FOCUS ON RESEARCH

Cancer Immunotherapy — The Endgame Begins

Louis M. Weiner, M.D.

Related articles, p. 2698 and 2704

In 1987, an editorial accompanying a report on the use of high-dose interleukin-2 therapy for cancer asked whether the field of immunotherapy was at "the beginning of the end" or "the end of the beginning."[1] In retrospect, I would say it was at the "beginning of the beginning." Have we made progress since then? Finn, in her review of tumor immunology in this issue of the *Journal* (pages 2704–2715), answers emphatically in the affirmative, and the report by Hunder et al., also in this issue (pages 2698–2703), underscores the remarkable potential of the immune system to eradicate cancer, even when the disease is widespread.

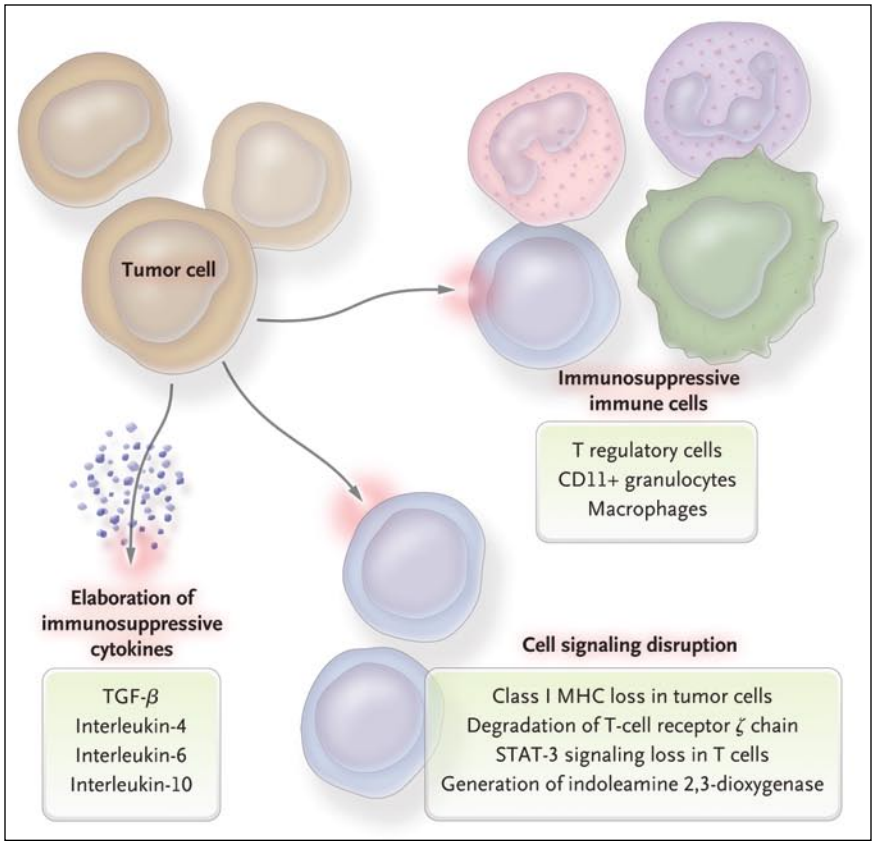
It has long been known that graft-versus-tumor effects underlie the success of allogeneic bone marrow transplantation for hematologic neoplasms and the efficacy of donor lymphocyte infusions in chronic myelogenous leukemia. These new results show that the immune system can eradicate a cancer, just as it can reject an allogeneic organ unless the recipient receives potent immunosuppressive agents. However, since the immune system perceives most cancers as "self," the allograft-rejection mechanism is not often operative in patients with cancer.

Nevertheless, the immune system can respond to some types of tumors. Interactions of developing tumors with the immune system can eliminate cancer cells that display highly immunogenic tumor antigens, thereby shaping the tumor's repertoire of cancer antigens and enhancing the ability of the surviving tumor cells to evade the immune system. It is also possible to activate the immune system into an antitumor state. About 15% of patients with metastatic melanoma or renal-cell carcinoma have clinically significant responses to activation of T cells by high-dose interleukin-2 therapy. Some of these responses are complete, durable, and apparently curative. Recently, Morgan et al. improved on these results by treating melanoma with lymphocytotoxic chemotherapy, followed by an infusion of autologous tumor-derived T cells in conjunction with interleukin-2 to sustain T-cell survival and activation.[2] Hence, there is a precedent for the remarkable results of the adoptive cellular therapy approach described by Hunder et al. These successes indicate that it is possible to induce a restricted kind of autoimmunity, targeted primarily against cancer-related antigens, with limited toxic effects on the patient.

