Overcoming radiation-induced immune suppression by targeting the PD1/PDL1 axis

James Welsh
MD Anderson Cancer Center, USA

Strategies for overcoming tumor evasion of the immune system have already started to translate into improved outcomes for lung cancer. Because most patients with unresectable lung cancer are treated with radiation, now is the time to expand our understanding of how radiation can influence immune evasion. Radiation is known to be a potent antigen stimulator, which can serve to prime the immune system to attack cancer cells. However, radiation was recently discovered to induce PDL1 expression by lung tumors, and PDL1 can blunt this immune response. Studies in melanoma have shown that combining radiation with new immunomodulating therapies, such as ipilimumab can result in immune-mediated responses at sites outside the irradiated area, a phenomenon described as the abscopal effect.

Radiation therapy can be highly effective in achieving local tumor control in lung cancer. However, until now it has not been able to control metastatic disease, the cause of death for most patients with lung cancer. We hypothesize that by combining inhibitors of the PD1/PDL1 axis with radiation; we can not only enhance local control but also reduce or eliminate the spread of metastatic disease. Anti-PDL1 therapies are already being tested as monotherapy or in combination with chemotherapy for lung cancer, and as such this is an excellent time to investigate the molecular basis for how these therapies work in combination with radiation. This talk will review the prior preclinical data describing the abscopal phenomena, along with our current laboratory work on this topic, followed by an overview of our clinical trial strategy for combing immunotherapy with radiation.

Biography

James Welsh, MD, specializes in the treatment of thoracic cancers at The University of Texas MD Anderson Cancer Center. He began his career in oncology at the Department of Molecular Oncology at Genentech Inc., where some of the first biological target therapies were developed (e.g., rituximab [Rituxan], trastuzumab [Herceptin], and bevacizumab [Avastin]). While at Genentech, he and his team discovered and cloned the Wnt-Induced secreted proteins (WISP) family of oncogenes. He later attended Dartmouth Medical School, where his laboratory work involved developing strategies to radiosensitize tumors by inhibiting AKT. He completed a residency in radiation oncology at the University of Arizona, where he also ran a laboratory focused on developing biologically targeted therapies as radiosensitizers and led several clinical trials combining biological therapies with ionizing radiation. He joined the clinical faculty at MD Anderson Cancer Center in 2008. His academic pursuits extend from the laboratory to the clinic, with a focus on translational research, developing novel therapeutics and immunotherapies to combine with radiation, with the goal of developing personalized therapy approaches for cancer.

JWelsh@mdanderson.org