Treatment of Kaposi Sarcoma With Oral Administration of Shark Cartilage in a Human Herpesvirus 8–Seropositive, Human Immunodeficiency Virus–Seronegative Homosexual Man

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The patient was repeatedly seronegative for human immunodeficiency virus, and his serial lymphocyte subset counts, complete blood cell counts, serum chemis-

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REPORT OF A CASE

A 45-year-old white man presented with a 2½-year history of a bruiselike area on the arch of his right foot (Figure 1). A skin biopsy specimen of the lesion revealed Kaposi sarcoma (KS) (Figure 2), with slitlike vascular spaces that were accentuated by CD34 immunostaining (Figure 3).

The patient was a sexually active homosexual man of English descent, with no Ashkenazi Jewish or Mediterranean family background. His medications included aspirin, St John’s wort, multiple and B complex vitamins, fluvastatin sodium, loratadine, and fexofenadine hydrochloride, and he occasionally used amyl nitrate nasally as a sexual stimulant.

Physical examination revealed a 1.5 × 3-cm slightly violaceous indurated plaque on the mid instep of the patient’s right foot. No other mucocutaneous lesions of KS were found, and there was no hepatosplenomegaly or peripheral lymphadenopathy. A chest x-ray film revealed no abnormalities. The assessment was early-stage KS (T0 T0 S0),1 with a performance status of 0.

Figure 2. Sections of skin in 1997 (A) and 1999 (B) showing decreased numbers of small vessels in papillary dermis (hematoxylin-eosin, original magnification ×40).

Figure 1. A, Erythematous patch of Kaposi sarcoma on the patient’s right mid instep in 1997. B, Patch has faded significantly in color by 1999.
try study results, and chest x-ray films were normal. Initial serological tests were positive for human herpesvirus 8 (HHV-8) at a titer of more than 1:160 (reference value, 1:20 [negative]) on immunofluorescent antibody assay (Specialty Laboratories, Santa Monica, Calif), and polymerase chain reaction testing of a serum sample showed positivity for HHV-8 DNA. After further laboratory testing, confirmation of the diagnosis, and clinical monitoring, a 3-month course of oral ganciclovir (1000 mg 3 times daily) was initiated, but the KS lesion did not improve.

**THERAPEUTIC CHALLENGE**

Intralesional vinblastine sulfate, interferon, intravenous foscarnet sodium, and cidofovir were considered as treatment options but were not used, because the progression of the lesion was slow and the adverse effects of the drugs were not acceptable to the patient. Also, locally aggressive treatments, such as excision, radiation therapy, and cryotherapy, were unacceptable to the patient owing to the potential for disfiguration and possible functional impairment. Alitretinoin was also considered, but the cost was prohibitive, and it was not available on a compassionate-use basis. Furthermore, local therapies would not address the underlying HHV-8 infection or the systemic nature of the disease.

**SOLUTION**

A trial of oral shark cartilage therapy was initiated at a dose of 3750 mg divided 2 times a day for the first 3 months and 4500 mg divided 3 times a day for the rest of the treatment period. After 3 months, the KS lesion had decreased in size (1.5 × 2.5 cm) and was less violaceous. By 6 months, it had faded significantly in color and was almost clinically undetectable. A biopsy specimen obtained at 9 months showed histopathologic evidence of regression of the KS (not shown). Clinical improvement continued (Figure 1), and by 21 months, a biopsy specimen showed even further histological regression (Figure 2). The regression was apparent, as there were fewer slitlike spaces and collections of small vessels in the papillary dermis that were enhanced by CD34 immunostaining (Figure 3).

The patient switched between 2 brands of shark cartilage (Swanson Health Products, Pittsburgh, Pa, and General Nutrition Center Natural Brand, Fargo, ND) (1 capsule equals 730 mg of shark cartilage powder) during the course of his treatment because of differences in cost. He did not experience any adverse or toxic effects.

**COMMENT**

This is the first reported case in which oral shark cartilage was used in the treatment of cutaneous KS, with documented clinical and histological regression over a 3-year follow-up period. Human herpesvirus 8 has been detected in almost 100% of KS lesions and is believed to play a role in the pathogenesis of KS. Recent findings implicate HHV-8–encoded interleukin-6 in creating an angiogenic state in KS by stimulating the expression of vascular endothelial growth factor. Our case is unique because it suggests that the use of shark cartilage as a treatment for KS may be a plausible alternative to traditional and possibly more toxic treatment modalities.

The use of shark cartilage products as an alternative therapy for cancer and angiogenesis-related disorders is becoming increasingly common. Although shark cartilage has not been approved by the Food and Drug Administration as a treatment modality for anticancer and/or antiangiogenesis therapy, peer-reviewed literature contains reports of the antiangiogenic properties of shark cartilage–derived products.

The presence of an inhibitor of tumor angiogenesis in the cartilage of basking sharks (Cetorhinus maximus) was first demonstrated in 1983 by shark-extract inhibition of neovascularization of tumors implanted in experimental corneas. Initial work exploring antiangiogenic factors in bovine and rabbit cartilage resulted in the isolation of a protein named collagenase-derived inhibitor. At least 2 more angiogenesis inhibitors have been isolated from shark cartilage. One of them, isolated from the blue shark (Prionace glauca), possesses both anti–human umbilical vein endothelial cell–migration activity and anticolagenolysis activity. There are a few reports on the treatment of various diseases with shark cartilage. Oral administration of shark cartilage resulted in a decrease in wound angiogenesis.
in healthy men, supporting the efficacy of orally administered shark cartilage in promoting antiangiogenesis.13 In another trial, a topically administered shark cartilage derivative (AE-941, Neovostat; AEterna Laboratories Inc, Quebec City, Quebec) was applied to the forearms of test subjects, and anti-inflammatory as well as anti-angiogenic properties were documented.14 However, a phase I/II trial in which patients with previously treated advanced breast, colon, and lung cancers were examined showed no effect on tumor growth with oral shark cartilage.15 This study, though, used a short-course, high-dose treatment regimen of 1.0 to 1.3 g/kg of shark cartilage over a 12-week trial.

