

Ten-year Follow-up of a Phase III Trial of the Duration of Elective Androgen Deprivation in Locally Advanced Prostate Cancer

Early studies of androgen-deprivation therapy (ADT) have demonstrated its clinical benefit, but have left many questions unanswered. Due to the need for prospective evidence to confirm the use of ADT plus radiotherapy in patients with locally advanced prostate cancer, a randomized phase III study in prostate cancer patients was performed. Patients (n=1,554) with T2c-T4 prostate cancer with no extra pelvic lymph node involvement and prostate-specific antigen (PSA) less than 150 ng/mL received 4 months of goserelin and flutamide before and during radiotherapy and then were randomly assigned to receive either no further ADT (short-term androgen deprivation [STAD] with radiotherapy) or 24 months of goserelin (long-term androgen deprivation [LTAD] with radiotherapy). The primary endpoint was an absolute 10% improvement in disease-free survival (DFS; from 40% to 50%). The study results, published in the May 20 issue of the *Journal of Clinical Oncology*, found that at 10 years, the patients who received LTAD had significant improvement compared to the patients who received STAD for all endpoints except overall survival (OS). The LTAD group, compared to the STAD group, had higher DFS (22.5% vs 13.2%; $P<.0001$) and disease-specific survival (DSS; 88.7% vs 83.9%; $P=.0042$). Other study endpoints, such as local progression, distant metastasis, and biochemical failure were also more improved in patients in the LTAD group. However, an analysis of 10-year OS demonstrated a similar rate in patients receiving STAD and LTAD (51.6% vs 53.9%; $P=.36$). When adjusted for PSA and T-stage, the LTAD group had significantly improved DFS ($P<.0001$), DSS ($P=.002$), local progression ($P<.0001$), distant metastasis ($P<.0001$), and biochemical failure ($P<.0001$) at 10 years, compared to the STAD group. In the subset of patients with a Gleason score of 8–10, those treated with LTAD had statistically significant improvements in DFS, DSS, and OS and a statistically significant decline in local progression, distant metastasis, and biochemical failure. The study findings support the recommendation that treatment with LTAD plus radiotherapy for locally advanced prostate cancer is superior to treatment with STAD plus radiotherapy. Additionally, the researchers concluded that LTAD plus radiotherapy should be the standard treatment for prostate cancer patients with a Gleason score of 8–10.

Racial and Ethnic Variations in Hepatocellular Carcinoma Incidence Within the United States

In recent years, the rising rate of fatal hepatocellular carcinoma, a primary malignancy of the liver, has become a growing public health concern. There are marked differences in the frequency of this carcinoma related to age, sex, race, and geographic location. Therefore, current screening and surveillance guidelines require updating in order to improve detection and prevention methods of this deadly cancer. Drs. Wong and Corley performed a retrospective cohort study using data collected by the Surveillance, Epidemiology, and End Results program to evaluate the deviations in the incidence of hepatocellular carcinoma. The study, which was published in the June issue of the *American Journal of Medicine*, evaluated sex-specific, race/ethnicity-specific, and age-specific differences in hepatocellular carcinoma from 1992 to 2004. Study findings showed the incidence highest among Asians (11/100,000 per year), followed by white Hispanics (8.8/100,000 per year) and Caucasians (2.6/100,000 per year). The study also noted that male subjects had a doubling of cancer rates every 10 years from the age of 30–50 years, whereas female subjects reached rates comparable to males 10–15 years later and peaked at considerably lower values across all race and ethnic groups. The researchers concluded that variations in the incidence of hepatocellular carcinoma may be attributed to risk factors such as viral hepatitis and that a distinct approach customized to specific risk profiles may improve the detection of treatable tumors.

