Gynecologic Oncology 130 (2013) 550–553

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Electrochemotherapy can be used as palliative treatment in patients with repeated loco-regional recurrence of squamous vulvar cancer: a preliminary study ☆

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HIGHLIGHTS

- Patients with recurrence of vulvar cancer were submitted to electrochemotherapy
- The treatment was effective to improve symptoms and easy to perform
- The treatment is able to achieve a local control of disease

ARTICLE INFO

Article history:
Received 4 May 2013
Accepted 20 June 2013
Available online 28 June 2013

Keywords:
Electrochemotherapy
Vulvar cancer
Recurrence
Palliative cure

ABSTRACT

Objective. Electrochemotherapy (ECT) is an attractive treatment for solid cutaneous tumours with a good response rate (55–92%). No studies have evaluated ECT performed in vulvar cancer. The aim of our study was to evaluate the safety, local tumour efficacy and relief of symptoms of ECT treatment in patients affected by recurrence of squamocellular vulvar cancer (V-SCC) unsuitable for standard treatments.

Methods. We enrolled nine patients with histological diagnosis of recurrence of V-SCC. Intravenous bleomycin was injected under general sedation after an accurate mapping of all lesions and ECT was performed. Patients were reviewed after one, three and six months. Response to therapy was evaluated using RECIST criteria and quality of life (QoL) was evaluated via questionnaires.

Results. The median age was 84 years (range 80–90 years). The main location of recurrences was the vulva (87.5%). Multiple lesions were present in 25% of cases. No peri-operative complications were observed. Response to therapy was complete in 62.5% of patients, partial in 12.5%, no change was observed in 12.5% and progression of disease in 12.5% of patients respectively. Evaluation of symptoms showed a significant reduction of pain, bleeding, odour ($p < 0.04$) and urinary discomfort ($p < 0.04$). We observed two relapses at four and seven months after treatment. After nine months fifty percent of patients were alive.

Conclusions. Our preliminary study showed that ECT is a suitable procedure in elderly patients with loco-regional vulvar cancer relapses. ECT can be used as palliative therapy and the treatment relieves symptoms and improves QoL.

Introduction

Vulvar cancer represents 5% of all female gynaecologic malignancies and its incidence is 10 times higher in patients over 75 years of age [1]. Treatment and management represent a challenge because of its anatomic location, tendency to spread to the lymph nodes and incidence in the elderly [2].

In the past radical surgery was the primary treatment option in both early and late stages. Nowadays surgery still has an important role but neo/adjuvant chemo and radiotherapy are used to decrease postoperative complications and improve prognosis [3].

Despite this multimodal approach recurrence, especially in advanced stages, is not rare [4]. Loco-regional recurrence is an important risk factor for distant metastatic disease, either synchrone or metachrone with a negative effect on quality of life (QoL) (local pain, vaginal bleeding,

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0090-8258/$ – see front matter
http://dx.doi.org/10.1016/j.ygyno.2013.06.028

burning and odour) [5]. Therapy for this pattern of recurrence is limited and options are based on the volume and site of the disease. After multidisciplinary treatment for recurrences surgical resection remains the preferred therapeutic approach [6]. However when surgery cannot be performed with a reasonable cosmetic and functional outcome, other options must be evaluated.

Electrochemotherapy (ECT) is a recent loco-regional therapy that combines low-dose cytotoxic drugs (bleomcyn and cisplatin), administered intravenously or intra-lesionally, and high intensity electric pulses to induce electroporation to improve drug delivery into tumour cells [7].

ECT is used in humans for the treatment of cutaneous neoplasms or the palliation of skin tumour metastases. Since 1995 literature has reported a 92% response rate in patients treated with ECT for disseminated cutaneous and subcutaneous melanoma lesions as a palliative cure [8,9]. In 2006 a multicentre study performed by the European Standard Operating Procedure for Electrochemotherapy (ESOPE) defined the parameters for using ECT. ECT can be proposed in cutaneous metastasis that cannot be excised because of the number and/or site of the tumour and in a palliative setting the procedure offers a good response (85%) and improves patient QoL [10].

In literature, no study has previously evaluated whether ECT could be used for local treatment in cutaneous recurrences of squamous cellular vulvar cancer (V-SCC).

The aim of this preliminary study was to evaluate the safety, local efficacy, acceptability and QoL of ECT with bleomycin in reducing the size of tumours in patients with V-SCC with loco-regional cutaneous recurrence submitted to multiple previous treatments (chemotherapy, radiotherapy and surgery) and unsuitable for standard treatments.

