

Weekly paclitaxel for advanced aggressive classic Kaposi sarcoma: experience in 17 cases

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Summary

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Key words

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Conflicts of interest

None declared.

Background Paclitaxel has proved to be highly effective in the treatment of severe AIDS-related Kaposi sarcoma (KS), for which it is now considered as a second-line monotherapy. Taxanes were recently shown to be active also in classic, endemic and post-transplantation KS.

Objectives To evaluate the clinical efficacy and tolerability of standardized paclitaxel treatment (100 mg weekly, intravenously) in a homogeneous group of 17 patients with advanced aggressive and refractory classic KS (cKS).

Methods Seventeen patients with aggressive refractory cKS (stage IIIBc–IVBcv) were treated with intravenous paclitaxel 100 mg weekly. The response to the therapy was evaluated after 12 weeks. A maintenance treatment every 2 weeks was introduced for most of the patients and a final evaluation was made.

Results A partial/complete response was achieved in 14 of 17 patients. Two patients had allergic reactions, for which treatment was discontinued. One patient had progression of disease despite initial improvement. Patients received a mean of 16.8 courses. The treatment was generally well tolerated. Mean time to recurrence was 4.5 months from the end of the therapy and 7.35 months from the 12th course. In four of 10 patients who relapsed at follow-up, the recurrence was mild and responsive to local treatment, while the other six relapsing patients repeated paclitaxel with good response in five of them.

Conclusions This study shows that low-dose paclitaxel proved to be effective and well tolerated in patients with aggressive refractory cKS, controlling the aggressiveness of the disease. The treatment can be repeated with good response.

Classic Kaposi sarcoma (cKS) is a rare angioproliferative disease related to human herpesvirus-8,¹ usually occurring in men aged over 50 years, with a higher prevalence in particular regions, such as the Mediterranean area.^{2,3} Therapy is influenced by the usually slow progression of the disease and by the advanced age of the patients.⁴ In our experience, compression therapy with elastic stockings and intralesional vincristine can be sufficient to manage patients in early stages.⁵ Advanced stages with diffuse cutaneous involvement and complications, such as lymphoedema, lymphorrhoea, ulceration and bleeding, cause functional impairment requiring systemic chemotherapy.

Vinblastine and bleomycin or vinblastine alone can be considered as first-line therapy,⁶ when chemotherapy is required. Etoposide, interferon alfa, anthracyclines, liposomal doxorubicin and gemcitabine have been used as second-line therapy, showing good results, and indicated in several studies as giving partial response (decrease of about 70% of the lesions),

with a variable remission period shown in a few large surveys.^{7–13}

Nevertheless, in elderly patients with cKS, such chemotherapies cannot always be suitable due to the frequent comorbidity (cardiovascular disease, depression and reduced bone marrow function are quite frequent). Thus, in quickly developing disease and symptomatic patients we need rapidly acting but tolerable drugs, in order to reduce complications and improve the quality of life.

Taxanes have recently been considered for treatment of refractory or life-threatening nonhuman immunodeficiency virus (HIV)-associated KS.¹⁴ The efficacy of these drugs, their antiangiogenic and microtubular protein disrupting function,^{15–17} have been reported in many large series of patients with AIDS-related KS (AIDS-KS) in whom treatment with taxanes has been approved as second-line monotherapy.^{4,15,18–24} The use of taxanes in cKS is quoted in anecdotal reports in only a few patients.^{14,25–28}

Herein, we evaluate the efficacy, rapidity and toxicity of the taxane paclitaxel in 17 patients with symptomatic, aggressive and refractory cKS treated with paclitaxel 100 mg weekly. We experienced rapid and extremely good response. The remission was often short term; nevertheless, the therapy slowed disease progression and permitted management by less aggressive therapies. When necessary, the therapy was reintroduced with good response, sometimes better than in the first cycle.

