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Electrochemotherapy in the Treatment of Kaposi Sarcoma Cutaneous Lesions: A Two-Center Prospective Phase II Trial

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ABSTRACT

Background. Electrochemotherapy (ECT) is an emerging treatment for cutaneous lesions of different tumor types. The combination of chemotherapy and electroporation enhances drug uptake into tumoral cells. However, its role in the treatment of Kaposi sarcoma (KS) has not yet been well defined, and to date, literature reports are scarce. We prospectively evaluated clinical activity and safety of ECT in KS patients. **Methods**. Twenty-three patients with histologically confirmed unresectable KS, not treatable by radiotherapy or intralesional vincristine therapy, were enrolled onto the study according to the European Standard Operating Procedures of Electrochemotherapy (ESOPE) guidelines and treated with a pulse generator. **Results.** A response to the first ECT session was obtained in all patients, with a complete response (CR) in 14 (60.9%) of 23 patients. A second ECT was performed in 5 (21.7%) and a third in 2, with a median interval between two sessions of 5.1 (range 2.5–25.5) months. Overall, a total of 15 patients (65%) experienced a CR. After a median follow-up of 1.5 years (range 2 months to 4.2 years), 16 patients maintained the response, 4 after repeated courses. Sustained local control of treated lesions was present in 20 of 23 patients. The overall survival rate was 74.4% at 2 years. **Conclusions**. ECT represents an additional therapeutic tool for the management of KS cutaneous lesions, characterized by a definite clinical activity and long-lasting remissions. The absence of systemic side effects and the low impact on the immune system also make this treatment suitable for elderly people, even with repeated courses.

Kaposi sarcoma (KS) was first described by Moritz von Kaposi in 1872 as a spindle cell malignant vascular tumor originating from endothelial cells, with a tendency to develop multifocally.1,2

Four clinical and epidemiological forms of KS have been recognized: (1) classic or sporadic, found in elderly men of Mediterranean origin and of Eastern European or Jewish heritage, with location of lesions usually on the lower extremities and/or trunk, rarely involving visceral organs, with a chronic and indolent

course; (2) African or endemic, an aggressive form of KS involving visceral and/or lymphatic organs, occurring in young adults and children of subequatorial Africa, in patients who are seronegative for human immunodeficiency virus (HIV); (3) iatrogenic or immunosuppression-associated form, found in individuals who received transplants, mainly renal transplants, after cyclosporin and corticosteroid therapy; it has a mild clinical course and affects skin, mucous membranes, and other organs; and (4) epidemic or acquired immunodeficiency syndrome (AIDS)-related form, the most aggressive and fatal variant, found in HIV-1-infected subjects.3,4

Clinically, KS is characterized by multiple firm, purple-blue or reddish-brown plaques and nodules, distributed mainly on the lower extremities and trunk and often associated with venous stasis, lymphedema, and/or hyperkeratosis.5,6 Clinicohistologic findings are identical for all variants.

Different therapeutic options are available: local treatments (surgical excision, laser, cryosurgery, radiotherapy, and intralesional injection and topical treatments with cytotoxic drugs) as well as systemic treatments (vinblastine, vincristine, vinorelbine, etoposide, bleomycin, liposomal anthracyclines, and paclitaxel).3 The choice of treatment is based on the clinical variant, disease stage, progression patterns, and immune status.7

Because KS mainly affects elderly people, often causes pain and disfigurement, and may lead to functional disability, a repeatable and safe therapeutic procedure that acts quickly on multiple lesions represents a relevant opportunity.

In this scenario, electrochemotherapy (ECT), a local treatment proposed for cutaneous metastatic nodules and primary skin tumors, can be considered. This promising technique combines the antitumoral activity of nonpermeant (e.g., bleomycin) or poorly permeant (e.g., cisplatin) anticancer drugs, to the delivery of short, intense electrical pulses (electroporation). The electrical pulses are delivered locally to increase cell permeability by enhancing drug uptake into tumoral cells, thus raising the intracellular concentration and toxicity of bleomycin and cisplatin.8,9 Among the several chemotherapeutic drugs that have been tested for their application with electroporation, intravenous or intralesional bleomycin and intralesional cisplatin were chosen because they had higher cytotoxicity.9–11

