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Electrochemotherapy in non-melanoma head and neck skin cancers: a three centers experience and literature review

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ABSTRACT

AIM

The main purposes of this study were to evaluate the efficacy of electrochemotherapy in head and neck tumours, to assess the local tumour control, the safety profile and its impact on the patients' quality of life.

METHODS

This is a multicenter prospective, non-randomized phase II trial.

This trial was carried out at the Dermatologic Clinic of University of Rome "La Sapienza", at the Dermatologic Clinic of University of Chieti and at the Dermatologic Clinic of University of Turin.

55 patients with head and neck cancers were recruited. The electrochemotherapy procedure was carried out according to the ESOPE guidelines. Statistical analyses were performed using Stata/SE12.0 Statistical Software

RESULTS

A significant clinical response was achieved in 50/55 patients with 91% of objective response rate (OR). 33 of 55 patients showed a CR (60%); 17 treated patients had a PR (31%). A significantly higher CR rate was obtained in patients

not previously treated by surgery (15/19; 79%), with respect to those with a previous excision of the tumour (14/30; 47%) (p=0.025). An additional parameter influencing response is represented by anesthesia: patients treated by ECT with general anesthesia were characterized by significantly higher CR rate (68%) than those treated with local anesthesia (27%) (p=0.014).

CONCLUSIONS:

Our experience confirmed high efficiency in local tumour control, excellent toxicity profile, tissue preservation with good cosmetic and functional results, even with repeated applications. ECT can represent a first-line treatment in the local management of head and neck cancers.

Keywords: Electrochemotherapy; head and neck cancers; treatment.

INTRODUCTION

Head and neck cancers (HNC) are the sixth most common cancer worldwide and accounts for approximately 350,000 deaths for year. In this category basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) represent more than the 90% of the diagnosis.[1] These tumours are associated with high morbidity when they are locally advanced. Treatment options are manifold. Surgery, radiation therapy, and chemotherapy are the mainstays of treating HNC, although they often leave the patient with disfigurement and long lasting adverse effects on physiologic functions. The success rate of multimodality treatment for patients with advanced disease is low, ranging between 10 and 20%.[2]

Given the poor response rates in patients with HNC and side effects associated with standard treatments, alternative therapeutic methods have to be developed. Electrochemotherapy (ECT) is a new local treatment for primary skin tumours and cutaneous metastatic nodules. This promising procedure combines the activity of anticancer drugs (e.g., bleomycin or cisplatin), to short, intense electrical pulses (electroporation), delivered locally to increase cell permeability by enhancing drug uptake. ECT not only magnifies drug cytotoxicity, but also produces antitumor vascular effects. Transient vasoconstriction leads to drug retention in the tumour cells and also endothelial cell destruction. The synergism of these effects explains

the favorable results of ECT.[3, 4]

Electroporation was introduced and developed at the Institute "Gustave Roussy" in the early 1980s to transfer genes into mammalian cells. During the following years, its application was extended to facilitate delivery of DNA, chemotherapeutic agents and other drugs into cells.

In HNC, ECT was first used in patients with cutaneous metastasis in 1991.[5] Subsequently, Panje et al. described their experience with EPT and intratumorally applied bleomycin in 10 patients with recurrent SCCs.[6] In 2006, the multicenter European Standard Operating Procedures of Electrochemotherapy (ESOPE) project has provided the necessary guidelines for the use of ECT.[7]

Our study describes 55 patients treated by ECT with intravenous bleomycin at three different Italian dermatologic centers. The aim was to evaluate the efficacy of ECT in achieving local tumour control; the toxicity profile of this modality and the impact on the patients' quality of life.

MATERIALS AND METHODS

Study design

This is a multicenter, prospective, non-randomized phase II trial carried out at the Dermatologic and Plastic Surgery Clinic of University of Rome "Sapienza", at the Dermatologic Clinic of University of Chieti and at the Dermatologic Clinic of University of Turin. The main purposes of this study were to evaluate the clinical efficacy of ECT in HNC, to assess the local tumour control and function and organ sparing.

