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Cancer immunotherapy comes of age

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It is 20 years since the demonstration that immune stimulation of metastatic tumors with interleukin-2 (IL-2) could cause the regression of established human cancers.[1] IL-2 is a lymphocyte immunoregulatory hormone that has no direct impact on cancer cells. The administration of IL-2 to cancer patients is based solely on its ability to mediate immune reactions directed against cancer antigens. Thus, the demonstration that IL-2 administration could reproducibly mediate tumor regression in 15–20% of patients with metastatic melanoma or renal-cell cancer established, for the first time, the power of immunotherapy for treating cancer. Approximately 50% of responders experienced complete tumor regression and 80% of these patients have maintained a complete response up to 20 years later. Thus it seems that metastatic melanoma and renal-cell cancer join the small group of metastatic solid tumors that can be 'cured' by systemic treatment.

On the basis of these data and dozens of other reports with similar results, the FDA approved IL-2 for the treatment of patients with metastatic renal-cell cancer in 1992 and for melanoma patients in 1998. Although early studies showed that IL-2 was associated with significant side effects, clinical experience has taught oncologists how to deal with these toxicities safely and, as a result, treatment-related mortality due to the administration of IL-2 in patients with metastatic cancer is now less than 0.5%.[2]

These clinical results led to studies being carried out to identify the lymphocytes responsible for tumor regression, which in turn led to the molecular characterization of the genes encoding cancer antigens.[3] Almost 100 human cancer antigens that are expressed in various tumor types have now been described. Although the success of attempts to develop direct immunization approaches (cancer vaccines) using antigens that are characterized at a molecular level has not yet been reproducible in mediating cancer regression, much work is ongoing in this area.

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More recently, additional immune manipulations capable of mediating cancer regression in humans have been described. Both stimulatory and inhibitory factors affect the function of immune lymphocytes. By administering a monoclonal antibody to block the effects of the inhibitory factor, cytotoxic T-lymphocyte-associated antigen 4, on the surface of lymphocytes, durable tumor regressions have been seen in patients with melanoma and renal cancer.[4]

The most effective application of immunotherapy for the treatment of human cancer is the administration of autologous lymphocytes with reactivity to tumor antigens. New approaches to cell transfer (or 'adoptive') therapy in patients involve lymphodepletion using non-myeloablative chemotherapy prior to autologous lymphocyte infusion. This approach can replace up to 80% of the immune system of cancer patients with lymphocytes possessing potent anti-cancer properties.[5] In these trials approximately 50% of all patients with metastatic melanoma refractory to treatment with both high-dose IL-2 and chemotherapy showed objective cancer responses.

Modern immunotherapy as it is applied to the treatment of patients with cancer is only 20 years old. The use of surgery to remove cancer was described in the Edmund Smith papyrus 4,500 years ago. The birth of radiation therapy dates to just 1 year after the discovery of X-rays by Roentgen, and modern chemotherapy began 60 years ago when nitrogen mustard was used to treat patients with a lymphoid malignancy. Immunotherapy is much younger and progress in its development for the treatment of patients with cancer is growing at a rapid pace. The promise for the future of this exciting and evolving field is much anticipated.

Supplementary information, in the form of a reference list, is available on the *Nature Clinical Practice Oncology* website.