Patients and methods

From 2000 to 2006, 17 patients with aggressive cKS were treated with paclitaxel. They were all followed and treated in cooperation with a dermatology department and an oncology department, with evaluation of the disease stage before and

after therapy, according to our classification of cKS (Table 1).²⁹ The selected patients had long-lasting cKS (mean 10.9 years, range 4–30), already treated with many other specific regimens (one to eight different chemotherapies; four patients also received radiotherapy). The disease stage ranged from IIIBc to IVBcv (two IVBcv, six IVBc, nine IIIBc) according to our scale for cKS. All of them presented complications such as lymphoedema, lymphorrhoea, ulceration and haemorrhage causing functional impairment, and all had rapidly developing disease. Their mean age was 71.4 years (range 59–81) and all but one were men. The characteristics of the patients are listed in Table 2. Informed consent was obtained from all the patients taking part in the protocol. The patients underwent weekly intravenous (i.v.) infusions of paclitaxel 100 mg, the first time over 3 h, then in 1 h if well tolerated. Premedica-

Table 1 Staging of classic Kaposi sarcoma²⁹

Stage	Prevalent skin lesions	Behaviour	Evolution	Complications ^a
I Macular/nodular	Macules and/or nodules	Nonaggressive (mostly limbs)	Slow (A) Rapid (B)	Lymphoedema Lymphorrhoea
II Infiltrative (± V)	Infiltrative plaques	Locally aggressive (mostly limbs)	Slow (A) Rapid (B)	Haemorrhage Pain
III Florid (± V)	Angiomatous nodules and plaques	Locally aggressive (mostly limbs)	Slow (A) Rapid (B)	Ulceration Functional impairment
IV Generalized (± V)	Angiomatous nodules and plaques	Disseminated aggressive	Slow (A) Rapid (B)	

^aAll of them prevalent in stage III and IV; lymphoedema and lymphorrhoea often observed in stage II; lymphoedema, ulceration and haemorrhage sometimes present in stage I. V, visceral involvement (pharyngo-oral cavity, gastroenteric tract, lymph nodes, bone marrow, lungs). Rapid = appearance of new lesions within 3 months.

Table 2 Characteristics of the patients

Patient	Sex/age (years)	Diagnosis year	Stage	No. previous therapies	Previous therapies
1	M/62	1988	IVBc	6	VBL × 2, VP16, VBL, VBL + BLM, RT
2	M/63	1999	IVBcv	6	RT, VBL, GEM, VP16, RT, indinavir
3	M/68	1998	IIIBc	4	ABV, RT, GEM, BLM
4	M/81	1975	IIIBc	10	VBL, VBL + VCR, ABV, VP16 p.o. × 2, VP16 i.v., GEM, oncocarbide, VNR, VP16 i.v.
5	M/75	1988	IVBcv	9	VNR, VBL, VP16, BLM, GEM × 2, ABV, oncocarbide, RT
6	M/80	1993	IVBc	3	IFN, VBL, EPI
7	M/77	1996	IVBc	4	VBL, GEM, VNR, GEM
8	M/77	1998	IVBc	6	ABV × 2, VBL × 3, THAL
9	M/80	1997	IIIBc	2	VBL, indinavir
10	M/59	1975	IIIBc	4	VBL × 2, GEM, VBL + BLM
11	M/79	1994	IIIBc	4	VBL, VBL + BLM, VP16, indinavir
12	M/75	1991	IVBc	6	VNR, VBL, VP16, BLM, GEM, oncocarbide
13	M/65	1994	IVBc	1	VBL + BLM
14	M/64	1997	IIIBc	3	VBL + BLM, VBL × 2
15	M/62	1997	IIIBc	1	VBL + BLM
16	M/77	2002	IIIBc	2	VBL + BLM, VBL
17	F/70	1998	IIIBc	2	IFN, VBL + BLM

VBL, vinblastine; VP16, etoposide; BLM, bleomycin; RT, radiotherapy; GEM, gemcitabine; VCR, vincristine; ABV, adriamycin + bleomycin + vincristine; VNR, vinorelbine; EPI, epirubicin; THAL, thalidomide; IFN, interferon; i.v., intravenously; p.o., orally.

Table 3 Response criteria

	Clinical benefit	Tumour response
Initial response	Reduction of complications	±
Partial response	Stable improvement of complications	Size reduction
Complete response	Total regression of complications	Smoothing of all the lesions, only pigmented inactive patches remaining
Disease progression	Increase of complications	Increase of the number and size of the lesions

tion consisted of dexamethasone 12–20 mg i.v., ranitidine 50 mg i.v., clorphenamine maleate 10 mg intramuscularly (i.m.).

