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Cause and effect relationship between application of deuterium-depleted water and improvement of chronic lymphocytic leukemia

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Abstract

The anticancer effect of deuterium depletion has been proved in various types of cancer in combination with conventional therapies. Here we report a case study of a patient diagnosed in 2006 with chronic lymphocytic leukemia (CLL). His stage at diagnosis did not require the immediate conventional therapy and so he started consuming deuterium-depleted water (DDW). Significant changes occurred already during the first three months; WBC count dropped from 16x10³ cells/μL to 7.7x10³ cells/μL, to the normal range and the cervical lymph nodes regressed. He continued drinking DDW uninterruptedly in the first three years (1,231 days) and periodically in the subsequent 11 years. PLT count significantly increased from 108x10³/μL to 232x10³/μL after two years' DDW-consumption. CD5+/CD19+ percentage showed significant decrease from 69% to 4% and the rate of chromosome trisomy 12 in interphase blood cells was reduced from 40% to 7% in the first three years. The study confirms that deuterium depletion as a single treatment is effective and delays the use of conventional chemotherapy.

Keywords: Chronic Lymphocytic Leukemia (CLL), B Lymphocytes, Fluorescence In Situ Hybridization (FISH), Deuterium (D), Deuterium-Depleted Water (DDW), Case Study, Fluorescence Activated Cell Sorting (FACS).

Introduction

Chronic lymphocytic leukemia (CLL) is one of the most common types of leukemia, with approximately 10,000 new cases yearly in the United States [1]. CLL affects B and T lymphocytes as well as natural killer cells, but the majority of CLL cases are of the B cell phenotype [2].

The median age at diagnosis lies between 67 and 72 years. More male than female patients (1.7:1) are affected. As the incidence rate rises with age, the prevalence and mortality of CLL are likely to increase further due to the demographic changes expected in the forthcoming decades [2].

The initial symptoms of CLL vary, but may include loss of energy, weight loss, enlarged lymph nodes, and splenomegaly [3]. CLL originates from the uncontrolled clonal growth mostly of small B lymphocytes in a manner that often leads to the crowding out of healthy cells. The disease affects bone marrow and peripheral blood, and can lead to pathological changes in lymph nodes, liver, and spleen [3]. Despite these, many patients remain asymptomatic for several years. Physicians typically monitor patients with CLL for signs of infection, autoimmunity, and bone marrow failure, which are common long-term complications [4].

Diagnostic evaluation and differential diagnosis are very important in cases of CLL, and the diagnoses are based on complete blood count with differential and chemistry panel. The diagnosis of CLL requires the presence of $\geq 10 \times 10^3$ cells/μL B lymphocytes in the peripheral blood, sustained for at least 3 months. The clonality of these B lymphocytes needs to be confirmed by demonstrating immunoglobulin light chain restriction using flow cytometry. Most cases are of B-cell lineage, the cells being characterized by IgM and IgD surface markers [5].

History and physical examination including bidimensional diameters of the largest palpable lymph nodes in the cervical, axillary, and inguinal nodal sites and dimensions of the liver and spleen are required parts of the diagnosis [6].

Interphase fluorescence in situ hybridization (FISH), performed on peripheral blood lymphocytes, can identify cytogenetic lesions in >80% of all CLL cases. The most common deletions are in the long arm of chromosome 13 (del(13q)). Additional, frequent chromosomal aberrations comprise trisomy of chromosome 12 and deletions in the long arm of chromosome 11 (del(11q)) and in the short arm of chromosome 17 (del(17p)) [6,7].

For this type of hematopoietic disease, the treatment protocol does not necessarily require medication to be initiated after diagnosis, it provides the patient the best chance for survival if the first chemotherapy is given as late as possible after diagnosis. Therefore, unless otherwise contraindicated, watchful waiting is used until white blood cell counts reach tenfold of the normal value, i.e. one hundred thousand [8].

Available treatments generally induce remission, although nearly all patients relapse, and CLL still remains an incurable disease. Early detection is practiced widely, but seemingly makes no difference to the patient's eventual outcome [9].

The stable isotopes of hydrogen, protium (H) and deuterium (D) have different chemical and physical behavior [10-12]. D-concentration in living organisms is 12 mmol/L and to investigate its role in cell cycle regulation, numerous studies have been conducted on cell lines in culture media prepared with deuterium-depleted water (DDW) [13,14].

