

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Cell Transfer and Other Immunotherapeutic Strategies

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H&O What are the principles behind the current development of immunotherapy in the treatment of cancer?

SR Previous studies have established the principle that it is possible to stimulate the immune system to cause cancer regression. The administration of interleukin-2 has no direct impact on cancer cells, but leads to objective responses in 15–20% of patients with metastatic melanoma and metastatic kidney cancer. Approximately half of these responses are complete responses and appear to be durable, with many patients disease free at 15 years.

More recently, many new immunotherapeutic strategies have begun to be developed. The description of numerous cancer antigens and the identification of their molecular nature have opened new possibilities. The most successful of the new approaches is cell transfer therapy, which can mediate cancer regression in approximately half of all patients with metastatic melanoma. In addition, there are new understandings about suppressive mechanisms in the immune system that can be overcome by the administration of antibodies.

H&O What is the role of cancer antigens in the development of immune therapies?

SR The ability to identify T lymphocytes that recognize cancer antigens enables the screening of cancer cells for expression of genes, and also enables identification of genes that encode cancer antigens. Close to 100 cancer antigens have been identified thus far. Knowing the molecular nature of these antigens makes possible the development of increasingly specific immune therapies.

H&O Do cancer antigens vary among tumor types?

SR Some antigens are unique to individual types of cancer, and some are shared among tumor types. For example, the MART1 and GP100 tumor antigens are present in the vast majority of melanomas. The MAGE series of cancer antigens are present in testicular cancer and some common epithelial tumors. These are just a few of the variety of antigens that can be used as targets of immune attack.

H&O How has the development of vaccines for cancer treatment proceeded?

SR A great deal of research has been done to find effective vaccines directed against cancer antigens. Vaccines that are effective in hematopoietic tumors have been developed. Dendritic cell vaccines to treat B-cell lymphomas have been described, as have some peptide vaccines that appear to mediate regression in some patients with myeloproliferative disease. In solid tumors, cancer vaccines have not yet been very effective.

However, cell transfer therapy—the generation of cells outside the body, with subsequent transfer back into patients—has been successfully used in patients with melanoma (Figure 1). In this approach, lymphocytes are taken from the patient's body, expanded, and then returned under the proper conditions. Approximately half of patients with metastatic melanoma respond to this approach, and research to extend this strategy to other types of cancer is ongoing.

H&O Why are melanoma patients good candidates for cell transfer therapy?

SR Melanoma has several advantages. It is very easy to grow in tissue culture, which many common epithelial cancers are not. This feature makes melanoma a good candidate for certain laboratory experiments. In addition, melanomas tend to express class II major histocompatibility complex antigens on their surface to a greater degree than many other tumors, which may render them more immunogenic.

H&O Could you further describe the process of cell transfer therapy?

SR The first step in cell transfer therapy is to identify lymphocytes in a patient that recognize tumor antigens. These lymphocytes are grown to large numbers outside the body and then returned to the patient. Lymphodepletion of patients prior to the transfer of these cells causes an increase in the antitumor activity of the cells. In some of the patients included in our study that was published in *Science* in 2002, 80% of the circulating natural killer cells were antitumor cells; these patients tend to experience dramatic regression of cancer as a result of this cell transfer therapy.

This treatment approach is still very experimental. A follow-up of our initial study in melanoma will be published in the *Journal of Clinical Oncology* in early 2005. This approach may be the most promising use of the immune system in the treatment of cancer and we will be working to see if it will be effective in other cancer types.

H&O What other immunotherapy strategies are currently being researched?

SR The recent description of cells that suppress the immune system has led to research to try to eliminate these suppressor influences in order to increase immune reactions. A molecule called anti-CTLA4 has been shown to mediate tumor regression in some patients. Thus, eliminating influences that prevent the immune system from working may also be an effective treatment for cancer.

H&O What factors might lead to a lack of response to cell transfer or other immune therapies?

SR It is possible that through immune therapy, the expression of antigens on cancer cells would be immunoregulated, rendering the cells less susceptible. It is also possible that tumors lead to tolerance in the immune system, or may suppress the immune system by secreting molecules such as transforming growth factor β or interleukin-10, both of which can suppress immune reactions. There are many complex reactions in the immune system of the host as well as potential immunogenicity of tumors that need to be better understood.

H&O Have these potential reactions been seen in the clinical trials conducted thus far?

SR There is evidence that T cells that recognize cancer antigens can be induced in patients at high levels and yet not cause cancer regression. The reason for this lack of response is not fully understood. One possible explanation is that the T cells that are generated do not have a

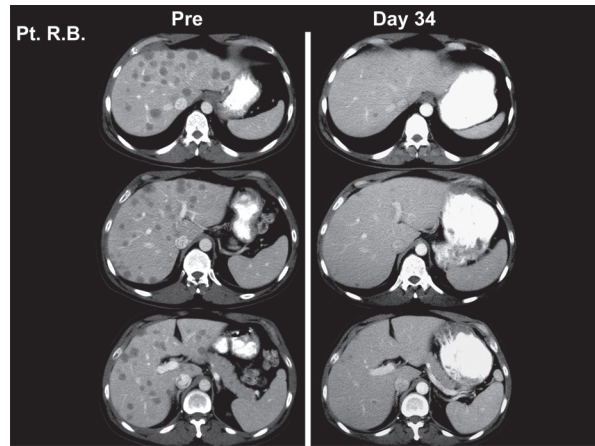


Figure 1. X-ray showing regression of cancer in patients who have undergone cell transfer therapy.

high enough affinity for the recognition of tumor antigens. It may also be that there are aspects of the immune system that can suppress immunity, or that the cancer can produce substances that can inhibit immune reactions. Each of these potential explanations serves as the basis for some important research.

H&O In addition to factors that may prevent the desired response, are toxicities observed with immunotherapy?

SR Intrusions into the immune system always carry the risk of the development of autoimmune disease. With some forms of immunotherapy, patients may experience destruction of normal tissues, as a function of the target antigen that serves as the basis for the therapy. However, immune reactions can be subverted using steroids and immunosuppressive reagents.

Suggested Reading

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