advanced and inoperable breast cancer¹⁴.

Some of the above techniques are currently used in several Portuguese hospitals^{15,16}.

Basal-cell carcinoma (BCC) is the most common malignant tumour in Caucasians. It is generally considered a low malignancy tumour, since it frequently presents as a slow growing, locally invasive lesion with excellent response to the conventional therapies, particularly when diagnosed early. However, cases of highly aggressive¹⁷⁻²⁰ and metastatic^{21,22} BCC have been reported, suggesting that this may be a very complex tumour capable of extremely aggressive behaviour, resulting in devastating destruction and cosmetic disfigurement. Moreover, in locations near the eyes nose or ears, it may even account for mortality because of contiguous and perineural invasion of the cranium^{18,20}.

Three cases of primary, advanced and aggressive basal-cell carcinoma, successfully treated by chemosurgery without systematised microscopic control, are herein reported to illustrate the method.

Method

Prior to treatment, the tumour is photographed, carefully measured and biopsied. Alternatively, since the paste fixes the tumour *in vivo*, the fragment required for the histologic examination can be removed the day after the first application and immediately processed without further fixation. The surrounding skin is protected with

adhesive tape, leaving the lesion and its apparent limits exposed. For the first procedures, a safety margin is not considered.

The paste, containing 45% zinc chloride in a special vehicle* that slowly releases the salt for about 24 hours, is applied over the entire surface of the tumour. The thickness of the layer of paste varies according to the degree of penetration desired, according to the criterion suggested by Mohs²⁰. The paste is kept in place by means of a non-occlusive dressing. Non-narcotic analgesics are prescribed for the 24 hours following treatment.

One or two weeks later (longer if the tumour is fibrous), depending on the structure of the cancer, the necrotic mass almost completely detaches itself from the underlying viable neoplastic tissue and is painlessly removed with forceps and/or scissors. After removal of all the necrotic tissue, another application of the paste is made, in a similar manner. The whole procedure is repeated as many times as necessary until complete extirpation of the tumour is achieved and there are no clinical signs of persistence of the disease. At the last two or three procedures, a safety margin is also treated, its width depending on the tumour's size and histology. Any clinically suspected sites are biopsied to ascertain the absence of neoplastic cells.

The resulting clean ulceration will, in most cases, heal by second intention. In some specific cases, plastic surgery will contribute to better cosmetic or functional results. The ultimate criterion of successful treatment is the absence of recurrence for a minimum of 5 years.

*Formula

Zinc chloride	45.0g
<i>Sanguinaria canadensis</i>	10.8g
<i>Alpinia officinarum</i>	7.2g
Deionised water	q.s. 100.0g

(European Patent no. 0025649)

Material

The three BCC described below were all primary, advanced and neglected. Adenopathies were not detected, on presentation, in any of the patients.

Case 1

A 69-year-old Caucasian woman had an ulceration on the distal part of the front of the right leg, for 4 years, which was being treated with topical antiseptics and kept progressing in surface.

On presentation, the entire lesion was ulcerated with clear-cut and raised borders, and measured 120mm×90mm and was about 10mm to 15mm thick. The surface was red, slightly irregular and bled easily (Fig.1).

Histologic examination revealed basal-cell carcinoma with areas of keratotic differentiation.

Immediately before treatment, which can be painful, particularly in large ulcerated lesions, an epidural catheter was inserted for adequate analgesia (buprenorphine). Two applications of the paste were made over a period of 20 days (Fig.2). The neoplasm plus the safety margin were chemosurgically excised. The final ulceration was very large and a graft was performed in order to prevent an unstable scar (Fig.3).

A control biopsy, 6 months later, on a suspected nodule on the border of the graft proved the absence of neoplastic tissue. The patient has been followed-up (Fig.4) for just over 5 years without signs of recurrence or metastases.

Case 2

An 88-year-old Caucasian woman noticed a small macule on the right cheek, one year before our first examination. A small,

firm, brown nodule developed and became pruriginous. The lesion had rapidly enlarged over the previous 6 months.

On presentation, there was a fetid, very protuberant, ulcerated mass, with necrotic areas, measuring 90mm×90mm, on the right cheek (Fig.5). The clinical diagnosis was of squamous-cell carcinoma. The patient was admitted and proposed for the simplified chemosurgical technique.

Histologic examination revealed a solid, undifferentiated basal-cell carcinoma with areas of necrosis.

Seven applications of the paste were made over a period of three weeks. On the last three procedures, an adequate safety margin was also treated. After gradual removal of the necrotic tissues (Fig.6), a clean ulceration was obtained (Fig.7) which healed, by second intention, in approximately 4 weeks.

The cosmetic result was excellent. The patient was followed up for 5 years (when she was almost 94 years old), with no signs of recurrence or metastases (Fig.8).

Case 3

A 66-year-old Caucasian, diabetic male had an erythematous, slightly scaly plaque on his back, with pruritus, for 5 years. The lesion had been diagnosed as a dermatitis and topical corticosteroid treatment had been prescribed. Subsequently, the lesion slowly enlarged, became protuberant, exudative and ulcerated, bleeding after minor trauma. The patient did not seek further medical advice during that long period of time.

On presentation, the tumour was ulcerated, very protuberant, with an irregular surface, and measured 87mm×75mm. The border was well defined but less raised than the central part of the lesion (Fig.9). The clinical diagnosis was of



Fig. 1 - Advanced BCC, before treatment.



Fig. 2 - Clean ulceration after complete removal of the tumour by simplified chemosurgery



Fig. 3 - After skin graft.



Fig. 4 - Two years after grafting.



Fig. 5 - Bulky and partially necrosed BCC, before treatment.



Fig. 6 - Four days after the last chemosurgical procedure.



Fig. 7 - Remaining ulceration, 2 weeks after Fig. 6.

squamous-cell carcinoma but histologic examination revealed an adenoid basal-cell carcinoma. The patient was hospitalized and proposed for simplified chemosurgery.

The first application of the paste was made over the tumour only. Two days later, the patient had a temperature of 38 °C and constitutional symptoms and signs resembling an infectious condition, with redness and oedema around the lesion.



Fig. 8 - Five years after cure.

Five days after the first chemosurgical procedure, biopsies were carried out on two points of the lesion's contour. At this stage, the necrotic mass resultant from the first application of the paste was still adherent to the underlying neoplastic tissue



Fig. 9 - Advanced protuberant BCC, before treatment.