Due to the peculiarity of this tumour and of its clinical manifestations, the following efficacy parameters were considered: (i) clinical benefit, (ii) tumour response and (iii) relationship between clinical benefit and tumour response. Thus response criteria were defined as the following: (i) initial response (IR), i.e. reduction of complications (lymphoedema, lymphorrhoea, ulceration, bleeding and pain); (ii) partial response (PR), i.e. size reduction of all the lesions with stable improvement of the complications; (iii) complete response (CR), i.e. total regression of all the complications and smoothing of the lesions with disappearance of the nodules and plaques or transformation to flat pigmented inactive patches (stage I); and (iv) progression of disease (PD), i.e. increase of lesions and/or symptoms (Table 3).

The first evaluation was performed after four cycles: in all the responders, therapy was continued up to 12 cycles. Therapy was discontinued when CR was obtained. When PR was obtained at the 12th week, the treatment was repeated every 2 weeks and was discontinued when a stable improvement of the lesions lasting for at least 4 weeks in the absence of

tumour progression or CR was achieved. The treatment was discontinued in case of (i) serious adverse events or (ii) PD.

Side-effects were reported according to the Common Terminology Criteria for Adverse Events (version 3.0).³⁰

Results

Seventeen patients with aggressive cKS were treated with paclitaxel. Treatment was discontinued in two patients for a serious systemic allergic reaction after the second infusion. The other 15 patients received a mean of 16.8 infusions (range 12–28).

The response to the therapy of the 15 evaluable patients is summarized in Table 4. All patients showed IR after four cycles with decrease of lymphoedema, lymphorrhoea, ulceration and bleeding, and improvement of the symptoms and of functional impairment. After 12 cycles 14 of 15 patients obtained a further clinical benefit, achieving PR up to CR, with flattening and decreased infiltration of the lesions, while PD was observed in one patient despite the initial improvement (patient 4). After 12 cycles, three patients achieved CR and discontinued the therapy; 11 patients continued the treatment every 2 weeks for a mean of eight courses (range

Table 4 Response to the therapy

Patient	No. of total courses	Initial stage	Response at four cycles	Response at 12 cycles	Final response	Stage after treatment	T to P from the 12th cycle (months)	T to P from the end of therapy (months)	FU (months)
1	16	IVBc	IR	PR	PR	IIIB	3	1	22
2	28	IVBcv	IR	PR	PR	IIIB	12	4	15
3	19	IIIBc	IR	PR	PR	IIA	10.5	7	33
4	12	IIIBc	IR	PD	PD	IIIBc	–	–	48
5	2	IVBcv	NV	NV	NV	NV	–	–	Lost to FU
6	12	IVBc	IR	CR	CR	IA	5	5	Lost to FU
7	2	IVBc	NV	NV	NV	NV	–	–	43
8	22	IVBc	IR	PR	CR	IA	10	5	16
9	12	IIIBc	IR	CR	CR	IB	3, slight	3, slight	15
10	18	IIIBc	IR	PR	PR	IIA	7	4	14
11	15	IIIBc	IR	PR	CR	IA	6.5, slight	5, slight	12
12	17	IVBc	IR	PR	CR	IA	10.5, slight	8, slight	33
13	18	IVBc	IR	PR	CR	IB	6, slight	3, slight	15
14	16	IIIBc	IR	PR	CR	IA/B ^a	–	–	–
15	17	IIIBc	IR	PR	CR	IA/B ^a	–	–	1
16	12	IIIBc	IR	CR	CR	IA/B ^a	–	–	1
17	18	IIIBc	IR	PR	CR	IA/B ^a	–	–	–

^aThese patients have a short follow-up, not sufficient for evaluation. T to P, time to progression; FU, follow-up; IR, initial response; PR, partial response; CR, complete response; PD, progression of disease; NV, not evaluable.

3–15), obtaining CR in seven patients and stable PR in four patients.

Thus, at the end of the therapy 10 patients achieved stable CR and four patients stable PR. Moreover, the responding patients were newly evaluated according to our staging scale after 3 months from the end of the treatment or after the therapy for the more recent cases, showing a general improvement of the clinical stage (Table 4).

