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The Emergence of Modern Cancer Immunotherapy

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The last two decades have seen the emergence of immunotherapy as an effective treatment for selected patients with metastatic cancer. Durable complete remissions can be induced in cancer patients solely by inducing immune responses against the growing cancer.

The clearest example of the effectiveness of immunotherapy to mediate cancer regression comes from studies of the administration of interleukin (IL)-2 to patients with metastatic melanoma and metastatic renal cancer.[1] IL-2 has no direct effect on cancer cells, and all of the antitumor effects resulting from its administration are the result of its ability to stimulate immune reactions in cancer patients. A total of 15% to 20% of patients with metastatic melanoma and metastatic kidney cancer experience objective regressions of metastatic disease, almost half of which are complete responses. Now, with 20-year follow-up in some patients, it seems that treatment with IL-2 probably "cures" patients who experience a complete response, because 80% of these patients have ongoing complete responses. In our own series in the Surgery Branch, National Cancer Institute, only 6 of 33 patients with either metastatic melanoma or kidney cancer who had complete cancer regressions have ever had disease recurrence.[1] The treatment can be safely administered with a treatment-related mortality of <. 5%.[2] Thus, it seems that patients with metastatic melanoma and metastatic renal cancer join that very small group of patients with solid tumors that can be cured by systemic treatment.

The article by Spanknebel et al.[3] in this issue of *Annals of Surgical Oncology* comparing two different dose schedules of high-dose IL-2 is one of many articles that corroborate these findings. Similar results from many series led the Food and Drug Administration to approve the use of high-dose IL-2 for patients with metastatic kidney cancer in 1992 and for patients with metastatic melanoma in 1998. The durability of complete responses was a decisive factor in the approval of these treatment regimens, which should be offered to all eligible patients with these metastatic cancers.

The realization that IL-2 administration could cause tumor regression led to studies that identified the lymphocytes responsible for these tumor regressions, and this in turn led to the identification of the molecular nature of multiple cancer antigens that have been extensively studied for use in cancer vaccines.[4] A variety of methods for immunizing patients with these molecularly defined cancer antigens have been shown to give rise to tumor-specific T lymphocytes, although there are currently no cancer vaccine approaches that can reproducibly mediate the regression of cancer in patients.[5] Research in this area is active, however, and the intensive study of new approaches holds the possibility for future success.

Other immunotherapy approaches have now been shown to mediate regression of metastatic cancer in patients. The adoptive transfer of autologous lymphocytes with antitumor activity, expanded in vitro and reinfused into patients, can mediate tumor regression,[6] and recent advances in this field have dramatically improved the effectiveness of this approach.[7] Lymphodepletion before the administration of autologous tumor reactive cells has led to

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objective responses in 18 (51%) of 35 patients with metastatic melanoma, including those refractory to high-dose IL-2 and combination chemotherapy.[8] These studies demonstrate the effectiveness of immune T cells when administered to hosts actively depleted of T-regulatory cells, as well as cells that compete for homeostatic cytokines.

A detailed understanding of the costimulatory molecules that affect the antitumor activity of lymphocytes has led to an increased understanding of the role of inhibitory factors that can influence antitumor immune reactions. The administration of a monoclonal antibody to CTLA-4, an inhibitory influence on both CD4 and CD8 lymphocytes, can lead to durable cancer regressions that are often accompanied by manifestations of autoimmune disease, thus demonstrating the similarity of immune tolerance to normal self-antigens and to tumors.[9]

There has, however, been considerable confusion in the field of cancer immunotherapy because clinical trials are often reported with nonstandard or surrogate end points instead of tumor regression to indicate clinical effectiveness. The ability to compare clinical trials evaluating treatment regimens in cancer patients is dependent on the use of standard accepted criteria for determining objective clinical responses. Two sets of criteria are in common use. In brief, the World Health Organization criteria[10] for objective clinical response are based on a 50% decrease in the sum of the products of the perpendicular diameters of all lesions, with no increase in any lesion and no appearance of new lesions. Alternatively, RECIST (Response Evaluation Criteria in Solid Tumors) criteria[11] for objective response are based on a 30% decrease in the sum of the longest diameters of target lesions, with no increase in any lesion. Deviation from these widely accepted criteria leads to considerable confusion. “Mixed responses” in which some tumors decrease and others increase do not qualify as objective responses in any standard criteria. An example is seen in the report by Spanknebel et al.,[3] which reports “10 objective responses in 46 evaluable patients after one course of IL-2 therapy.” However, five of these are mixed responders, and thus the true objective response rate is not 22%, but, rather, 11%.