Fig. 10 - After removal of the fixed tissues by electrocision. Note the oedema and inflammation around the tumour.

and, in order to hasten the treatment (the patient was very anxious to return home), the fixed tissue was removed by electrocision (Fig.10), followed by another application of the paste, again without safety margin. The fever continued at the same level and the inflammation became much more intense, extending approximately 150mm all around the tumour border, and the patient's dorsum was very warm, red and swollen (Fig.11). This condition was interpreted as the natural, although unusually intense, reaction to chemosurgery. The fever, always around 38 °C, lasted 8 days. Fearing a secondary infection, on the 7th day a large spectrum antibiotic, cephadrine, was administered, but the fever subsided on the next day. During this period of sustained temperature, routine tests and analyses were made and, excepting the high levels of glycaemia, all values were normal. The white blood cells count displayed no significant altera-

tions during this period and was always around 7,000-8,000/mm³.

The second application of paste was not thick enough to fix the remaining tumour and the response was very unusual: the residual cancer, underneath the fixed layer, kept decreasing daily, without any other treatment, evolving to a clean, granulating ulceration. The intense inflammation around the lesion subsided very slowly.

Nineteen days after the beginning of treatment, several biopsies were performed in the ulceration and its contour. Histologic examination revealed intense inflammation with oedema and innumerable neutrophils and monocytes, but no neoplastic cells. Two months later, another biopsy was made in a suspected site at the edge of the ulceration, which histology showed a chronic inflammatory infiltrate and vascular proliferation (Fig. 12).

The patient refused the proposed skin graft, so the healing occurred by second



Fig. 11 - Six days later, the inflammation had extended over a large area surrounding the lesion.



Fig. 13 - Three months after Fig. 11, almost completely healed by second intention.

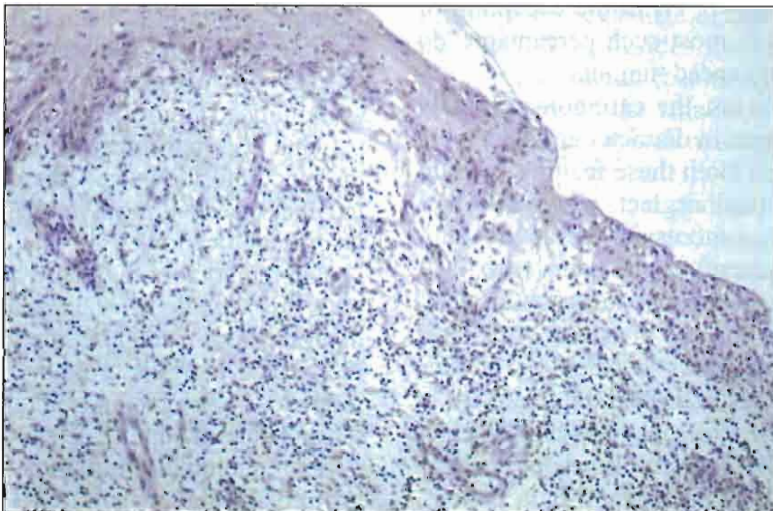


Fig. 12 - Histologic features of the ulceration border, displaying polymorphic nuclear leukocytes and monocytes and newly formed vessels.

intention (Fig.13). Another biopsy was made 6 months after treatment in the remaining ulceration, revealing intense chronic inflammatory infiltrate, without neoplasm. Healing was complete one month later. The patient has been followed up for 4 years and 4 months, and there have been no signs of recurrence or metastases. This patient will be encouraged to maintain regular follow-up examinations for 10 years.

Comments

The behaviour of basal-cell carcinoma depends on a variety of parameters. Major factors associated with recurrence are the location (nose, ear and near the eyes), size (more than 20mm in diameter) and histologic subtype (morpheaform, metatypical and infiltrative are more aggressive)^{16-19,23,24}.

Five year recurrence rates for treated primary BCC range from 1% with Mohs' surgery and 2% with cryosurgery to an average of 8.7% when considering curettage and electrodesiccation, surgery and radiation therapy²⁶. With the exception of Mohs' method, most such percentages do not refer to advanced tumours.

In our patients, the carcinomas largely exceeded 20mm in diameter and they were all advanced. Both these features, associated with patient neglect, would favour a prognosis of unsuccessful therapy, unanticipated complications and recurrence.

Chemosurgery without systematised microscopic control provides cure rates comparable to Mohs' method. The first published series described the treatment of 212 basal-cell and squamous-cell carcinomas, all with 5-year follow-up, with no recurrences⁸. Unpublished data concerning the same method and a further, slightly larger number of patients treated, accounts for a total of well over 400 cases

of BCC and SCC followed up between 5 and 10 years, with absolutely no recurrences and only one case of persistence of the tumour (SCC) of the ear.

In 34 patients suffering from advanced SCC with diameters between 30mm and 190mm, 25 patients (73.5%) were cured¹⁰. Of this same series, 5 patients had been proposed for amputation (3 of the hand and 2 of the leg) by various departments of surgery; amputation was prevented in 3 (2 hands and 1 leg).

Eight patients with primary, nodular melanomas of Clark levels IV and V were successfully treated with simplified chemosurgery¹³. Their follow-ups ranged from 9 months to 5 years.

Fifteen women suffering from advanced and inoperable breast cancer were also treated by simplified chemosurgery —after a modified protocol to suit these tumours and denominated "chemomastectomy" by the author¹⁴. Clinical cure was achieved in one third of patients, and local eradication of the cancers in a total of 12 women.

These three primary and advanced BCC, with major axes between 87mm and 120mm, would have been difficult to treat by other therapeutic methods. Cure was achieved with chemosurgery without systematised microscopic control. Two patients required only two applications of the zinc chloride paste; the carcinoma on the cheek needed more applications due to its critical location.

The remarkably high cure rates obtained with this technique when comparing with other methods cannot be solely attributed to the treated margins around and under the lesions —other methods adopt similar criterion without identical outcome. In our opinion, the intense inflammatory reaction around the lesion triggered by the zinc chloride paste (particularly evident in Case 3 - Figs.11 and 12) plays a major role in tumour eradication and, very likely, has an

important action on the silent outgrowths that extend peripherally and unpredictably from the detectable tumoural mass.

In Case 3, the established protocol was not followed as to the rule stating that the entire cancer must be removed and that an adequate safety margin must also be treated. When we observed the huge inflammation surrounding the carcinoma and the neoplastic mass “vanishing” over the days following the second application of the paste, we realized that the inflammation might be capable of actually suppressing the residual carcinoma and even the possible peripheral extensions. We knew that the layer of paste applied on the last chemosurgical procedure was insufficient to fix the remaining tumour, and that the safety margin had not been treated, yet, the evolution was unexpectedly similar to what should have happened if the protocol had been observed. Several biopsies were performed, on various sites and on separate occasions, that confirmed the absence of neoplastic tissue. Should there be no persistence of tumour or recurrence after this incomplete chemosurgery, we shall have clinical proof of the efficacy of the intense inflammation in contributing towards eradication of the cancer, at least in this particular case. The patient was informed of the scientific interest of this experiment and of the risk of persistence or recurrence of the tumour, and agreed to keep all appointments in order to guarantee a strict follow-up. Four years and 4 months after treatment, the patient is well and without any evidence of persistence or recurrence of the carcinoma.

