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Background: Aviscumine is an Escherichia coli-derived recombinant type II ribosome-inactivating protein with potent antitumor activity in vitro and in vivo. It is the recombinant counterpart of natural mistletoe lectin-I. The current study was performed to determine the safety profile, dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of the intravenous (i.v.) administration of aviscumine in cancer patients. Translational research included the evaluation of pharmacokinetics and monitoring of plasma cytokine and anti-aviscumine antibody induction after administration of the drug.

Patients and methods: Aviscumine was given twice weekly as a 1 h central i.v. infusion in patients with advanced, refractory progressive, solid malignant tumors who had not been previously exposed to natural mistletoe preparations. They had histologically or cytologically verified disease, were ≥18 years old, had an Eastern Cooperative Oncology Group performance status ≤2 and adequate bone marrow, liver and renal function. DLT was defined as any non-hematological grade 3–4 toxicity (National Cancer Institute Common Toxicity Criteria version 2.0), neutrophil count <500/μl for ≥7 days, febrile neutropenia or thrombocytopenia grade 4. The MTD was defined as the dose at which >20% of patients experienced DLT during the first treatment cycle. The Continual Reassessment Method was used to determine the number of patients required per dose level.

Results: Forty-one fully eligible patients (19 male, 22 female) with a median age of 56 years (range 37–74) were enrolled. Colorectal, ovarian, renal cell and breast cancer were the most common tumor types. Dose levels of aviscumine ranged from 10 to 6400 ng/kg. The median number of cycles was two (range one to eight). Common clinical toxicities in cycle 1 were fatigue, fever, nausea, vomiting and allergic reactions. Fatigue grade 3 was dose limiting in one of six patients at 4000 ng/kg and reversible grade 3 liver toxicity (elevation in alkaline phosphatase, transaminases and/or γ-glutamyltransferase) occurred in one of 10 patients at 4800 ng/kg and in two of five patients at 6400 ng/kg. The best response (RECIST criteria) was stable disease in 11 patients, lasting for two to eight cycles. The pharmacokinetic evaluation revealed a short half-life of 13 min and linear kinetics on dose levels ≥1600 ng/kg. Aviscumine stimulated the immune system with a release of cytokines such as interleukin (IL)-1β, IL-6 and interferon-γ, and induced immunoglobulin (Ig) G- and/or IgM-anti-aviscumine antibodies of uncertain clinical relevance.

Conclusions: The recommended dose for further clinical trials is 5600 ng/kg twice weekly. Based on the short half-life of the recombinant protein observed in this trial, the exploration of prolonged infusion schedules of aviscumine is warranted.

Key words: aviscumine, CD75s, phase I study, recombinant mistletoe lectin, ribosome-inactivating proteins, solid tumors

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