

Sirolimus Use for Kaposi Opens Door to Research

BY BRUCE JANCIN
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ZURICH — The effectiveness of sirolimus for treatment of Kaposi sarcoma arising in solid organ transplant recipients has opened the door to development of novel therapeutic approaches in the often more aggressive AIDS-related form of the malignancy, said Dr. Erwin Tschachler.

Sirolimus itself would be inappropriate for use in AIDS patients, since it is a potent immunosuppressive agent. But the drug also is believed to have antitumor properties resulting from its ability to block the mammalian target of rapamycin (mTOR), he said at the annual meeting of the European Society for Dermatological Research.

The mTOR molecule occupies a key role in the Akt signaling pathway by which human herpesvirus 8 (HHV-8) directs endothelial cell proliferation and transformation along with elaboration of angiogenic factors including vascular endothelial growth factor, ultimately resulting in Kaposi sarcoma (KS), explained Dr. Tschachler, professor of dermatology at the Medical University of Vienna.

In recent years, it has become clear that HHV-8 is the etiologic agent in all forms of KS. "There is no Kaposi sarcoma without HHV-8," he said. The incidence of KS in transplant recipients is roughly 500-fold greater than in the general population. In organ transplant recipients who either have preexisting latent HHV-8 infection or acquire the virus from an infected organ donor, the average time from initiation of chronic immunosuppressive therapy to development of KS is about 2 years.

Cyclosporine, the linchpin of chronic antigrft-rejection therapy, figures prominently in KS in transplant recipients. The drug has tumor-promoting effects. The traditional approach to managing transplant-related KS has been to reduce cyclosporine or discontinue it, he continued.

A major development in transplant medicine occurred several years ago when investigators at the University of Bari (Italy) reported that upon switching 15 kidney-transplant recipients with KS from cyclosporine to sirolimus, all cutaneous KS lesions disappeared within 3 months. Histologic confirmation of remission was obtained by biopsy at the former lesion sites at 6 months. KS remission was achieved without any episodes of graft rejection or reduction in donor-kidney function (N. Engl. J. Med. 2005;352:1317-23).

This report prompted discussion as to whether the tumor regression might have been brought about by halting cyclosporine. However, the consensus is that most of the observed benefit resulted from sirolimus-induced inhibition of angiogenesis and tumor cell proliferation, according to Dr. Tschachler.

He singled out as particularly influential the work of Silvia Montaner, Ph.D., of the University of Maryland, Baltimore, who has shown that a single HHV-8 gene encoding a chemokine-like viral G protein-coupled receptor called vGPCR is sufficient to induce formation of KS-like tumors in mice. Pharmacologic inhibition of the Akt signaling pathway prevented vGPCR-induced endothelial cell proliferation and tumor formation in the animal model (Cancer Res. 2006;66:168-74).

Dr. Tschachler reported having no conflicts of interest. ■

Paclitaxel Tops Second-Line Choices For AIDS-Related Kaposi Sarcoma

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ZURICH — Intravenous paclitaxel is the treatment of choice in patients whose AIDS-related Kaposi sarcoma isn't responsive to liposomal anthracyclines, Dr. Erwin Tschachler said at the annual meeting of the European Society for Dermatological Research.

"It's more cytotoxic, has more side effects, but works in a considerable percentage of patients in which other cytotoxic therapies have failed. So it's not a first-line treatment," explained Dr. Tschachler, professor of dermatology at the Medical University of Vienna. For localized Kaposi sarcoma, surgery, cryotherapy, radiation therapy, intralesional cytotoxic agents, photodynamic therapy, and topical retinoids remain good options.

But for rapidly progressive cutaneous or symptomatic visceral disease, liposomal anthracyclines have replaced older combination chemotherapy regimens because they have higher remission rates and are

much better tolerated, said Dr. Tschachler.

These liposomal agents and paclitaxel—all of which are approved by the Food and Drug Administration for the treatment of AIDS-related Kaposi sarcoma—are given with palliative rather than curative intent.

Dr. Tschachler and colleagues typically start treatment with liposomal doxorubicin (Doxil) at 20 mg/m² IV every 2-3 weeks, although it can be given at up to 40 mg/m². Remission rates of 38%-92% have been reported. Liposomal daunorubicin (DaunoXome) is slightly less effective. The dosing is 40-60 mg/m² IV every 2 weeks.

Eventually the Kaposi sarcoma is likely to return despite liposomal anthracycline therapy, which is when it's time to switch to paclitaxel (Taxol), he said. Paclitaxel has double the response rate and twice as long an average duration of remission. The recommended dosing is 135-175 mg/m² IV given over 3 hours every 3 weeks initially, then 100 mg/m² every 2 weeks to maintain remission.

Dr. Tschachler reported having no conflicts of interest. ■

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Galderma Laboratories, L.P., 14501 N. Freeway, Fort Worth, TX 76177 CET-886A Printed in USA 01/08