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ASCO15:

Hot Topics & Research Sneak Peeks

BY SARAH DIGIULIO

The theme for this year's ASCO Annual Meeting is "Illumination & Innovation: Transforming Data into Learning." That was chosen, ASCO President Peter Paul Yu, MD, FACP, FASCO, explained, because oncologists and all health care providers need to be able to make sense of the bombardment of data that comes along with advances such as the promise of precision medicine and the digitalization of clinical health.

"It's about how we make sense of the world around us and derive insight into improving the lives of our patients," said Yu, Director of Cancer Research at Palo Alto Medical Foundation. "Perhaps most of the data is background noise. But identifying and understanding the important pieces of data lead to models or algorithms that help us understand the behavior of cancer—or other human

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Skin Cancer Mortality Shown to Increase after Organ Transplantation

BY MARK FUERST

SAN FRANCISCO—Mortality from skin cancer increased among patients undergoing organ transplantation—in particular, for Caucasian men older than age 50, according to a U.S. population-based study presented here at the American Academy of Dermatology Annual Meeting.

"The skin cancer rate is increased in transplant recipients, especially in white men over age 50," said Sarah Tuttleton Arron, MD, PhD, Assistant Professor of Dermatology in Residence and Associate Director of the University of California, San Francisco Dermatologic Surgery and Laser Surgery. "Oncologists need to have a high index of suspicion that these patients will have a poor outcome after transplantation and treat them accordingly."

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New HCV Therapy Effective across Disease Spectrum

BY ED SUSMAN

VIENNA, Austria—The latest entry into direct-acting antiviral treatment for hepatitis C virus (HCV) infection—a leading cause of liver cancer—allows patients to achieve sustained virologic responses across a broad spectrum of conditions, researchers reported here at the International Liver Congress.

The investigational combination, being developed by Merck, is a fixed-dose tablet containing 100 mg of the HCV NS3/4A protease inhibitor grazoprevir and 50 mg of the HCV NS5A replication complex inhibitor elbasvir that is taken once daily for 12 weeks.

In the pivotal C-Edge Phase III randomized, placebo-controlled trial, 299 of 316 patients—95 percent of the study population—achieved a sustained virologic response 12 weeks after the treatment ended (SVR12, considered a functional cure of the disease).

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PERIODICALS

SKIN CANCER MORTALITY SHOWN TO INCREASE AFTER ORGAN TRANSPLANTATION

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There is limited population based data on skin cancer mortality after organ transplantation, she noted. "Our objective was to determine the U.S. incidence of skin cancer mortality after transplantation using the Organ Procurement and Transplant Network database, which captures all transplants, including cause of death."

Arron, who is also Chief of Mohs Micrographic Surgery of San Francisco VA Medical Center and Director of both the High Risk Skin Cancer Program and the Dermatology Clinical Research Unit, explained that she and her colleagues researchers set out to identify the U.S. incidence density rate of skin cancer death after organ transplantation, the risk factors for skin cancer death after organ transplantation, and specific high risk subgroups for skin cancer death after organ transplantation.

Study Methods

Using the database, the team identified approximately 531,000 transplants between 1987 and 2013. There were nearly 1,000 deaths due to skin cancer, for an incidence rate of 3.3 per 100 person years and a cumulative incidence of one percent at 20 years.

The researchers constructed a regression model for skin cancer death on significant covariates, including male sex, age, thoracic transplant, white race, and year of transplant.

> "Some studies suggest lowering immunosuppression to manage melanoma in transplant recipients."

"We used classification and regression tree analysis to identify specific high risk groups—notably white men over 50," Arron said. The thoracic incidence density ratio of 18.5 per 100 person years had a reversed hazard ratio of 5.51. The abdominal incidence density ratio of 6.5 per 100 person years had a reversed hazard ratio of 2.09.

"These data demonstrate a low rate of skin cancer deaths, but identify the population at high risk," Arron said. "The reported incidence is expected to be an underestimate due to misclassification of cause of death, particularly from cutaneous squamous cell carcinoma."

An ongoing Transplant Skin Cancer Network incidence study will capture additional data on skin cancer incidence and mortality after transplant, she said.

