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Electrochemotherapy as "*new standard of care*" treatment for cutaneous Kaposi's sarcoma

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Abstract

Background: Electrochemotherapy (ECT) is a novel modality for the treatment of skin nodules and cutaneous or subcutaneous tumors that allows delivery of low and non-permeant drug into cells. The aim of this prospective single-center study was to evaluate ECT efficacy in the local treatment of Classic Kaposi's sarcoma (CKS) skin localization stage I–II sec. Brambilla et al.

Methods: Nineteen consecutive patients affected by classic KS were included in this study. All patients underwent blood sampling and concurrent incisional biopsy for histological diagnosis and Kaposi's sarcoma related herpes virus 8 (HHV-8) molecular analysis. ECT treatment of KS cutaneous lesions were performed according to the European Standard Operating Procedures of Electrochemotherapy (ESOPE). The primary endpoint of the study was the evaluation of ECT efficacy in the treatment of KS skin nodules and the assessment of HHV-8 viral load in the peripheral blood following the ECT therapy.

Results: Complete response (CR) was observed in 14 (73.6%) patients after first ECT session, while 3 (15.7%) and 2 (10.5%) out of 19 patients received a second and a third ECT treatment, respectively. Clinical response dragged out the whole follow-up period that ranged between 6 and 31 months with a median of 16 months.

Conclusions: Clinical management of CKS skin localizations still represents a challenging task for surgeons and oncologists. Therefore, according to this and other author's recent experiences, ECT is claimed to become the "*new standard of care*" as first line treatment strategy for stage I–II CKS patients.

Keywords: Kaposi's sarcoma; Electrochemotherapy; HHV-8

Introduction

Kaposi's sarcoma (KS) was first described in 1872 by the Hungarian dermatologist Moritz Kaposi.[1] It has been defined as a mesenchymal tumor involving blood and lymphatic vessels.[2] Kaposi's sarcoma is characterized by four different clinical and epidemiological settings[3]: 1) epidemic or AIDS-associated KS, 2) endemic or African KS, 3) iatrogenic post-transplantation KS, and 4) Mediterranean or classic KS (CKS). In the late 1994, DNA sequences of a new KS-associated virus, the human herpesvirus type 8 (HHV-8), were consistently identified in AIDS-associated KS.[4] This virus has been demonstrated to be the etiological agent of all clinic-epidemiological forms of KS.[5–7] HHV-8, however, is necessary but not sufficient to cause KS and other factors such as immunosuppression have been shown to play a major role in tumor development.[8]

Classic KS mostly affects elderly Eastern European Jewish or Mediterranean men (male/female ratio: 10–15/1). Lesions occur mostly on the skin and subcutaneous tissue of the lower limbs and, more rarely, in internal organs.[9] Classic KS is usually chronic, persisting over many years, but is not life threatening. The risk factors for CKS include advanced age, diabetes, and the use of corticosteroid medication.[10,11] Age and corticosteroid medication are also associated with CKS progression.[12] If immunosenescence

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cannot be modified, then an immunodeficiency (exogenous or endogenous) that could potentially be corrected should always be sought. Clinically, KS is characterized by multiple firm, purple-blue or reddish-brown plaques and nodules, often associated with venous stasis, lymphedema, and/or hyperkeratosis.[13] Classic KS is usually indolent and slowly progressive (mean survival, 10–15 years).[14] However, the clinical course of CKS may be characterized by lymph node and visceral involvement and by local complications that may seriously impair quality of life. These more aggressive forms require systemic therapy with antiproliferative drugs. Clinico-histologic findings are identical for all variants. Skin lesions often cause pain and disfigurement and may lead to functional disability. A recent CKS staging system based on objective criteria has been proposed by Brambilla et al.[15] Because classic KS frequently occurs in elderly patients, a repeatable and safe therapeutic procedure that acts quickly on multiple lesions represents a relevant opportunity. Classic KS often represent a therapeutic challenge, due to the number, localization and size of the lesions. For localized forms, the available options are radiotherapy, surgical excision, laser, cryosurgery intralesional injections and topical treatments with cytotoxic drugs. Unfortunately, none of them has been proven to be superior to the others.[16] Although many options are available, standard therapeutic guideline hasn't been stated for this condition.