Host-tumour relationships involve several factors that can enhance or suppress neoplastic growth. Systemic and local immunity are representative of this feature and may have a role in preventing the development of basal-cell carcinoma. The

T-cell seems to be the most involved cell giving rise to the infiltrate surrounding tumour islands²⁸. Also, topical application of primary or recall antigens eradicates 60% to 90% of tumours²⁹, probably by giving rise to a non-specific local immune response³⁰. Reports of intra-lesional IFN- α and IL-2 therapies also showed good results³¹. Again, these therapies gave rise to an enhanced T-cell mediated immune response, with infiltrating CD4+ cells and increased expression of adhesion molecules (ICAM 1).

Mohs' surgery —which is not widely available outside the United States— has the distinct advantage of maximal preservation of normal tissue around the cancer, while providing invaluable histologic monitoring and reliability in objectively determining adequate margins of excision. However, it does not provoke any significant inflammation, either in the original method, because the fixed tissue was removed before it could induce the appearance of inflammatory cells, or in the “fresh-tissue” technique which is biologically similar to conventional surgery.

The main advantage of this chemosurgical method —besides the excellent cure rates and cosmetic results obtained in the management of the smaller carcinomas⁸— is its simplicity, which makes it easily available to any specialist. The method is, indeed, easy to learn and to perform, does not require sophisticated equipment and, in most cases, can be performed on an outpatient regimen. Its low cost, plus the fact that it can be used effectively in the treatment of many extensive and advanced cancers are added benefits that make it an invaluable therapeutic modality.

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COMMENT

I will summarize the first two cases with recourse to the photographic evidence: Figure 1 - Extensive basal-cell carcinoma on the leg of a 69-year-old woman, measuring 120mmX90mm and 10mm-15mm thick. Legend to Figure 2 - Clinically cured after two applications of the ZnCl paste. Legends to Figs. 3 and 4 - A skin graft was performed. The patient was followed for 5 years without recurrence.

Figures 5-8 - An 88-year-old woman without operative conditions presented with a solid, undifferentiated basal-cell carcinoma, measuring 90mmX90mmX15mm. She was

clinically cured after 8 applications of the paste and was followed for 5 years without recurrence.

Figures 9 and 10 - This case has actual immunologic significance and I would like to ask partial readers (by partial readers I mean those who will not be motivated into reading the totality of this re-edition) to concentrate on this very important case. There were many suggestions of immunologic activity in my work, but, in this case, immunological enhancement is clinically evident.

Chimiochirurgie sans contrôle microscopique pour des carcinomes cutanés avancés

J Méd Esth Chir Derm 1991;18(7):205-210.

In 1991 I published, in another journal, this paper of which I will outline the Abstract: thirty-four patients (14 men and 20 women, aged 23-91) suffering from squamous-cell carcinomas, 24 located on the head and the remaining on the limbs, measuring between 30mm and 190mm were treated by simplified chemosurgery. Cure was obtained in 25 patients; two died

during treatment, due to cerebrovascular disease, with reduction of the tumour; in two patients the tumours persisted, and amputation could not be prevented (one leg and one hand); and five patients eventually died due to metastases. The complications were: lesion of the cervico-facialis nerve (two cases) and arterial break (three cases).

An attempt at reducing pain in cancer patients treated by chemosurgery without systematised microscopic control

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Key Words. Chemosurgery. Chemosurgical technique, simplified. Squamous-cell carcinoma. Basal-cell carcinoma. Pain.

Abstract. An open study comparing two methods to prevent or reduce pain after treatment by chemosurgery without systematised microscopic control was carried out. Prior to chemosurgery, group I, consisting of 44 patients, underwent one freezing by liquid nitrogen (contact probe or open spray, depending on the size of the tumour), and group II, consisting of 35 patients, received local anaesthesia by subcutaneous injection of 70% alcohol. In both groups the pain was prevented or greatly reduced, and there was a marginally significant statistical difference in favour of the former group. In view of the results, choice of either method should be clinical, but bearing in mind that the latter method is less adequate for larger cancers, since the anaesthesia by alcohol may produce intoxication.

Caustic substances have been used to treat skin cancer from antiquity to the beginning of this century¹. One of the most interesting is zinc chloride, which therapeutic activity was described by Canquoïn and Bougard² and Stelwagen³. The latter developed, in 1990, a remarkable method to treat skin cancers with a zinc chloride paste. In 1975, when one of us (JCAG) was working in the Lisbon Centre of the Portuguese Institute of Oncology, he

developed –in collaboration with A. C. Ascensão– a simplified chemosurgical technique to treat skin cancers using a zinc chloride paste*. In a short pilot trial, 12 patients were treated and a protocol was established.

In 1986, *Gonçalves and Ascensão* published their experience with the first group of patients (not including those of the pilot trial), which consisted of 179 basal-cell carcinomas (BCC) with diameters between 5mm and 35mm, and 33 squamous-cell carcinomas (SCC) with

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*Formula:

Zinc chloride	45g
<i>Sanguinaria canadensis</i>	10.8g
<i>Alpinia officinarum</i>	7.2g
Deionised water q.s.	100g
(European Patent no.0025649)	

diameters between 7mm and 45mm⁴. All patients had more than 5 years follow-up and no tumour persistence or recurrence was observed. This study continued until 400 skin cancers (BCCs and SCCs) had been treated; only one persistence (SCC) had occurred (unpublished data). One therapeutic failure in 400 cases meant an extremely high cure rate (99.75%), and simplified chemosurgery became a routine treatment at the Institute, due to its high efficacy, low cost and simplicity.

Motivated by this success, JCAG decided to extend this chemosurgical treatment to larger and invading tumours, developing adequate protocols for various types of external cancers and respective anatomic locations. Many advanced SCCs, for which conventional treatment was difficult or not feasible, were treated by this simplified method of chemosurgery⁵. In a group of 34 patients with advanced cutaneous SCCs, 29 were cured⁶. Two patients with very advanced SCCs of the hand, both proposed for amputation and who were also beyond the possibilities of cryosurgery – JCAG also developed a cryosurgical protocol for such advanced cancers⁷, but which was not indicated for these two cases – were treated by his chemosurgical method. Two fingers of each hand were amputated by successive applications of the paste, and the carcinomas were cured without recurrence⁸. Recently, two similar cases were successfully treated (as yet unpublished),

Fifteen patients with advanced breast cancer (5 primary, 5 recurrent after surgical mastectomy, and 5 which persisted after other, previously administered treatments) were treated by his technique of chemomastectomy. Local eradication was achieved in 12 patients, most of whom subsequently died of metastatic disease; three patients were

clinically cured with survival between 2 and 3 years without signs of recurrence⁹.