It follows from the above that a way of treatment that efficiently blocks or reduces the multiplication of abnormal B cells with no or minimal side effects could be an optimal solution for CLL patients to remain symptom-free for extended periods. Based on the existing knowledge on the role of deuterium (D, heavy hydrogen [15,16]) in cell cycle regulation [17], consumption of deuterium-depleted water (DDW) could fulfil the mentioned requirements and be of effective therapeutic benefit in CLL.

The apoptosis-triggering effect of DDW was demonstrated both *in vitro* and *in vivo* [14,18]. D-depletion also exerts an influence on proto-oncogenes and tumor suppressor genes, and the expression of c-myc, Ha-ras, and p53 genes induced by carcinogen exposure was significantly weakened when the animals were given DDW to drink [19]. Administration of DDW as drinking water resulted in complete or partial tumor regression in mice xenotransplanted with MDA-MB-231 or MCF-7 human breast adenocarcinomas or PC-3 human prostate tumor [13,14]. Lung cancer patients undergoing DDW treatment in addition to conventional treatments achieved longer MSTs, and DDW was also successfully applied in lung cancer complicated by brain metastases [20].

CLL is the rare type of cancer in which the protocol does not require immediate treatment after diagnosis. The application of DDW in CLL as only intervention may provide compelling evidence for the anticancer effect of deuterium depletion. The aim of the present retrospective case study was to investigate the impact of D depletion on the outcome of CLL. The daily water intake of the patient was replaced with DDW (105-65 ppm D) for 15 years, in one or two cures per year lasting for several months, without the use of conventional chemotherapy regimens. The primary study endpoints were the response to DDW and the progression-free interval.

Case Description

A 41-year-old male patient was diagnosed with CLL in December 2005. He had elevated white blood cell counts (WBC) of $16x10^3$ cells/μL and low PLT ($108x10^3$/μL). In addition, significant enlargement of the cervical lymph nodes was described, the spleen became twice as large as normal, and ultrasound confirmed the presence of an abdominal lymph node conglomerate about 9 cm in size.

The patient started consuming DDW (Deuterium-depleted water) within two months after diagnosis, continued drinking it uninterruptedly in the first three years (1,231 days) and periodically in the subsequent 11 years (Table 1).

Table 1: DDW-consumption during the follow-up period

	Start of DDW-consumption	End of DDW-consumption	Duration of DDW cures (days)
1	26-Feb-06	10-Jul-09	1,231
2	4-Jan-10	10-Apr-10	96
3	28-Jul-11	5-Dec-11	131
4	15-May-12	10-Dec-12	210
5	15-Jan-13	6-Jun-13	143
6	15-Sep-13	15-Dec-13	92
7	10-Apr-14	10-Aug-14	123
8	10-Feb-15	12-May-15	92
9	2-Sep-15	21-Dec-15	111
10	7-Mar-16	17-Jun-16	103
11	27-Oct-16	4-Oct-17	343
12	9-Mar-18	1-Feb-19	330
13	9-Dec-19	16-Mar-20	99
14	16-May-20	15-Jul-20	61
15	25-Sep-20	13-Oct-20	19

Table 1 shows the DDW-consumption periods over a time span of 15 years. Significant changes occurred already during the first three months; WBC count dropped from $16x10^3$ cells/µL to $7.7x10^3$ cells/µL, to the normal range and the cervical lymph nodes regressed. PLT count significantly increased from $108x10^3$/µL to $232x10^3$/µL after two years' DDW-consumption. The changes of WBC during the first 3 years and the subsequent period are summarized in Figure1.