Other endpoints were safety and tolerability of this treatment and its ability to improve the quality of life for the best aesthetic results.

This trial was approved by each hospital ethical committee and all patients provided written informed consent before ECT treatment.

Patients

55 patients, 41 men and 14 women with a median age of 80 years (range 42-94), were recruited into the study from October 2005 to March 2013.

Inclusion criteria were the following: presence of a cutaneous tumour localized in the head and neck area, patient unable and unwilling to undergo surgery or radiotherapy, recurrent cancers after other therapies, measurable cutaneous tumour

lesions with a maximum depth of 3 cm, normal hepatic and renal function, performance status between 0-2 seconds the scale of the Eastern cooperative Oncology Group (ECOG).[8] Exclusion criteria: history of allergic reactions or hypersensitivity to bleomycin, liver or kidney failure, reduced lung function, history of epilepsy, severe cardiac arrhythmias, condition of pregnancy or lactation, previous treatment with bleomycin at the maximum cumulative dose (250 000 IU/m2).

The clinical and pathological characteristics of patients and tumours located in the head and neck district and treated by ECT are summarized in *Table 1*.

About to the localization 26 (48%) lesions were on the scalp; 7 (13%) involved the ear; 7 (13%) the nose; 3 (5%) the front; 3 (5%) the cheek; 3 (5%) the ocular region and 6 (11%) in other head and neck areas.

The histological characteristics of the different tumour subtypes were evaluated with biopsies. 25 patients enrolled had SCC (45.5%) and 24 BCC (43.6%); the 6 remaining patients had different tumour types (2 Merkel cell carcinoma and 1 respectively Kaposi sarcoma, angiosarcoma, parotid adenocarcinoma and metastatic rhabdomyosarcoma).

The T2 classification was the most frequent, particularly for SCC (84% of cases). Treated lesions had a diameter ranged widely between 5 mm and more than 150 mm

(median 30 mm).

The majority of patients (64%) received already one or more treatments before ECT, specifically 20 patients (36%) were treated previously only with surgery, 11 patients (20%) with surgery and other treatments; 4 (8%) with cryotherapy; 20 patients (36%) had not received any treatment before ECT.

ECT procedure

The technical procedure was carried out according to the ESOPE guidelines.[7]

A total of 55 cutaneous lesions were treated in 78 (68%) courses of ECT. All the patients received at least 1 ECT course; 11 (12%) patients were treated with two cycles (20%), 12 (11%) with three (21,8%). The subsequent courses were repeated after a 2 to 3 month from the previous ones.

Before treatment, the medical histories of patients were collected, and physical examination, laboratory tests, electro-cardiography and imaging studies were performed.

ECT was performed in the majority of cases under general anesthesia (44 cases, 80%); local anesthesia plus sedation was however used in 11 patients (20%). Mild general anesthesia consisted of premedication with oral benzodiazepine (chlordemethyldiazepam), induction with a short-acting intravenous anesthetic

agent (propofol 2.5 mg/kg), inhalation of anesthetic vapor (sevoflurane 2%), and assisted ventilation air/oxygen 40%; local anesthesia consisted of intratumoural injection of only lidocaine or lidocaine and epinephrine. All the patients were treated with intravenous bolus of bleomycin at a dosage of 15 mg/m2 injected in 60 seconds. Eight minutes after the infusion, the electrical pulses (variable amplitude with 1-5000 Hz delivery frequencies) were delivered by a square wave pulse generator: CliniporatorTM (IGEA, Carpi, Italy). Three different types of electrodes were used, chosen according to lesions' features. The hexagonal needles were the most frequently used (42 patients, 76.4%), followed by the linear (11 cases, 20%) and plates (only 2 cases, 3.6%). The electroporation was completed within 28 min from bleomycin infusion. The complete coverage of the tumour area and the effectiveness of pulse delivery were ensured.

The procedure was performed either on a Day hospital setting or during an one-day hospitalization with a maximum observation period of 24 hours. Following treatment, patients underwent regular clinical visits. The median follow-up after treatment was 8 months with a range of 3-27 months.

