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NCCAM/NCI phase I study of mistletoe extract and gemcitabine in patients with advanced solid tumors.

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Background: European mistletoe (*viscum album* L.) extracts (EMEX) are used for cancer treatment in Europe. Clinical efficacy remains controversial. Controlled safety and toxicity data are lacking. Objectives of this novel phase I dose-escalation study of an EMEX/gemcitabine (GEM) combination were 1) safety, toxicity, and MTD in patients with advanced solid cancers (ASC), 2) neutrophil count recovery, 3) formation of mistletoe lectin antibodies (ML ab), 4) plasma concentrations of IL-6, IL-12, IFN*g*, and *TNF-a*, 5) clinical response.

Methods: ASC patients (n=44, breast 12, pancreas 10, colorectal 17, NSCLC 5, f:m=21:23, average age 55 years) received escalating doses of EMEX (HELIXOR A, Helixor GmbH, Rosenfeld, Germany) during stage 1 (20-250 mg s.c. daily) and increasing doses of GEM during stage 2 (750 - 1680 mg/m^2 over 30 minutes i.v. on day 1 and 8, 3-week cycle) for 3 cycles. GEM plasma concentrations (Cp, baseline and week 8 (stable EMEX dose for 7 days) were determined during stage 1 by HPLC with UV detection. Plasma cytokine and MLab concentrations were measured by ELISA.

Results: Five dose-limiting toxicities were observed: grade 4 neutropenia (2), grade 4 thrombocytopenia, grade 3 cellulitis, and grade 4 acute renal failure. GEM 1380 mg/m^2 and EMEX 250 mg were the MTD. Of 44 patients 24 developed Non-neutropenic fever and flu-like syndrome. GEM pharmacokinetics were unaffected by EMEX. All patients developed ML3 IgG antibodies. Plasma cytokine concentrations were minimally affected. ANC values showed a trend to increase between baseline and C2 in stage I. Partial response and stable disease were found in 6% and 42% of patients, respectively. All partial responses occurred in patients with pancreatic cancer. Median survival was 190 days. Compliance with EMEX injections varied from 78.6-100%.

Conclusions: The EMEX/GEM combination demonstrated limited toxicity, no alterations of GEM Cp during infusion of EMEX, clinical benefit in 48% of patients, good tolerability and excellent EMEX compliance. Addition of EMEX may allow for use of higher doses of GEM and increase the ANC nadir. No effects on the measured cytokines were observed. The long-term utility, safety, and tolerability of EMEX plus GEM warrant further study.

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