Phase I clinical and pharmacokinetic study of BBR 3576, a novel aza-anthrapyrazole, administered i.v. every 4 weeks in patients with advanced solid tumors: a phase I study group trial of the Central European Society of Anticancer-Drug Research (CESAR).

Abstract:
BBR 3576 is a novel aza-anthrapyrazole with limited potential for cardiotoxicity in preclinical models. This phase I clinical and pharmacokinetic study was performed to determine the maximum tolerated dose, the dose-limiting toxicity (DLT) and the pharmacokinetic profile of BBR 3576 administered i.v. as a 1-h infusion repeated every 4 weeks. In total, 27 patients were treated at doses starting from 1 to 150 mg/m². The dose levels 1, 2, 4, 8, 16, 32, 64, 90, 125 and 150 mg/m² were investigated in one, three, one, three, two, one, three, four, three and six patients, respectively. The DLT was a grade 3 stomatitis at 150 mg/m². At this dose level as well as at 125 mg/m², neutropenia grade 3 and 4 were frequently seen, but not reaching the criteria for DLT. Time to neutrophil nadir was about 2 weeks and recovery took place within 1 week. Other bone marrow toxicities were mild; lymphopenia was also observed. No significant drug-induced cardiotoxicity was observed. The plasma concentration versus time curves of BBR 3576 showed a biexponential profile with a linear kinetic behavior. A very large volume of distribution, a high plasma clearance and long elimination half-lives were calculated.
Renal unchanged drug excretion was less than 10% and therefore a minor excretion route. No objective antitumor responses were found. On the basis of this study, the recommended dose for phase II studies is 150 mg/m², although the maximum tolerated dose as per protocol definition was not reached. This trial showed that BBR 3576 has a manageable toxicity profile on a 4-week schedule. Phase II studies have started in patients with solid tumors, as suggested by preclinical data in different in vivo model systems.