The first eight cases of malignant melanoma (Clark levels IV and V) treated by this method were published¹⁰. These were very elderly patients and the lesions were eradicated without recurrence. Five patients died of unrelated diseases between 9 months and 5 years post treatment; the three remaining patients survived between 4 and 8 years, without recurrence. Although this is not a statistically significant number, he considers it highly improbable that, with any other treatment, no recurrence would have occurred with these patients. One case of an inguinal metastasis of malignant melanoma, measuring 110mm×90mm×60mm, was resistant to chemotherapy (CCNU, Procarbazine, Vincristine and POC), possibly due to the large tumoural mass. The metastatic melanoma was almost entirely removed with the chemosurgical method. Subsequently, the tumour remnants surrounding the femoral artery were successfully treated with two cycles of the mentioned chemotherapy. The patient has a 12-year follow-up in good general condition and without recurrence¹¹.

Three very advanced cases of BCC were successfully treated by this simplified chemosurgery, with follow-up of 5 years or more. One of these cases was particularly interesting: the carcinoma, located on the dorsum, measured 87mm×75mm and was very thick. Two applications of the zinc chloride paste reduced it to two thirds of its original thickness. A strong inflammation developed, measuring 150mm all around the tumour, occupying almost the entire dorsum, accompanied by high fever. The remaining cancer did not receive any further treatment but kept reducing, until it completely disappeared and was replaced

by healthy granulation tissue. There was no recurrence after 9 years' follow-up¹².

The main advantages of this simplified chemosurgery are: the high cure rate –much higher than that of conventional treatments; the permanence of necrotic tissue in place that provokes a strong inflammation (a defence mechanism against peripheral extensions of the cancer, which enhances the immunological response) as demonstrated in the above mentioned case¹². The simplicity of the method and its low cost are also important factors¹³.

Pain, however, is a considerable disadvantage and can persist for some 20 hours after treatment. In the first 212 treated patients, 13.95% had intense pain, 55.86% referred moderate pain that subsided or improved with analgesics, and 30.19% did not refer any pain⁴. Generally, when treating very advanced and extensive cancers^{5-7,9-12}, patients referred intense pain.

For many years, JCAG searched for various ways to solve this problem, with limited success. Eleven years ago, remembering that cryosurgically treated lesions become insensitive, he tried to apply one freezing, by cryosurgery, on the whole tumour, immediately before chemosurgery –we shall, henceforth, refer to this as "method A". Three years later, he recalled an ancient method to treat pain and uncontrollable itching (subcutaneous injection of 70% alcohol, which produces local anaesthesia that persists for a few weeks¹⁴), and he also tried it –henceforth referred to as "method B".

The aim of this study was to assess the effectiveness of these two methods to reduce pain after simplified chemosurgery. Since the treatment groups were not homogeneous and there are several potential confounding effects on pain, we

controlled statistically for the following effects: treatment group, histological type and area of tumour, and sex and age of patient.

Material and Methods

Patients

Group I, treated with method A, consists of 44 Caucasian patients, 20 men and 24 women with ages ranging from 50 to 101 years (31 were 75 or older - mean of 77 years). The referred time of evolution was between a few months and 20 years, and was unknown in 13 cases. However, this information, when given by such elderly people, should not be considered as reliable in either group –in his experience, JCAG finds that very elderly patients often have a vague and undependable notion of time.

The histological diagnoses were: 18 basal-cell carcinomas, 24 squamous-cell carcinomas, 1 lentigo maligna melanoma and 1 trichofolliculoma. The latter is a benign tumour, clinically diagnosed as BCC but, since the aim of the study was the sensibility to pain, it was maintained in the series.

Major axes (M) ranged from 10mm to 50mm (mean M 26mm; mean area 413mm²). The TNM classification of BCCs was: T1N0M0 in 9 cases, T2N0M0 in 8 and T3N0M0 in one case. The SCCs were T1N0M0 in 5 cases, T2N0M0 in 18 and T3N0M0 in one case. The lentigo maligna melanoma was pT1sN0M0. The anatomic location of the tumours was: 32 on the face, 2 on the neck and 10 on the limbs.

Group II, treated with method B, consisted of 35 Caucasian patients, 14

men and 31 women with ages ranging from 54 to 97 years (25 were 75 or older - mean of 76 years). The reported time of evolution was between two months and 20 years, and 8 patients were unable to indicate any time.

The histological diagnoses were: 15 basal-cell carcinomas and 20 squamous-cell carcinomas. Major axes measured between 6mm and 41mm (mean M 20mm; mean area 151mm²). The TNM classification of BCCs was: T1N0M0 in 12 cases and T2N0M0 in 3 cases. The SCCs were T1N0M0 in 9 cases and T2N0M0 in 11. The anatomic location of the cancers was: 28 on the face, 6 on the limbs and one on the neck.

Both groups were constituted mainly by rural people, with approximately the same low level of education.

Chemosurgical protocol

In both groups, a history was taken, the tumour was measured and photographed, its anatomical location registered and a biopsy was done. Both protocols have phases 1 and 2. Phase 2 is identical in both groups.

Group I, phase 1: the lesion is anaesthetised and undergoes one freezing, by probe contact cooled by liquid nitrogen, with hydrophilic gel between the probe and the tumour (lesions up to 20mm-23mm), or by open spray (larger tumours), without temperature control. In phase 2, limitation of the target to be submitted to chemosurgery (the cancer plus adequate safety margin) is done with two layers of 4cm-8cm-wide adhesive tape, depending on the quantity of paste to be applied and on the anatomic location. The zinc chloride paste is applied over the

cancer and safety margin with a wooden spatula. JCAG follows Mohs' recommendations in "Factors affecting penetration of fixative"², where the thickness of the paste to be applied is related to the intended thickness of neoplastic tissue to be fixed. A non-occlusive dressing is used. When the cancer is bulky, requiring a thick layer of paste, a ring of cotton-wool is placed around the lesion and a layer under the dressing, to prevent running off of the paste, which tends to occur when it is heated by body temperature.

The dressing is removed 24 hours later, when the tumour and safety margin are fixed, grey and necrotic, with inflammatory signs around it, which increase in the following days. Between 6 and 10 days, a clear demarcation appears between the fixed tissue and the normal looking skin. This becomes more pronounced originating a groove that isolates the fixed tissues. By 10 to 15 days, the tumour sloughs off spontaneously or is easily removed with forceps. Careful measuring of the resulting ulceration and its clinical evaluation are fundamental steps in this protocol. If the measurements, in the surface and depth are considered satisfactory, in terms of the established safety margin, and if the surface of the ulceration is clean and smooth, the wound is allowed to heal by second intention. If the safety margin, in periphery and/or in depth is not sufficient, a second or more applications are made. Likewise, if there is clinical suspicion of persistence of the tumour, a biopsy is taken and one or more applications are made (Figs.1-9).

