

This Week's Citation Classic

Gutterman J U, Blumenschein G R, Alexanian R, Yap H-Y, Buzdar A U, Cabanillas F, Hortobagyi G N, Hersh E M, Rasmussen S L, Harmon M, Kramer M & Pestka S. Leukocyte interferon-induced tumor regression in human metastatic breast cancer, multiple myeloma, and malignant lymphoma.

Ann. Intern. Med. 93:399-406, 1980.

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Anderson Hosp. and Tumor Inst.; Depts. Med. and Microbiol., Baylor Coll. Med., Houston, TX;

and Dept. Chemotherapy, Hoffmann-La Roche, and Roche Inst. Molecular Biology, Nutley, NJ]

This paper was the first demonstration of the ability of leukocyte (alpha) interferon to induce regression of metastatic solid tumors and consistent remissions of hematologic malignancies. The paper demonstrated the plasma pharmacokinetics of leukocyte interferon, its side effects, and its potential as an antitumor agent and catalyzed research on the biological therapy of cancer. [The SC* indicates that this paper has been cited in over 355 publications.]

Interferon Induces Tumor Regression in Cancer Patients

Jordan U. Gutterman
M.D. Anderson Cancer Center
University of Texas
Houston, TX 77030

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In April 1975, while working on the immunotherapy of cancer as an associate professor of medicine at the University of Texas M.D. Anderson Cancer Center, I attended an international conference on interferon organized by Mathilde Krim in New York City, where I heard several exciting presentations on the potential antiviral and antitumor activities of interferon. Tom Merigan's work at Stanford University on viral diseases and Hans Strander's work in Sweden on osteogenic sarcoma so impressed me that I decided to begin work on interferon.

But one concern had the potential to hinder my entry into the field. Because interferon is species-specific, purified human interferon was required for clinical studies, and the only interferon sufficiently pure for clinical work was being produced in Helsinki at the Finnish Red Cross by Kari Cantell. Interferon cost \$50.00/10⁶ units.

Though I began work in spite of the difficulties, attempts to obtain funding for clinical work were unsuccessful until Mary Lasker, of the Albert and Mary Lasker Foundation in New York, made a commitment to purchase sufficient amounts of partially purified leukocyte (alpha) interferon to start clinical investigations.

Our initial objectives were to determine if interferon could induce tumor regression in patients with metastatic breast cancer and remissions in patients with B-cell neoplasms. The first clinical study was started on February 12, 1978; as luck would have it, the first two patients with metastatic breast cancer showed sufficient tumor regression (partial re-

sponses) to tell me we were on the right track. I collaborated with a variety of hematologists/oncologists at M.D. Anderson (listed as coauthors in the manuscript) and with Sidney Pestka and his colleagues at Hoffmann-La Roche to assay the antiviral effects and to study the plasma pharmacokinetics. In addition, we completed our clinical study, finally including 38 patients.

The subject of this paper, that first clinical trial, was first formally presented at the American Association for Cancer Research in New Orleans in May 1979 and was finally published in the *Annals of Internal Medicine* in 1980. We reported the first evidence that a biological cytokine could induce regression of established metastases and remissions of hematopoietic neoplasms. Initial reactions to the work were far from positive. Chemotherapy and radiation therapy were mainstays for the treatment of advanced cancer; that biological therapy (or what has become known as biological response modifiers) could have an impact on human cancer was a very foreign idea in 1980 and most oncologists remained skeptical.

A year after this work was published, we started the first clinical investigation with recombinant DNA-derived α -interferon, the first purified lymphokine studied in human cancer.¹ In 1983 we demonstrated for the first time that renal cell carcinoma was sensitive to α -IFN.² My colleagues, Dr. J.R. Quesada and Dr. E.M. Hersh, and I discovered dramatic activity in a B-cell tumor, hairy cell leukemia (HCL).³ In 1986 my colleague, Dr. M. Talpaz, and I published data that for the first time showed significant remissions in patients with chronic myelogenous leukemia (CML) and selective suppression of the Philadelphia chromosome in some patients.⁴

I believe this work has been highly quoted because it was the first demonstration that a biological cytokine could induce regression of established metastases in patients with advanced cancer. The applicability of the discovery was wide as this observation has now been extended to other cytokines such as IL-2. This paper, therefore, had a large impact on influencing the development of biological therapy of cancer. Today, α -interferon is used widely throughout the world for a variety of human malignancies and viral diseases. Alpha-IFN was approved by the Food and Drug Administration in the US in June 1986 for the treatment of HCL and later for Kaposi's sarcoma and condylomata acuminata. Worldwide, interferon has been approved for a variety of other neoplasms, including renal cell carcinoma, multiple myeloma, malignant melanoma, and CML.

1. Gutterman J U, Fine S, Quesada J, Horning S J, Levine J F, Alexanian R, Bernhardt L, Kramer M, Spiegel H, Colburn W, Trown P, Merigan T & Dziewanowski Z. Recombinant leukocyte A interferon: pharmacokinetics, single-dose tolerance, and biologic effects in cancer patients. *Ann. Intern. Med.* 96:349-56, 1982. (Cited 275 times.)
2. Quesada J R, Swanson D A, Trinidad A & Gutterman J U. Renal cell carcinoma: antitumor effects of leukocyte interferon. *Cancer Res.* 43:940-7, 1983. (Cited 190 times.)
3. Quesada J R, Reuben J, Manning J T, Hersh E M & Gutterman J U. Alpha interferon for induction of remission in hairy cell leukemia. *N. Engl. J. Med.* 310:15-8, 1984. (Cited 420 times.)
4. Talpaz M, Kantarjian H M, McCredie K, Trujillo J M, Keating M J & Gutterman J U. Hematologic remission and cytogenetic improvement induced by recombinant human interferon alpha_n in chronic myelogenous leukemia. *N. Engl. J. Med.* 314:1065-9, 1986. (Cited 160 times.)

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