Combination of vinblastine and bleomycin as first line therapy in advanced classic Kaposi’s sarcoma

L Brambilla,∗† A Miedico,‡ S Ferrucci,† A Romanelli,† M Brambati,† M Vinci,‡ L Tedeschi,‡ V Boneschi†

† Institute of Dermatological Sciences, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Via Pace 9, 20122 Milan, Italy
‡ Oncology Department, San Carlo Borromeo Hospital, Via Pio II, 3, 20153, Milan, Italy

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*Corresponding author, tel. +39 255035112; fax +39 2550335562; E-mail: luciabrambilla1@tiscalinet.it

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Abstract

Background Classic KS (CKS) mainly affects elderly people, has an irregular course, and is relatively benign for years. However, sometimes the disease may progress rapidly and spread to internal organs, thus necessitating systemic chemotherapy. We therefore decided to carry out a prospective trial using vinblastine and bleomycin, which are active, easy to administer and control, and low cost.

Methods We treated 29 patients affected by CKS with vinblastine i.v., up to 10 mg in combination with bleomycin i.m., 15 IU every 3 weeks. We administered a median of seven cycles of therapy.

Results All the 29 enrolled patients were evaluated: 21% reached a complete response and 76% had an intermediate response. Toxicity was limited. The maximal response was attained in a median of 5 months, with a mean duration of 4 months.

Conclusion The combination of vinblastine and bleomycin achieved a high rate of objective responses in a subgroup of elderly and symptomatic patients, without considerable toxicity. We recommend the combination as first line chemotherapy for advanced CKS.

Introduction

Kaposi’s sarcoma (KS) is a rare vascular tumour mainly affecting the skin, and is strictly related to a viral infection. It has different clinical manifestations and behaviour in spite of similar histological features, as shown in Table 1.

Classic KS (CKS) affects elderly people of Mediterranean, Eastern European or Jewish heritage. Peak incidence occurs in the sixth decade of life. CKS generally has a chronic and irregular course that can begin with one or more angiomatous patches, plaques or nodular skin lesions, usually limited to the lower extremities. Pathologically it is characterized by vascular proliferation of well-formed vascular structures and immature endothelial spindle cells in storiform pattern with interstitial erythrocytes and inflammatory lymphoplasmocytic infiltrate. The course can be indolent and relatively benign for years with slow enlargement of the original tumour and/or development of new lesions. In time, complications develop, such as lymphoedema, ulceration with bleeding and superimposed infections, which compromise the patient’s quality of life. The disease may sometimes progress rapidly and spread to internal organs such as the gastrointestinal tract, lymph nodes and lungs or involve contiguous bones. Patients survive an average of 10–15 years before dying, most often of unrelated causes.

Other than genetic and immunological factors, human herpesvirus-8 (HHV-8) plays an important role in the pathogenesis of CKS. This virus is present in 100% of
examined pathological tissue specimens, as are antibodies anti-HHV-8 in affected patients. HHV-8 can be transmitted sexually or by other means such as maternal–infant transmission.4–6 Moreover, the viral load in peripheral blood mononuclear cells seems to correlate with the activity of KS.7

Because of the highly variable clinical evolution of the disease it is often difficult to decide whether and when to treat these, frequently old, patients. In fact, there is no standard therapy policy for KS and the treatment must be tailored to the individual patient.8

Unlike AIDS-related KS, there is no universally accepted stage classification for CKS. We decided to use a new staging system based on objective criteria that more closely follow the clinical variability of CKS and make therapeutic choices easier. This staging system comprises four stages (I–IV) based on skin lesions and localization, and the presence or absence of complications and visceral involvement9 (Table 2).

In stages I and II (slow evolution) therapeutic strategy includes different approaches depending on the features of the tumour: clinic monitoring, surgical removal (also important for histological confirmation of the diagnosis), radiotherapy (in selected cases),10 elastic stockings for the prevention of lymphoedema and, finally, intralesional chemotherapy with vincristine.11 Patients in stage II with rapid evolution or complications, and in stage III or IV require systemic chemotherapy. Many drugs are effective in the treatment of naive, refractory or relapsed KS: interferon alfa, vinca alkaloids,12,13 bleomycin, doxorubicin, liposomal doxorubicin,14,15 gemcitabine,16 etoposide,17 and paclitaxel.18 Due to the rarity and distribution of cases, there is little information about which is the best therapy,19 and only a randomized trial involving CKS has been published so far.20 The majority of studies of KS has been carried out on the AIDS-related form. In this particular form of KS, research on treatment with high efficacy and minimal side-effects for both young and frail patients has emphasized the importance of liposomal doxorubicin. This is in fact the drug indicated for first line treatment in AIDS-KS.21 CKS mostly affects an elderly population, which in some respects is as frail as those affected by AIDS-related KS. It is therefore important to have new chemotherapeutic strategies for CKS that act rapidly, have limited side-effects, and could be used for long periods and overcome resistance to previous treatments, without neglecting economic aspects.