ECT has recently entered clinical practice, especially in the management of melanoma cutaneous metastases, which is the most commonly treated tumor.10,11 Our encouraging results in 14 melanoma patients showed a 93% overall response rate.12 On the other hand, literature reports on KS treated with ECT remain scarce. Indeed, the use of ECT use in a KS patient was first reported by Heller et al. in 1998: four lesions treated by ECT achieved a complete response (CR), while the three sites that received bleomycin only showed disease progression.13 Curatolo et al. described the complete regression of a case of isolated genital KS after one course of ECT, underlining its efficacy and high tolerability in difficult anatomic sites.14 Another case report demonstrated the disappearance of human herpesvirus 8-positive cells at treated sites after ECT.15 Cases of KS were also included in the European Standard Operating Procedures of Electrochemotherapy (ESOPE) trial.10

Our study describes 23 KS patients treated by ECT with systemic bleomycin at two different Italian dermatologic centers. The aim was to evaluate the efficacy of ECT in achieving local tumor control; the toxicity profile of this modality; and its impact on the patients' quality of life.

PATIENTS AND METHODS

Study Design

This prospective, nonrandomized phase II trial aimed at the evaluation of the clinical activity and safety of ECT in KS patients was carried out at the Dermatologic Clinic of University of Rome “La Sapienza” and at the Dermatologic Clinic of University of Turin.

The application and study of ECT treatment in patients was approved by the ethical committees of both hospitals, and all patients provided written informed consent before treatment.

The primary objective was the assessment of the clinical response rate; secondary end points were toxicity evaluation, local tumor control and time to treatment failure, and quality-of-life assessment.

Patients

Twenty-three patients, 13 men and 10 women with a median age of 77 years, were enrolled onto the study between October 2005 and September 2010 (Table 1). Most of the patients manifested the classic form of KS; 3 had an iatrogenic form, 1 due to lung transplant and the other 2 to Hodgkin and non-Hodgkin lymphoma, respectively; only 1 patient had an AIDS-related form. Treated lesions were located mainly on lower limbs, in 3 cases also extended to the trunk and upper limbs, and in 1 were localized to genital and perineal areas. A total of 532 cutaneous lesions consisting of papules, plaques, and nodules were treated, with an average number of lesions per patient of 23.

Patient enrollment was carried out according to the ESOPE criteria.10,11 Inclusion criteria were as follows: histologically confirmed KS with cutaneous lesions not treatable by surgery, radiotherapy, or intralesional vincristine; absence of extracutaneous involvement radiologically confirmed; age >18 years, Karnofsky performance status of >70; and a washout period of at least 4 weeks after previous treatments. One patient was considered eligible for ECT according to these criteria but was excluded as a result of a high anesthesiologic risk resulting from age and comorbidities.

Sixteen patients could not be treated by surgery, radiotherapy, or intralesional vincristine because as they had multiple (10 to 50) cutaneous lesions, located on the lower limbs or disseminated (Table 1); moreover, 4 of them had experienced recurrence of disease after previous systemic chemotherapy and 3 after interferon therapy. For the other 7 patients with fewer lesions, 2 had disease refractory to radiotherapy (patients 10 and 21), 1 after intralesional vincristine (patient 4), and 2 after systemic chemotherapy (patient 14 and 20; patient 20 had been treated with a bleomycin-containing regimen). Patient 8 developed KS after receiving a lung transplant; he showed a large infiltrated plaque on his right leg measuring 15 cm in diameter that had been refractory to previous radiotherapy. Patient 6 had seven large plaques located on both lower limbs, from 5 to 10 cm in diameter, not treatable by intralesional vincristine or radiotherapy.

