

Experts Highlight Big Advances in Treating Urologic Malignancies

Some of the foremost experts on urologic malignancies met at the sixth annual Oncology Congress in San Francisco, CA, on October 17, 2010, to reflect and discuss several remarkable achievements over the past year.

Dr. William Oh from Mount Sinai School of Medicine updated the audience on recent developments in the treatment of castration-resistant prostate cancer (CRPC). He reminded those in attendance that it has been nearly 70 years since Charles Huggins and Clarence Hodges at the University of Chicago published their Nobel prize-winning work on the benefits of androgen-deprivation therapy for prostate cancer. Since that time, there have been major improvements in the design of anti-androgen therapies with therapeutic benefit. Unfortunately, most patients eventually develop CRPC, a situation where PSA rises despite low serum testosterone levels. Summarizing a wealth of recent clinical data, Dr. Oh emphatically stated that, "CRPC is not hormone-refractory cancer, but is frequently hormone ultra-sensitive." A number of mechanisms have been found to contribute to the development of CRPC, including androgen receptor (AR) amplification, AR point mutations, and expression of AR co-activators. Fortunately, several new, more potent anti-androgens are in clinical trials. Abiraterone, which blocks testosterone synthesis from the adrenal gland, has performed well in phase III clinical trials and is expected to be FDA approved in 2011. In addition, MDV3100, a second-generation anti-androgen that potently binds the AR to inhibit its nuclear translocation and DNA binding, has generated great excitement because of its performance in early phase clinical trials for CRPC. On the basis of these promising results, a phase III clinical trial of MDV3100 is rapidly moving forward for this indication.

Dr. Sandy Srinivas from Stanford University opened up her remarks by saying this is a "Remarkable time for patients with prostate cancer and those who care for them." She discussed the April 2010 FDA approval of sipuleucel-T for the treatment of metastatic castrate resistant prostate cancer (CRPC). A major milestone for the tumor immunotherapy field as a whole, sipuleucel-T is the first approved therapeutic "vaccine" against cancer. More accurately, sipuleucel-T is a personalized cellular immune product that is manufactured by collecting peripheral blood mononuclear cells from prostate cancer patients, enriching them for dendritic cells (DCs), and incubating these with a recombinant protein found in most prostate cancer cells (prostatic acid phosphatase or PAP). The activated DCs are then infused back into the patient where they tend to instruct the immune system to recognize and attack the prostate cancer cells. In a phase III clinical trial of 127 men with previously untreated metastatic CRPC, those randomized to receive sipuleucel-T lived an average 4.1 months longer than the placebo group (25.9 vs 21.4 months, respectively; $p=0.01$). At the 3-year preplanned survival analysis, 34% of sipuleucel-T-treated patients were alive compared to 11% of placebo-treated patients ($p=0.0046$). The treatment was generally well-tolerated with low-grade fever and rigor being the most common side effects. Dr. Srinivas pointed out a number of issues that need to be weighed when considering sipuleucel-T for this indication, including the laborious nature of the treatment (multiple infusions) and high cost.

Dr. Matthew Galsky from the Mount Sinai School of Medicine reviewed recent advances in the treatment of bladder cancer. Stating that we “may have hit the ceiling with traditional cytotoxics”, Dr. Galsky highlighted several promising targeted agents for advanced bladder cancer. In particular, there is compelling evidence that signaling from the HER2/ErbB receptor family contributes to tumor cell survival in bladder cancer. As such, there are several early phase clinical trials ongoing to test whether the kinase inhibitor lapatinib or the anti-EGFR antibody cetuximab may be beneficial. In addition, Dr. Galsky outlined a number of clinical trials to test the anti-angiogenesis agent bevacizumab in patients with bladder cancer.

Dr. Thomas Hutson from Baylor-Sammons Cancer Center reviewed the achievements over the past few years in the treatment of advanced renal cell carcinoma (RCC) with targeted agents. In 2004, the overall survival for treatment naïve patients with metastatic RCC was 7-9 months. Recent clinical trials of the multikinase inhibitor sunitinib have reported median overall survival rates of approximately 26 months for these patients. Dr. Hutson outlined a number of ongoing phase III clinical trials to determine which targeted agents are superior as first-line therapy against various subtypes of RCC. Moreover, the biggest questions currently revolve around second-line therapy for patients with advanced RCC who progress on therapy—a topic that is actively being addressed through clinical trials. Dr. Hutson outlined what he considered the five biggest challenges in RCC treatment today as: “Toxicity, cost, maintenance of therapy, development of resistance, and individualizing therapy.”

By any measure, it has been a remarkable year for those fighting urologic malignancies. Given the number of new agents in clinical trials, one gets the sense that this is just the beginning.