

## Bortezomib Does Not Prevent the Occurrence of Kaposi's Sarcoma in Patients with Haematological Malignancies: Two Case Reports

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Kaposi's sarcoma (KS) is a rare angioproliferative tumour that affects skin and mucosa. Kaposi's sarcoma herpes virus (KSHV or human herpes virus-8 (HHV-8)) is thought to be the causal agent (1). Besides endemic cases, KS induced by HHV-8 reactivation has been described among immunocompromised patients, such as those with AIDS and those with iatrogenic immunosuppression, mainly transplant recipients (2–4).

Bortezomib is a proteasome inhibitor used for the treatment of multiple myeloma and plasma cell dyscrasias, such as AL amyloidosis. No previous cases of KS occurring after bortezomib therapy have been reported.

### CASE REPORTS

**Case 1.** A 69-year-old woman of Afro-Caribbean origin was referred in November 2012 for acute renal failure associated with lumbar pain and weight loss. She had no significant medical history. Clinical and biological investigations revealed IgG-lambda multiple myeloma with bone, renal and haematological complications (Table S1<sup>1</sup>).

Chemotherapy with bortezomib (1.3 mg/m<sup>2</sup> subcutaneously on days 1, 4, 8, 11, on a 21-day cycle), oral dexamethasone (20 mg twice a week) and cyclophosphamide (750 mg/m<sup>2</sup> intravenously (IV) on day 1), was initiated. After 3 cycles, the patient reached both renal (creatinine 152 µmol/l) and haematological partial remission.

In February 2013, violaceous macules and papules were noticed on her left forearm and right arm, followed by similar bilateral lesions on both legs (Fig. 1A, B).

Cutaneous biopsy demonstrated pathological features of typical KS. PCR of HHV-8 DNA was highly positive in tumour lesions, but negative in blood cells.

HIV serology was negative. Oesophago-gastro-duodenoscopy, thoraco-abdominal computed tomography (CT) scan and F-18 FDG PET/CT (<sup>18</sup>F-fluorodeoxyglucose-positron emission tomography–CT) showed no visceral involvement of KS.

Treatment with bortezomib and cyclophosphamide was interrupted and lenalidomide was introduced as second-line treatment for myeloma, after renal function dose-adjustment (15 mg every other day), associated with dexamethasone (20 mg once a week).

The cutaneous lesions regressed completely 2 months after initiation of lenalidomide. Blood HHV-8 PCR remained negative. The patient showed an excellent haematological response and renal function continued to improve. After a 3-year follow-up, the patient is still receiving lenalidomide maintenance therapy with sustained haematological remission. No KS relapse has been observed to date.

**Case 2.** A 63-year-old woman of North African origin was referred in July 2013 for nephrotic syndrome associated with acute renal failure. Her medical history was significant for diabetes mellitus and hypertension, but also for cirrhosis due to hepatitis



Fig. 1. Baseline Kaposi's sarcoma lesions in patient 1.

C, treated with PEG-interferon-alpha and ribavirin, with sustained virological remission.

She reported recent history of marked asthenia, associated with diarrhoea and vomiting. On admission, physical examination was unremarkable. Biological and pathological investigations revealed renal and digestive AL lambda amyloidosis (Table S1<sup>1</sup>). Cardiac imaging and thoraco-abdominal CT were normal.

Treatment with bortezomib (1.3 mg/m<sup>2</sup> subcutaneously on days 1, 8, 15 and 21, of a 28-day cycle), oral dexamethasone (20 mg twice a week) and oral cyclophosphamide (500 mg on days 1, 8, 15), was initiated in August 2013. Despite initial haematological response, nephrotic syndrome persisted with rapid deterioration of renal dysfunction, leading to initiation of haemodialysis in October 2013.

During the third cycle of therapy, the patient developed extended papular lesions of the thighs (Fig. S1<sup>1</sup>). Skin biopsy showed characteristic features of KS with positive cutaneous HHV-8 latency-associated nuclear antigen (LANA) staining. HHV-8 viraemia was positive, with a viral load of 792 copies/ml (2.9 log). No visceral localization of KS was found on F-18 FDG PET/CT and thoraco-abdominal CT scan.