Group II, phase 1: the lesion is anaesthetised and an injection of 70% alcohol is administered immediately under the apparent base of the tumour and



Fig. 1 - Squamous-cell carcinoma, measuring 40mmx35mmx25mm, on an 84-year-old patient.



Fig. 3 - Four days after treatment, the tumour is fixed. The patient felt no pain.



Fig. 2 - The healthy skin around the tumour is protected with adhesive tape.



Fig. 4 - Three months after simplified chemosurgery.

its safety margin, to induce long term insensitivity. Phase 2 is identical to that of group I (Figs.10-15).

All patients, in both groups, were prescribed the analgesic Clonixine (300mg), and instructed to take it if required.

Pain

Thorough and objective measurement of pain is impossible. The description given by the patients is obviously subjective and influenced by their personality and educational status. In an attempt to improve and simplify the clinical assessment of pain, a score from 0 to 3 was established, as follows: 0 = non-existent; 1 = slight –the patient did not need to take any analgesics and slept well; 2 = moderate

–the patient took an analgesic, the pain subsided and sleep was not affected; 3 = intense –the pain did not subside with analgesics and disturbed sleep.

The surface area of each tumour was estimated from the measurements of the major (M) and minor (m) axes, assuming an elliptical shape, using the formula: $\pi.M.m / 4$. Tumours were significantly larger in group A (median 413mm²) than in group B (median 151mm²) (Wilcoxon test: $Z=-3.12, P<0.005$).

The probabilities of different pain scores were investigated by fitting logistic regression models using maximum likelihood with the following factors: treatment group (I or II), histological type (BCC or SCC, the two patients with different tumour types were excluded from



Fig. 5 - Squamous-cell carcinoma on the forearm, measuring 38mmx35mm.



Fig. 6 - The surrounding skin is protected with bandages before cryosurgery.



Fig. 7 - Further protection with adhesive tape before simplified chemosurgery.

the analysis) and area of tumour, and sex and age of patient. A minimum adequate model was found by a stepwise backward deletion procedure. The highest order interaction was removed from the full model if it was not significant ($P > 0.05$),



Fig. 8 - The measurements of the ulceration after sloughing off were similar to those of the tumour. A second application of the zinc chloride paste was made on the contour. In the center, oxide zinc was applied as protection. The patient referred slight pain.



Fig. 9 - Two months after treatment, completely healed. He died, of an unrelated disease, three years later, without recurrence.

and a reduced model was fitted. The highest order non-significant interaction with the highest P -value was then removed, and a new reduced model was fitted. Non-significant factors or interactions were maintained in the model when any higher-order interactions, including the factor or interaction, were significant. This procedure was repeated until the model included only significant factors and/or interactions. Statistical analyses were done with JMP Version 3.2 for Macintosh (SAS Institute Inc.).



Fig. 10 - Basal-cell carcinoma measuring 20mmx13mm.



Fig. 11 - Ulceration after treatment.



Fig. 12 - Resulting scar, two months later. No recurrence after 8 years.

Results

Oedema was present in all patients. The time of healing could not be established, because most patients did not keep their appointments, due to their advanced age, economic difficulties, lack of accompanying person, etc. In fact, the failure to keep appointments seriously impeded treatment, since the established

protocol could not be followed as is mandatory.

From **group I** (44 patients), 23 were cured and are alive with no signs of recurrence or metastases; the follow-up ranges from 6 months to 9 years (mean of 4 years). Seventeen patients died of unrelated diseases, between 4 months and 8 years (mean of 3 years), after successful treatment. Three patients eventually died of recurrence and/or metastases; all these had SCCs with major axes measuring 40mm and 50mm. A fourth patient with recurrence (SCC) is now under treatment. The cure rate for group I was of 91%.

From **group II** (35 patients), 22 were cured and are alive with no signs of recurrence or metastases; the follow-up ranges from 6 months to 7 years (mean of 4 years). Nine patients died of unrelated diseases, between 1 and 8 years (mean of 4 years), after successful treatment. Three patients with SCC had recurrences and eventually died; these tumours' major axes measured between 22mm and 31mm. Another recurrence occurred 1 year post-treatment; the patient underwent plastic surgery and now, 3 years later, she is well. The cure rate for group II was of 88.60%.

Pain

In group I, the pain was: non-existent (0) in 16 patients; slight (1) in 16; moderate (2) in 10; and intense (3) in two patients.

In group II, it was: non-existent (0) in 16 patients; slight (1) in 12; moderate (2) in 3; and intense (3) in 4 patients.

The minimal adequate model showed significant effects of treatment group and tumour type on pain (Table I). Patients from group II reported marginally higher pain scores than those from group I and patients with BCC showed more pain than



Fig. 13 - Squamous-cell carcinoma, measuring 40mmx15mm, on a 94-year-old patient.



Fig. 14 - Third application of the zinc chloride paste on a suspicious site.

those with SCC. The factors tumour area, and patient's age and sex were not significantly related to pain, but the interactions treatment group by tumour area, treatment group by patient age and tumour area by tumour type were all significant (Table I).

Discussion

The very high cure rates achieved with chemosurgery without systematised microscopic control (simplified chemosurgery) over the past 23 years^{4,6,8-12} clinically suggests that it triggers an immunological response. The above mentioned case of the large and thick BCC¹² in which the simplified chemosurgery caused a strong inflam-



Fig. 15 - The patient was clinically cured and healed, two months later. She died of senility a few months later.

matory reaction that resulted in the cure of two thirds of the existent cancer that had not yet received any treatment appears to substantiate such response, but laboratory studies confirming this had not been done. As this paper was being prepared, however, R.S. Kalish and collaborators¹⁵ reported that when induced K1735 melanomas in mice were fixed by a zinc chloride paste, the mice developed considerably increased resistance to the subsequent intradermal injection of the same tumour. This is an important study that proves the value of the zinc chloride paste in enhancing immunological defence, and helps to explain the efficacy of simplified chemosurgery.

The recurrence rate in the present study (91% for group I and 88.5% for group II) was higher than that obtained with simplified chemosurgery when the protocol is correctly followed^{4,12}.

The clinical records of all patients who had recurrences were carefully reviewed and it was found that they all failed to keep their appointments after application of the zinc chloride paste, having been observed several days after sloughing off of the tumours. The resulting ulcerations already were undergoing healing and could not, therefore, be adequately measured and clinically evaluated for the possible need of further applications. It is absolutely essential that this step of the protocol be followed.

The hospital where this study was conducted is situated in a rural district, and serves a population that resides within a radius of some 40Km. The low educational status of most subjects in this study and their advanced ages made it very difficult to obtain their full co-operation. They either did not understand that they must keep their appointments on the set

dates, or forgot those dates, or had insurmountable difficulties to return to the hospital as asked. One possible solution would be to hospitalise the more uncooperative patients. However, since one of the advantages of this chemosurgical technique is the fact that it can be performed on an out-patient basis, it is not easy to justify admittance to the health care services, plus the fact that inactivity of old patients in the wards significantly contributes to vascular cerebral accidents.

