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Potential of New Treatments for Prostate Cancer

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More than 240,000 men will be diagnosed with prostate cancer this year and more than 28,000 will die of their cancer [1]. Moreover, prostate cancer therapies can cause severe, permanent damage to the patients, such as incontinence and erectile dysfunction. Clearly, new therapies are needed. The ideal cancer therapy would cure patients of their cancer without causing concurrent or subsequent side effects.

Immunotherapy is one such possibility for creating a potent new cancer therapy with minimal side effects, if it can appropriately activate the patient's immune system. The power of the immune system is illustrated by the fact that the immune system initially has an immunosurveillance system to recognize and kill the precancerous and cancerous cells that frequently develop [2]. Unfortunately, sometimes, a cancer cell can escape immunosurveillance and grow to a point where it is no longer killed by the NK cells and cytotoxic T cells of the immunosurveillance system. The cytotoxic T cells that would otherwise kill the cancer cells are said to have developed tolerance to the cancer cells [2].

The immune system can still recognize and bind to cancer antigens on the cancer cells. This continued recognition can be seen by the presence of tumor-infiltrating lymphocytes (which include cytotoxic T cells) that specifically bind to the cancer cells [3]. However, since the lymphocytes have developed tolerance to the tumor cells, they do not kill the tumor cells and are said to be anergic. Thus, the key to creating a new cancer therapy is to break tolerance, allowing the patient's immune system to attack and kill the cancer cells. Such an immunotherapy that could fully activate the immune system against the cancer cells would be very, very potent.

Several approaches to immunotherapy have been investigated clinically. First, Provenge (Sipuleucel-T) employs a patient's own dendritic cells that are treated *in vitro* with a fusion protein composed of granulocyte-macrophage colony stimulating factor (GM-CSF) to stimulate the dendritic cells and prostatic acid phosphatase to provide antigen to induce T cell proliferation. Second, GVAX uses a combination of two prostate cancer cells to provide antigen, one of which is transfected to secrete GM-CSF. Third, PROSTVAC-VF uses GM-CSF inoculation plus injection of vaccinia virus that has been genetically modified to make prostate specific antigen, B7, ICAM-1, and LFA-3. These immunotherapies have had limited effect: 4 month increase in survival with Provenge [4], no increase in survival with GVAX [5], and 8.5 month increase in survival with PROSTVAC-VF [6]. This is probably because these immunotherapies focus on generating new cytotoxic T cells that may still be suppressed by either pre-existing or newly generated immunoregulatory cells.

An alternative immunotherapy that focuses on breaking tolerance may give better activation of the host immune system. Interleukin-15 (IL-15) is a potent activator molecule that can break tolerance and that has several advantages as an immunotherapy. IL-15 stimulates the production and proliferation of helper and cytotoxic T cells while avoiding the stimulation and proliferation of immunoregulatory cells [7]. Also, it enhances the survival of memory cytotoxic T cells and activates lymphocytes that have a stronger cytotoxicity against tumor cells than those activated by IL-2 [7]. For example, in one study, using mice bearing TRAMP-C2 prostate cancers, systemic administration of IL-15 led to about 20% survival [8]. Survival could be increased to 60% when IL-15 therapy was combined with two antibodies that block regulatory T cells. However, there may be some concerns about systemic administration of IL-15 in man, as toxicity has been noted in an IL-15 preclinical study in non-human primates [9].

One mechanism of avoiding systemic administration of IL-15 is to *in vitro* treat immune cells with IL-15. Indeed, harvested human dendritic cells, treated *in vitro* with IL-15 and re-inoculated, caused 10^5-10^6 fold *in vivo* proliferation of tumor antigen-specific memory T cells and inhibited immunoregulatory cell expansion [10]. However, the antigen-specific memory T cells would still be susceptible to the action of immunoregulatory cells.

Another mechanism is to administer a whole-cell cancer vaccine that contains IL-15. This would provide a localized treatment of tumor-infiltrating lymphocytes that would then have a systemic effect. The localized treatment would minimize the side effects of the treatment itself. The systemic effect would be the killing of cancer cells that may have metastasized throughout the patient's body.

Indeed, in a mouse study, RM-1 prostate cancer vaccine cells induced to accumulate cell-associated IL-15, when lethally irradiated and inoculated, protected 60% of mice against challenge with live RM-1 prostate cancer cells [11]. The inoculated IL-15-based cancer vaccine cells are recognized by tumor-infiltrating lymphocytes. The irradiation-induced lysis of the vaccine cells releases sufficient IL-15 locally to activate the tumor-infiltrating lymphocytes, causing them to proliferate, to wander, and to kill cancer cells wherever they are found.

In summary, while current immunotherapies focusing on activation of dendritic cells and T cell proliferation have shown promise of increased survival time, IL-15-based immunotherapies that break tolerance would appear to hold promise for curing patients. Moreover, the use of cell-associated IL-15 may limit side effects due to its local release.

References

1. http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics
2. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD (2002) Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 3: 991-998.
3. Rosenberg SA, Spiess P, Lafreniere R (1986) A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes. Science 233: 1318-1321.
4. Fong MK, Hare R, Jarkowski A (2012) A new era for castrate resistant prostate cancer: a treatment review and update. J Oncol Pharm Pract 18: 343-354.
5. Higano C, Saad F, Somer B, Curti B, Petrylak D, et al. (2009) A phase III trial

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of GVAX immunotherapy for prostate cancer versus docetaxel plus prednisone in asymptomatic, castration-resistant prostate cancer (CRPC). ASCO GU Symposium.

6. Kantoff PW, Schuetz TJ, Blumenstein BA, Glode LM, Bilhartz DL, et al.(2010) Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol 28: 1099-1105.
7. Steel JC, Waldmann TA, Morris JC (2012) Interleukin-15 biology and its therapeutic implications in cancer. Trends Pharmacol Sci 33: 35-41.
8. Yu P, Steel JC, Zhang M, Morris JC, Waitz R, et al. (2012) Simultaneous inhibition of two regulatory T-cell subsets enhanced Interleukin-15 efficacy in a prostate tumor model. Proc Natl Acad Sci U S A 109: 6187-6192.
9. Berger C, Berger M, Hackman RC, Gough M, Elliott C, et al. (2009) Safety and immunologic effects of IL-15 administration in nonhuman primates. Blood 114: 2417-2426.
10. Romano E, Rossi M, Ratzinger G, de Cos MA, Chung DJ, et al. (2011) Peptide-loaded Langerhans cells, despite increased IL15 secretion and T-cell activation in vitro, elicit antitumor T-cell responses comparable to peptide-loaded monocyte-derived dendritic cells in vivo. Clin Cancer Res 17: 1984-1997.
11. Wu TG, Perdigão JR, Umhoefer TK, Cao J, Ansari DA, et al. (2009) Heterogeneous interleukin-15 inducibilities in murine B16 melanoma and RM-1 prostate carcinoma by interferon-alpha treatment. J Interferon Cytokine Res 29: 719-728.