TABLE 1 Clinical characteristics of patients, previous treatment, and follow-up data

Patient no.	Sex, age (years)	Previous treatment	No. of lesions	Localization	Response[a]
1	M, 85	Vinblastine	28	Lower limbs	CR
2	M, 76	RT	33[b]	Lower limbs	CR
3	F, 70	None	35	Lower limbs	PR
4	F, 81	Intralesional VCR	4	Lower limbs	CR
5	F, 72	Doxorubicin, RT, Navelbine	38[b]	Lower limbs	CR
6	M, 70	None	10	Lower limbs	CR
7	M, 65	IFN	41	Lower limbs	CR
8	M, 44	RT	1	Lower limbs	CR
9	F, 86	None	39[b]	Lower limbs	PR
10	M, 76	RT	6	Lower limbs	PR
11	M, 77	None	22	Lower limbs	CR
12	M, 86	Vinblastine	50	Lower limbs	PR
13	F, 84	None	7	Lower limbs	CR
14	M, 81	Vinblastine	5	Genitalia	CR
15	M, 84	None	30[b]	Lower limbs	PR
16	M, 84	None	30	Lower limbs	CR
17	F, 51	Doxorubicin	27	Disseminated	CR
18	F, 82	None	23	Lower limbs	PR
19	M, 60	IFN	38	Disseminated	CR
20	M, 77	Vinblastine, vinblastine–bleomycin	8[b]	Lower limbs	PR
21	F, 43	RT	9	Lower limbs	CR
22	F, 54	IFN	20	Disseminated	PR
23	F, 86	None	28	Lower limbs	CR

IFN interferon, *RT* radiotherapy

[a] At the end of last ECT course

[b] Total number of lesions treated considering all ECT courses

ECT Treatment

Treatments were carried out at the Dermatologic Clinic of Rome University “La Sapienza” and at the Dermatologic Clinic of the University of Turin with the Cliniporator™ device (IGEA, Modena, Italy).

Mild general anesthesia or spinal anesthesia was provided. Mild general anesthesia consisted of premedication with oral benzodiazepine (chlordemethyldiazepam), induction with a short-acting intravenous anaesthetic agent (propofol 2.5 mg/kg), inhalation of anesthetic vapor (sevoflurane 2%), and assisted ventilation air/oxygen 40%. Postsurgical analgesia was provided by intravenous paracetamol (1 g). Three different types of electrodes (IGEA) were used depending on the type of lesion. Type I electrodes were made up of two parallel stainless steel plates with varying distances between 6 and 8 mm, used for the treatment of small superficial lesions. Needle electrodes were suitable for treatment of thicker and deeper-seated tumor nodules. Type II electrodes were made up of two parallel arrays of needles with a 4-mm gap between them for treatment of small nodules. Type III electrodes were a hexagonal array of electrodes (six needles forming a hexagon and one needle at its center with an 8-mm gap between them) for larger nodules (1 cm in diameter). The electrical pulses were generated and applied with the Cliniporator™ device, which generates square-wave electric pulses of variable amplitude with 1–5000 Hz delivery frequencies. All the patients were treated with intravenous bleomycin, which was also preferred to intralesional administration in cases of few lesions. The intravenous administration allowed for a

homogeneous drug concentration, thus avoiding irregular distribution within the tumor. Bleomycin was provided at a dose of 15 mg/m2 for 30 s to 1 min; electric pulses were delivered from 8 to 28 min after bleomycin infusion to obtain an optimal response utilizing the most appropriate drug concentrations in tissues. A time interval of 20 min was enough to treat up to 50 lesions.

Treatment was performed on an inpatient basis, with a maximum observation period of 24 h after treatment.

Response Criteria Evaluation and Follow-up

Measurements of the treated lesions were carried out on day 0, at follow-up at weeks 4, 8, and 12, and every 3 to 6 months thereafter. Clinical response to treatment was assessed 4 weeks after the ECT session. The clinical measurements were taken by calipers, considering the sum of the largest diameter of the lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST).16 Up to seven lesions were chosen in each patient as index lesions. Response was evaluated according to the RECIST as follows: progressive disease for an increase in sum of diameters of >20%; partial response (PR) for a decrease of 30% for at least 4 weeks; no change for an increase of <20% or a decrease of <50%; and CR for total clinical disappearance of the lesion.

Repeated ECT courses in a single patient were performed in the presence of the following: multiple lesions not manageable in a single session, PR lesions after the first course, and appearance of new cutaneous lesions in untreated areas.

A total of 18 of our patients were provided a single ECT session (78.2%). A second treatment was performed in 5 patients (4 PR and 1 CR after the first course); 2 of them underwent a third ECT treatment.