An important conclusion is that communication with the relatives of patients was inadequate. When conducting pilot trials, full co-operation from the subjects should be a strict criterion for inclusion in the study group.

Although the statistical study showed a small advantage in reducing pain by method A, we feel that the use of either method should depend on clinical indications, local facilities and personal preference. In fact, method A is more adequate for larger cancers, because the use of substantial quantities of alcohol in large body areas could cause intoxication.

TABLE I

Minimum adequate logistic regression model for pain on 77 patients ($\chi^2 = 15.924$, $df=7$, $p<0.05$). The sign of the effects and interactions indicate the direction of increasing pain. Each factor and interaction was tested by a likelihood ratio test, relative to a reduced model excluding the factor or interaction.

Factor	Sign	df	LR
Group [A-B]	-	1	4.010 *
Type [BCC-SCC]	+	1	4.035 *
Area		1	0.466 NS
Age		1	2.545 NS
Group * Area	-	1	4.849 *
Group * Age	+	1	5.201 *
Area * Type	-	1	5.282 *

df = degrees of freedom

LR = likelihood ratio

NS, $P>0.05$; *, $P<0.05$

One of the many advantages of simplified chemosurgery is that it is readily accepted by elderly patients who often fear conventional surgery and/or are a high risk for general anaesthesia. Post-treatment pain, however, has been a considerable drawback. The development of two optional methods that help reduce pain is an important improvement, namely for physicians who are required to treat patients in out-patient facilities, when low cost is an important factor.

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COMMENT

For some 22 years I unsuccessfully searched for a method to diminish or abolish the pain, which was the only disadvantage of simplified chemosurgery. One day, while driving to work, I suddenly remembered an ancient treatment for persistent pruritus of vulvar lichen sclerosus with dermal injections of alcohol. Some weeks

later, it occurred to me that, after cryosurgery, even very painful cancers become completely painless, due to damage to the respective sensitive nerves. This paper shows that both can eliminate pain. A young scientist [RBRA] currently doing research in the U.S. performed the statistical study.

Experimental Rationale for Treatment of High-Risk Human Melanoma with Zinc Chloride Fixative Paste

Increased Resistance to Tumor Challenge in Murine Melanoma Model

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BACKGROUND. Fixed-tissue micrographic surgery (Mohs) of melanoma has been shown by retrospective analysis to improve 5-year survival.

OBJECTIVES. To determine whether zinc chloride fixative paste acts as an immune adjuvant to increase host resistance to melanoma.

METHODS. We performed a murine study using the poorly immunogenic B16 melanoma of C57Bl/6J mice, and the more immunogenic K1735p melanoma of C3H/HeN mice. Tumors were treated with zinc chloride paste and excised 24 hours later (Group 1), or simply excised (Group 2). Mice were challenged 7

days later with injection of melanoma cells at a distant site, and tumor growth in this second site was followed.

RESULTS. K1735p melanomas developed at the challenge site in 69% of mice treated with excision versus 32% of mice treated with zinc chloride fixation ($P < 0.025$). Development of B16 melanoma was not altered by zinc chloride fixation.

CONCLUSION. Zinc chloride fixation of the more immunogenic K1735p melanoma increased resistance to subsequent tumor challenge, suggesting that zinc chloride fixative paste acts as an immune adjuvant. © 1998 by the American Society for Dermatologic Surgery, Inc. *Dermatol Surg* 1998;24:1021-1025.

The conventional treatment of cutaneous melanoma has been excision with a deep and wide margin of normal surrounding tissue depending upon the depth and thickness of the tumor. Adjuvant therapy has been recommended for melanoma patients in whom clinical and histopathological parameters indicate a high risk of relapse. Interferon α -2B has been approved by the U.S. Food and Drug Administration for treatment of such high-risk primary melanomas.¹ However, the survival from high-risk melanomas remains poor, and additional modalities are needed.

Clinical evidence suggests that an old modality, zinc chloride fixative paste, may improve the prognosis of high-risk melanoma. Retrospective data using historical control comparisons indicate that the use of zinc chloride fixative as an adjuvant to surgery significantly improves 5-year survival relative to conventional surgery

for high-risk melanoma. In 1977, Frederic E. Mohs published data on 103 consecutive patients with advanced melanomas treated with zinc chloride fixative (64% level 5 lesions, 20% regional lymph node involvement).² The 5-year survival rate was compared with a series of melanomas treated conventionally at the Massachusetts General Hospital, and stratified by level of invasion (Clark's level).³ Both studies were completed in 1968. In the conventional surgery series, all the melanomas were primary tumors without regional lymph node metastases, and the incidence of level 5 invasion was one-sixth that of the zinc chloride fixative cases. Despite the 20% incidence of nodal metastases in the zinc chloride fixative series, a significant ($P = 0.003$) improvement in 5-year survival was noted favoring the zinc chloride fixation with Mohs surgery.⁴

This remarkable result has not been fully appreciated, possibly because the mechanism of action of zinc chloride fixation has not been well understood. When applied before surgery, zinc chloride paste penetrates deeply, killing and histologically preserving the tissue. It was initially proposed that this acts to prevent iatrogenic spread of melanoma, and reduce the excision margins.⁵ This paper presents evidence that zinc chloride fixative acts additionally as an immune adjuvant, increasing host resistance to the melanoma.

A controlled murine study was performed comparing zinc chloride paste fixation with simple excision of

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melanoma. The murine melanoma lines used were K1735p and B16-F1. Mice were injected intradermally with melanoma cells, and the subsequent tumors were treated either by excision, or zinc chloride fixative paste followed by excision. After a 1-week rest, the mice were challenged at a different site with a second injection of the same melanoma cell line, and tumor appearance at the second site was monitored. Mice with K1735p melanoma treated with zinc chloride fixative paste had a significant reduction in tumor development at the second challenge site, suggesting that zinc chloride fixation had induced host resistance to the melanoma.

Materials and Methods

Mice

C57Bl/6J and C3H/HeN female mice, 5 weeks of age, were obtained from Jackson Laboratories. Mice were housed in the Department of Laboratory Animal Resources facility at SUNY at Stony Brook, and fed Purina chow and water ad lib. All animal protocols were approved by the Institutional Animal Care and Utilization Committee, and the animal facility is approved by AAALC.

Murine Melanomas

The K1735p melanoma line, which arose in a C3H/HeN mouse,⁶ was obtained from Margaret Kripke (Dept. of Immunology, MD Anderson Cancer Center, University of Texas). B16-F1 melanoma was obtained from ATCC (NBL line 6323). This tumor arose in a C57Bl/6J mouse. Both melanoma cell lines were cultured in RPMI 1640 media (Gibco, Grand Island, NY), supplemented with 10% fetal bovine serum (HyClone), 4 mM glutamine, and 5 μ g/mL gentamicin (both from Gibco).

