

Safety of the proteasome inhibitor disulfiram combined with capacitive hyperthermia in the treatment of advanced solid tumors

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Background: Disulfiram is an old drug used to treat alcoholism. Recently some authors has demonstrated antineoplastic activity in preclinical settings on various cancer types. The mechanisms of action is not fully understood but seems to rely mainly on the inhibition of proteasome, comparable to that of other specific drugs like bortezomib. Previous complexation of disulfiram with heavy metal ions, mainly Cu and Zn, is mandatory for disulfiram activity.

Hyperthermia on the other hand proved to be synergistic with proteasome inhibition in cancer cell lines. On these basis we started a phase I trial to test the safety of concurrent combination of disulfiram with zinc supplementation and hyperthermia in the presence or absence of chemotherapy.

Materials and methods: Disulfiram 400 mg and zinc sulphate 200 mg daily were both given orally without interruption. External capacitive hyperthermia (40-43°C range) was performed on target lesions twice a week for 1 hour with an EHY2000 equipment. Concomitant chemotherapy was allowed. Re-evaluations were done every 2 months. Treatment was protracted until disease progression.

Results: 15 patients with different pretreated solid malignancies entered the study, 7 of them were also given concurrent chemotherapy with various drugs. Absence of important co-morbidities at the time of enrolment was mandatory. In the absence of chemotherapy the main toxicity was diarrhea G1-2 which occurred in 4 out of 8 patients. Occasional mild fatigue and nausea were also observed. One patient discontinued treatment because of reappearance of symptoms of a pre-existing cardiac failure (NYHA 2). One patient died of unknown causes after one month and was not evaluable for response.

Treatment was well tolerated also when chemotherapy was added although toxicity was increased. However only two patients, experienced G3 toxicities, fatigue and neutropenia respectively. No toxicities related to hyperthermia were observed.

Overall we observed 1 CR (7 %), 2 PR (14 %), 7 SD (50 %) and 4 PD (29 %) with a disease control rate of 71 %. On the target lesion we recorded Interestingly partial responses were observed in a sarcoma and glioblastoma in the absence of chemotherapy.

Conclusions: Disulfiram with zinc supplementation and hyperthermia is feasible and safe alone or in combination with chemotherapy. However attention has to be used when treated patients with a history of cardiac failure. Although this study was not designed to assess efficacy, a moderate activity seems to be present as responses were recorded both with and without chemotherapy, together with an high disease control rate.