Response Evaluation and Follow-up

For each patient the tumour size was measured by calipers considering the sum of the largest diameter of the lesions according to the Response Evaluation Criteria in

Solid Tumours (RECIST).[9]

The formal evaluation of clinical response was performed after 8 weeks from the ECT procedure; thereafter lesions were evaluated, photographed and measured at monthly intervals.

The clinical response was evaluated according to the RECIST as follows: progressive disease (PD) for an increase in sum of diameters of >20%; partial response (PR) for a decrease of 30% for at least 4 weeks; stable disease (SD) for an increase of <20% or a decrease of <50%; and complete response (CR) for total clinical disappearance of the lesion.

Case Record Forms (CRF) were filled with patient's data before and after the treatment; for each patient quality of life was assessed by a questionnaire (EQ-5D).[10]

Statistical analyses

Pearson's chi squared and Student's t-tests were used to compare categorical and continuous variables, respectively on the achievement of a complete response in patients with the two mayor histologies. Logistic regression was used to evaluate the association between clinical feature and the complete response. For the model Maximum size was assumed as linear, type of anesthesia, previous surgery, gender, scalp site were assumed as categories. Scalp site was used in the multivariate logistic

model as single site compared to the other as this location report different response rate according to literature data. All statistical tests were two sides. P-values <0.05 were considered significant. Statistical analyses were performed using Stata/SE12.0 Statistical Software (STATA, College Station, TX). *Table 2*

RESULTS ECT sessions

A significant clinical response was achieved in 50/55 patients with 91% of objective response rate (OR). 33 of 55 patients showed a CR (60%); 17 treated patients had a PR (31%); 4 patients presented a SD (7%) and only 1 underwent a PD (1,8%). All tumour responses were confirmed by biopsy and histological examination. *Fig. 1* A-B

A complete response was obtained in 67% of patients with BCCs in 52% of patients with SCCs and in all the patients with Merkel cell carcinoma (2 cases) angiosarcoma and Kaposi sarcoma (1 case each). In 9% ECT had a palliative role (3 SCC, 1 parotid adenocarcinoma, 1 rhabdomyosarcoma) and in 1.8% a neoadjuvant role (1 SCC).

A series of parameters were evaluated to identify predictive factors associated to a higher likelihood of obtaining a complete response (CR) in BCC and SCC patients. Age, gender, BCC vs. SCC, tumour site and tumour classification were not

associated to a different CR rate. On the other hand, a significantly higher CR rate was obtained in patients not previously treated by surgery (15/19; 79%), with respect to those with a previous excision of the tumour (14/30; 47%) (p=0.025). *Fig. 2* A

When stratifying patients according to the tumor size, it appears that the unfavorable predictive value of previous surgery on the ECT response rate is maintained for lesions larger than 2 cm, but not for smaller lesions. Indeed, in patients previously treated by surgery, a CR was obtained in 7/11 (64%), with tumour size smaller than 2 cm but in only 7/19 (36%) with larger tumours. *Fig. 2* B

Another parameter associated to a higher CR rate is local *vs* general anesthesia: patients treated by ECT with general anesthesia were characterized by a significantly higher CR rate (26/38; 68%) than those treated with local anesthesia (3/11, 27%) (p=0.014). *Table 3*

Patients Outcomes

48 patients maintained the response after a median follow-up of 13 months (range 6 - 36, average 21) from the treatment. None of the lesions that achieved a CR relapsed after a median follow-up period of 14 months (range, 6 - 36 months). At the time of writing, 2 out of 17 PR patients maintained their clinical response, whilst the other 15 PR patients have been submitted to further ECTs or other treatments. Two patients died for disease progression outside the treated area and 1 patient died for

local progression. Two further patients died of unrelated causes.