Ten of 14 responding patients relapsed, and the four remaining patients had a very short follow-up (1 month or less), not sufficient to evaluate the length of the response. The mean time to recurrence was 7.35 months (range 3–12) from the 12th cycle and 4.5 months (range 1–8) from the end of the maintenance therapy. Although recurrence was experienced in 10 patients, it was mild in four of them and they received only local treatment such as single-nodule infiltration with vincristine or compression therapy with elastic stockings.

Paclitaxel was reintroduced in the remaining six relapsed patients, with achievement of intermediate response/good response in five of them: one patient is under treatment and the other four experienced progression after 1, 3, 5 and 8 months. Response was always rapid and therapy well tolerated.

The therapy was very well tolerated with low toxicity. In particular, haematological toxicity was extremely low: only grade 1 neutropenia was recorded in two patients, asthenia and diarrhoea in four and one patients, respectively, and grade 1 neurological toxicity was recorded in one patient.

Two patients had a serious systemic allergic reaction during the second infusion with facial erythema, dyspnoea and hypotension, that cleared with high-dose steroid infusion, liquids *i.v.* and oxygen. Nevertheless, these patients already showed a reduction of the symptoms after the first paclitaxel cycle.

Discussion

Seventeen patients with long-lasting aggressive cKS were treated with standardized low-dose paclitaxel therapy (100 mg *i.v.* weekly). Fifteen patients showed rapid initial improvement and relief of the symptoms within 1 month (four infusions), while a stable PR/CR was obtained in 14 of 15 patients, with progression of one patient (patient 4) after the fourth course. Better to define the improvement and the evolution of the disease, we evaluated again the patients' stage after 3 months, when such a follow-up was available, obtaining a considerable improvement of the clinical stage (Table 4).

cKS has a wide spectrum of clinical manifestations and aggressiveness, with the balance with the immune system being crucial for disease course and prognosis.^{4,31} Due to the peculiarity of this disease, in our experience it is particularly important to define the stage with a classification considering the type of lesions, complications, functional impairment and evolution time. This classification scheme permitted a more precise and homogeneous evaluation of the disease with a resulting standardized planning of the treatment.²⁹

All the patients had been treated with numerous chemotherapeutic agents during their long-lasting disease, which had become refractory and rapidly progressive. In some patients it was not possible to repeat chemotherapies which proved to be effective before, due to the maximum total dose allowed (*i.e.* bleomycin). Moreover, it was not possible to repeat some effective but less tolerable therapies the patients had undergone 10–20 years before, when their general conditions were better. In contrast to other studies,^{8–10} we generally did not use interferon alfa, because of the serious psychiatric effects we often observed in elderly patients.

Paclitaxel is a drug highly effective in the treatment of several neoplasms, including ovarian, breast and lung carcinomas.¹⁷ It is a microtubule-stabilizing drug that causes dividing cells to arrest and then undergo apoptosis. It also has antiangiogenic activity because it alters cytoskeletal structure, affecting migration and invasion. Recently, paclitaxel has also been found to be active in patients with advanced HIV-associated KS and it has been approved for AIDS-KS as a second-line therapy after anthracycline-based regimens. Good results were also reported in some anecdotal reports in non-HIV-related KS, classic, endemic and post-transplantation KS,^{4,15,18–28} and confirmed in a 12-patient French series.¹⁴

In our study the low dose of paclitaxel was chosen in order to improve tolerability in our elderly patients. We experienced very good results with rapid response (Fig. 1). The mean time to recurrence was 7.35 months (range 3–12) from the 12th cycle and 4.5 months (range 1–8) from the end of the therapy. The remission period was shorter than in the French study (8.9 months; range 6.8–11.2), in which other non-HIV-related types of KS were considered, apart from cKS; also docetaxel was used and different therapeutic schemes were applied. In fact, paclitaxel was used in three patients only, with a similar final dose but a different regimen. Docetaxel has been reported to be more effective as an antiangiogenic drug,³² which could explain the better result but also the lower tolerability: haematological toxicity was much higher, requiring a supportive treatment with granulocyte colony-stimulating factor in several patients. In contrast, in our study the drug was not associated with any other supportive treatment and haematological toxicity was very low.

