Gene Transfer Shows Efficacy for Skin Lymphomas

BY BRUCE JANCIN
Denver Bureau

ZURICH — Intralesional adenoviral vector–delivered interferon-gamma gene transfer is a novel and promising immunotherapy for primary cutaneous lymphomas, Dr. Mirjana Urosevic said at the annual meeting of the European Society for Dermatological Research.

Although adenovirus is the most utilized vector in the field of gene therapy, in the setting of primary cutaneous lymphoma the adenoviral vector is not merely a gene therapy delivery system. It has therapeutic activity in its own right, according to Dr. Urosevic of the University of Zurich.

She and her colleagues found that adenoviral vector activates innate immunity and induces type 1 interferons, most prominently interferon-α (IFN-α), a toll-like receptor agonist that stimulates antitumor immunity and has strong antiproliferative and antiangiogenic effects. They demonstrated this in gene expression profile studies of skin lesions obtained before and after treatment in 20 patients with various primary cutaneous lymphomas.

The appeal of adenovirus-mediated interferon-gamma (IFN-γ) gene transfer is that it provides a complementary two-pronged approach to immunotherapy, calling forth both innate and adaptive immunity. The adenovirus induces IFN-α, while the gene insert comprised of human cDNA induces IFN-γ, a type II interferon. Both IFN-α and IFN-γ are believed to be crucial for the most efficient tumor rejection.

In preliminary studies, the researchers found that adenovirus-mediated IFN-γ gene transfer provided impressive clinical efficacy. Favorable responses have been universal in the small number of treated patients with cutaneous B-cell lymphomas. The majority of patients with cutaneous T-cell lymphomas have also responded.

The adenovirus-mediated interferon-gamma gene transfer provides a two-pronged approach by calling forth both innate and adaptive immunity.

Although direct intralesional injection of IFN-α or IFN-γ also results in tumor regression, adenovirus-mediated IFN-γ gene transfer is better tolerated, as it induces the patient's own cells to produce the interferons. It's a local intralesional therapy without systemic toxicity, said Dr. Urosevic.

The chief side effect is pain at the injection site lasting no longer than an hour. A strong local erythematous reaction can also occur. In addition, patients lacking antibodies to adenovirus experience febrile episodes in response to the initial injections.

The primary cutaneous lymphomas are uncommon malignancies characterized by accumulation of clonal T or B lymphocytes in the skin. Most are indolent chronic diseases with a good prognosis, so the preference is for low-morbidity treatments that provide good control for long periods, she said. The primary cutaneous lymphomas don't offer tumor antigens as targets for immunotherapy, but nonspecific immunostimulation can be applied using cytokines such as IFN-α and IFN-γ.

The primary cutaneous B-cell lymphomas are a heterogeneous group of disorders defined by skin involvement without extracutaneous disease at the time of diagnosis. They account for about one-quarter of all primary cutaneous lymphomas.

Two of the three major subtypes of primary cutaneous B-cell lymphomas in the World Health Organization classification—marginal zone B-cell lymphoma and follicle center lymphoma—particularly lend themselves as a testing ground for less aggressive treatments such as immunotherapy because they are low-grade lymphomas that progress slowly, often over decades. The third major subtype—large B-cell lymphoma, leg type—is considerably more aggressive and doesn't qualify for immunotherapy, Dr. Urosevic explained.

There are at present no approved therapies for primary cutaneous B-cell lymphomas. The most widely used treatments are surgery and radiotherapy. Off-label therapies include corticosteroids, rituximab, and imiquimod.

Adenovirus-mediated IFN-γ gene transfer is being developed by Transgene SA of Strasbourg, France, the company that funded the study. A phase II clinical trial in 40 patients with radiotherapy-resistant primary cutaneous B-cell lymphomas is under way.

The treatment regimen entails once-weekly injections for 3 weeks followed by a 2-week pause to assess for disease progression. If the disease is stable or there is an objective response, weekly treatment resumes. Recently, however, Dr. Urosevic and colleagues showed that if the genes for IFN-α and IFN-γ are induced shortly after treatment starts, a later favorable therapeutic response is predicted.

Successfully treated lesions—and in many cases untreated ones as well—slowly disappear, with complete responses often seen after three to six injections. ■

Non-Hodgkin's Lymphoma Helped by Immunomodulator + Radiotherapy

BY SHERRY BOSCHERT
San Francisco Bureau

LOS ANGELES — Two rare types of non-Hodgkin's lymphomas responded to treatment with intratumoral injections of an investigational immunomodulator plus radiotherapy in a pilot study of seven patients, Dr. Anjali V. Morales reported at the annual meeting of the Society for Investigative Dermatology.