Toxicity and Quality-of-life Assessment

The systemic toxicity of the treatment was graded according to World Health Organization criteria. Quality of life was assessed by means of the Patient Global Assessment (PGA).17 The PGA evaluation question was, “On the basis of any way which illness and/or health conditions affect you at this moment in time, please mark the line below to show how well you are doing.” The 0-mm end of the line was marked “very well” and the 100-mm end of the line was marked “very poorly.” All the patients completed the test at baseline before treatment and after 4 weeks from ECT at the time of response evaluation.

Statistical Analyses

Statistical analyses were performed by SPSS software for Windows, version 12 (SPSS, Chicago, IL). The differences in the distribution of objective responses of the nodules were tested by contingency tables and the chi-square test.

Local tumor control in the treated lesions was estimated as a function of time by the Kaplan-Meier product limit method and was calculated as the time from achievement of response to the demonstration of either relapse in CR lesions or a >25% size increase in PR metastases, or last follow-up date.

Time to treatment failure was measured from the first day of treatment with ECT to either disease recurrence requiring a different treatment, therapy discontinuation for any reason, death from any cause, or last date of follow-up for patients treated with repeat ECT sessions.

Overall survival was measured from the first day of treatment with ECT to either death from any cause or last date of follow-up, counting all deaths as events.

RESULTS

First ECT Treatment

A total of 23 patients with multiple or recurrent KS cutaneous lesions were treated with ECT. A response to the first ECT treatment, scored at 4 weeks, was obtained in all patients, with a complete regression (CR) of the treated lesions in 14 (60.9%) of 23 and a PR in 9 patients (39.1%) (Figs. 1, 2, 3).

Responses were obtained in both plaques and nodules. No difference in the overall response rate was observed according to the size of cutaneous lesions; however, the CR rate of lesions >3 cm in maximum diameter was lower than that obtained in smaller lesions (47.1% vs. 61.1%; $\chi 2$ test, P = 0.007).

Further ECT Treatments

A second ECT session was performed in 5 patients (21.7%). Three patients were retreated for the development of new lesions in previously untreated areas (1 CR and 2 PR after the first course), and further achieved 1 CR and 2 PR. Two patients underwent a second session to treat the nodules that remained after the first course; one experienced CR and the other PR. Two patients underwent a third treatment for both new and previously treated lesions and always maintained a PR with respect to the initial measurement. The median interval between two ECT sessions was 5.1 (range 2.5–25.5) months.

Overall, ECT treatment led to a CR in 15 patients (65%), in 14 after the first session and in 1 after the second. The likelihood of experiencing CR was analyzed on the basis of clinical KS features. A CR was obtained in 2 of 3 iatrogenic cases, in 11 of 19 classic KS, and in 1 AIDS-related form. When CR was evaluated according to the body site, it was observed in 12 of 19 patients with lower limb lesions, in the patient with exclusively genital localization, and in 2 of 3 patients with involvement of trunk and limbs. Furthermore, ECT led to CR in 6 of 9 patients who experienced relapse or whose disease was refractory to treatment after previous chemotherapy or immunotherapy.