Materials and methods

In our prospective preliminary study we recruited nine women with histological diagnosis of single or multiple loco-regional recurrences of V-SCC. Patients were unsuitable for standard treatments because of tumour characteristics (previous multiple surgeries or previous radiotherapy) and general status and were invited to participate in the study to undergo palliative therapy with ECT.

Inclusion criteria and technical procedures followed the European Standard Operating Procedures of ECT Study (ESOPE) [11]. The study was approved by the local ethical committee and all patients signed an informed consent form before enrolment.

Before initiating the procedure accurate digital mapping of all lesions was performed and the area involved was sketched. All nodules were measured and the tumour area was calculated [11]. If multiple nodules were present the area was the sum of the area of each lesion. A full clinical history, clinical examination, routine blood biochemistry, computer tomography scan (CT) and 18 F-FDG-PET/CT to evaluate distant metastasis were required.

The procedure required a hospital stay of 24 h and general sedation.

Intravenous Bleomycin (Bleomicina Nippon K fl) was injected in an i.v. bolus (30 s) at a dose of 15000 UI/m2. Electrical pulses started eight minutes after bolus and treatment was completed 28 min after the end of infusion [11]. ECT electroporation was performed using a Cliniporator device with type III electrodes placed into the lesion (Igea S.p.A. Carpi Italy). Pulse delivery frequency was 5 kHz at a duration of 100 μs. Electrodes were gently inserted into the skin of the area affected at a depth of one centimeter; the procedure was repeated progressively covering all of the area to be treated.

Patients were seen again four weeks after the procedure and then every four months. During follow-up treatment efficacy was determined by careful inspection of genitalia and the pelvic region and all new suspected lesions were mapped and a histological sample was taken. ECT response criteria was defined according to the WHO Handbook for Reporting Results of Cancer Treatment [12]: complete response (CR) when the tumour nodule was not palpable; partial response (PR) when the tumour size decreased by more than 50% in the products of the largest perpendicular diameters of the measurable lesions; no change (NC) when the lesion had a reduction <50% and an increase of up to 25%; progressive disease (PD) when the tumour size had increased by more than 25%.

To evaluate an improvement in QoL following ECT treatment we administered visual analogue score (VAS) for pain and vulvar cancer subscale (VCS) part of functional assessment of vulvar cancer therapy (FACT-V) for QoL [13], before and four weeks after the procedure. Willingness to undergo further ECT treatment, if necessary, was asked to patients.

Statistical analysis

All continuous data are expressed in terms of mean and standard deviation of the mean and range. Unpaired T test was performed to investigate response to VCS before and after ECT. $p < 0.05$ was considered significant. Statistical analysis was carried out by means of the Statistical Package for the Social Sciences (SPSS) software version 9.0 (SPSS Inc., Chicago, USA).

Results

Between 2009 and 2012, nine women were eligible for the study according to the inclusion criteria and were enrolled in the study. Patient age was 84 ± 3.9 years (mean ± SD) at time of enrolment.

Diagnosis stage of primary tumours, according to the FIGO system, was: one patient at stage IA, (11%), one patient at stage IB (11%), three

Table 1
Patients characteristics.

Patients	NR[a]	Type R[b]	Location[c]	*ab* before ECT(cm^2)[d]	Response	Δab After ECT (cm^2)[e] (%)	Time R after ECT (days)	Location [f]
1	1	S	1r	1.4	PD	−0.8 (57)	–	–
2	0	M	2r–2l	2.5–2	CR	0 (100)	230	1
3	2	S	3	0.32	CR	0 (100)	–	–
4	4	S	5	10	PR	8.9 (89)	–	–
5	3	S	4	2.5	CR	0 (100)	–	–
6	1	S	1l	1.5	CR	0 (100)	124	1
7	1	S	6r	2.6	SD	2.3 (11)	–	–
8	1	M	3	3	CR	0 (100)	–	–

NR = number of recurrence before ECT.
R = Recurrence.
[b] S = singular recurrence or lesion, M = multiple recurrence or lesion.
[c] 1 = labium mayus, 2 = labium minus, 3 = posterior commissure, 4 = paraurethral region, 5 = emivulva, 6 = inguinal region, l = left, r = right.
[d] *a* = largest diameter of the tumour nodule, *b* = diameter of the tumour nodule perpendicular to *a*.
[e] Δ *ab* = *ab* before ECT – *ab* after ECT.
[f] 1 = same site treated, 2 = other site.