

This Week's Citation Classic®

Rosenberg S A, Lotze M T, Muul L M, Chang A E, Avis F P, Leitman S, Linehan W M, Robertson C N, Lee R E, Rubin J T, Seipp C A, Simpson C G & White D E. A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high dose interleukin-2 alone. *N. Engl. J. Med.* 316:889-97, 1987. [National Cancer Institute and Clinical Center, National Institutes of Health, Bethesda, MD]

One hundred and fifty-seven patients with metastatic cancer for whom standard therapy had failed received treatment with either high-dose interleukin-2 (IL-2) alone (49 patients) or lymphokine-activated killer cells plus IL-2 (108 patients). Nine patients underwent complete regression of metastatic cancer and 20 additional patients underwent at least a 50 percent reduction in their cancer. [The *SC[®]* indicates that this paper has been cited in more than 1,250 publications.]

The End of the Beginning

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In 1985, we published our first results with the use of high-dose interleukin-2 (IL-2) given in combination with lymphokine-activated killer cells in patients with advanced cancer.¹ Our earlier Phase I studies in humans using high-dose IL-2 alone had not shown any anticancer responses, but experimental studies did demonstrate an antitumor effect of IL-2 administration in mice with established lung metastases. We thus renewed clinical efforts using a more aggressive regimen of high-dose IL-2 in cancer patients and the following year reported anticancer responses in 3 of 10 patients with advanced melanoma treated with high-dose IL-2 alone.² These papers stimulated a substantial interest in experimental and clinical studies using IL-2 and in tumor immunology in general. Our own efforts to develop this immunotherapy intensified and between December 1984 and August 1986, we administered 180 courses of treatment to 157 patients with metastatic cancer for whom other treatments had failed. The re-

sults of this study were published in this *Citation Classic®* paper. Most of the patients had advanced kidney cancer or melanoma and both complete elimination of cancer and substantial partial regressions were seen. We concentrated on these two cancers because they appeared to be most responsive to this treatment in our early studies of patients with a variety of cancer types. In the early development of these IL-2 based immunotherapies there was considerable concern about the toxic side effects of IL-2 that limited its application. As we learned to deal with these effects the safety of IL-2 administration increased, and we have now treated over 400 consecutive patients with IL-2 without a treatment-related mortality. Dozens of clinical studies confirmed the anticancer effects of these high-dose IL-2 based regimens and led ultimately in 1992 to the approval by the Food and Drug Administration of the use of IL-2 for the treatment of patients with advanced metastatic kidney cancer.

This paper firmly established that immunotherapy alone could lead to the regression of even bulky cancers in selected patients and stimulated research aimed at improving these immunotherapies. In an accompanying editorial, John Durant, president of the Fox Chase Cancer Center, wrote "perhaps we are at the end of the beginning of the search for successful immunotherapy for cancer." Our own efforts moved to the study of a more potent immune cell we called a tumor infiltrating lymphocyte (TIL) that resulted in improved clinical effectiveness in patients with melanoma.³ This work led us directly to the first insertion of foreign genes into humans using the bacterial gene for neomycin phosphotransferase transduced into TIL⁴ and to attempts to use gene therapy for cancer treatment using TIL transduced with the gene for tumor necrosis factor.⁵

1. Rosenberg S A, Lotze M T, Muul L M, Leitman S, Chang A E, Ettinghausen S E, Matory Y L, Skibber J M, Shiloni E, Vetto J T, Seipp C A, Simpson C & Reichert C M. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N. Engl. J. Med.* 313:1485-92, 1985. (Cited 1,090 times.) (See also: Rosenberg S A. The development of immunotherapy for cancer. *Citation Classic. Current Contents /Clinical Medicine* 21(16):8. 19 April 1993.)
2. Lotze M T, Chang A E, Seipp C A, Simpson C A, Vetto J T & Rosenberg S A. High-dose recombinant interleukin-2 in the treatment of patients with disseminated cancer responses, treatment-related morbidity and histologic findings. *JAMA—J. Am. Med. Assn.* 256:3117-24, 1986. (Cited 290 times.)
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5. Rosenberg S A. Gene therapy for cancer. *JAMA—J. Am. Med. Assn.* 268:2416-9, 1992.

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