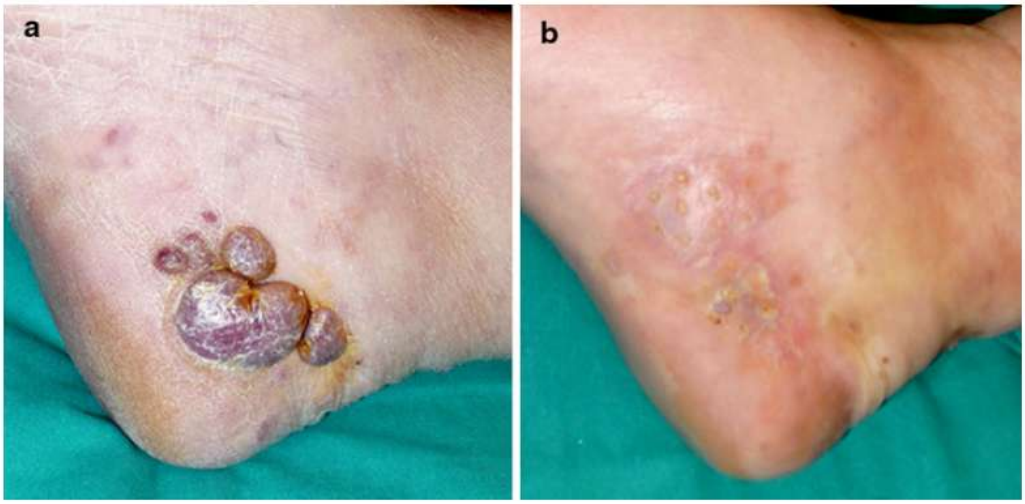

Fig. 1 Patient with multiple lesions on legs. a Confluent nodular lesions up to 4 cm in diameter located on the heel. b Complete remission after treatment

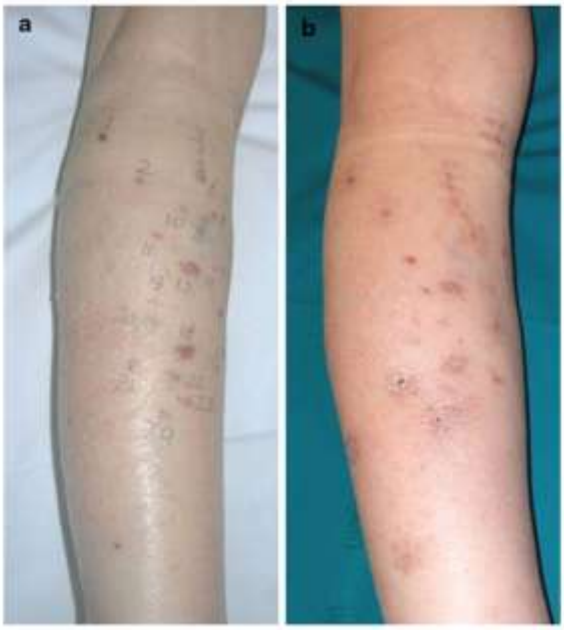

Fig. 2 a Disseminated papules and small plaques sized 1–2 cm on the left calf. b Partial remission after treatment

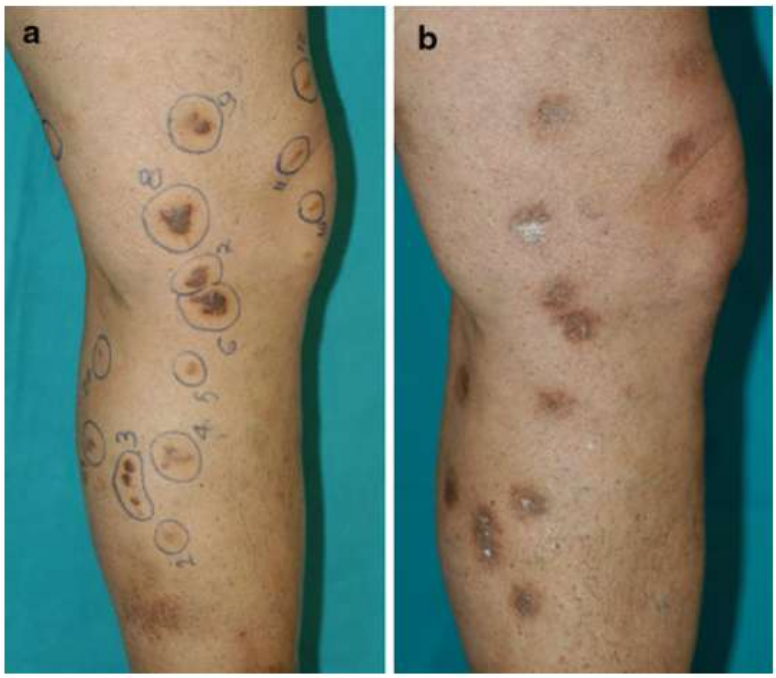

Fig. 3 a Disseminated papules and nodules on the left leg. b Complete remission of treated lesions with residual hyperpigmentation and atrophic scars

Follow-up

After a median follow-up of 1.5 years (range 2 months to 4.2 years), 16 patients maintained the response, 4 after repeated courses. Twelve of these patients experienced a CR and 4 a PR. These 4 PR

patients were not retreated with ECT, nor did they undergo further treatment, because the response was considered satisfactory on the basis of the indolent behavior of the disease and their good quality of life.