Chemotherapy by bortezomib and cyclophosphamide was therefore stopped, and a combination of lenalidomide (5 mg 3 times a week, following dialysis) and dexamethasone was started in January 2014, in order to control plasma cell dyscrasia. Although the haematological response remained good after modification of chemotherapy, the patient died from septic shock in March 2014, due to enterococcal bacteraemia. No modification of the cutaneous lesions was observed before the fatal outcome.

### DISCUSSION

We report here 2 cases of KS that developed following treatment with bortezomib and cyclophosphamide.

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Bortezomib (Velcade®) is a reversible proteasome inhibitor used for the treatment of plasma cell disorders (5), which has been approved by the US Food and Drug Administration (FDA) for first- or second-line treatment of patients with multiple myeloma and mantle cell lymphoma. Recent data suggest that bortezomib also has some activity against gamma herpes virus (GHV)-associated cancers. Association between KS and HHV-8 is well established (1), but several other malignancies are HHV-8-driven, such as primary effusion lymphoma (PEL) (6), plasmablastic lymphoma and multicentric Castleman's disease. Interestingly, bortezomib has even more pronounced cytotoxic effects against PEL cells than against multiple myeloma cell lines (7) and could block the virus lytic cycle (8).

The presumed *in vitro* efficacy of this drug against HHV-8 contrasts with the occurrence of KS in the 2 bortezomib-treated patients reported here. Iatrogenic forms of KS have been well described in individuals receiving different cytotoxic or immunosuppressive drugs. The most frequently reported therapies associated with drug-induced KS are corticosteroids (3–5), azathioprine (3), cyclosporine A (4) and cyclophosphamide<sup>2</sup>.

In the 2 cases reported here, KS may have been induced by cyclophosphamide and/or dexamethasone. Nevertheless, KS was diagnosed shortly after initiation of treatment, suggesting that addition of bortezomib to cyclophosphamide does not prevent HHV-8 reactivation and may have a synergistic immunosuppressive effect leading to development of KS.

Although iatrogenic KS can partially regress after the reduction of immunosuppression, disseminated or symptomatic forms often require specific therapy (9). Treatment of KS lesions is based on surgical excision and/or radiation therapy, sometimes associated with cytotoxic drugs, such as doxorubicin or etoposide. Sirolimus (10) has been used recently in transplantation-associated KS. In parallel, other studies have shown that thalidomide is sometimes associated with beneficial effects on both HIV- and non-HIV-related KS (11), despite multiple toxicities, such as neuropathy or thrombosis (11, 12).

Lenalidomide is an immunomodulatory drug derived from thalidomide, which shows both anti-angiogenic and immune-stimulatory properties, together with direct effects on tumour and stroma cells (12). Its use has been approved for the treatment of multiple myeloma, in association with dexamethasone.

Several cases have been published to date (13, 14), reporting HHV-8-associated diseases responding to lenalidomide, after failure of conventional chemotherapy. In the 2 cases reported here, no specific chemotherapy was given for KS, in the absence of visceral organ involvement, but bortezomib and cyclophosphamide were stopped, in order

to hamper progression of KS. Lenalidomide was initiated to treat plasma cell dyscrasia, hoping that it would also be beneficial for KS lesions. Interestingly, in one of the cases, regression of KS lesions was observed only a few months after initiation of lenalidomide, similarly to previously reported cases. In the second case, we were not able to observe the potential effect of lenalidomide on KS, as the patient died from infectious complications shortly after introduction of the drug.

More information on effectiveness and tolerance are necessary before considering lenalidomide as a new drug for KS. Nevertheless, our data, in combination with previous reports, suggest that this immunomodulatory drug could be proposed as a second-line agent in patients with drug-induced KS, especially in patients with underlying plasma cell disorders.

*Conflicts of interest:* CL: advisory boards for MSD, BMS, Roche, Novartis Amgen. The other authors declare no conflicts of interest.

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