Gemcitabine for the Treatment of Classic Kaposi's Sarcoma: A Case Series

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Abstract. *Radiation-refractory and progressive Kaposi's sarcoma remains a challenge for the oncologist. Systemic chemotherapy has improved, but results are poor. Gemcitabine is largely employed in oncology for its high therapeutic rates. We report four cases of patients with radiation-refractory and progressive classic Kaposi's sarcoma, two of whom were pre-treated with chemotherapy and then underwent treatment with gemcitabine. All patients had an objective response with long progression-free survival. Gemcitabine seems to be very effective and safe in the treatment of classic Kaposi's sarcoma.*

Kaposi's sarcoma (KS) is a rare multifocal lymphoangio-proliferative disease related to human herpesvirus-8 (1). Four clinical patterns have been described: classic or Mediterranean KS, acquired immunodeficiency syndrome (AIDS)-related KS, KS secondary to other immuno-suppressive diseases, and endemic or African KS (2).

The classic or Mediterranean variant of KS affects mainly elderly males, usually involves the lower limbs and has an indolent clinical course. Early-stage treatment is localized: radiotherapy (3), intralesional vinca alkaloids (4, 5) and nicotine dermal patch (5), with satisfying disease control. There are some aggressive KS variants with early spread to the skin, lymph nodes and visceral organs, for which chemotherapy is needed. Various anti-blastic drugs (single or in combination), including α-interferon, vinblastine, bleomycin, dacarbazine, anthracyclines and paclitaxel, have been studied, with an overall response rate up to 80% (6-8). Gemcitabine is widely-used in oncology practice and has a good toxicity profile, so that it is often included in chemotherapy combinations and used as single chemotherapy agent in the elderly (9). Gemcitabine is a pyrimidine analogue and replaces cytidine in DNA helix during DNA replication. Gemcitabine does not affect lymphocyte immuno-reactivity in patients with solid tumors and seems to be synergistic with immunotherapy in animal models (10, 11).

We report four cases of patients with progressive classic KS successfully treated with gemcitabine as a single agent.

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Key Words: Kaposi's sarcoma, gemcitabine, chemotherapy, case series.

Case Report

Case 1. In February 2007, a 73-year-old man diagnosed with classic KS of the lower limb came to our attention with disease progression. Cutaneous lesions involved the upper and the lower limbs, with subcutaneous dissemination to the left thigh accompanied by a conspicuous oedema (see Figures 1 and 2). The patient had already undergone radiation, α-interferon and chemotherapy (vimblastine, pegylated liposomal doxorubicin and paclitaxel). Treatment with gemcitabine at a fixed infusion rate of 10 mg/m^2/min on days 1, 8, 15 every 28 days was started. After the first administration the patient underwent abdominal surgery for an acute peritonitis due to a bowel perforation. Six weeks later, he resumed chemotherapy. The clinical pattern of the lower limbs and of the left thigh had improved dramatically immediately after the first gemcitabine administration. The improvement was confirmed after three courses of chemotherapy, and at the end of the chemotherapy program of a total of six courses, as shown in Figures 1 and 2. The patient entered a follow-up program and after 24 months experienced disease progression; the same therapy was repeated obtaining another disease response after six courses. The patient is now receiving a further nine courses of gemcitabine because of further progression. His disease has been under control with gemcitabine for 78 months and the patient is doing very well.

Case 2. In November 2011, a 54-year-old man sought to our observation. The patient had been diagnosed with KS in 2004 and treated with α-interferon for three years. Due to

