Rush Hour Traffic: Directing T Cells to Tumor
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In 2010, the Food and Drug Administration approved sipuleucel-T for the treatment of asymptomatic or minimally symptomatic castration-resistant metastatic prostate cancer based on demonstration of an improvement in overall survival in a randomized phase III clinical trial (1), one of three recent positive large controlled vaccine trials in a variety of human cancers that show that specific T cells can be elicited by vaccination (2,3). Sipuleucel-T is a patient-specific cellular product that is prepared by culturing autologous peripheral blood mononuclear cells ex vivo with a recombinant human fusion protein consisting of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony stimulating factor (GM-CSF). The final infusion product is comprised of a mixture of cells, including antigen-presenting cells (APC), T cells, B cells, natural killer (NK) cells, and others. Although sipuleucel-T is categorized as autologous cellular immunotherapy, its postulated mechanism of action suggests that it is a form of therapeutic cancer vaccine. The PAP serves as the tumor-associated antigen and is likely taken up by APCs during the in vitro culture and processed and presented on their surface in the context of major histocompatibility complex molecules. GM-CSF presumably acts as an adjuvant to activate APCs to enhance antigen presentation to T cells. Following administration to the patients, the APCs expressing PAP-derived peptides induce PAP-specific T cells that in turn might exert antitumor effects. Indeed, T-cell proliferative and IFN-γ immune responses against the fusion protein, PAP-GM-CSF and PAP alone were observed in the peripheral blood in patients following sipuleucel-T administration (1). Antibody responses against PAP-GM-CSF and PAP alone were also observed. However, whether the induced T cells traffic to the tumor site, a prerequisite to achieve tumor eradication, is unknown. Understanding the effects in the tumor microenvironment is necessary to develop strategies to enhance the potency of sipuleucel-T. In this issue of the Journal, Fong and colleagues investigated this in an elegantly designed neoadjuvant trial in patients with localized prostate cancer scheduled to undergo radical prostatectomy (4).

In this single-arm, open-label, multicenter phase II study, patients received the standard three doses of sipuleucel-T at two-week intervals. Tumor biopsies were obtained at baseline and radical prostatectomy was performed two to three weeks after the final infusion of sipuleucel-T. The primary objective was to determine changes in immune cell infiltrates in the paired tumor tissues. In the 37 evaluable patients, the authors found a statistically significant increase in CD3+ T-cell infiltration at the tumor interface after sipuleucel-T compared with baseline biopsies. Further analysis showed that both CD4+Foxp3+ effector T cells and CD8+ T cells were increased at the tumor interface but not NK cells. Although the investigators did not assess the function of the infiltrating T cells, analysis of peripheral blood T cells showed proliferative and IFN-γ responses against PAP-GM-CSF and/or PAP alone. Importantly, such changes in T cell infiltrates were not observed in the control group of 12 patients with localized prostate cancer that underwent radical prostatectomy but did not receive sipuleucel-T preoperatively. While a randomized trial would have been ideal, the patients selected for comparison were well matched for clinical risk criteria and thus, provided a good control. Comparing the tumor infiltrates between prostatectomy specimens and needle biopsies is also not ideal, but the absence of T cell infiltrates in the control group suggests that the observed changes in the treated group are because of sipuleucel-T.

The results of this study provide further insights into the mechanism of action of sipuleucel-T. They suggest that PAP-specific T cells are likely induced in the periphery and traffic to the tumor site following sipuleucel-T administration. The study also showed some unexpected findings. For example, T cells expressing the coinhibitory molecule PD-1 and the immunosuppressive CD4+Foxp3+ regulatory T cells (Tregs) were increased at the tumor interface in addition to the effector T cells. Expression of PD-1 may indicate infiltration with activated T cells, and this was supported by the observation that the majority of the infiltrating T cells were proliferating, indicated by Ki-67+ stain. The increase in Tregs may be because of direct induction of Tregs by sipuleucel-T or may be a physiological response to infiltration by effector T cells. These observations imply that combination strategies with agents that block PD-1 (5,6) or Treg function (7,8) may enhance the efficacy of sipuleucel-T. However, several questions remain unanswered, including the maturation phenotype (eg, central vs effector memory) of the infiltrating T cells, the cytotoxic activity of the T cells, expression of other activation and coinhibitory molecules, effect of booster vaccination, long-term persistence, and correlation with clinical outcome. Investigation of multiple phenotypic and functional features of infiltrating T cells is difficult when tissue samples are limited, but whole genome gene expression profiling could be a valuable tool to evaluate such changes in small tissue samples (9). Despite the T cell infiltration into tumors after sipuleucel-T, downregulation of the tumors was not observed compared with baseline. It is possible that this may be because of the short interval between sipuleucel-T infusions and radical prostatectomy. Unlike cytotoxic chemotherapy, clinical response after active immunotherapy can be slow and take weeks to months. But it is also possible that clinically evident tumor response may not occur after sipuleucel-T.
reductions in prostate-specific antigen levels were detected in only 2.6% of metastatic prostate cancer patients treated with sipuleucel-T. Nevertheless, an improvement in overall survival was observed in the metastatic setting (1). It is possible that this conundrum may be because of the alteration of the natural history of the disease mediated by infiltration of antitumor T cells into the tumor following sipuleucel-T (10).

In summary, this is the first study to demonstrate that activated T cells traffic to tumor sites after sipuleucel-T immunotherapy. Although conducting such studies using paired tumor biopsies is cumbersome and expensive, these studies are essential and should be performed early in the development of novel therapies to better understand their mechanism of action and to develop approaches to enhance their efficacy. In this respect, the neoadjuvant trial design by Fong and colleagues could serve as a model for future trials of novel immunotherapies and targeted agents in prostate cancer and other malignancies.

References

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