Electrochemotherapy (ECT) is a recent therapeutic method used in primary and metastatic skin tumors. It is a safe procedure that can be considered for KS patients, especially when multiple lesions are present. The rationale behind this technique is that electroporation, obtained by the application of electric fields, temporarily increases the permeability of cell membrane by creating transient pores, thus allowing the direct diffusion of different molecules within cells.[17] It combines the administration of highly cytotoxic drugs (like bleomycin or cisplatin) followed by the applications of high intensity electric pulses in tumor lesions on the skin or subcutaneous tissue. At the appropriate pulse parameters, pore formation on the cell membrane allows low permeant drugs like bleomycin or cisplatin to enter the cell and thus locally increase thereby their toxicity: up to 10,000 times for bleomycin and 80 times for cisplatin.[18] In addition to drug-induced cell killing, electroporation is responsible for changes in the tumor region. A "vascular lock," consisting in a reflex constriction of vessels after electric pulse delivery, produces a temporary reduction in perfusion of tumor tissue and an interstitial edema. This effect appears to last longer in tumor tissue compared with normal tissue. For this reason, the cytotoxic drugs must be administered prior to electroporation. Furthermore, other vascular effects exerted by ECT include endothelial cell destruction and neovascular reorganization due to a local reduction in angiogenic factors production.[19–21]

The use of ECT in a KS patient was first reported by Heller et al., in 1998 and to date only few reports are present in the current literature on this issue.[22] The aim of our study is to evaluate if ECT can be considered as a first line therapy and a new standard of care in patients with stage I–II CKS.

Material and methods

Patients and samples

This was a prospective, single-center study including nineteen consecutive patients with classic KS lesions of the inferior limbs (16 males and 3 females) that were referred to the National Cancer Institute of Naples from January 2010 to June 2012. Brambilla CKS staging system based on objective criteria, was accounted to select patients. Twelve patients had stage I characteristics while the remaining 7 cases were classified as stage II (Table 1).

Each patient was asked to give a written informed consent to participate to the study and was invited to fill an epidemiologic questionnaire regarding lifestyle, risk factors and anamnestic data. Furthermore, demographic features including origin, age at onset, gender of the patient, as well as clinical features such as localization of lesions, treatment modalities, results and tumor recurrence at the time of observation were also recorded. All patients underwent concurrent incisional biopsy and blood sampling for histological examination and HHV-8 DNA viral load determination at the time of enrollment. A second blood sample was obtained at a six-month follow-up visit after the end of ECT treatment to monitor the HHV-8 viral load. Each cutaneous biopsy was divided in two sections, one processed for pathological examination and the other was stored in RNAlater stabilizing solution (Ambion, Austin, TX) at −80 °C. Ten ml of fresh blood was processed within one hour for PBMCs isolation by Ficoll density gradient

Table 1
Patients characteristics.

Patient no.	Sex, age (years)	Localization	Response	Stage
01	F, 85	Right foot	CR	I
02	F, 74	Lower limb	CR	I
03	F, 63	Lower limbs bilateral	CR	II
04	M, 44	Lower limbs bilateral	CR	II
05	M, 69	Foot	CR	I
06	M, 61	Foot	CR	I
07	M, 74	Lower limbs bilateral	CR	II
08	M, 72	Foot	CR	I
09	M, 75	Foot	CR	I
10	M, 83	Foot	CR	I
11	M, 59	Foot	CR	I
12	M, 84	Lower limbs	CR	II
13	M, 65	Left foot	CR	I
14	M, 58	Genitalia	CR	II
15	M, 73	Lower limbs	CR	II
16	M, 68	Lower limbs	CR	I
17	M, 66	Foot	CR	I
18	M, 70	Lower limbs	CR	II
19	M, 73	Lower limb	CR	I

CR: complete response.