CRM197 (nontoxic diphtheria toxin): effects on advanced cancer patients

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Source: Cancer Immunology, Immunotherapy, Volume 53, Number 11, November 2004 , pp. 1041-1048(8)
Publisher: Springer

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Abstract:

Purpose: Many years ago, diphtheria toxin (DT) showed antitumor activity in mice and in humans, but it was unclear whether this depended on the toxicity of the molecule only or on its strong inflammatory-immunological property as well. To deal with this open question, we planned to treat a group of cancer patients with cross-reacting material 197 (CRM197). CRM197 is a nontoxic mutant of DT that shares the immunological properties of the native molecule and its ability to bind to heparin-binding epidermal growth factor (HB-EGF), the specific cell-membrane receptor for DT that is often overexpressed in cancer. Methods: 25 outpatients with various advanced tumors who were refractory to standard therapies (23 subjects) or had refused, in whole or in part, conventional therapies (2 subjects) were treated with CRM197 injected subcutaneously in the abdominal wall, on alternate days, for 6 days. Three different dosages (1.7, 2.6, or 3.5 mg/day) were used according to the patient's degree of immunological reactivity to DT/CRM197 (none, moderate, or high). Results: After the first administration of CRM197, a significant increase in the number of circulating neutrophils and in the serum level of TNF-α was detected. Toxicities were minimal. Only patients with delayed-type hypersensitivity to DT/CRM197 had irritating skin reactions in the injection sites and a flu-like syndrome with fever. Pharmacokinetics showed a mean peak concentration (12.7 ng/ml) 12 h after the first injection and a mean half-life of 18.1 h. There were two complete and one partial responses (metastatic breast carcinoma, neuroblastoma, and metastatic breast carcinoma) lasting 4, 45+, and 15 months, respectively. Six cases of stable disease, lasting from 1 to 15 months, were also recorded. Conclusions: CRM197 injected subcutaneously elicited an inflammatory-immunological reaction, caused tolerable toxicities, was absorbed to a good extent into the circulatory system, and exerted some degree of biological antitumor activity. A possible role of neutrophils and TNF-α in the mode of action of the molecule is hypothesized.

Keywords: Antitumor activity; Clinical trial; Nontoxic diphtheria toxin
Document Type: Research article
DOI: 10.1007/s00262-004-0546-4
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