First SCC Calls for Change in Immunosuppression

BY BRUCE JANCIN
Denver Bureau

AMSTERDAM — The appearance of a first squamous cell carcinoma in an organ transplant recipient is an appropriate time to discuss revising the immunosuppressive regimen to prevent subsequent skin cancers, Dr. Sylvie Euvrard said at the 11th World Congress on Cancers of the Skin.

"We think it is crucial. There is no test to assess the right level of immunosuppression. We think in many cases skin cancer means over-immunosuppression," said Dr. Euvrard, a transplant dermatologist at Edouard Herriot Hospital in Lyon, France.

The risk of squamous cell carcinoma (SCC) in organ transplant recipients is up to 250 times greater than in the general population. Roughly 80% of organ transplant recipients (OTRs) who develop an

Median time to a skin cancer was 1,126 days in the withdrawal group and 491 days for controls.

DR. EUVRARD

invasive SCC will develop one or more new ones within the next 3 years.

The risk of SCCs in OTRs is of secondary concern to many transplant physicians. Their main focus is on preventing graft rejection, so they are reluctant to fiddle with the immunosuppressive regimen, but they are often persuaded to do so by the argument that SCC in transplant recipients is associated with an increased rate of primary internal malignancies suggesting over-immunosuppression, Dr. Euvrard said.

Both the how and when of modifying immunosuppression to prevent skin cancer in OTRs remain controversial issues that are being addressed by ongoing randomized trials. A case for revising immunosuppression can be made in patients with multiple keratotic skin lesions based upon a recent study in which Dr. Euvrard was a coinvestigator. The study showed that OTRs with 50 or more such lesions had a 12.1-fold increased risk of SCC, compared with those who had none.

There are two general approaches to modification of immunosuppression. One is to reduce the dosing of cyclosporine and/or tacrolimus. The other approach is to substitute an mTOR (mammalian target of rapamycin) inhibitor such as sirolimus or everolimus for the calcineurin inhibitor. The latter approach is particularly attractive in light of evidence from both in vitro and mouse studies that the calcineurin inhibitors have oncogenic effects independent of their immunosuppressive activity, while the mTOR inhibitors have distinct anticancer effects, she said at the congress cosponsored by the Skin Cancer Foundation and the department of dermatology at Erasmus University, Rotterdam.

A recent international study by the Rapamune Maintenance Regimen Study Group bolsters the case for substitution with sirolimus. Three months following renal transplantation, 430 OTRs were randomized to remain on their immediate posttransplant regimen of cyclosporine, sirolimus, and corticosteroids or to withdrawal of cyclosporine and an increase in sirolimus such that trough levels doubled.

At 5 years' follow-up, the median time to a first skin carcinoma was 1,126 days in the cyclosporine withdrawal group, compared with 491 days in controls. There was a reduction in the total number of skin cancers in the cyclosporine withdrawal group as well. Moreover, the incidence of nonskin cancers was 4.0% in the cyclosporine withdrawal group, compared with 9.6% in those who remained on the calcineurin inhibitor (J. Am. Soc. Nephrol. 2006;17:581-9).

Also intriguing was an analysis of the United Network for Organ Sharing's kidney transplant registry, Dr. Euvrard continued. This observational study showed that after 963 days of immunosuppression the incidence of any new malignancy was 0.6% in patients on an mTOR inhibitor without a calcineurin inhibitor, an identical 0.6% in those on drugs from both classes, and 1.8% in patients on cyclosporine/tacrolimus without an mTOR inhibitor (Transplantation 2005;80:883-9).

Dr. Charlotte M. Proby said that at Barts and The London, Queen Mary's School of Medicine and Dentistry, where she practices dermatology, minimizing immunosuppression is the first-line measure when a patient develops skin cancer, even before prescribing acitretin for chemoprevention. ■