Toxicity and Quality of life

Local and systemic toxicity were graded according to Common Terminology Criteria for Adverse Events CTCAE 3.0. The treatment was generally well tolerated, with the majority of patients experiencing no toxicities (31 cases; 56%). Anesthesia was well tolerated by all patients and no adverse events were reported. No hematological toxicity due to bleomycin have been observed. The most frequent side effect was pain, which occurred after 24-48 from the procedure in 12 patients. This was reported as mild in 9 and severe only in 3 patients. The occurrence of pain was related to the development of post-treatment ulceration. Indeed, ulceration occurred only in 6 patients and all of them complained for pain. Other less frequent side effects, occurred in less than 10% of patients and in all cases mild and transient, were represented by redness with or without edema at the site of electric pulses delivery, pruritus, asthenia and fever. Patients' quality of life, assessed with the EQ5D visual analog scale, was improved after 2 months compared with baseline assessment.

DISCUSSION AND REVIEW OF THE LITERATURE

In this article we report the results of a prospective non-randomized phase II trial aimed at the evaluation of the clinical efficacy of ECT in HNC. 55 patients were enrolled from three separate Italian centers and were treated with the same protocol,

according to the ESOPE procedures, using the Cliniporator.[7, 11] To our knowledge, our study represents the largest case series of head and neck tumours cases treated with ECT.

Indeed, only few papers on small patient series or case reports have been specifically focused on the evaluation of clinical activity and toxicity of electroporation with bleomycin in HNC. *Table 4*

Belechradek et al. reported the results of a trial on eight patients with 42 nodules of head and neck SCCs treated with intravenous bleomycin followed by electroporation. Complete remission was observed in 23 nodules and partial remission in six.[12]

Hofmann et al. treated 10 patients with advanced stage head and neck SCC, obtaining 5 CR and 3 PR, while the remaining two patients had only part of the tumour treated.[13]

After an initial prospective study by Panje on 10 patients treated with ECT, Allegretti and Panje used this approach to treat 4 additional patients with HNC. In a total of 14 patients 6 patients had a CR, 6 had a PR, and 2 did not respond (OR 85.7%).[6, 14]

Tijink B.M. et al. presented a case series of 7 patients, with recurrent or metastatic HNC, for a total of 17 tumors, treated with ECT. Local tumour control was reached in 14/17 lesions (82.4 %).[15]

Bloom D.C. et al. demonstrated, in a group of patients with advanced head and neck

SCC, that a clinically significant response and palliative benefits are obtained with intratumoral bleomycin followed by electroporation, while intratumoral bleomycin alone had a poor response rate.[16]

A case series of 6 patients with skin cancer of the head and neck treated using ECT with intratumoral bleomycin were reported by Landstrom F.J.et al: in 4 out of 6 patients, one treatment was enough to eradicate the tumour with satisfactory cosmetic results.[17]

In 2011 Marenco F. et al. reported a case of recurrent SCC of the scalp treated with ECT, getting a good local control of the disease.[18]

Gargiulo et al. reported encouraging results (100% OR, 72% CR) on 25 patients affected by primary or relapsed cutaneous and subcutaneous non-melanoma cancers in the head and neck region treated with ECT and intravenous bleomycin.[19]

In 2012 Mevio et al. published preliminary results of their clinical trial; of the 31 lesions measurable 29 showed an OR (94%).[20]

Seccia et al. in 2014 explored the application of ECT in 14 recurrent or persistent SCCs in the head and neck area. 4/14 lesions exhibited a CR, 6/14 a PR (71,4% OR).[21]

In 2014 Campana et al. reviewed a 2-centre database, and found 39 patients with 24 SCCs, 9 BCCs and 6 adenocarcinoma. OR and CR rates were 59% and 38%, respectively. Tumour response was significantly better in patients with small,

primary tumours and also with intravenous bleomycin. The patient who was given bleomycin intravenously, followed by electroporation with a plate electrode, achieved a CR. BCC responded better.[22]

Our results, in agreement with literature data, confirm the effectiveness of this technique, showing an OR rate of 91%.

