Cryo-immunotherapy

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Cryotherapy for Prostate Cancer

Cryoablation has rapidly become an accepted technique for the management of localized prostate cancer (PCa). The concept of cryotherapy dates back to the 1850s when physicians used local applications of a salt solution containing crushed ice to treat advanced cancers that were accessible to treatment such as those of the breast and uterine cervix. In the early 1990s, cryotherapy was reintroduced for the treatment of prostate cancer after study in animals and human trials in the 1970s and 1980s. On the basis of these experimental and clinical studies, an optimal drop in temperature of -40°C is required to achieve total cell death.[i, ii] Although many theories were suggested for the underlying mechanism of the cryo-ablative tissue effect, the vascular component of initial vasoconstriction followed by reperfusion injury (increased capillary permeability) triggered by the thawing phase is considered to be the primary mechanism of tissue damage.[iii] However, intracellular crystallization and subsequent water shifting during the thawing phase also contribute significantly to the rupture of the cell membrane and irreversible cellular death.[2]

The introduction of ultrasound guidance allowed the freezing process to be controlled and monitored in real time. In 1996, the American Urological Association recognized cryoablation as an option for the treatment of localized PCa. In 2000, the third-generation of cryotherapy was ushered in with the development of gas-driven probes using the Joule-Thompson principal in which pressurized gas is permitted to depressurize through a small (1.5-mm) narrow nozzle located in the tip of the probe. Argon gas is used for cooling and helium for warming during the freeze-thaw cycles, respectively (two cycles are recommended).[iv] Concomitant with the development of these new units was the use of thermocouples to aid the operator in the real-time monitoring of temperature levels in critical areas such as the rectal wall and urethra and within the vicinity of the neurovascular bundles responsible for erectile function. The use of urethral warmers also contributed significantly in reducing urethral damage and sloughing related urinary retention postoperatively.[v]

Cryo-immunotherapy

While the last decade has seen numerous advances in the treatment of carcinoma with modulation of the immune system,[vi, vii, viii] nascent immune effects after cryotherapy were observed as far back as the 1970s in the treatment of PCa when investigators anecdotally

noted spontaneous regression of distant metastases.[ix, x] These reports, in which Albin et al first coined the term "cryo-immunotherapy," stimulated much interest in the immunomodulatory effects of cryoablation. Multiple studies ensued in animal models in an attempt to elucidate and measure this effect.[xi, xii, xiii]

Several recently published studies have indicated that preoperative immune response modifications may have a role in improving survival benefit. In fact, cryo-immunotherapy, as a novel approach for extending the therapeutic effect from local to systemic treatment of prostate cancer, has received more interest recently. Necrosis after cryotherapy releases large amounts of tumor antigens and inflammatory signals that are necessary for triggering dendritic cell maturation. Dendritic T cells are the primary antigen-presenting cells of the immune system and have the ability to interact with immune effector cells such as T and B cells, natural killer cells. Tumor antigen loading followed by dendritic cell activation promotes specific tumor cell necrosis, which theoretically increases the extent of the cryotherapy effect. Results of early preclinical studies are encouraging and await confirmation in a clinical setting.[xiv] The application of immunotherapy to supplement primary minimally invasive treatment in patients with high-risk disease is appealing; however, large controlled studies are needed before the widespread application of this interesting concept to early prostate cancer.

Clinical Application

Despite the antitumor immunity stimulated by cryotherapy, most reports recognize that the effect is minimal in most cases and would require amplification in order to fully mobilize a host immune system to destroy residual or metastatic disease either at the time of local treatment or at some future point in time.[xv] There are a number of new PCa immune therapies currently under investigation or recently approved for use in advanced or metastatic disease that may suit such a purpose for newly diagnosed cancer or the setting of salvage cryotherapy.[xvi] It remains to be seen, however, how these therapies would interact with cryo-immunotherapy and whether the mechanisms as a whole would be synergistic. Investigation of this effect via cellular immune assays with and without additional immune modulation treatments after cryotherapy must be studied.

Clinical Endpoints for Cryo-immunotherapy

Any therapy for prostate cancer must also have a directed endpoint, preferably one that correlates strongly with and hence can be used as a surrogate for overall survival or prostate-cancer specific survival. To date, most clinicians and study investigators have used

serum prostate-specific antigen (PSA) as a marker of outcome, however, there have been numerous reports of its deficiencies with respect to cancer immunotherapy.[xvii, xviii] Namely, although some prostate cancer immunotherapies have been shown to benefit overall survival, they have had little or no impact on PSA kinetics, sometimes even increasing despite positive therapeutic effect. Some have tried to use disease burden, measured radiographically and quantified through Response Evaluation Criteria in Solid Tumors (RECIST) criteria, as a surrogate to meaningful clinical response or outcome, but again, showed disappointing results with this intermediate marker as some patients lived longer despite showing "progression" based on these definition.[xix],[xx] Finally, some groups have advocated the use of circulating tumor cells (CTCs), where ≥ 5 CTCs/7.5 mL blood has been shown to correlate to worse outcome as compared to men with fewer than 5 CTCs/7.5 mL blood.[xxi] A well-defined marker must be determined in advance and the definition for disease progression should be made carefully, especially in light of immune system kinetics and delayed response times.

To this end, with the advent of cancer immunotherapy over the last 15 years, the statistical analyses and study designs have been questioned with regards to the kinetics of immunotherapy responses. Hoos et al have rightly pointed out that there exists several problems with the methodologies in studies to date;[xxii] namely, he notes the lack of standards in cellular immune response assays, novel patterns of anti-tumor response patterns not classifiable with current RECIST or World Health Organization (WHO) criteria, and delayed separation of Kaplan–Meier curves in randomized immunotherapy trials, affecting the power (β) of the trial and the number of responders needed to obtain statistically significant results. He makes specific recommendations to address these pitfalls in previous studies, including assay harmonization, use of immune-related response criteria (irRC) adapted from RECIST and WHO criteria, and use of modified statistical analyses to account for delayed kinetics of immune responses that can affect power of a study to detect a clinical outcome.

Acronyms and Abbreviations

CTC - circulating tumor cell
irRC - immune-related response criteria
PCa - prostate cancer
PSA - prostate-specific antigen
RECIST - Response Evaluation Criteria in Solid Tumors
WHO - World Health Organization

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