Zinc Chloride Fixative Paste

Zinc chloride fixative paste was obtained from the School of Pharmacy, University of Wisconsin, (Madison, WI). The paste is composed of zinc chloride, stibnite, and *Sanguinarin cinnamensis*.⁷ A detailed description of the composition and use of this fixative paste has been published by Mohs.⁸

Initial Tumor Injection

Mice were shaved on the back and injected intradermally with 2.5×10^5 K1735b cells, or 5×10^5 B16 cells in a volume of 0.1 mL.

Anesthesia

Mice were anesthetized with a ketamine/xylazine mixture composed of three parts ketamine (Ketaset 100 mg/mL; Avenco, Dodge, Iowa), three parts sterile 0.9% saline (Kendall Laboratories, Irvine, CA), and two parts xylazine (Rompun 20 mg/mL; Haver, McBay, Shawnee, KA). The anesthetic mixture was injected intraperitoneally (0.03 mL per mouse).

Excision Technique for Melanomas

When maximal tumor diameter reached 6.0 mm, mice were alternately assigned to excision or zinc chloride fixative paste

treatment. Mice were anesthetized as above. The skin over the tumor was lifted with a forceps and a hemostat was clamped 3–4 mm below the tumor. The tumor was then shaved off with a scalpel, directly above the hemostat, and the linear wound was sutured with nylon sutures. Mice were housed in individual cages for 1 week after surgery.

Procedure for Treating Melanoma with Zinc Chloride Fixative Paste

Mice assigned for zinc chloride fixation were anesthetized, and the skin over the tumor was first treated with a cotton swab dipped in dichloroacetic acid (Sigma, St. Louis, MO). Zinc chloride fixative paste was then applied to the tumor in a thin layer using a cotton swab. The treatment site was occluded with gauze backed by cloth adhesive tape. Vaseline was applied to the gauze, and the dressing (vaseline, gauze, tape) was sutured over the tumor by one suture in each corner. The mice were housed in individual cages. On the following day the zinc chloride-fixed tumors were excised as above.

Tumor Challenge in Right Flank

One week after the completion of tumor treatments, all mice were injected subcutaneously in the right flank with either 1.5×10^5 K1735p cells, or 1×10^5 B16 cells in a volume of 0.1 mL. Mice were always challenged with the same tumor line as the initial back tumor. Cross challenge with different melanoma lines was not possible because the B16-F1 and K1735p melanomas arose in mice with different major histocompatibility antigens (C57Bl/6J vs C3H/HeN).

Observation of Mice for Tumor Development

Mice were examined twice weekly for the development of tumors in their flank. The mice injected with B16-F1 were examined for 60 days, and the mice injected with K1735p were examined for 90 days. After tumors reached 1.0 cm in diameter, the mice were sacrificed. No tumors were noted to regress.

Results

Zinc Chloride Fixation of the K1735 Melanoma Increased Resistance to Subsequent Tumor Challenge, Relative to Excision Alone

C3H/HeN female mice were injected with K1735p melanoma cells intradermally in their back. When the tumors reached 6 mm maximal diameter, the mice were alternately assigned to either excision, or zinc chloride fixative treatment followed 24 hours later by excision. One week after treatment, resistance to melanoma challenge was determined by injection of all mice with K1735p melanoma cells subcutaneously in the right flank. Mice were observed for tumor development.

Treatment with zinc chloride fixative paste resulted in significant resistance to subsequent challenge with the same melanoma cell line (Table 1 and Figure 1). The results were reproduced in 4/4 experiments, and when

Table 1. Zinc Chloride Fixation of K1735p Melanoma Induced Resistance to Subsequent Tumor Challenge

Group	Exp 1	Exp 2	Exp 3	Exp 4	Pooled No.
A. Zinc chloride	1/9*	3/8	5/10	3/11	12/38 (32%)
B. Simple excision	4/10	9/11	10/13	9/12	32/46 (69%)*

* Number of mice with tumors/total number of mice.

† $P < 0.025$ by Chi-square.

pooled were statistically significant (Chi square: $P < 0.025$).

Zinc Chloride Fixation of the Poorly Immunogenic B16-F1 Melanoma Had No Effect on Subsequent Tumor Challenge, Relative to Excision Alone

C57Bl/6j mice were injected with B16-F1 melanoma cells in the back, and treated with zinc chloride fixative paste followed by excision, or excision alone, as described above. The mice were then challenged with a second injection of B6-F1 cells subcutaneously in the right flank. There was no significant difference in tumor development between mice treated with excision, and mice treated with zinc chloride fixative paste followed by excision (Table 2 and Figure 2). This suggests that response to zinc chloride fixative paste is a function of the immunogenicity of the tumor.

Histologic Exam of Melanomas Fixed with Zinc Chloride Paste

K1735p melanomas were fixed with zinc chloride fixative paste for 24 hours, then excised. The excised tumors were placed in formalin, embedded in paraffin, and stained with hematoxylin & eosin (Figure 3). The architecture and cellular detail of the tumor was well preserved. There was a modest inflammatory infiltrate at the tumor margin composed of mononuclear cells and

Figure 1. Percent of mice free of K1735p melanoma. Mice were treated for a K1735p melanoma on their back with zinc chloride fixative paste, or excision alone, then injected with K1735p cells in their right flank.

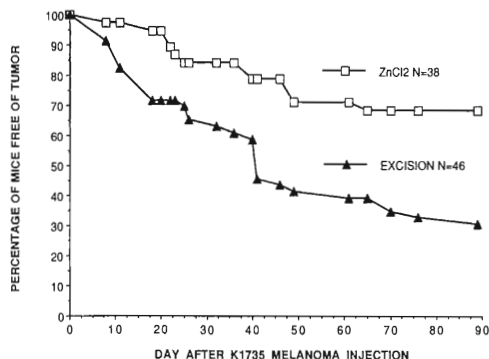


Table 2. Zinc Chloride Fixation of B16-F1 Melanoma Did Not Have a Significant Effect on Resistance to Subsequent Tumor Challenge

Group	Exp 1	Exp 2	Exp 3	Pooled No.
A. Zinc chloride	2/6*	2/9	8/12	12/27 (44%)
B. Simple excision	6/8	2/9	7/11	15/28 (53%)

* Number of mice with tumors/total number of mice.

neutrophils. Scant infiltration of mononuclear cells and neutrophils was also seen in the margins of K1735p tumors excised without zinc chloride fixation (Figure 4).