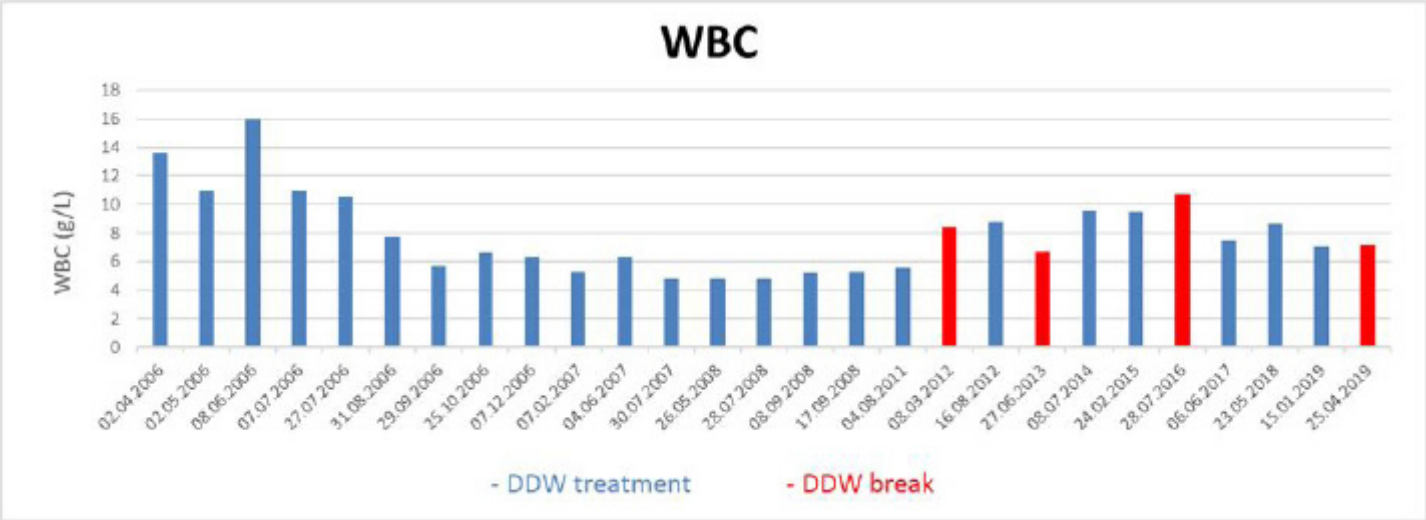

Figure 1: The changes in WBC count

By the end of the first 3 years' period, the enlarged cervical lymph nodes regressed almost completely, the spleen size normalized, and the abdominal lymph node conglomerate disintegrated.

Moderate progression of cervical lymph nodes was detected 2.5 months later the patient had stopped DDW-consumption, and the size of abdominal lymph node increased from 3.5 cm to 4.5 cm. After starting the next cure with DDW four months later the abdominal lymph node size was 2 cm and the cervical lymph nodes regressed again. The patient applied DDW during the last 15 years 14 times after this first pause, at intervals of a few months, altogether for 3,184 days (8.7 years) and phases of moderate progression and regression followed during the break and consumption of DDW, respectively. Up to present, there was no need for conventional chemotherapy.

Fluorescence Activated Cell Sorting (FACS) and Fluorescence In Situ Hybridization (FISH) examinations were regularly performed during the follow up of the patient. FACS tests were performed on samples obtained by bone marrow biopsy. The important disease-specific parameters are the percentages of CD markers at the lymphoid gate, in this case, CD5+/CD19+ cells. The results are summarized in Figure 2.

