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Mistletoe and gemcitabine in patients with advanced cancer: a model for the phase I study of botanicals and botanical-drug interactions in cancer therapy.

Mansky PJ, Grem J, Wallerstedt DB, Monahan BP, Blackman MR.

National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD 20892-2669, USA. manskyp@mail.nih.gov

Plant extracts of the European mistletoe (MTE), *Viscum album*, the most widely used cancer treatment in Germany, have been used in European countries as sole intervention or as adjunct to conventional cancer therapies for more than 80 years. Preclinical data suggest immunostimulatory and cytotoxic effects of MTE. While the clinical efficacy of MTE in cancer is being investigated, toxicity and potential interactions of MTE with standard chemotherapeutic agents are unknown. Gemcitabine is an approved antimetabolite chemotherapeutic agent effective as single agent in patients with solid tumors (ST). The documented metabolism and pharmacokinetics of gemcitabine make this agent well suited for the study of botanical-chemotherapy drug interactions (BDIA) in cancer. Based on reports of altered drug metabolism associated with botanical preparations, research into BDIA has intensified. The phase I, 2-stage, dose-escalation study outlined here will test MTE with gemcitabine as a paradigm for the phase I investigation of botanical-drug combination treatments in patients with advanced ST. The protocol including the following components has been reviewed and approved by the National Cancer Institute Institutional Review Board (IRB), the National Naval Medical Center IRB, and the Navy Clinical Investigation Program (study 02-074): (1) use of a standardized MTE, approved by the Food and Drug Administration for investigational use; (2) independent verification of key MTE components considered biologically active; (3) identification of contaminants and adulterants; (4) pharmacokinetics of gemcitabine and its principal metabolites before and upon exposure to MTE; (5) safety and toxicity data collection; (6) assays of plasma ML antibody production in vivo; and (7) pharmacodynamic studies of the botanical-drug combination.

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