Recombinant Factor VIIa Fails to Modify Outcomes after Intracerebral Hemorrhage

In an earlier trial conducted in 2005, researchers found that recombinant activated factor VIIa (rFVIIa) weakened hematoma growth, reduced mortality at 90 days (from 28% to 18%), and improved functional outcomes in patients with intracerebral bleeding. rFVIIa is a procoagulant that improves coagulation at the site of vascular injury; it has been successful in managing bleeding in people with congenital and acquired disorders of hemostasis. In order to substantiate previous study findings, a larger phase III trial was recently completed; results were reported in the May issue of the *New England Journal of Medicine*. The study randomly assigned 842 patients with cerebral hemorrhages to receive placebo (n=268),

rFVIIa 20 mg/kg (n=276), or rFVIIa 80 mg/kg (n=297) administered within 4 hours of onset of stroke. The primary endpoint of poor clinical outcome (severe disability or death) was assessed by the modified Rankin scale 90 days after stroke occurred; computed tomography scans were also used to assess outcomes. Study findings showed that patients receiving 80 mg/kg of rFVIIa had a smaller increase in intracerebral hemorrhage volume compared to patients receiving 20 mg/kg and placebo (11% vs 18% vs 26%, respectively). The growth in volume of intracerebral hemorrhage was reduced by 3.8 mL (95% confidence interval [CI], 0.9–6.7; $P=.009$) in the high dose rFVIIa group and by 2.6 mL (95% CI, -0.3–5.5; $P=.08$) in the lower dose rFVIIa group compared to the placebo group. Although a reduction in bleeding was seen in both rFVIIa groups, there was no significant difference among the 3 groups in the proportion of patients with poor clinical outcome (placebo, 24%; rFVIIa 20 mg/kg, 26%; rFVIIa 80 mg/kg, 29%). Mortality at 90 days was also similar among the 3 groups (approximately 20%); odds ratios for survival, compared to placebo, were 1.1 for the high dose rFVIIa and 0.8 for the lower dose rFVIIa. Thromboembolic serious adverse event rates were comparable in the 3 groups, but arterial events were more common in the high dose rFVIIa group (9%) compared to the placebo group (4%; $P=.04$). The researchers concluded that hemostatic therapy with rFVIIa did reduce the growth of hematoma, but it did not support the findings of the earlier study, as improvement in survival and functional outcomes after intracerebral hemorrhage were not observed.

Researchers Find p53-mTOR Link, How Tumor Suppressor Inhibits Cell Growth

Researchers at the University of California, San Diego School of Medicine, are one step closer to describing the mechanism of how p53 regulates and protects cells against DNA damage that might lead to cancer. Two p53 target

genes—Sestrin1 and Sestrin2—were found to link p53, a tumor suppressor, and mammalian target of rapamycin (mTOR), a central regulator of cell growth whose activity is inhibited by rapamycin.

The 2 Sestrin genes are the missing piece of the puzzle that explains how p53 can inhibit the mTOR pathway and thereby negatively regulate cell growth, said investigator Andrei V. Budanov, PhD, postdoctoral fellow at UCSD. Scientists previously knew which p53 target genes inhibit cell proliferation, but not for cell growth inhibition.

Previous studies showed Sestrin1 and Sestrin2 proteins, which are expressed in response to genotoxic stress, to provide protective function. Sestrin1 and 2, and p53 have also been found to control the accumulation of reactive oxygen species (ROS), which are involved in cell signaling. Levels of ROS under genotoxic stress are known to increase dramatically, triggering significant damage to cell structures and resulting in oxidative stress.

In this study, which was published in the August 8 issue of the journal *Cell*, the UCSD researchers investigated what target genes allowed p53 to inhibit cell growth. They found that in addition to controlling ROS accumulation, Sestrin1 and 2 activate the adenosine monophosphate-responsive protein kinase and target it to phosphorylate TSC2, stimulating its GTPase activating protein activity and resulting in the inhibition of mTOR. Consequently, Sestrin2-deficient mice fail to inhibit mTOR signaling. This also explained the role of p53 as a potent regulator of many aspects of cell physiology, providing protection against DNA damage and stress.

According to researchers, knockout mouse models of Sestrin1 and 2 will be an important tool for future studies of their role in carcinogenesis. Investigator Michael Karin, PhD, professor of pharmacology in the Laboratory of Gene Regulation and Signal Transduction at UCSD, added that molecules that mimic the molecular actions of the Sestrins can be used to control cell metabolism and regain control over cancer cells that have lost p53.