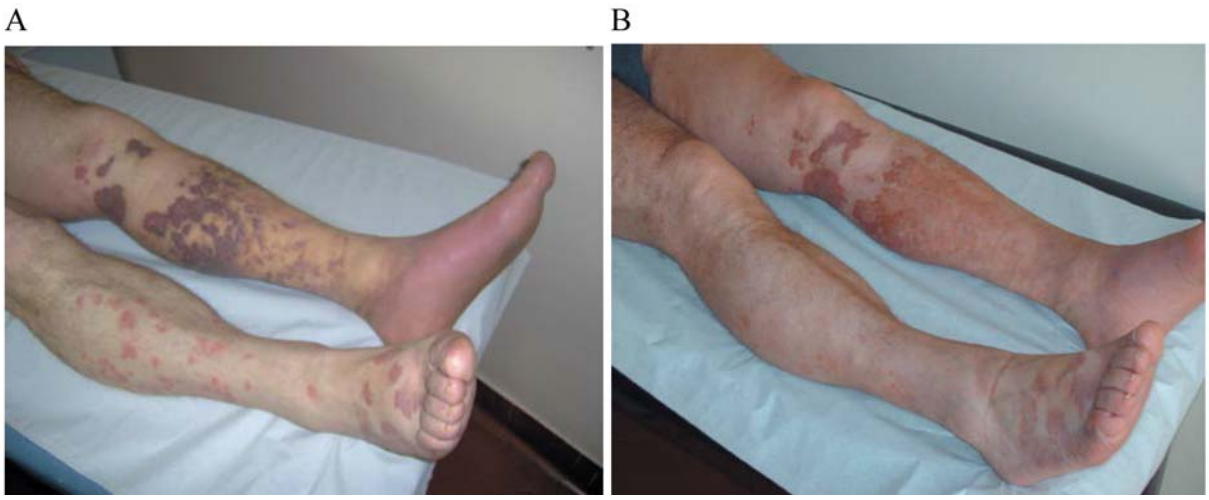

Figure 1. *Case 1: Cutaneous pattern of the inferior limb before (A) and after (B) gemcitabine treatment.*

progressive systemic disease, he underwent therapy wiyh vimblastine, paclitaxel, liposomal doxorubicin, everolimus and pazopanib, with tumor progression both on skin and oral, nasal and pharyngeal mucosa. In May 2012, the patient started therapy of gemcitabine at 1000 mg/m^2 over a 100-min infusion on days 1, 8, 15 every four weeks, with a rapid reduction of the faster growing mucosal lesions and a stabilization of the numerous indolent cutaneous lesions. The only side-effect reported was swelling of the left leg due to the presence of a large skin lesion and to the edematogenic effect of gemcitabine administered at 10 mg/m^2/min (12). The patient continued treatment until October 2012 then committed suicide probably due to his depressive state.

Case 3. In March 2012, a 69-year-old man was diagnosed with cutaneous classic KS of the left leg. No radiation was suggested, the patient started therapy with gemcitabine at 1000 mg/m^2 on days 1 and 8 every three weeks. Previously, in 2010, he was treated with surgery and radiotherapy for prostatic cancer with regular following-up. After three courses of gemcitabine, the clinical evaluation showed a partial response which was confirmed after six courses of the same therapy with a contrast-enhanced CT scan of thorax and abdomen, which excluded visceral progression. Treatment was stopped and the patient entered follow-up. In August 2013, he was still in follow-up without signs of progression and his lesions continue to fade (see Figure 3).

Case 4. In October 2012, a 72-year-old man with progression of classic KS came to our attention. First diagnosis was made in 1999 after the excision of a nodule of the left ear, then in August 2002 two more lesions appeared on the right leg and biopsy confirmed the diagnosis of KS. A contrast-enhanced CT scan excluded visceral and lymph nodal involvement and the patient was evaluated for radiation therapy. Cycles of radiation were administered to the inferior limbs from 2002 to October 2011. In September 2012, a new progression on the inferior limbs occurred, contrast-enhanced CT scan excluded visceral and lymph nodal involvement. Therapy with gemcitabine at 1000 mg/m^2 on days 1, 8 and 15 every four weeks was started. After three courses, the cutaneous pattern was stable, with a modest reduction of lesions, and after six courses of gemcitabine, the patient had partial remission (see Figure 4). Follow-up was started and up to August 2013, no progression had occurred.