Discussion

Fixation of the K1735p melanoma with zinc chloride fixative paste resulted in resistance to subsequent challenge with the same tumor. Similar treatment of the poorly immunogenic B16-F1 melanoma did not result in resistance to tumor challenge, indicating that the response to zinc chloride fixative paste was a function of the immunogenicity of the tumor. It is hypothesized that the zinc chloride fixation had an immune adjuvant, or vaccine-like effect, that induced host cell-mediated resistance to the K1735p melanoma. Nonspecific inflammation alone did not suffice to explain the result, since zinc chloride fixative paste did not induce resistance to the poorly immunogenic B16-F1 melanoma.

It remains possible, although unlikely, that the effect of the $ZnCl_2$ treatment is the result of the $ZnCl_2$ treatment alone, and not that of the $ZnCl_2$ treatment plus melanoma. If this is the case, one would need to propose that the inflammation induced by $ZnCl_2$ treatment results in a nonspecific immunity at a distant site lasting for up to 1 week, and resulting in tumor rejection, selectively, of the more immunogenic melanoma.

Histology revealed only a modest inflammatory in-

Figure 2. Percent of mice free of B16-F1 melanoma. Mice were treated for a B16-F1 melanoma on their back with zinc chloride fixative paste, or excision alone, then injected with B16-F1 cells in their right flank.

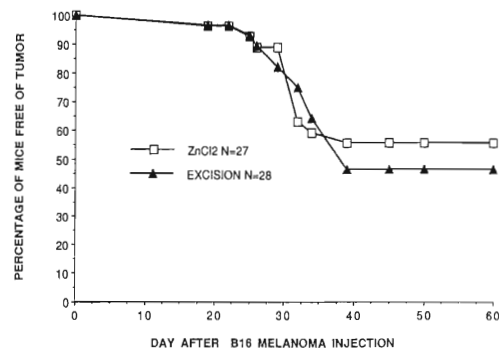




Figure 3. Histology of K1735p melanoma fixed with zinc chloride fixative paste for 24 hours: A) $\times 25$; B) $\times 250$.

filtrate at the tumor margins after fixation with zinc chloride fixative paste. This suggests that an adjuvant effect of zinc chloride fixation is manifest in draining lymph nodes, rather than at the site of the tumor.

There is a great need for new and additional modalities for the treatment of high-risk melanoma. The gain in survival with interferon therapy, although statistically significant, is disappointing.¹ Vaccines are being investigated as potential adjuvant therapies for intermediate and high-risk melanomas,⁹⁻¹¹ and immunotherapy with antigen-pulsed dendritic antigen presenting cells is currently attracting much interest.¹²

K1735 melanoma has been used in many studies of the immunotherapy of melanoma. Transfection of K1735 tumor cells with the co-stimulatory molecule B7-1 (CD80) results in a highly immunogenic tumor line capable of protecting against inocula of nontransfected K1735 cells.¹³⁻¹⁶ K1735 cells without such manipulations are much less immunogenic. In contrast, the B16 melanoma is very poorly immunogenic, on the basis of low expression of class I major histocompatibility antigens.¹⁷ Unlike K1735, the response to B16 melanoma is poor after immunization with B7-1-transfected tumor

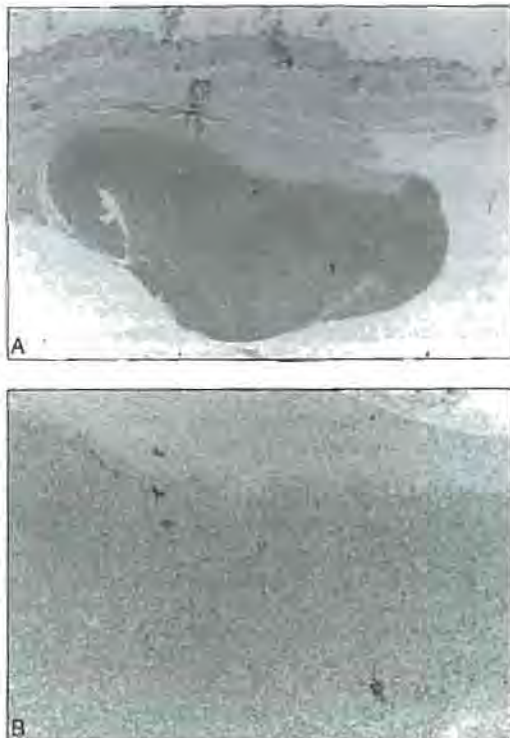


Figure 4. Histology of K1735p melanoma excised without zinc chloride fixative paste: A) $\times 25$; B) $\times 250$.

cells.¹⁸ This lack of response can be corrected by treatment with interleukin 12.

Based on the lack of effect of the zinc chloride fixation on the poorly immunogenic B16-F1 melanoma, it would be predicted that this treatment would not be of benefit to patients with tumors of low immunogenicity. However, it has been shown in experimental systems that interleukin 12 and gamma-interferon are able to improve the response of poorly immunogenic tumors such as B16 to immunotherapy.^{19,20} It is possible that cytokine therapy may improve the response of poorly immunogenic melanomas to zinc chloride fixation.

Enhancement of antitumor immunity with zinc chloride paste could potentially reduce metastases in melanoma patients. This is consistent with the finding that treatment of human melanoma with zinc chloride fixative paste results in improved 5-year survival. One possible clinical application of this technique may be to apply zinc chloride fixative paste to high-risk or advanced melanoma after an incisional biopsy.

The use of zinc chloride fixative paste for Mohs surgery of melanoma should not be confused with the fresh tissue technique, which uses frozen sections of unfixed tissue. A recent retrospective study of Mohs

surgery for melanoma with fresh tissue technique found no difference in survival from historical controls.²¹

Hybrid Mohs surgery, in which the tumor is first excised as fresh tissue, and the base of the wound is treated with zinc chloride fixative paste, has also been used for human melanoma. Comparison of 113 cases treated with the hybrid technique, with 61 cases treated with fresh tissue technique, demonstrated no advantage for the hybrid Mohs technique for thin or intermediate level melanomas.²² This demonstrates that zinc chloride fixative paste alone, in the absence of melanoma cells, has no benefit in the treatment of human melanoma. Based on the results of the historical control study,⁴ and the findings in this experiment, it appears that the benefits derived from zinc chloride require fixation of the melanoma to induce the immune response.

In conclusion, zinc chloride fixative paste acted as an immune adjuvant to induce resistance to melanoma in mice. These data provide an experimental basis for the use of zinc chloride fixation for human melanoma, and support the need for a randomized clinical trial.

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COMMENT

This important paper that closes this Special Issue does not require an elaborate comment. In any case, I could not do it with the indispensable penetrating analysis, since immunology is not my field of research. However, I would like to stress the fact that the zinc chloride paste is the only treatment that seems to enhance the defence against melanoma, as was demonstrated by

Kalish and collaborators. This type of research is not fashionable (in Medicine also, there are too many fashions!), but I hope that some open-minded researcher will continue this important immunologic study. Each year thousands of new patients are diagnosed with malignant melanoma; they merit the interest of researchers, even if the suggested method is not in fashion.

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