No data are reported in literature as to the clinical parameters associated to a higher clinical response rate in HNC. On the other hand in all types of tumour, the parameters associated with response to ECT are represented by tumour size, histology and location, dose and route of administration, electrode type and accuracy in electrode placement and intensity of pulse delivery. Mali B. et al showed that ECT was less effective on tumours larger than 3 cm compared to tumours smaller than 3 cm.[23, 24] Our results demonstrated that age, gender, BCC or SCC, tumour site and tumour classification do not affect CR rate. Furthermore, we observed a significantly higher CR rate in patients not previously treated by surgery (79%), with respect to those with a previous excision of the tumour (47%) (p=0.025). As to tumour size in patients previously treated by surgery, a CR was obtained in 64% with tumour size smaller than 2 cm but in only 36% with larger tumours. The difference in response can be explained both by the more malignant behavior of tumours that relapse after proper surgical treatment and by the alterations in blood flow after surgery with subsequent irregular drug distribution. In fact, we observed that patients with a

surface tumour size of 5-10 cm^2 or maximum tumour size 2-5 cm^2 benefit most from ECT as first-line treatment, even though this phenomenon was not verified in squamous cell carcinoma and in lesion on the scalp. An additional parameter influencing response is represented by anesthesia: patients treated by ECT with general anesthesia were characterized by significantly higher CR rate (68%) than those treated with local anesthesia (27%) (p=0.014); narcosis probably allows a more accurate electrode placement and coverage of the tumour area and repeated pulse delivery, while a treatment conducted in local anesthesia may be unpleasant for the patient and thus influence duration and completion of the session.

CONCLUSIONS

HNC represent a challenge in terms of therapy and management for the involvement of important anatomic structures and the elder age of patients. Although surgery remains the gold standard of treatment, it can cause functional and aesthetical impairment without always achieving radicality. Moreover, chemotherapy and radiotherapy are often ineffective and disabling, or contraindicated for the

anatomical site or general conditions of the patient.

Our experience confirmed the well-known advantages of ECT: high efficiency in local tumour control, excellent toxicity profile, tissue preservation with good cosmetic and functional results, even with repeated applications, and finally favorable cost-effectiveness ratio.

The efficacy of ECT in the treatment of skin and mucosal tumours is proved by the fact that from a palliative role for painful and bleeding lesions, it can now be seen in neoadjuvant or curative settings.[25, 26]

Also in the local management of HNC ECT confirms its valid therapeutic tool and can represent a first-line treatment, especially in selected cases with limited disease, indolent behavior or elderly patients, avoiding demolitive surgery that would cause cosmetic and functional impairment.

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Table 1. Clinical - pathological characteristics of patients before ECT

Table 2. LOGISTIC REGRESSION on the complete response (n=49)

Table 3. BCC and SCC: parameters predictive of complete response

Table 4. Review of the literature

Figures 1 A - B.
A) Basal cell carcinoma, infiltrating the dermis, the parotid gland and the sternocleidomastoid and masseter muscles (80x70x50 mm). Before ECT session.

B) Complete remission after 20 months after ECT session.

Figures 2 A - B.
A) Results: a significantly higher CR rate was obtained in patients not previously treated by surgery (p=0.025).

B) Results: CR was obtained in 7/11 with tumours <2 cm but in only 7/19 with larger tumours.

Table 1. Clinical - pathological characteristics of patients before ECT

Factor	Basal cell carcinoma (n=24)	Squamous cell carcinoma (n=25)	Others (n=6)	Total (n=55)
Gender				
- Male	17 (71%)	21 (84%)	3 (50%)	41 (75%)
- Female	7 (29%)	4 (16%)	3 (50%)	14 (25%)
Age at treatment				
- Median	75	84	84.5	80
- range	42-94	61-93	58-88	42-94
Max tumour diameter				
- median (mm)	24	30	32.5	30
- range	8-154	5-115	15-80	5-154
Tumour classification:				
- T1	8 (33%)	2 (8%)	2 (33.5%)	12 (22%)
- T2	14 (59%)	21 (84%)	2 (33.5%)	37 (67%)
- T3	2 (8%)	2 (8%)	1 (16.5%)	5 (9%)
- NA	-	-	1 (16.5%)	1 (2%)
Tumour site				
- nose	6 (25%)	1 (4%)	-	7 (13%)
- front	1 (4%)	2 (8%)	-	3 (5%)
- cheek	1 (4%)	2 (8%)	-	3 (5%)
- ocular region	3 (12%)	-	-	3 (5%)
- ear	2 (8%)	5 (20%)	-	7 (13%)
- scalp	10 (42%)	13 (52%)	3 (50%)	26 (48%)
- NA	1 (4%)	2 (8%)	3 (50%)	6 (11%)
Previous treatments:				
- none	7 (29%)	8 (32%)	5 (83%)	20 (36%)
- surgery	13 (54%)	7 (28%)	-	20 (36%)
- surgery plus others*	3 (13%)	7 (28%)	1 (17%)	11 (20%)
- cryo	1 (4%)	3 (12%)	-	4 (8%)
ECT sessions:				
- 1	12 (50%)	18 (72%)	2 (34%)	32 (58%)

