Childhood Malignant Diseases: Which is the Carnitine's Role?

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Carnitine (β-hydroxy-γ-trimethylaminobutyric acid) is an essential cofactor for the transport of long-chain fatty acids across the inner mitochondrial membrane into the mitochondrial matrix, where they are broken down via β-oxidation.[1] In addition to its principal function, carnitine also buffers potentially toxic acyl-CoA metabolites and modulates the ratio of acyl-CoA/CoA.[2] The latter regulates the activity of many mitochondrial enzymes involved in the citric acid cycle, gluconeogenesis, the urea cycle, and fatty oxidation.[2]

Although 99% of the carnitine amount is intracellular, the relationship between serum acylcarnitine (AC) and free carnitine (FC) is highly sensitive to intramitochondrial metabolic alterations.[3] Such alterations occur in different situations both normal and abnormal. Normal conditions include fasting, aging, and pregnancy. Pathologic situations with abnormal ratio AC/FC can be seen several inborn errors of metabolism in mainly organic acidurias, heart failure, diabetes, chronic renal failure, demyelinated diseases, and iatrogenic situations such as those treated with valproate and zidovuline.[4]

Abnormal ratio AC/FC may occur in all types of malignancies. Inadequate intake of carnitine or cachexia is not the only cause of these metabolic changes. Metabolic alterations that result from therapy or from the neoplastic process could also be responsible.[5]

In patients with malignancies, the carnitine system appears abnormally expressed both in tumor and nontumor involved tissue.[5] It is known that cancer cells are developed deriving energy from glycolysis.[6,7] One of the defensive mechanisms of the organism against this process is probably the suppression of glycolysis with decreasing production of energy through β-oxidation. Carnitine's insufficiency appears as a result of its increased consumption in β-oxidation. As it is known β-oxidation seems to play a protective role for the tissues, which are cancer affected.[8] This suggestion is supported by the fact that the ketogenic diet has an inhibitory effect on the growth of tumor cells.[9]

The aggressive multimodal therapy may also be directly or indirectly responsible for the metabolic difference observed in cancer patients.[10] These changes in carnitine's system may lead to decreased β-oxidation in favor of glycolysis[6] and also could be explained by increased loss of carnitine through the kidney as a result of chemotherapy.[5]

Malnutrition, carnitine's decreased absorption during the treatment, and the lack of nutrition caused by the undesirable effects of chemotherapy (anorexia, vomiting, nausea, diarrhea) could be other reasons for carnitine's deficiency in cancer patients, with repercussions in the growth, especially in children who are continuously developing organisms, both physically and mentally.

In pediatric patients with cancer, the initially normal carnitine levels are decreased after the chemotherapy.[10] The prevalence of malnutrition during the therapy in that study was higher than at diagnosis, but it was not significant and itself could not explain the carnitine's insufficiency. Metabolic changes that result from therapy and/or the neoplastic process may be responsible for that decrease.[10]

Toxicity and other side effects of chemotherapy could be reserved by carnitine treatment without affecting its anticancer therapeutic efficacy.[5]

Administration of carnitine could prevent the drug-induced mitochondrial damage in drug exposed cells.[11] In selected patients L-carnitine supplementation may be effective in alleviating chemotherapy-induced fatigue.[12]

It is demonstrated that carnitine treatment significantly prevents or decreases both acute and delayed forms of cardiomyopathy provoked by anthracyclines in animal models[5] and also inhibits the cisplatin-induced injury of the kidney and small intestine.[13]

There is evidence that, at high doses, L-carnitine may mimic some of the biologic activities of glucocorticoids,[14] which is an important therapeutic agent in childhood leukemia. Could carnitine have a synergic action or increases the efficacy of glucocorticoids?

In conclusion, a more complex approach to mechanisms that underlie tumor growth, which takes into account the altered metabolic pathways in cancer

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disease, could represent a challenge for the future of cancer research. From this point of view, the study of the carnitine system represents a tool to understand the molecular basis underlying the metabolism in normal and cancer cells. Could carnitine's supplementation minimize/prevent some of the chemotherapy-induced toxicity in children with malignant disease?

All metabolic changes and chemotherapy-induced toxicity are more severe in children with malignant diseases in comparison with adults, because of the growth process in children is not yet complete. Every effort in decreasing the side effects of the anticancer drugs, without affecting their antineoplastic efficacy, would be of major importance, as a better quality of life could be provided.

Could carnitine help in that effort?

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