Deuterium depletion results in several fold increases in the median survival time of cancer patients during oncotherapy

Gábor Somlyai[1], Mária Debrődi[1], Ildikó Somlyai[1], Orsolya Abonyi[1], László G. Boros [2,3,4]

[1]HYD LLC for Cancer Research and Drug Development, Budapest, Hungary, [2]Department of Pediatrics, Harbor-UCLA Medical Center, UCLA School of Medicine, Los Angeles, CA 90502, USA, [3]The Los Angeles Biomedical Research Institute (LABiOMED), Torrance, CA 90502, USA, [4]SIDMAP, LLC, Culver city, CA 90063, USA

The central role of hydrogen is well known in regulating chemical reaction kinetics and the role of its stable heavy isotope, deuterium (D), is also important in regulating chemical and structural protein interactions and functions. The deuterium/hydrogen (D/H) mass ratio is the largest among stable isotopes of the same element, which causes dramatic, sometimes ten-fold differences in the chemical behavior between the two hydrogen isotopes [1, 2]. The concentration of deuterium is about 150 ppm (over 16 mM/L) in surface water and 12-14 mM/L in living organisms, which is a relevant concentration considering that the Ca^{2+} normal value in human blood is only 2.24-2.74 mM/L. In order to reveal the possible role of naturally occurring D in living organisms, the replacement of surface water with deuterium-depleted water (DDW) in a range from 25 ppm to 135 ppm was investigated in cell cultures, animal studies, as well as in prospective blinded and retrospective clinical trials.

Deuterium-depleted water inhibited cell growth of multiple cancer cell lines in *in vitro* culturing studies [3-6] and readily induced tumor xenograft regression in immune compromised mice [3, 5]. Replacement of normal daily water intake with DDW induced complete or partial tumour regression in dogs and cats with various spontaneous tumours [4] as the result of the very first deuterium-depleted anticancer drug registered for veterinary use in Hungary, in 1999.

To explore the efficacy of deuterium depletion (DD) when included in oncotherapy both prospective and retrospective studies have been reported. Double blind, controlled, human Phase II clinical trial with prostate cancer, in compliance with GCP principles exhibited a significant difference between the control (22 patients) and treated (22 patients) groups with respect to end point parameters and confirmed the anti-tumour efficacy of DDW. Seven patients in the treated group and one patient in the placebo group achieved partial response ($p = 0.046$) during the four months treatment period with DDW. In the treated group net decrease in prostate volume was three times higher (160.3 cm^3 vs. 54.0 cm^3; $p = 0.0019$), urination complaints ceased at a higher rate (8 (DDW) vs. 0 (control) patients, $p = 0.0041$), and the one-year survival rate was also higher (2 (DDW) vs. 9 (control) deaths; $p = 0.034$) [7].

To gain additional information on DDW efficacy, the data matrices of 1827 cancer patients consuming DDW were evaluated in an open label retrospective study. The cumulative follow-up period of patients covers over 6881 years from the diagnosis of the disease, with DDW consumption of 2265 cumulative years. Median survival time (MST) of the 1827 control patients treated with standard oncotherapy, which represent all major tumor types, was 121.2 months (10.1 years). MST correlated with the length of DDW consumption in treated groups, such as; DDW treatment (DDW-T) for at least 91 days (n=1689 patients) resulted in an MST of 115 months (9.6 years), (DDW-T) for at least 151 days (n=1312 patients) showed an MST of 132 months (11 years), (DDW-T) for at least 211 days (n=1060 patients) showed

