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Addition of Immunotherapy Prolongs Survival in Kidney Cancer

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Adding the experimental immunotherapy AGS-003 (Argos Therapeutics) to standard targeted therapy with sunitinib (*Sutent*, Pfizer) prolonged expected survival time in patients with advanced kidney cancer.

This finding comes from a small single-group phase 2 study of patients with metastatic renal cell carcinoma. The results were presented by Asim Amin, MD, PhD, codirector of the Levine Cancer Institute in Charlotte, North Carolina, at the 2013 Genitourinary Cancers Symposium (GUCS) in Orlando, Florida.

All of the 21 patients had an unfavorable prognosis. For poor-risk patients, predicted overall survival was around 8 months; for intermediate-risk patients, it was 22 months. However, more half of the patients survived for more than 30 months, and one third are still alive after 4 years or more.

This "striking" prolongation of survival has prompted a larger phase 3 study, which has already started enrolling patients, according to Argos Therapeutics.

Fully Personalized Immunotherapy

AGS-003 is produced by extracting messenger RNA from a sample of a patient's tumor (obtained at the time of nephrectomy) and incorporating it into the patient's dendritic cells (obtained during a single leukapheresis procedure). This is a fully personalized immunotherapy, Dr. Amin told *Medscape Medical News*.

It is different from the prostate cancer vaccine, sipuleucel-T (*Provenge*, Dendreon), which is "personalized, but only in part," he noted. For the production of sipuleucel-T, dendritic cells are collected from patients, but these cells are then programmed with a 'generic' prostate cancer antigen; the same antigen is used in every patient, he explained. In AGS-003, the dendritic cells of each patient are programmed with antigens from their own tumor, he added.

"The issue with kidney cancer is that we have not identified any major antigens, unlike in melanoma and prostate cancer.... This is why we need to use the patient's own tumor," he said.

According to Argos Therapeutics, the tumor RNA is used to "program" the dendritic cells with the entire disease-antigen repertoire to trigger a response against the patient's specific tumor. In the phase 2 trial, blood samples indicate that patients have antitumor memory T cells. There is a correlation between overall survival and the number of these cells that are induced.

Prolongation of Survival

The prolongation of survival is not a complete surprise. "This has been seen before with immunomodulation," Dr. Amin noted. Some of kidney cancer patients treated with high-dose interleukin-2 are living for 10 to 15 years. However, because of the toxic events associated with this therapy, it is only applicable to about 10% of patients, he said.

Tyrosine-kinase inhibitors such as sunitinib have "revolutionized the treatment of kidney cancer; now everybody can get a drug treatment," he said. However, although they do prolong survival, the responses are not durable.

In this trial, Dr. Amin and colleagues have shown that adding immunotherapy to standard therapy increases the durability of the response, and AGS-003 is not associated with any toxic events, other than injection-site reactions and erythema, he said.

The researchers chose to combine AGS-003 with sunitinib because it also has some immunomodulatory properties; it suppresses T regulatory and myeloid suppressor cells. Other tyrosine-kinase inhibitors used in the treatment of kidney cancer might not be such a good match. For instance, sorafenib inhibits dendritic cell function, Dr. Amin noted, so could interfere with the mechanism of action of AGS-003.

In this trial, all patients were treated with standard 6-week cycles of sunitinib. AGS-003 was administered once every 3 weeks,

for 5 doses, and then every 12 weeks until the disease progressed.

Median progression-free survival was 11.2 months and the final median overall survival was 30.2 months, Dr. Amin reported.

However, when the patients were subdivided according to baseline risk, the 11 intermediate-risk patients had a median progression-free survival of 19.4 months and a median overall survival of 39.5 months. The 10 poor-risk patients had a median progression-free survival of 5.8 months and a median overall survival of 9.1 months.

For comparison, Dr. Amin noted that a pivotal trial in which sunitinib was used alone showed that median overall survival was 5.3 months for poor-risk patients and 20.7 months for intermediate-risk patients.

The addition of immunotherapy to sunitinib led to a "near doubling of the expected progression-free and overall survival for unfavorable-risk subjects," he concluded.

Larger Trial Already Underway

The American Society of Clinical Oncology, which cosponsored GUCS, highlighted this abstract in its press materials. Leonard Gomella, MD, FACS, a member of the GUCS news planning team, noted that such prolonged survival is "very encouraging," but it will need to be confirmed in larger number of patients.

A larger trial is already underway. It is expected that the phase 3 ADAPT study, a randomized multicenter open-label trial, will enroll 450 patients, mainly in the United States. It will compare the immunotherapy plus sunitinib with sunitinib alone. The plan is to administer AGS-003 in 8 doses over the initial 12 months, followed by booster shots every 3 months for patients who are continuing to benefit.

Results from the phase 3 study will likely not be available until 2015, Dr. Amin said.

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