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ICRF-193 is the most cytotoxic of the bis(dioxopiperazine)s, a group of compounds originally synthesized as membrane permeant metal chelators on the hypothesis that metal chelation is crucial to the efficacy of many anticancer drugs. Subsequent work by many laboratories has not supported this hypothesis, but has shown that bis(dioxopiperazine)s are very potent catalytic inhibitors of human topoisomerase II. However, several lines of evidence argue against simple catalytic inhibition of topoisomerase II as the basis of cytotoxicity and antineoplastic activity in the bis (dioxopiperazine)s. We have found that ICRF- 193 is a substantial topoisomerase II poison both *in vivo* and *in vitro*. We find that topoisomerase II poisoning by ICRF-193 is very dependent on the protein denaturant used in the assay. The commonly used denaturant, SDS, is very inefficient at trapping ICRF-193- stabilized topoisomerase II-DNA cleavage complexes as irreversible protein-DNA crosslinks. The strong chaotropic protein denaturant, guanidinium HCl however works well. In this respect, ICRF-193 resembles the quinoxaline antitumor drug, CQS (Gao, H. et al., Ca Res. 60:5937, 2000). A variety of in vivo and *in vitro* assays indicate that ICRF-193 has significant selectivity for topoisomerase IIß as a topoisomerase poison, although this ß- isozyme selectivity is not as great as that of the quinoxaline antitumor drug XK-469 (Gao, H. et al., PNAS 96:12168, 1999).

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THE BIOLOGICAL EFFECT OF DEUTERIUM-DEPLETED WATER. A POSSIBLE NEW TOOL IN CANCER THERAPY

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It is known that the deuterium/hydrogen (D/H) mass ratio is the largest of stable isotopes of the same element, causing differences in the physical and chemical behaviour between the two hydrogen isotopes. In spite of the fact that the concentration of D is about 150 ppm (over 16 mM) in surface water and more than 10 mM in living organisms the possible role of the naturally occurring deuterium has been ignored for six decades.

The experiments with deuterium-depleted water (DDW) revealed that due to the D-depletion the various cell lines (PC-3, human prostate; MDA, human breast; HT-29, human colon; M14, human melanoma) required longer time to multiply *in vitro*. DDW caused tumour regression in xenotransplanted mice (Ml)A and MCF-7, human breast; PC-3) and induced apoptosis *in vitro* and *in vivo*. The application of DDW induced complete or partial tumour regression in dogs and cats with different tumours (rectum, breast, lymphoid leucosis, etc.)

Double blind controlled Phase II clinical trial with prostate cancer, in compliance with GCP principles confirmed a significant difference between the control and treated groups with respect to the examined parameters that indicated the anti-tumour effect of the preparation.

a) At the time of the 5th and 6th visits, the ratio of patients showing an increased efficacy (PR) was significantly higher statistically (5th visit: p= 0.0096, 6th visit: p = 0.021) in the treated group.

b) The volume of the prostate decreased significantly (p = 0.043) in the treated group, whereas it could be regarded as unchanged in the control group.

c) The number of patients with a decreased prostate volume was significantly higher (exact Armitage-test: p = 0.015; exact Fisher-test: p = 0.011).

d) Significantly more patients reported a positive change in symptoms in the treated group (exact Armitage-test: p = 0.0009; exact Fisher-test: p = 0.0018).

e) The survival rate in the treated group was significantly higher (p = 0.050).

From the results of the clinical trial, it can be concluded that the decrease in the deuterium concentration in the patients' body, caused by the administration of DDW, may have an effective use in the treatment of tumours.

We suggest that the cells are able to regulate the D/H ratio and the changes in the D/H ratio can trigger certain molecular mechanisms having key role in cell cycle regulation. We suppose that not the shift in the intracellular pH, but the concomitant increase in the D/H ratio is the real trigger for the cells to enter into S phase. The decrease of D concentration can intervene in the signal transduction pathways thus leading to tumour regression. This assumption is supported by the observation that the D-depletion has an influence on the expression of genes (c-myc, Ha-ras and p53) playing a key role in tumour development.