Recombinant Interleukin 2 Monotherapy for Classic Kaposi Sarcoma

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

An 83-year-old Japanese man was referred to our clinic with a 3-year history of multiple cutaneous lesions on both feet, which had slowly increased in size and number. A physical examination revealed scattered blue-red papules up to 5 mm in diameter on both feet, mainly on the soles. The largest dome-shaped nodule (10 mm in diameter) was present on the ventral aspect of his right first toe. The inguinal lymph nodes were not palpable. Results of computed tomographic scanning showed no metastatic lesions in the liver or other abdominal organs. The results of laboratory studies were within normal limits, including urinalysis, CD4+ and CD8+ lymphocyte counts, and CD4/CD8 ratio. Serologic test results for human immunodeficiency virus (HIV) 1 and HIV-2 were negative. The patient had IgG antibodies to cytomegalovirus. He was otherwise healthy except for having hypertension, for which he was taking alacepril. The largest nodule located on his right first toe was excised with 1-cm margins, and the defect was covered by a full-thickness skin graft. A specimen of the excised nodule revealed bland spindle tumor cells forming vascular channels proliferating with slight inflammatory lymphocytic infiltration in the dermis. These clinical and histological findings confirmed the diagnosis of classic Kaposi sarcoma (KS) in stage IIA, according to the classification by Kriegel et al. Weekly intrallesional doses of $35 \times 10^4$ units of recombinant interleukin 2 (rIL-2) (Shionogi & Co Ltd, Osaka, Japan) were injected into the skin lesions in the sole of the patient’s right foot. The papular lesions began to regress and subsequently flattened, becoming variously sized purpura after the 10th injection (3 months) of rIL-2. A biopsy specimen of 1 of these purpuric macules revealed a marked decrease in the number of tumor cells with elongated nuclei. However, atypical tumor cells were focally detected between collagen bundles with fibrosclerotic changes. No mitotic figures were detected. Mod-

SOLUTION

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Figure 1. Many violaceous macules and nodules of Kaposi sarcoma (KS) on the sole of the patient’s right foot before therapy with recombinant interleukin 2. Note the postoperative site of a full-thickness skin graft for the former largest nodule of KS (arrow).
erate inflammatory infiltration, including eosinophils and extravasation of erythrocytes, was also noted in the dermis (Figure 3). Terminal deoxynucleotidyl transferase–mediated deoxyuridine 5-triphosphate–biotin nick end labeling (TUNEL) staining was performed as previously reported using biopsy specimens both before and after treatment with rIL-2 to visualize apoptotic cell death at the cellular level. Although we detected some TUNEL-positive tumor cells in specimens both before and after treatment, the positive cells after treatment outnumbered those before treatment. Injections of rIL-2 into the right foot were continued for a total of 26 weeks. After the 26th injection, which was equivalent to a total dose of \(91 \times 10^5\) units of rIL-2, almost all skin lesions, including both papules and purpuric macules, were completely resolved on the soles of both feet (Figure 4). There have been no recurrences of the resolved lesions in the 13 months following discontinuation of therapy. No local or general adverse effects or laboratory abnormalities were noted during treatment.

**COMMENT**

The classic form of KS is a rare neoplasm that principally affects the skin of the lower extremities in a multifocal fashion. The lesions slowly increase in size and number, spreading proximally and coalescing into plaques. In this form of KS, which develops in generally immunocompetent patients who usually present with limited cutaneous disease, the disease-related mortality rate has been reported to be between 10% and 20%. However, an additional 25% of patients die of a second malignant tumor. Epidemiological evidence indicates an infectious origin of KS. In several recent studies, human herpesvirus 8 DNA sequences were identified in...
Various treatments have been used to treat classic KS, although no definitive cure is known at present. Surgery, formerly recommended, is no longer indicated apart from tissue analysis. The tendency toward multifocality makes radiation therapy or chemotherapy, or both, the preferred mode of treatment. Radiation therapy is an important treatment, used for many years in classic KS. Lesions of KS are highly radiosensitive, and the treatment is well tolerated and temporarily controls large localized lesions. Adverse effects include residual hypopigmentation, radiodermatitis, and ulceration of the skin. In classic KS with limited cutaneous disease, as in the present case, intralesional cytotoxic chemotherapy seems more desirable than systemic chemotherapy. Intralesional injection of vinblastine sulfate is the most commonly used treatment regimen because it is fast, inexpensive, and shows high response rates in the treatment of skin lesions. Adverse effects include pain, skin irritation, and ulceration at the site of injection. However, both radiation therapy and chemotherapy are toxic and/or only temporarily effective. Researchers have sought nontoxic approaches to the treatment of KS. Recently, treatment with interferon alfa administered subcutaneously has been reported to be effective in classic KS as well as in KS related to the acquired immunodeficiency syndrome. Costa da Cunha et al report that recombinant interferon alfa was of benefit in 8 patients with non–HIV-related KS including classic KS, which was previously unresponsive to conventional chemotherapy. However, toxic effects in patients receiving interferon alfa have also been reported, including transient fever, fatigue, weight loss, transient neutropenia, and a depressive syndrome, which sometimes require reduction of the drug dosage.

