DICHLOROACETATE-INDUCED NEUROPATHY IN HIGH GRADE FOLLICULAR LYMPHOMA PATIENT

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Curative therapy for follicular lymphomas (FLs) has not been established yet. FLs respond well to chemotherapy and radiation. A large number of current studies confirmed an improved overall response if rituximab was added to chemotherapy. Dichloroacetate (DCA) can be used to inhibit tumor growth. There have been reports that DCA leads to neuropathy. In non-Hodgkin’s lymphoma (NHL), DCA leads to antineoplastic action against cell lines and apoptosis of tumor cells, which reduces the metabolism and the number of tumor cells. We present a patient with NHL-FL Grade 3a who took alternatively DCA therapy. In our case report, DCA did not show any treatment benefit but only serious sensorimotor neuropathy as a result of DCA therapy.


Key words: follicular lymphoma, dichloroacetate, neuropathy

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Introduction

Follicular lymphomas (FLs) are the second most frequent subtype of nodal lymphoid malignancies in Western Europe. The annual incidence of this disease has rapidly increased during recent decades and has risen from 2–3/100,000 during the 1950s to 5/100,000 recently (1).

Curative therapy for FLs has not been established yet. The choice of therapy is based on clinical risk factors, symptoms and prognostic disease factors. Systemic therapy has not given results in asymptomatic patients and is appropriate for use only with the occurrence of symptomatic disease. Early initiation of rituximab (R) resulted in improved progression-free survival, but without survival benefit. FLs respond well to chemotherapy and radiation. A large number of current studies confirmed an improved overall response if rituximab was added to chemotherapy. The choice of chemotherapy is based on patient comorbidity indexes, mostly in the light of anthracycline introduction (2).

Dichloroacetate (DCA) has been used for the genetic mitochondrial diseases and treatment of cancer. There have been reports that DCA leads to neuropathy (3). DCA can be used to inhibit tumor growth. This is done by transferring the cell into oxidation and phosphorylation into mitochondria, which lead to apoptosis and the formation of oxygen radicals, superoxide, that also lead to a decrease in tumor volume (4). The mechanism of DCA action includes the inhibition of pyruvate dehydrogenase kinase (PDK), which deactivates the PDK complex. This complex blocks the activity of mitochondria, and therefore there is no mitochondrial oxidative phosphorylation, so that glycolysis is switched into cytoplasm, which leads to lactic acidosis (5). Lactic acidosis facilitates tumor growth by the degradation of an extracellular matrix that allows expansion of tumor cells and initiates their mobility, increasing their metastatic potential and activation of angiogenesis. DCA reduces lactic acidosis and indirectly reduces tumor growth (6). When the mitochondria in the tumor cell are active, it means that they are having the Krebs cycle or glucose oxidation. Being hyperpolarized, they open the mitochondrial pores from which exit cytochrome C and other pro-apoptotic factors that caused tumor cell apoptosis (7).

In non-Hodgkin’s lymphoma (NHL), DCA causes antineoplastic action against cell lines and apoptosis of tumor cells, which reduces the metabolism and the number of tumor cells. A decrease in lactic acidosis in lymphoma cells leads to anti-proliferative, anti-metastatic and anti-angiogenic effects on the tumor. DCA causes a significant dose-dependent decline in tumor cell survival. DCA induces dose-dependent apoptosis in Dalton’s lymphoma (DL) cells (8, 9).
Case report