T-cell therapy is promising, but there are many other examples of effective cancer immunotherapy. For example, monoclonal antibodies with clinical activity in non-Hodgkin's lymphoma and breast cancer interact with the immune system. Treatment of non-Hodgkin's lymphoma with rituximab, an anti-CD20 (B-cell) antibody, is more effective in patients with the amino acid 158 (V/V) polymorphism in CD16A, the low-affinity Fcγ receptor expressed by natural killer cells. This variant receptor promotes antibody-dependent cellular cytotoxicity and contributes to efficient immune clearance of antibody-coated targets. Recently, the beneficial effect on breast cancer of trastuzumab, a monoclonal antibody against HER2/*neu*, was found to be associated with the induction of T-cell responses against HER2/*neu*.[3] Vaccines that prevent primary hepatitis B virus (HBV) infection also prevent the development of HBV-induced hepatocellular carcinoma, and similar benefits for cervical-cancer prevention are anticipated from human papillomavirus vaccines.

In contrast to vaccines directed against infectious agents that can initiate neoplasia, cancer vaccines have focused on cancer-cell–related antigens. Many such vaccines can elicit immune responses mediated by T cells or antibodies against tumor antigens. Although there have been occasional hints of clinical benefit, no cancer vaccine has had sufficient clinical activity to warrant approval of its use for cancer therapy. Progress in this field would be greatly accelerated if many agents with immunologic efficacy that are not used to treat cancer, such as interleukin-12, were readily available to use in combination with cancer vaccines. Even high-dose interleukin-2 therapy, which can be curative in advanced melanoma and renal-cell carcinoma, is frequently ineffective and has proved to be a limited platform for effective derivative treatments. Despite these limitations, every clinical investigator who has witnessed remarkable tumor regressions in some patients treated with immunotherapy has been intrigued and tormented by the idea that immunotherapy can trigger powerful and durable cancer control, even as the definitive targets and mechanisms of action remain elusive, perched at the outer limits of our knowledge.

In an era when huge, randomized clinical trials are frequently required to demonstrate the efficacy of new treatments, there is still a role for an illuminating, carefully performed, and thought-



Tumor-Derived Immunosuppression.

Tumors evade or defeat the host tumor response to obtain a host-specific selective survival advantage through elaboration of immunosuppressive cytokines, the production of immunosuppressive immune cells, and disruption in cell signaling. In a recent study, researchers were able to infuse expanded autologous CD4+ T-cell clones to overcome tumor-derived immunosuppression in a patient with metastatic melanoma. MHC denotes major histocompatibility complex, STAT-3 signal transducer and activator of transcription 3, and TGF-β transforming growth factor β.

fully analyzed pilot study or case report. Virtually everything that was important to learn about the future of monoclonal-antibody therapy of lymphoma was described in a small trial reported by Miller et al. in 1982.[4] Similarly, the case report by Hunder et al. lays out important principles. The success of their novel strategy and the clear immune mechanisms of action point to a feasible new direction for adoptive cellular therapy of cancer. Hunder et al. infused only 10^8 purified CD4+ T cells, which were expanded by coincubation with antigen-presenting cells that displayed melanoma-derived peptides bound to the patient's class II major-histocompatibility-complex antigens, thereby driving the proliferation of CD4+ T cells that recognize cancer-relevant targets. They showed that such CD4+ T cells can coordinate an effective, prolonged antitumor immune response. Moreover, the infused CD4+ T cells produced their own survival factors when they encountered their cognate targets, thereby eliminating the need for exogenous interleukin-2 and hence minimizing acute toxicity. In addition, Hunder et al. found that the induction of an effective antitumor immune response against a cancer-rejection antigen elicited responses against other antigens of the patient's melanoma. This broader immune response most likely blocks escape routes, such as loss of expression of the targeted antigen, that otherwise could allow a tumor to circumvent immune control.

This type of approach will not always work. Variability in the immune response and the biology of the tumor will require customized immunotherapy regimens that take these complexities into account. For example, cancers use a variety of immunosuppressive mechanisms to defeat potentially effective immune responses (see diagram).[5] Although the CD4+ T cells infused by Hunder et al. were able to overcome tumor-derived immunosuppression, this will not always be the case, and it may prove necessary to therapeutically target immune-suppression mechanisms on an individualized basis.

Do the findings of Hunder et al. represent a mirage, an oasis, or an early sighting of the destination? Time will tell, but I suspect that if the destination is not yet at hand, it is in sight. The endgame has begun.

Dr. Weiner reports receiving research grant support from Amgen and Eisai Research Institute. No other potential conflict of interest relevant to this article was reported.

Dr. Weiner is director of the Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC.

1. Durant JR. Immunotherapy of cancer: the end of the beginning? N Engl J Med 1987;316:939-41.
2. Morgan RA, Dudley ME, Wunderlich JR, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. Science 2006;314:126-9.
3. Taylor C, Hershman D, Shah N, et al. Augmented HER-2 specific immunity during treatment with trastuzumab and chemotherapy. Clin Cancer Res 2007;13:5133-43.
4. Miller RA, Maloney DG, Warnke R, Levy R. Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody. N Engl J Med 1982;306:517-22.
5. Rabinovich GA, Gabrilovich D, Sotomayor EM. Immunosuppressive strategies that are mediated by tumor cells. Annu Rev Immunol 2007;25:267-96.