Discussion

The present cases all exhibit a long-lasting response with radiation and chemotherapy progressive classic KS using single-agent gemcitabine administered at a fixed infusion rate on days 1, 8, 15 every 28 days, or with other classic schedules.

A review of the literature indicated only one prior report of gemcitabine for treatment of the classic variant of KS. Brambilla *et al*. administered gemcitabine with a standard schedule of 1,200 mg/m^2 over a hypothetical 30-min infusion (time of infusion not reported in the paper) on days 1, 8 every 3 weeks to 11 patients with refractory classic KS. The authors obtained an overall response rate of 100% with one complete response and 10 partial responses.

Our cases' outcomes confirmed these results. All patients had a partial response and all but the one who committed suicide are experiencing long progression-free survival (of 24, 5+ and 17+ months respectively). Case 1, in particular, is experiencing a disease control with gemcitabine administered

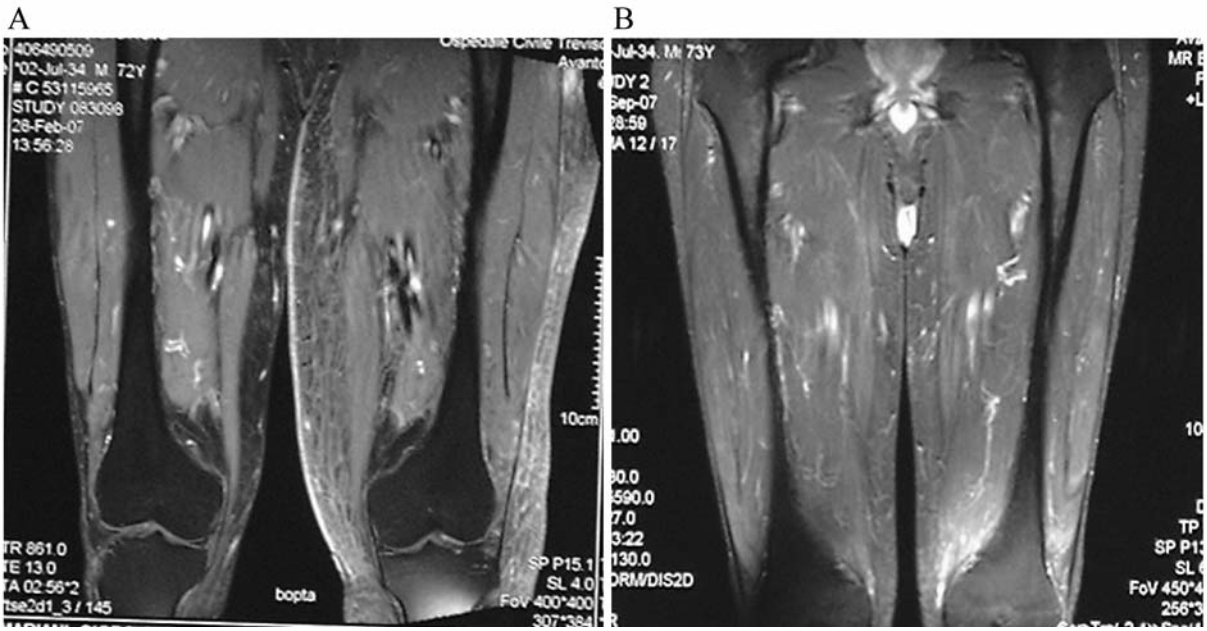

Figure 2. *Case 1: Nuclear magnetic resonance with contrast pattern of the left thigh before (A) and after (B) gemcitabine treatment.*