"Oncologists need to partner with dermatologists on the transplant team as we learn the dermatologic effects of novel cancer therapies and which drugs are safe in transplant patients," Arron added.

Melanoma in Transplantation

Early-stage melanoma patients also show significantly worse outcomes after transplantation, according to a separate report by Alvin H. Chong, MBBS, MMed, Senior Lecturer in Dermatology at the University of Melbourne in Australia.

Chong gave an update on melanomas in transplant recipients, discussing melanoma in transplant recipients in post-transplant melanomas, pre-transplant melanomas, and melanomas from donor organs.

"Melanomas are the third most common malignancy in Australian renal transplant patients, and skin cancer deaths account for 37 percent of all cancer deaths," he said.

In a study of approximately 7,500 renal transplant patients in Australia, 11 percent of all deaths were due to skin cancer. Melanoma accounted for 7.8 percent of all cancer deaths in these renal transplant recipients.

SCOPE Centers

Prognosis of de novo melanomas post-transplantation is poor in Europe as well, Chong noted: A voluntary study in 53 Skin Care for Organ Transplant Patients (SCOPE) centers in Europe compared survival rates among transplant recipients with melanomas with those of U.S. melanoma patients who did not have transplants and were matched for age, sex, Breslow thickness, and ulceration, using data from the American Joint Committee on Cancer (AJCC).

The overall prognosis of SCOPE transplant recipients with de novo melanomas was worse than the American cohort. The five-year overall survival in the SCOPE cohort was 54 percent compared with 82 percent in the AJCC cohort. Post-transplant survival outcome for less invasive melanomas in the SCOPE cohort was no different from in the AJCC cohort. However, the survival outcome was worse for SCOPE patients than the AJCC controls in those with more invasive melanomas, Chong said.

He cited a 2011 study of malignant melanoma in approximately 700 post-transplant recipients from Mayo Clinic, UNOS, and Israel Penn Databases. A total of 133 post-transplant melanomas with known Breslow thicknesses were found. Survival rates were stratified and compared with those in the Surveillance, Epidemiology and End Results (SEER) database for expected survival.

"The overall survival at three years was worse for transplant melanoma patients, compared with SEER data," Chong said, adding that cause-specific survival was worse only for transplant melanomas that were 1.5 to 3 mm. He noted that current data is not population-based, counts on voluntary reporting, and is non-contemporaneous.

"A recent systematic review of melanoma incidence and prognosis in solid organ transplant recipients concluded that population-based studies that account for melanoma stage and risk factors are needed for patients and clinicians to better understand the prognosis of pre- and post-transplant melanoma," he said.

SARAH TUTTLETON ARRON, MD, PHD, noted that an ongoing Transplant Skin Cancer Network incidence study will capture additional data on skin cancer incidence and mortality after transplant.

> "Oncologists need to partner with dermatologists on the transplant team as we learn the dermatologic effects of novel cancer therapies and which drugs are safe in transplant patients."

Australian Study

A recent Australian national, population-based, matched-cohort study

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identified approximately 8,000 melanoma patients in a transplant database. The Australian cancer database includes all Australian kidney transplant recipients with de novo invasive melanoma, who were identified by linkage.

Non-transplant recipients with invasive melanoma were randomly selected from cancer registry records, matched for age, sex, state of residence, and year of diagnosis—up to three per case. Similarly for transplant recipients without melanomas, who were randomly selected from database records and matched for age, sex, and state of residence—also up to three per case.

Data were collected by body site, histology, Breslow thickness, Clark's level, concurrent nevus, ulceration, and overall AJCC pathologic stage. The data were analyzed to compare clinicopathologic characteristics for the probability of overall survival, including predictors of all-cause mortality.

The researchers found 75 kidney transplant recipients with melanomas, three-quarters of them male, about half who were diagnosed in the 1990s, with a median age at diagnosis of 55. The median time between transplantation and diagnosis was four years.

Three-quarters of these transplant recipients with melanomas died with a median of 6.6 years since diagnosis. In contrast, of more than 200 matched non-transplant melanoma patients, 30 percent died after a median of 27 years since diagnosis.

"There was no significant difference in Breslow thickness or histological subtype in transplant versus non-transplant melanoma," Chong said. But there was a significant difference in AJCC pathologic stage and Clark's level in transplant versus non-transplant patients. For overall survival, transplant patients with melanoma did significantly worse."