Of the remaining 7 patients, 2 died of unrelated causes (myocardial infarction and relapse of Hodgkin lymphoma) while maintaining CR. The remaining 5 patients developed a cutaneous disease progression (2 in previously untreated areas and 3 in treated body sites) that was no longer manageable with ECT. All these patients were treated with standard systemic chemotherapy (3 with liposomal doxorubicin, 1 with gemcitabine, and 1 with vinblastine); 2 of them died as a result of extended cutaneous and extracutaneous disease progression.

The local tumor control rate at 2 years was 76.2% (Fig. 4). Sustained local control of treated lesions was achieved in 20 of 23 patients.

The median time to treatment failure has not yet been reached (>4.2 years). The overall survival rate was 74.4% at 2 years and remained stable thereafter.

Side Effects and Quality of Life

Cutaneous infection was observed in 2 patients and was treated with oral antibiotics, leading to a complete remission within a few days. Two patients complained of local pain during the first few days after treatment; no other subjective symptoms were reported, and no systemic toxicity occurred. General anesthesia was well tolerated by all patients, and no adverse events were reported.

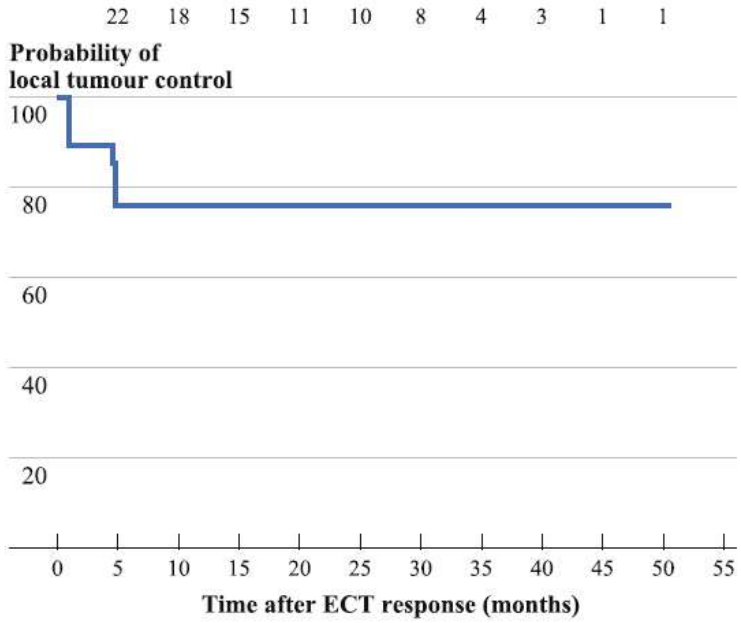

Fig. 4 Local tumor control in 23 patients with KS treated by ECT. Numbers above the graph represent number of patients still in follow-up at the corresponding time interval

The benefit in terms of improvement of quality of life obtained by patients after ECT was evaluated by the PGA. In 22 patients (95%), an improvement in the quality of life was scored; this improvement was not necessarily related to complete remission.

DISCUSSION

This study reports the results of a prospective nonrandomized phase II trial aimed at the evaluation of the clinical activity and toxicity of ECT with intravenously administered bleomycin in the treatment of KS cutaneous lesions. Patients were enrolled from two separate Italian centers in Rome and Turin and were treated with the same protocol, according to the ESOPE guidelines, using the Cliniporator™ device.10,11 To our knowledge, this is the largest series of KS cases treated with ECT.

Our results demonstrate that ECT results in a marked clinical activity and a good toxicity profile in KS patients. In fact, a clinical response was obtained in all cases, regardless of tumor size, with 60.9% experiencing a CR after the first session; moreover, one further CR was obtained after a repeat session. Despite the overall excellent response rates, far higher CR rates were scored in patients with lesions sized <3 cm (61.1% vs. 47.1%).

The high response rates were coupled with a long remission duration: 20 of 23 patients experienced sustained local tumor control. No systemic toxicities occurred, and only 2 patients reported transient pain after treatment. ECT was also associated with an improvement in quality of life as determined by the PGA.