We present a case of a 44-year-old Caucasian male with asymptomatic swollen lymph nodes of the neck and under the jaw. In June 2014, he noticed enlarged tonsils and vegetative-infiltrative tumor of the right tonsils was verified by examination. Bilateral tonsillectomy was performed in June 2014 on the right lateral lymph node biopsy. Histopathology indicated NHL-FL Grade 3a. Immunohistochemistry was typical: CD20+, CD79a+, B SAP (PAX5)+, CD10+, bcl2+, bcl6+, CD43+/-, MUM1-, CD3-, CD5-, CD15-, CD23-, CD30-, CD138-, CyclinD1-, EMA-, CK AE1/AE3-, EBV -, Ki67+ in range of 20% - 25%. The patient did not have B symptoms. During the staging procedures, the following was verified: ECOG 0 KI 100. Multi-sliced computed tomography (MSCT) of the whole body was performed and it revealed: microlymphadenopathy of the right axillary lymph nodes up to 12 mm. Laboratory analysis: erythrocyte sedimentation - 15, Hct 38.1% (low), Hb 124g/L, RBC 4.17X 10¹²/L, WBC 4.7 X 10⁹/L, Neu 2.9 X 10⁹/L, Ly 1.3 X 10⁹/L, PLT 283 X 10⁹/L. Biochemistry findings: glucose 5.4 mmol/L, urea 3.5 mmol/L, creatinine 102 μmol/L, uric acid 330.3 μmol / L, total proteins 73.9 g/L, albumine 42.9 g/L, AST 18 U/L, ALT 21 U/L, ALP 104.8 U/L, LDH 322 U/L, GGT 17.7 U/L, CRP 1.5 mg/L, total bilirubin 10 μmol/L, Fe 12.7 μmol/L, Ca 2.72 mmol/L, Na 141 mmol/L, K 4.8 mmol/L. He was HIV, HBsAg negative. Plasma immunoglobulins: IgG 10.50 g/L, IgM 0.97 g/L, IgA 2.32 g/L, IgG 2.09 g/L.there are many studies where treatment with DCA has been discontinued despite the fact that thiamine was used as a prevention of nerve toxicity. DCA leads to encephalopathy and peripheral neuropathy. In Brandsma D et al.’s case report it was noticed that DCA encephalopathy and peripheral neuropathy were reversible but not entirely because small consequences remained, although the patient took the recommended dose range of thiamine. Due to the apparent toxicity of DCA, it is recommended to use it only in clinical trials. Peripheral neuropathy was more common in adults (86%) than in children (10%) (12). DCA damage the Schwann cells (SCs) and dorsal root ganglia (DRG) neurons by inhibiting the synthesis of myelin. As a consequence of DCA’s direct action on the morphology of SC cells, there is an evidence-based and dose-dependent change in morphology. The partial recovery of myelination was noticed when exposed to 5 mM of DCA under the same conditions. Also, myelination was completely reversible in SC and neurons of DRG (13).

Our patient had DCA intake in the dose range of 750mg with thiamine neuroprotection. However, his lymph nodes have enlarged slightly. During the follow-up, the patient remained still asymptomatic. We assume this asymptomatic phase is the consequence of natural biological flow of FL and is not influenced by DCA. We have only found serious sensorimotor neuropathy as a result of DCA therapy.
In conclusion, our case presented here did not show any treatment benefit with DCA, but only serious adverse event in the sense of neuropathy. Therefore, this case provides information to medical community on the negative consequences of DCA treatment for NHL.

References


Prikaz bolesnika

NEUROPATIJA IZAZVANA DIHLOROACETATOM KOD BOLESNIKA SA FOLIKULARNIM LIMFOMOM VISOKOG GRADUSA

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Kurativna terapija folikularnog limfoma (FLs) još uvek nije uspostavljena. FLs odlično reaguje na hemoterapiju i radioterapiju. Veliki broj sadašnjih studija potvrdio je bolji ukupni odgovor ako se rituximab koristi uz hemoterapiju. Dihloracetat (DCA) može biti korišćen zbog inhibicije tumorskog rasta. Postoje izveštaji da DCA dovodi do neuropatije. U ne-Hočkinskom limfomu (NHL) DCA dovodi do antineoplastičkog efekta cellijskih linija i apoptoze tumorskih cellija, što smanjuje metabolizam i broj tumorskih cellija. Mi predstavljamo bolesnika sa NHL-FL gradusa za koji je uzimao DCA kao alternativnu terapiju. U našem prikazu slučaja DCA nije pokazao terapijski benefit, već samo ozbiljnu senzo-motornu neuropatiju kao rezultat DCA terapije.


Ključne reči: folikularni limfom, dihloracetat, neuropatija

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