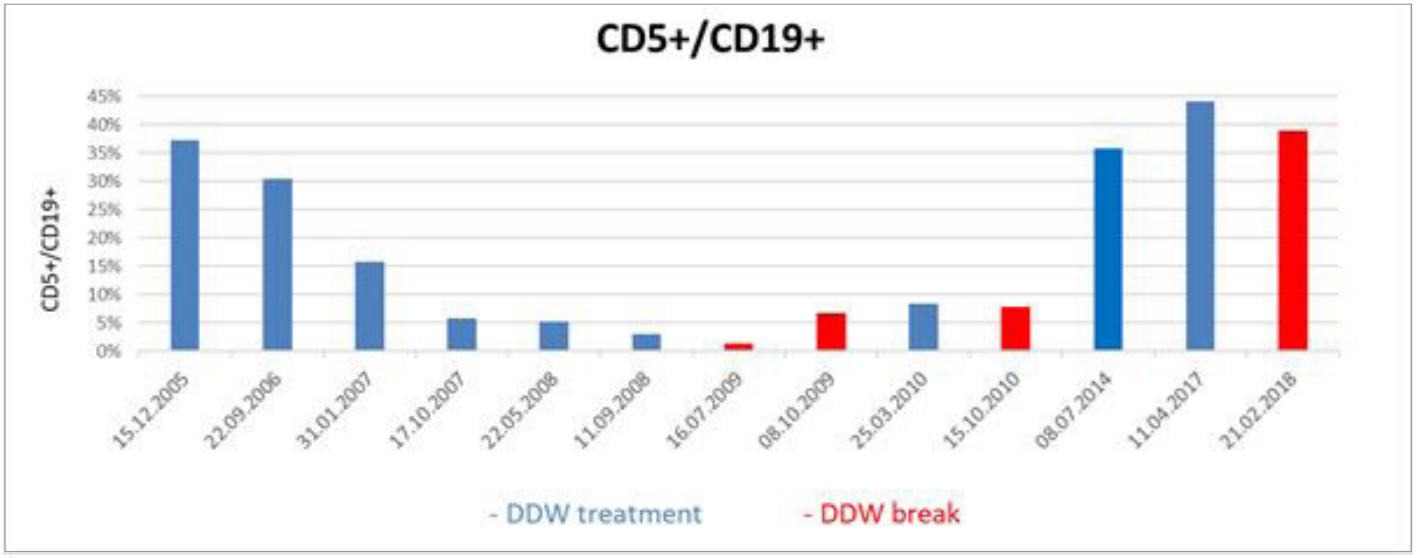

Figure 2: The rate of CD5+/CD19+ cells for the whole blood

The CD5+/CD19+ percentage showed significant decrease during the first three years of the treatment period and a distinct increase after stopping DDW-consumption.

FISH tests were done on blood cells. The aim of the examination was to determine the rate of chromosome trisomy 12 in interphase blood cells. Figure 3 shows the outcome of this test.

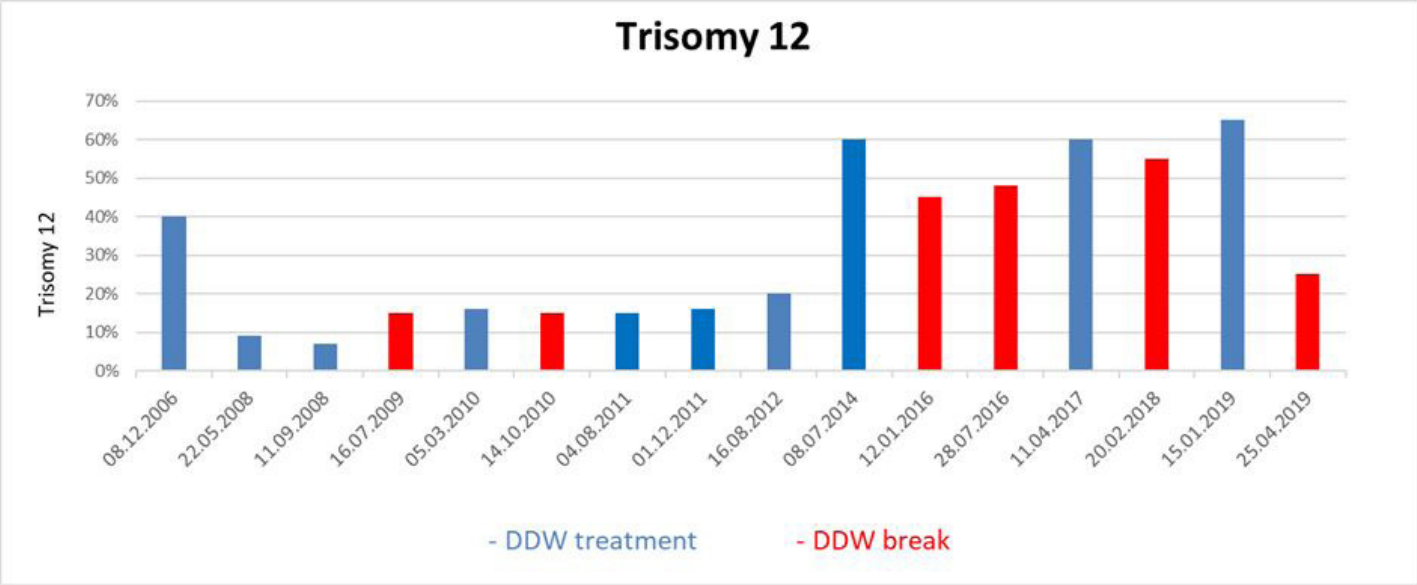

Figure 3: The rate of trisomy 12 in interphase blood cells

Improvement occurred in the first 3 years. When DDW was paused, findings showed progression. The data also shows that the elevated trisomy from 2014 on, that remained nearly constant despite short DDW cures (see Table 1), could be reduced from 65% to 25% by one-year consumption of DDW between March 2018 and February 2019.

The beneficial action of DDW may take some time to take effect. The CD5+/CD19+ percentage and trisomy 12 data from 08 July 2014 were quite high although on that day a cure has been running for 90 days. Similarly, both indicators were high in April 2017, in the middle of a one-year cure, but were lower in February 2018 when the cure was over by four months.