A favorable spin is often imparted to results based on the use of negative data to meet preconceived biases by using nonstandard criteria as surrogates for clinical response. Thus, reports of “tumor necrosis,” “lymphocyte infiltration,” “antigen loss,” “shrinkage of some lesions,” “symptom improvement,” or “survival longer than expected” appear in many articles and often obfuscate the truth.[5] These unusual criteria may often be part of the natural course of disease or are so subjective as to be open to considerable patient and investigator bias.

The article by Spanknebel et al.[3] confirms again that the administration of high-dose IL-2 can mediate regression of cancer in patients with metastatic melanoma or kidney cancer, although conclusions cannot be drawn comparing the two dose levels administered to these patients (720,000 vs. 600,000 IU/kg). In dozens of reports, the objective response rate to both regimens of high-dose IL-2 is 15% to 20%. It would require 1502 patients per arm to detect a 5% difference in response between these regimens at a significance level of .05 (power of .9) and would require 956 patients per arm to detect a 10% difference. The total of 47 patients divided into 2 different IL-2 treatment regimens by Spanknebel et al.[3] is not sufficient to compare the two IL-2 dose levels used.

The Spanknebel et al.[3] article in this issue, however, further emphasizes that a high-dose IL-2 regimen can be safely administered to patients and can mediate objective regressions in patients with metastatic melanoma or renal cancer. This is an effective treatment that should be offered to patients with these metastatic cancers. Twenty years after the first descriptions of the effectiveness of IL-2,[12,13] immunotherapy has come of age, and substantial improvements based on increased scientific understanding are on the way.

References

1. Rosenberg SA, Yang JC, White DE, Steinberg SM. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. Ann Surg 1998;228:307–19. [PubMed: 9742914]
2. Kammula US, White DE, Rosenberg SA. Trends in the safety of high dose bolus interleukin-2 administration in patients with metastatic cancer. Cancer 1998;83:797–805. [PubMed: 9708948]
3. Spanknebel K, Cheung KY, Stoutenburg J, et al. Initial clinical response predicts outcome and is associated with dose schedule in metastatic melanoma and renal cell carcinoma patients treated with high-dose interleukin 2. Ann Surg Oncol. in press
4. Rosenberg SA. Progress in human tumour immunology and immunotherapy. Nature 2001;411:380–4. [PubMed: 11357146]
5. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. Nat Med 2004;10:909–15. [PubMed: 15340416]
6. Rosenberg SA, Packard BS, Aebersold PM, et al. Use of tumor infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. *Preliminary report*. N Engl J Med 1988;319:1676–80. [PubMed: 3264384]
7. Dudley ME, Wunderlich JR, Robbins PF, et al. Cancer regression and autoimmunity in patients following clonal repopulation with anti-tumor lymphocytes. Science 2002;298:850–4. [PubMed: 12242449]
8. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23:2346–2357. [PubMed: 15800326]
9. Phan GQ, Yang JC, Sherry RM, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci USA 2003;100:8372–7. [PubMed: 12826605]
10. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207–14. [PubMed: 7459811]
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16. [PubMed: 10655437]
12. Rosenberg SA, Lotze MT, Muul LM, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. N Engl J Med 1985;313:1485–92. [PubMed: 3903508]
13. Lotze MT, Chang AE, Seipp CA, Simpson C, Vetto JT, Rosenberg SA. High dose recombinant interleukin-2 in the treatment of patients with disseminated cancer: responses, treatment related morbidity and histologic findings. JAMA 1986;256:3117–24. [PubMed: 3491225]