

Vitamin D as an adjuvant treatment in melanoma

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Summary

Melanoma is a type of skin cancer derived from pigment-producing melanocytes. Not only it is one of the deadliest forms of skin neoplasms, but its incidence has been on the rise over the last decades. Current innovations in treatments for the disease focus on either novel immunotherapies with immune checkpoint inhibitors or targeted therapies. One of the targeted pathways is the MAPK pathway, which is altered in up to 70% of melanomas. This pathway is targeted using drugs that inhibit mutated proteins such as BRAF and MEK. Regardless of the recent innovative therapies, melanoma remains a major clinical challenge.

Vitamin D is a hormone with pleiotropic biological properties. Besides its role in calcium homeostasis, vitamin D has also been found to exhibit several antitumor properties, including melanoma, affecting tumour growth, differentiation and proliferation. What is more, it was also proven that vitamin D enhances the efficacy of various forms of anti-melanoma therapy.

Therefore, in search for novel adjuvant settings to improve the efficacy of anti-melanoma treatments, the current study aimed to assess the response of the A375 melanoma cell line to cobimetinib, a MEK inhibitor, used in combination with the biologically active form of vitamin D, 1,25(OH)₂D₃. The effects of this combination strategy were tested in regards to cell proliferation, motility, cell cycle distribution and the expression of several genes associated with vitamin D and drug metabolism.

It was found that calcitriol significantly decreased the IC₅₀ value of cobimetinib by over 60%, enhancing the cytotoxic effect of the drug. Additionally, pretreatment with calcitriol reduced motility and induced an arrest in the G0/G1 cell cycle phase in melanoma cells subsequently exposed to cobimetinib. Calcitriol used prior to cobimetinib treatment increased the expression of vitamin D receptor (VDR) and other enzymes responsible for vitamin D metabolism and its activation at mRNA level. It also affected, at mRNA level, the expression of the main enzyme responsible for the metabolism of cobimetinib, CYP3A4, which additionally also activates vitamin D. These results indicate that vitamin D could be considered as a relevant adjuvant treatment enhancing the efficacy of cobimetinib in melanoma cells, although further extensive research is required to reliably assess its potential clinical benefits.