an MST of 141 months (11.7 years), (DDW-T) for at least 271 days (n=889 patients) showed an MST of 158 months (13.2 years), and (DDW-T) for at least 331 days (n=765 patients) reaffirmed MST of 158 months 13.2 years). It was found that 171 out of 1827 patients started DDW consumption in a tumor free stage and only 11 patients died during the 801 years cumulative follow up, which suggests that DD can drastically reduce disease relapse with a significant extension of disease free survival. The MST of small, homogenous prostate-, breast-, lung- and pancreas cancer populations was also calculated. The MST was 64.8 months in prostate cancer patients (n=20) having bone metastases within one year after diagnosis, which is a 3-fold increase when compared to 15-20 months in patients with standard oncological care without DDW [7]. The 74 breast cancer patients with stage IV disease with distant metastases in 135 cumulative number of organs the DDW-treated group showed an MST of 4.3 years in comparison with ~2.0 years MST [8] of control patients. One of the striking results was that only one patient died during the 221 years cumulative follow-up period out of the 48 breast cancer patients who started to consume DDW in remission [8]. The MST was 25.9 months in male patients (n=78) and 74.1 months in female patients (n=51) with lung cancer which is a 3 to 7 fold increase in comparison with control patients receiving conventional oncotherapy [9]. Unresectable pancreatic cancer patients entering DDW trial within or after 60 days of diagnosis were also evaluated. The MST for patients starting the DDW treatment within 60 days after diagnosis (n=18) achieved 39 months MST. In contrast, patients joining the DDW trial 60 days or later after diagnosis (n=14) showed a 16 months' MST [10]. The basic concepts of dosing DDW as part of standard oncotherapy will be discussed.

References:

[1] Jancsó G.: Isotope Effects**.** In: Handbook of Nuclear Chemistry, Volume 2. (Eds: Vértes A. Nagy S. Klencsár Z.) Kluwer Academic Publishers. Dordrecht, Netherlands, 2003. pp. 85-116.

[2] Katz J.J., Crespi H.L.: Isotope Effects in Biological Systems. In: Isotope Effects in Chemical Reactions. (Eds: Collins C. J., Bowman, N. S.). Van Nostrand Reinhold. New York, 1971. pp. 286-363

[3] Somlyai G, Jancsó G, Jákli Gy, Vass K, Barna B. et al. Naturally occurring deuterium is essential for the normal growth rate of cells. *FEBS Lett*. 1993; 317: 1–4. doi: 10.1016/0014-5793(93)81479-J

[4] Somlyai G., Laskay G., Berkényi, T. et al.: Naturally occuring deuterium may have a central role in cell signalling. In: Synthesis and Application of Isotopically Labelled Compounds (Ed.: J. R. Heys és D.G. Mellilo) John Wiley & Sons Ltd. New York, 1998.

[5] Somlyai G., Laskay G., Berkényi T. et al.: The Biological Effects of Deuterium-Depleted Water, a Possible New Tool in Cancer Therapy. *Z. Onkol. /J. Oncol.* 1998. 30, 4

[6] Cong F.S., Zhang Y.R., Sheng H.C. et al.: Deuterium-Depleted Water Inhibits Human Lung Carcinoma Cell Growth by Apoptosis. *Exp. Ther. Med.* 2010. 1. 277-283

[7] Kovács A., Guller I., Krempels K., Somlyai I., Jánosi I.Z., et al. Deuterium depletion may delay the progression of prostate cancer. *J. Cancer Ther*. 2011; 2: 548-556. doi: 10.4236/jct.2011.24075

[8] Krempels K., Somlyai I., Gyöngyi Z., Ember I., Balog K., Abonyi O., Somlyai G. A retrospective study of survival in breast cancer patients undergoing deuterium depletion in addition to conventional therapies. *J. Cancer Res. Ther.* 2013; 1(8): 194-200. doi:10.14312/2052-4994.2013-29

[9] Gyöngyi Z., Budán F., Szabó I., Ember I., Kiss I., et al. Deuterium Depleted Water Effects on Survival of Lung Cancer Patients and Expression of Kras and Bcl2 Genes in Mouse Lung. Nutr Cancer. 2013; 65(2):240-246. doi: 10.1080/01635581.2013.756533

[10] Boros, L. G., et al. (2014).Fumarate hydratase and deuterium depletion control oncogenesis via NADPH-dependent reductive synthesis: mitochondrial matrix water, DNA deuteration and epigenetic events. DOI: 10.1158/1538-7445.AM2014-1426 Conference: AACR, At San Diego, Volume: Cancer Res 2014;74 (19 Suppl)