Two of 17 patients had to discontinue the therapy due to a severe allergic reaction at the second infusion. Allergic reactions are a well-known dose-independent adverse event of treatment with paclitaxel,³³ that justify premedication with dexamethasone 12–20 mg *i.v.*, ranitidine 50 mg *i.v.* and clorphenamine maleate 10 mg *i.m.* In these patients a treatment with docetaxel could be suggested, as indicated in allergic reactions to paclitaxel for other tumours when the use of taxanes is recommended.³⁴

This is the first study on the use of standardized low-dose paclitaxel in a series of 17 patients with long-lasting, aggressive, refractory cKS. Despite the usual although often milder recurrence, the therapy was very successful in slowing down disease progression in elderly patients with chronic disease where no other therapy proved to be effective, thus often



Fig 1. Patient 8. (a) Before treatment, (b) after 12 infusions and (c) at the end of treatment (22 infusions).

permitting an easier management using local treatment (single-nodule infiltration with vincristine, compression therapy with elastic stockings). The therapy was repeated in case of relapse with good response, and only one patient experienced chemoresistance.

In our experience low-dose paclitaxel proved to be a useful drug, with low toxicity, that was extremely active in elderly patients affected by advanced and heavily pretreated cKS. In particular, it rapidly and greatly improved the classical complications of the disease, permitting a functional recovery with

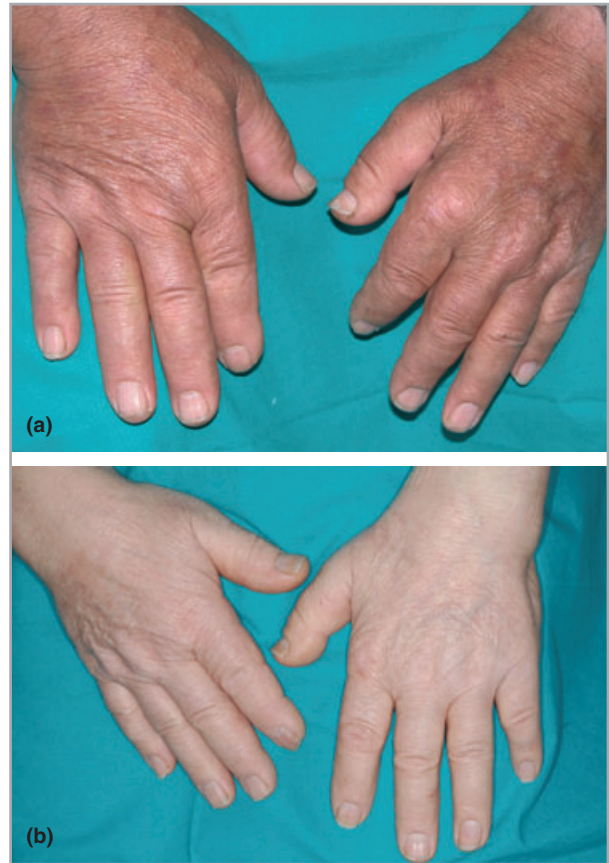


Fig 2. Patient 13. (a) Before treatment and (b) at the end of treatment (17 infusions).

great impact on the quality of life (Fig. 2). This is truly important as cKS is a chronic disease in which improvement of the quality of life is the first aim of the therapy, rather than complete remission. Consistently, the evaluation response should also consider the same criteria.

Considering the rapidity to induce response and the efficacy of paclitaxel used as third, fourth or more line of therapy, in our opinion this drug should be assessed as second-line therapy for advanced and complicated cKS (stage IIIB–IVBc) in controlled prospective clinical trials, just as was done in advanced HIV-associated KS. Only in this way can the real contribution of this drug in this uncommon pathology be clarified and maybe it will be possible to define treatment guidelines for advanced stages of cKS. The use of paclitaxel in cKS has been evaluated in anecdotal reports in only a few patients and it is difficult to compare the results with those obtained with other drugs such as vinblastine, bleomycin or doxorubicin used as first-line or second-line treatment. The few available studies, including our series, show short-term recurrence that is, on the other hand, common in multiply treated cancer patients. This could be due to the repeated premedication with steroids, as the iatrogenic effect of immunosuppressive drugs is well known in cKS,³⁵ and thus this treatment cannot be recommended as first-line therapy for the moment. For this purpose, further study and investigation

are required to define the best therapeutic schedule and the most suitable taxane to be used.

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