Conclusion

In summary, we can conclude that deuterium depletion, as sole intervention after diagnosis of CLL, resulted in a significant improvement in the patient's condition in all main parameters, including blood counts and the regression of lymph nodes. During the break in DDW-consumption, progression of the disease occurred, the size of the cervical lymph node increased, but a restarted DDW cure resulted in regression again and the cure was repeated several times during the follow-up time. This observation is in line with earlier findings on different tumor types including prostate, breast, lung and pancreatic cancer where integration of DDW into conventional therapy resulted in severalfold increases of the median survival time.

This case study proves that application of DDW can provide significant improvement in patients diagnosed with CLL, can delay progression and can postpone the need for conventional chemotherapy with several years.

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References

1. Ansari M, Auerbach M, Bahrain H (2015) A case of CLL that was successfully treated resulted in the immediate development of AML from a coexistent myeloid line that had been suppressed. Clin Case Rep 3(3):165-169.
2. Hallek M (2010) Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. Cancer Cell 17(1): 28-40.
3. Gonzalez KD, Noltner KA, Buzin CH, Gu D, Wen-Fong CY, et al. (2009) Beyond Li Fraumeni Syndrome: Clinical Characteristics of Families With p53 Germline Mutations. JCO 29 (8).
4. Boelens J, Lust S, Vanhoecke B, Offner F (2009) Chronic lymphocytic leukaemia. Anticancer Res 29(2): 605-615.
5. Sweet DL Jr, Golomb HM, Ultmann JE (1977) Chronic lymphocytic leukaemia and its relationship to other lymphoproliferative disorders. Clin Haematol 6(1): 141-157.
6. Caligaris-Cappio F, Dighiero G, Döhner H, Hillmen P, Keating M, et al. (2018) iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 131(25): 2745-2760.

7. Döhner H, Stilgenbauer S, Benner A, Leupolt E, Kröber A, et al. (2000) Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 343(26): 1910-1916.
8. Keating MJ, O'Brien S, Lerner S, Koller C, Beran M, et al. (1998) Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. Blood 92(4): 1165-1171.
9. Dighiero G, Hamblin TJ (2008) Chronic lymphocytic leukaemia. Lancet 371(9617): 1017-1029.
10. Katz JJ, Crespi HL (1971) Isotope effects in biological systems. In:Collins CJ, Bowman NS, eds. Isotope Effects in Chemical Reactions. New York, NY: Van Nostrand Reinhold; 286-363.
11. Rundel PW, Ehleringer JR, Nagy KA (1988) Stable Isotopes in Ecological Research. New York, NY: Springer
12. Jancsó G (2003) Isotope effects. In: Vértes A, Nagy S, Klencsár Z, eds.Handbook of Nuclear Chemistry, Volume 2. Dordrecht,Netherlands: Kluwer Academic; 85-116.
13. Somlyai G, Jancsó G, Jákli G, Vass K, Barna B, et al. (1993) Naturally occurring deuterium is essential for the normal growth rate of cells. FEBS Lett 317(1-2): 1-4.
14. Somlyai G, Laskay G, Berkényi T, Jákli Gy, Jancsó G (1998) Naturally occurring deuterium may have a central role in cell signalling. In: HeysJR, Melillo DG, eds. Synthesis and Applications of IsotopicallyLabelled Compounds.New York, NY: John Wiley and Sons; 137-141.
15. Wylie AW (1946) Deuterium or heavy hydrogen. Aust J Sci 9(2):43-50.
16. Katz JJ (1960) The biology of heavy water. What happens to experimental organisms that have been raised on water in which the hydrogen is not the common isotope of mass one but the heavy isotope of mass two?. Sci Am 203:106-116.
17. Boros LG, D'Agostino DP, Katz HE, Roth JP, Meuillet EJ, et al. (2016) Submolecular regulation of cell transformation by deuterium depleting water exchange reactions in the tricarboxylic acid substrate cycle. Med Hypotheses 87:69-74.
18. Somlyai G, Laskay G, Berkényi T, Galbács Z, Galbács G, et al. (1998) The biological effects of deuterium-depleted water, a possible new tool in cancer therapy. J of Oncology 30:91-94.
19. Gyöngyi Z, Somlyai G (2000) Deuterium depletion can decrease the expression of c-myc, Ha-ras and p53 gene in carcinogen-treated mice. In Vivo 14:437-439.
20. Gyöngyi Z, Budán F, Szabó I, Ember I, Kiss I, et al. (2013) Deuterium depleted water effects on survival of lung cancer patients and expression of Kras, Bcl2, and Myc genes in mouse lung. Nutr Cancer 65:240-246.