- 2 - 3 - >3	4 (17%) 5 (20%) 3 (13%)	4 (16%) 3 (12%) -	3 (50%) 1 (16%) -	11 (20%) 9 (16%) 3 (6%)
Clinical response - CR - PR - SD - PD	 18 (75%) 6 (25 %) - -	 13 (52%) 8 (32%) 3 (12%) 1 (4%)	 4 (66%) 1 (17%) 1 (17%) -	 33 (60%) 17 (31%) 4 (7%) 1 (2%)

Table 2. LOGISTIC REGRESSION on the complete response (n=49)

CR		OR	P	IC
MAX SIZE(mm)	Linear	.9830643	0.234	.9557846 1.011123
SCALP SITE		1.431046	0.606	.366487 5.587898
HISTOLOGY	SQUAMOUS *VS* BASAL CELL CARCINOMA	.2688105	0.096	.0571091 1.265282
PREVIOUS SURGERY PERFORMED		.2949917	0.133	.0600501 1.449124
ANESTHESIA	GENERAL *VS* LOCAL	7.789997	0.038	1.125847 53.9008
SEX	MALE *VS* FEMALE	.5555184	0.501	.1003824 3.074252

Table 3. BCC and SCC: parameters predictive of complete response

		Complete response	Non complete response	p
	Basal cell carcinoma	16	8	ns
	Squamous cell carcinoma	13	12	
Localization	Scalp	14	9	ns
	No scalp	15	11	
Tumour surface	< 1cm	5	5	ns
	1-1.99	4	4	
	2-4.99	5	5	
	5-9.99	7	7	
	10-19.99	3	3	
	>=20	5	6	
Tumour max size	<1 cm	3	1	ns
	1-1,99 cm	9	3	
	2-4.99 cm	12	8	
	>5 cm	5	8	
Previous Surgery	yes	14	16	0.025
	no	15	4	
Pain	yes	7	5	ns
	no	22	15	
Narcosi	yes	26	12	0.014
	no	3	8	

Table 4. Review of the literature

	N° patients treated	N° nodules	Histology	Drug and route	Objective Response (CR+PR)
Belechradek, 1993[12]	8	42	SCC	Bleomycin i.v.	69%
Hofmann, 1999[13]	10	10	SCC	Bleomycin i.t.	80%
Allegretti and Panje, 2001[14]	14	14	SCC	Bleomycin i.t.	85,7%
Tijink, 2006[15]	7	17	SCC, Merkel Cell Carcinoma, Melanoma, Sarcoma	Bleomycin i.t.	82,3%
Bloom, 2005[16]	54	69	SCC	Bleomycin i.t.	56,5%
Landstrom, 2010[17]	6	6	BCC, SCC	Bleomycin i.t.	66,6%
Marenco, 2011[18]	1	1	SCC	Bleomycin i.v.	100%
Gargiulo, 2012[19]	25	25	BCC, SCC, Bowen Disease	Bleomycin i.v.	100%
Mevio, 2012[20]	15	31	SCC, BCC, Merkel Cell Carcinoma	Bleomycin i.v.	94%
Seccia, 2014[22]	9	14	SCC	Bleomycin i.v.	71,4%
Campana, 2014[23]	39	81	SCC, BCC, Adenocarcinoma	Bleomycin i.v., Bleomycin i.t., Cisplatin i.t.	59%