> "There is a fourfold increased risk of death associated with melanomas in transplant recipients, controlling for demographic and clinicopathological characteristics."

In terms of melanoma-specific mortality, melanoma was reported as the cause of death in 22 of 55 (40%) of transplant melanomas and 26 of 61 (42%) in non-transplant melanomas. "Melanoma-specific mortality for transplant patients was 2.59," he said. "Increased risk of melanoma-specific death was observed in transplant patients with Stage I, but not with Stages II, III, or IV disease," although the study was likely underpowered to detect a mortality difference between stages.

"In this population-based study, non-transplant and transplant melanomas were contemporaneous, with identical methods for non-transplant and transplant. There was a long follow-up time. However, there was no centralized pathology review and no treatment data."

In summary, Chong said: "Melanomas in kidney transplant recipients versus non-transplant appear to be thicker [i.e., Clark's level] and more advanced AJCC stage at diagnosis and have lower overall survival, even with thin invasive melanomas. There is a fourfold increased risk of death, controlling for demographic and clinicopathological characteristics."

Possible Mechanism of Action

The possible mechanism, he said, is inhibition of immune response to melanoma cells by iatrogenic immunosuppression from enhanced tumor growth and spread, and "biological aggressiveness."

Another likely cofactor is a greater prevalence of comorbid conditions. "Recent advances in immunotherapy target inhibitory receptor ligand pairs immune checkpoints, anti-cytotoxic T lymphocyte 4 [ipilimumab], and anti-programmed cell death-1 [nivolumab, lambrolizumab]," he noted.

"Circulating tumor cells are found in immunosuppressed patients, but more data is needed. Currently, there is lack of evidence regarding the benefits of reducing, altering mTOR inhibition, or discontinuing immunosuppression."

There is also little evidence about the management of melanoma in transplant recipients, he continued. Expert opinion suggests the use of surgical excision with standard recommended margins and sentinel lymph node (SLN) biopsy generally at least for patients with AJCC Stage 1b disease. But SLN biopsy can be considered if melanoma has a thickness of 0.75 to 1 mm, is Clark level IV, and has increased mitoses, regression, and tumor-specific lymphocytes, he said.

Some studies suggest lowering immunosuppression to manage melanoma in transplant recipients. Consider using anti-angiogenic mTOR inhibition as immunosuppression, Chong said. "Sirolimus has a lower rate of malignancy compared with calcineurin inhibitors. Circulating angiogenic factors may inhibit T cell responses and promote melanoma."

Patient Education

Clinicians need to enhance patient education strategies as well, Chong said. "Educate patients to bring suspicious lesions to medical attention and to get an annual skin examination by a professional. High-risk patients should have frequent examinations. There is a low threshold for biopsy of pigmented lesions."

ALVIN H. CHONG, MBBS, MMED: "Melanomas in kidney transplant recipients versus non-transplant patients appear to be thicker and more advanced and patients have lower overall survival, even for those with thin invasive melanomas."

For a patient with prior history of melanoma pre-transplant, "do not wait for in-situ melanomas," he said. For invasive melanomas, current guidelines state to wait two to five years, depending on the melanoma and clinical situation. "There may be a role for SLN biopsy in thin primaries to determine wait time. If the lesion is more than 2 mm, consider a five-year wait."

> "Management of melanomas in transplant recipients requires multidisciplinary input."

He cited a recent systematic review of donor cancer transmission in 18 kidney transplant recipients that found a prognosis of five-year survival for donor-transmitted melanoma of less than 30 percent, even after graft removal and reduction/cessation of immunosuppression. In comparison, the five-year survival for the 20 renal cancer patients in the study was 75 percent.

"For de novo melanomas post-transplantation, recent population-based data show that prognosis is poorer than immuno-competent patients, even for thin primary melanomas," Chong summed up. "Management of melanomas in transplant recipients requires multidisciplinary input. The roles of SLN biopsy, lowering of immunosuppression, and mTOR inhibition is unclear. Caution is required for transplant recipients with a prior history of melanoma. Donor transplanted melanomas have a poor prognosis."