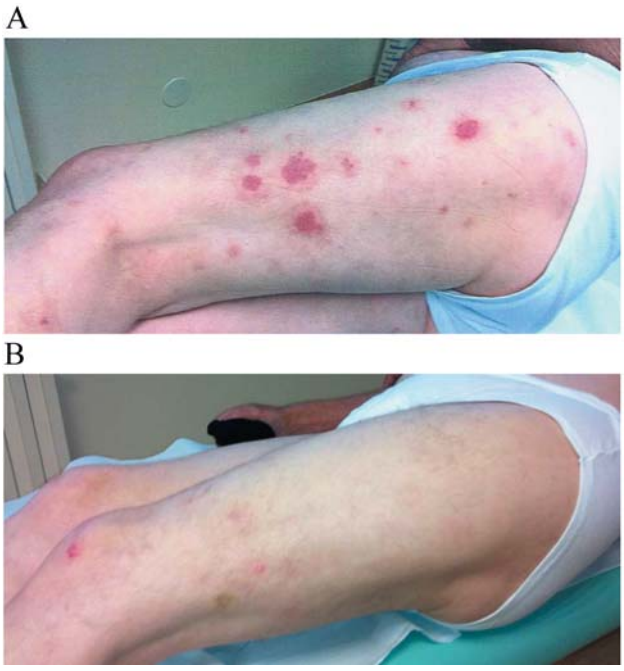

Figure 3. *Case 3: Cutaneous lesions of the left inferior limb before (A) and after (B) three courses of gemcitabine treatment.*

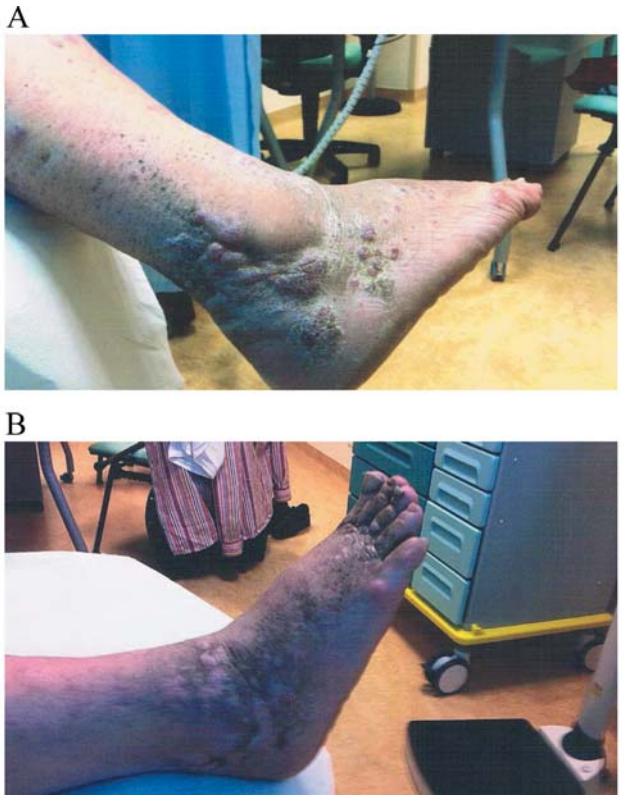

Figure 4. *Case 4: Cutaneous lesions of the right foot before (A) and after (B) six courses of gemcitabine treatment.*

at three different periods since February 2007 for a total of 21 cycles over six years and six months. At the present time, this patient (see Figure 1 for initial disease pattern) is doing very well, with no symptoms from his disease.

Moreover, toxicity has been mild and standard for gemcitabine, with no grade 3-4 adverse events.

Gemcitabine, unlike other cytotoxic agents, does not affect lymphocyte immunoreactivity in patients with solid tumors and seems to be synergistic with immunotherapy in animal models (10, 11). In a prior report, we showed that the treatment of patients with advanced renal carcinoma is feasible and safe using gemcitabine at a fixed infusion rate of 10 mg/m^2/min in combination with α-interferon or interleukin-2 (12).

In conclusion, our results and the previous data from Brambilla *et al*. (13) support treatment with gemcitabine for patients with refractory and progressive diffused KS. Fixed infusion rate administration modality should be preferred and its combination with immunotherapy should also be considered, expecially if it has not been administerd before.

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Received September 23, 2013
Revised October 24, 2013
Accepted October 25, 2013