Interleukin 2, which is 1 of a wide variety of cytokines, mediates lymphocyte proliferation. Continued exposure of human lymphocytes to IL-2 activates cells to mediate lymphokine-activated killer (LAK) activity. Cells mediating LAK activity are able to lyse a wide variety of fresh natural killer (NK)–sensitive and NK-resistant tumor cells, indicating a potential use in the treatment of neoplastic diseases. Lymphokine-activated killer cells are dependent on IL-2 for maintenance of antitumor activity and continued proliferation in vivo. Purified human rIL-2 is readily available because of recent progress in genetic engineering. The mechanism of action of rIL-2 seems to be its activation of both NK and LAK cells, although the precise mode of action is not yet clear. Recently, there have been reports that both rIL-2–stimulated NK cells and cells mediating LAK activity have the capacity to induce apoptosis in various kinds of tumor target cells. In contrast, interferon alfa–activated effector cells did not appear to activate the apoptotic pathway in the target cell as their means of cytotoxicity. Recombinant interleukin 2 is a widely accepted effective therapeutic modality for angiosarcomas in Japan. Although the protocol of rIL-2 therapy is not fully established in the treatment of angiosarcoma developing in the skin, daily administration of 35 to 70 × 10⁴ units of rIL-2 has often been tried systemically, which might be effective for cutaneous macular lesions of the disease. In fact, the successful treatment of angiosarcomas with rIL-2 has been reported. But there are several adverse effects reported in the use of rIL-2, such as general fatigue, anorexia, transient fever, and eosinophilia. The most significant among the adverse effects of rIL-2 therapy is a vascular leakage syndrome resulting in anasarca and multiorgan system dysfunction, especially when high doses of rIL-2 are systemically administered.

We performed a clinical trial of administration of rIL-2 alone in a case of classic KS classified along with malignant vascular tumors such as angiosarcomas. For the treatment of KS related to the acquired immunodeficiency syndrome, there have been reports of the use of rIL-2 combined with other therapeutic modalities. Klimas et al report that adoptive therapy with activated autologous CD8+ T cells and rIL-2 infusion led to partial regression of the disease in patients with KS related to the acquired immunodeficiency syndrome. Furthermore, they could not exclude the possibility that these partial responses were due to rIL-2 infusion alone. Ghyka et al report that treatment with IL-2 in combination with interferon alfa induced a more rapid involution of cutaneous lesions in classic KS than interferon alfa monotherapy. This is, to our knowledge, the second case of non–HIV-associated, classic KS treated with rIL-2. Efficacy of the treatment was observed within 3 months of commencement of therapy, with smaller lesions, including both papules and purpuric macules, showing the best response to rIL-2 treatment. After a treatment period of about 6 months, complete regression of all measurable lesions was observed. A beneficial effect on distant lesions was also noted; both papular and purpuric lesions on the un.injected left foot disappeared as well as those on the sole of the right foot, suggesting that intralesional injection of rIL-2 had a systemic effect. After the withdrawal of rIL-2 therapy, the patient has shown no signs of developing any new lesions with a follow-up of 13 months. In this case, the patient did not experience any adverse effects.

Important histopathological changes were seen between pretreatment and posttreatment biopsy specimens. On hematoxylin-eosin staining, the posttreatment specimen revealed a marked decrease in the number of KS cells, fibrosclerous modifications of collagen bundles in the dermis, and infiltration of lymphocytes, especially eosinophils with extravasation of erythrocytes. These changes reflected the efficacy of rIL-2 monotherapy. Moreover, apoptosis measured by TUNEL staining in biopsy specimens taken before and after rIL-2 treatment showed a higher incidence of TUNEL-positive nuclei in the posttreatment than in the pretreatment specimen. This finding indicates that rIL-2 administration induced apoptotic death of KS cells.

In conclusion, our clinical trial of rIL-2 immunotherapy has shown encouraging results in a case of clas-
sic KS, suggesting that immunotherapy with rIL-2 may be a safe and effective therapeutic modality for the treatment of the cutaneous lesions in classic KS. However, long-term, close follow-up of the patient will be necessary to confirm that he does not develop new lesions over time. Larger, controlled trials are required to evaluate the efficacy of rIL-2 monotherapy in classic KS.

REFERENCES


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