Six patients with mycosis fungoides and one patient with primary cutaneous B-cell lymphoma (CBCL) underwent low-dose radiotherapy to a single tumor site on day 1 and 2 plus injections of CpG 7909 to the same tumor within 24 hours before and after the radiotherapy. This treatment regimen was repeated weekly for a total of nine sessions. Noninjected tumors were monitored to assess systemic effects of the treatment.

CpG 7909 is an agonist to the protein TLR 9 (toll-like receptor 9) and belongs to a new class of immunomodulators that activate B cells and plasmacytoid dendritic cells. It showed promise as monotherapy for cutaneous T-cell lymphoma in a previous trial, said Dr. Morales of Stanford (Calif.) University.

In the current study, the combination of CpG 7909 and low-dose radiotherapy produced partial responses in two patients with mycosis fungoides and the one patient with CBCL. Another patient with mycosis fungoides showed a minor response, and the other three patients had stable disease, she reported.

A partial response was defined as greater than a 50% reduction in tumor volume or severity-weighted assessment tool (SWAT) score, compared with baseline. A minor response was defined as a 25%-50% reduction in tumor volume or SWAT score, compared with baseline.

The responses appeared after 6-9 weeks in patients with mycosis fungoides and after 4 weeks in the patient with CBCL. "We did note that responses were short-lived," so the protocol has been amended to enhance the systemic antitumor response, Dr. Morales said.

The investigators are enrolling patients now in a study that will administer low-dose radiotherapy and CpG 7909 injections to one tumor site on day 1 and 2, followed by two weekly CpG 7909 injections. At week 4, a second tumor site will be treated with radiotherapy and injections, followed by four weekly injections of CpG 7909. Nontreated lesions will be assessed for response.

The treatment appeared to be well tolerated, with grade 1-2 adverse events in all patients, she said. These included erythema, pain, and induration at the injection sites plus fever and fatigue in all patients. Six patients reported myalgia and arthralgia, three complained of headache, and one had nausea.

Researchers have theorized that intratumoral injection of CpG 7909 activates dendritic cells, which migrate to lymph nodes and promote a systemic antitumor immune response.

The study was initiated by Stanford faculty and funded by the National Institutes of Health, Dr. Morales said. ■

Consider Melanoma Thickness Before Sentinel Node Biopsy

BY JOHN R. BELL
Associate Editor

NEW YORK — Although melanoma is known for metastasizing to various sites, the most common site of metastasis is the locoregional lymph nodes, according to Dr. Richard Shapiro. They can be large and bulky or microscopic.

In a review of the literature on sentinel lymph node biopsy (SNLB), he noted that lymph node metastasis has been greatly associated with a decline in patient survival. However, "patients with nonpalpable, microscopic melanoma metastases tend to do much better than the patients who present with palpable metastases," he said at the American Academy of Dermatology's Academy 2007 meeting.

The thickness of a melanoma is key to its likelihood of having metastasized, he said. Thin melanomas—less than 0.76 mm in Breslow thickness—have a very small chance of having regional or distant metastases. However, patients with thick melanomas—4 mm or greater often have distant metastatic disease at presentation, said Dr. Shapiro of New York University, New York.

"It's the patients with so-called intermediate thickness lesions—that are approximately 0.76 mm to 4 mm thick—that have a much higher likelihood of having microscopic metastatic disease when they present than they do with having distant metastases. And so it would make sense in that intermediate thickness melanoma group to remove the lymph nodes in those patients and to see if we can decrease recurrence and increase survival."

Approximately 100 retrospective trials in the last 50 years have assessed associations between melanoma thickness and survival, with the only survival advantage seen in the patients with intermediate-thickness melanomas. However, prospective trials have found no survival advantage to elective lymph node dissection in patients with no clinical evidence of metastatic melanoma in the regional lymph nodes at presentation, Dr. Shapiro noted.

"Right now I would say the ideal candidate to undergo sentinel lymph node mapping and biopsy is the patient with a primary cutaneous melanoma 1 mm thick or greater, with no clinical evidence of regional lymph node metastases and in a patient where successful scintigraphy preoperatively can be performed and demonstrate regional lymph node draining," he said. ■