We therefore decided to carry out a prospective multicentric trial using a particular schedule of combination vinblastine and bleomycin, which are active, easy to administer and control, and are low cost. Vinblastine is a drug that can be used at low doses for a prolonged period without significant side-effects. Bleomycin can also be used for a prolonged period at single doses < 30 IU and up to the maximum total dose of 200–250 IU in the elderly, because of possible pulmonary toxicity, characterized by an interstitial pneumonitis that can lead to fibrosis.22

### Materials and methods

From January 2002 to September 2004 we enrolled 29 patients in the study (24 men and five women) with a median age of 74 years (range 58–89). Fifteen patients were undergoing first line chemotherapeutic treatment and 14 patients had previously received two or more regimens of therapy, which for some patients had included vinblastine and bleomycin.
Patients were classified according to the stage classification featured above (Table 2). Eligibility criteria included histologically confirmed diagnosis of CKS, HIV negativity, < 90 years of age, a performance status of 0 to 2, an adequate bone marrow reserve (WBC = 3000/µL, absolute neutrophil count = 1500/µL, platelet count = 130 000/µL), no renal or hepatic failure, absence of severe broncopulmonary disease, absence of other tumours except small non-melanoma skin cancers, and stages II (infiltrating) in the variant B (rapid), III (florid) and IV (generalized). All patients were evaluated by thorax radiography, ultrasound abdomen echography and/or computerized tomography and pulmonary function tests (FEV1 and DLCO). When possible, and bearing the age of the patient and gastrointestinal symptoms in mind, we completed the staging with endoscopy. Pulmonary function tests were repeated at the end of therapy; instrumental analysis was also repeated if positive at the initial staging.

Of the patients enrolled, four were in stage IIB, 18 were in stage III (nine in stage IIIB, eight in IIIBc and one in IIIBv) and seven were in stage IV (six in IVBc and one in IVBcv). Patients’ characteristics are shown in Table 3.

### Treatment schedule

Vinblastine was administered i.v. on days 1, 8 and 15 with dose escalation (4–6–8 mg) for 3 weeks (starting with 4 mg) and then at the maximum tolerated dose (up to 10 mg total dose) in combination with bleomycin, 15 IU (total dose) i.m., on day 1 every 3 weeks (Table 4).

An objective response was evaluated every 3 weeks by careful clinical observation. Red cells, white cells and platelet count were determined weekly during dose escalation and subsequently every 3 weeks.

It is difficult to define the response on the basis of WHO criteria in this tumour; therefore, we distinguished three levels of response: initial, intermediate and complete. Initial response was a reduction of associated complications (i.e. oedema, pain, ulcerations, haemorrhage, functional impairment, lymphorrhoea). Intermediate response was a consolidated, lasting reduction of number, width and thickness of all of the lesions, and improvement of complications. Complete response was the total regression of all complications, the planing of lesions with disappearance of nodules and plaques or their transformation in plain purple inactive lesions.

Toxicity was evaluated according to WHO criteria. Treatment was administered until a complete response, intermediate, consolidated response, disease progression, maximal bleomycin dose, or toxicity was observed.

### Results

All 29 enrolled patients were evaluated (Table 5): twenty-eight achieved an objective response and one patient experienced disease progression during treatment, after an initial response. Twenty-one per cent (6/29 patients) reached a complete response and 76% (22/29 patients) gave an intermediate response.

We administered a median of seven cycles of therapy (range 2–14). Initial response was observed at a median of 2 (range 1–7) months. The median time necessary to achieve the maximal response was 5 months. We calculated the median duration of response, 4 months (range...
1–25+), after the end of therapy because we stopped it at different levels of response or toxicity.

As regards toxicity, we observed 11 cases of neutropenia, three of which were grade IV; patients with neutropenia received G-CSF (granulocyte-colony stimulating factor).

Neurotoxicity grade I was recorded in two patients. One patient suffered from nausea and vomiting. No pulmonary toxicity, evaluated by pulmonary function tests before and at the end of treatment, was observed. All patients except two are still alive; one died of an acute myocardial ischaemic attack (not related to therapy) and one of renal cancer.

Compliance to the treatment schedule was high due to rapid reduction of symptoms related to KS.

Discussion

Although CKS is described as a disease with a long indolent course, not infrequently it shows a rapid progressive acceleration that necessitates systemic chemotherapy.

Considering patients’ median age and the importance of improving quality of life, the need to employ a convenient treatment schedule with few side-effects and at a limited cost is evident.

In the literature most reports focus on treatment of epidemic or post-transplant variant; only a few homogeneous series of classic type are published.

Our past experience has made us appreciate vinblastine as a single chemotherapeutic agent in first line treatment for its efficacy, convenience and tolerability. In one of our previous studies we treated 31 patients with vinblastine, 18 of whom achieved an objective response (CR + IR) with a median maximal response time of 8.5 months for CR and 6 months for IR and very limited toxicity.

Given the debilitating collateral events related to this tumour in stages > II, it is also important to have a treatment schedule that acts rapidly. Furthermore, elderly patients do not accept treatment with serious side-effects and that result in prolonged and repeated hospitalization. We therefore had to consider these problems before drawing up a treatment schedule for CKS, so as to obtain maximum compliance.

In our experience, combination vinblastine and bleomycin achieved a high rate of objective responses (97%) with acceptable toxicity, except for three patients who developed grade IV neutropenia during the initial phase of therapy.

The response was attained very rapidly (median of 2 months) and in a median of 5 months patients had a maximal response. The mean duration of response was 4 months (range 1–25+), calculated from the end of treatment.

Our results showed that 7–8 cycles of this schedule could produce a significant and quick response in a subgroup of elderly and symptomatic patients, without considerable toxicity and with remarkable improvement of quality of life. Moreover, the response was maintained for a significant period of time after discontinuation of chemotherapy.

In our experience, we consider that the combination of vinblastine with bleomycin can give good and rapid therapeutic results. These two drugs act in synergy at different points of the cellular cycle and have different side-effects.

Compared to other chemotherapeutic regimens we have used in the past (single chemotherapeutic agents such as vinblastine, etoposide, vinorelbine), we appreciated the good response rate (97%), the limited number of collateral effects and the rapidity in obtaining the maximal response. All these factors led to good patient compliance towards the therapeutic schedule. Moreover, the drugs are easy to administer and are low cost.

For these reasons, we recommend the combination of vinblastine and bleomycin as first line chemotherapy for aggressive CKS.

References