There is no standard therapy policy for KS; therapeutic options depend on disease stage, distribution of lesions and evolution pattern, clinical type, and immune status. Surgical procedures can be applied only on few and well-defined lesions; other local therapeutic strategies include radiotherapy18 as well as topical and intralesional therapy. Cutaneous KS is highly responsive to radiotherapy, with overall response rates ranging 85–98% and good tolerability.19–22

Among intralesional treatments, vincristine injections demonstrated a higher clinical activity with lower injection-related pain when compared to vinblastine and bleomycin.23–25 A recent prospective study of 151 patients with classic KS treated with intralesional vincristine reported a total response rate of 98.7%, with 76.1% CR; adverse events were limited to erythema and itching in 13.9% of cases, and no systemic toxicity was observed.23 Although the satisfactory toxicity profile of all these intralesional treatments, their application on a wide number of lesions is not possible, also considering the need to preserve the immunocompetence of patient. Our patients had an average number of lesions of 23, with up to 50 lesions treated on a single ECT session. Therefore, many of these patients may have not been eligible for intralesional treatments and would have received systemic chemotherapy.

Many drugs are effective in both single- and multiple-agent chemotherapy (vinca alkaloids, etoposide, liposomal doxorubicin, bleomycin). A phase III clinical trial comparing oral etoposide versus intravenous vinblastine demonstrated the efficacy of both drugs with no differences in terms of response rate (74% etoposide, 58% vinblastine), duration of response, or survival.26 In the vinblastine arm, the median maximum response time was 8.5 months for CR and 6 months for initial response. Despite myelotoxicity, vinca alkaloids are usually well tolerated. A phase II study on low-dose etoposide in AIDS-related KS confirmed its efficacy and safety, with the most frequent adverse effects being neutropenia and opportunistic infections.27 Liposomal doxorubicin is approved as first-line treatment of disseminated AIDS-related KS; two recent retrospective studies evaluated its activity and safety in KS as first- and second-line therapy, respectively.28–30 As first-line therapy, liposomal doxorubicin result in an overall response rate of 71%, with a 29% CR rate; grade III and IV toxicity was observed in 45% and 9% of patients, respectively. As

second-line therapy, it resulted in a CR in 10% of patients and a major response in 70%; grade III and IV toxicity occurred in 40% and 5% of cases, respectively. Brambilla et al. administered vinblastine–bleomycin in 29 patients and recorded a 97% objective response, with 21% CR and a median response duration of 4 months; this regimen registered 11 cases of neutropenia (38%, with 3 grade IV) and 2 cases of grade I neurotoxicity (7%).31

Despite the small number of cases and the nonrandomized patient accrual, we obtained promising results. In fact, with respect to standard systemic chemotherapy, ECT achieved a comparable clinical activity with an even higher CR rate; ECT responses were also obtained in patients who had experienced relapse or whose disease was refractory to standard systemic chemotherapy. Moreover, systemic treatments report considerable toxicity, while no serious adverse events occurred with ECT. The absence of toxicity and the mild general anesthesia needed for ECT treatment permitted repeated sessions. The electroporation induced with electric pulses, increasing the cytotoxicity of the chemotherapeutic agent, allows for the administration of a lower dose, thus limiting not only drug-related toxicity but also immunodepression. In our opinion, this is a remarkable achievement, especially considering that most patients in our series were elderly; as is well known, KS prognosis is strictly related to immunosuppression. Brenner et al. showed in 248 KS patients that age and immunosuppression are important prognostic factors for progression; immunosuppression alone is also predictive of dissemination.32 Most of our patients were affected by the classic Mediterranean form of KS, which is the most frequent variant in our geographic area.2,4 However, ECT was able to induce responses in the disease of 2 of 3 patients with iatrogenic KS and in 1 patient with the AIDS-related form; in this latter variant, the frequent visceral spreading limits the use of ECT.

In conclusion, our study shows that ECT is an additional therapeutic tool in the management of disseminated cutaneous KS lesions, characterized by a definite clinical activity and long-lasting remission. The absence of systemic adverse effects and the low impact on immunosystem functions also allow the treatment of elderly people with repeated courses.

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