In contrast, our therapy was based on a continuous low-dose regimen. This method of therapy is distinct and is based on the results of several studies of the effects of antiviral and chemotherapeutic agents on antiangiogenesis. A 1-year trial evaluating oral ganciclovir in the treatment of cytomegalovirus retinitis also found that such therapy decreased the risk of KS by 75%.16 This may be mediated by an effect on angiogenesis rather than by ganciclovir's antiviral effect on HHV-8, as the dosages used appear subtherapeutic. At a dosage of 3 g/d, the peak plasma concentration is only 0.004µM, which is well below the in vitro concentration of 2.7µM to 4.0µM that is needed to inhibit 50% of HHV-8 replication.17,18 No in vivo susceptibility testing for HHV-8 currently exists. Also, antiviral drugs, such as ganciclovir, target lytic viral replication, and because most of the spindle cells in KS are latently infected, the importance of the small population of susceptible spindle cells in the lytic stage is unknown.

Similarly, interferon, a primarily antiviral agent, is also used as an angiogenesis inhibitor that may function indirectly by inhibiting the spindle cells of KS and hemangiomas. Studies using interferon alfa-2a for the treatment of hemangiomas found that a long-term, low-dose regimen (daily treatment for at least 1 year) was necessary to prevent recurrence of the hemangiomas.19,20 These studies have shown that for the treatment of vascular lesions, long-term therapy at lower dosages was necessary for efficacy. This method presumably exploits a susceptibility of the angiogenic stimulus in the tumor and enhances antiangiogenic targeting or the immunomodulatory properties of the drug to alter the cytokine environment.

The efficacy of such antiangiogenic scheduling has also been demonstrated in animal and in vitro studies using continuous low-dose administration of chemotherapeutic agent to treat lung carcinoma, breast carcinoma, and neuroblastoma xenografts in mice.21,22 It is hypothesized that the tumor endothelial cells are more susceptible to chemotherapy than are the stable endothelial cells in normal tissue and therefore undergo more sustained apoptosis. Also, in contrast to traditional maximum tolerated dosing schedules requiring a treatment-free recovery period, the continuous schedule prevents the tumor cells from having a rest period in which to repair cellular damage. By simply changing the dosing schedule, one can redirect the action of a drug with antiangiogenic potential. Through this technique, the risk of drug resistance is decreased, and even a highly drug-resistant form of Lewis lung carcinoma, the most refractory murine tumor used in screening chemotherapeutic agents, could be eradicated by preferentially targeting the vascular tumor bed.22 This method may be even more beneficial for relatively slower-growing tumors, such as KS, because cytotoxic pressure can be prolonged. These studies show how the antiangiogenic and antitumor activities of these many agents can be independently accentuated based on the dosing regimen.

Since no prior studies exist regarding any dosing regimens with shark cartilage and KS, our continuous low-dose regimen was empirically determined to potentiate the inherent antiangiogenic action of shark cartilage based within the preceding framework of evidence. Our patient is unusual because he is a human immunodeficiency virus–seronegative homosexual man who is HHV-8 seropositive and does not fall into one of the 4 main subtypes of KS. He does have risk factors that predispose him to HHV-8 infection, and he uses condoms during anal intercourse but not during oral sex, which is consistent with data indicating that orogenital sex is significantly associated with HHV-8 seroconversion.23,24

Although the natural course of KS is gradual progression, we cannot discount the possibility of spontaneous regression in this patient. However, our patient's KS lesion, which had not responded to another treatment (ganciclovir), regressed dramatically in color and thickness as well as histopathologically during oral shark cartilage therapy. This outcome suggests that the oral shark cartilage was responsible for the regression of the KS.

The adverse effects and drug interactions of shark cartilage are presently unknown, and there are no reports of any toxic effects in the literature. Although shark cartilage is not subject to review by the Food and Drug Administration because it is classified as a dietary supplement instead of a drug, the Food and Drug Administration has not identified shark cartilage as unsafe, nor has it restricted its use owing to safety concerns. The cost of the 2 brands (Swanson Health Products and General Nutrition Center Natural Brand) of shark cartilage mentioned in this article is $1.08 and 1.32, respectively, per day, prices that compare with those of ganciclovir ($16 per 1000-mg tablet), alitretinoin gel ($1992 for 60 g), interferon alfa-2a ($24 per 3 million units), vinblastine ($8 per 10-mg/10-mL vial), foscarnet ($56 per 6-g/250-mL intravenous bottle), cidofovir ($664 per 375-mg vial), cryotherapy ($300 per treatment), and excisional surgery ($650).

Advantages of shark cartilage therapy include absence of systemic adverse effects; prevention of further morbidity, such as tumor-associated edema and necrosis; and patient satisfaction with the cosmetic results. The treatment was also consistent with the patient's medical philosophy of alternative medicine.

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REFERENCES


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