Review Article

Vitamin K: A potential Liver Cancer treatment way

Abstract

A review on different vitamin K effects on hepatocellular cancer and their tumour cell biology mechanism indicate possible synergistic treatment strategies. Monitoring of dysfunctional carboxylation of the vitamin K dependent coagulation factor II, with the commercial ELISA test PIVKA-II has been used as a hepatocellular cancer marker. Its relevance is also reviewed. Currently the PIVKA-II test has been withdrawn due to marketing reasons by Stago.

Performance of PIVKA-II as a HCC tumour marker

Multiple studies have shown increased PIVKA-II in HCC patients, and PIVKA-II is considered a valuable complement to AFP. Whereas the AFP measure reflects intrahepatic tumour burden, PIVKA-II correlates with vascular invasion and extra hepatic disease [6]. A suggested mechanism of action of PIVKA-II is that it facilitates the secretion of matrix metalloproteinase (MMP) 9 and MMP-2 through the ERK1/2MAPK pathway [7]. These proteolytic enzymes have the ability to degrade extracellular matrix and facilitate metastasis [8]. PIVKA-II has also been suggested to function as an autocrine/paracrine mitogen for HCC cells by stimulating the Met-JAK-STAT pathway [9]. The mechanism underlying the PIVKA-II increase is not completely understood, but several explanations have been proposed. For instance, animal experiments have shown decreased gamma-carboxylase activity in hepatic tumour tissue [10]. Other suggestions are vitamin K insufficiency in the tumour cells [11], defective vitamin K uptake [12] and excessive synthesis of prothrombin precursors [13].

Several studies comparing the diagnostic capability of different biomarkers for HCC exist. Using PIVKA-II in combination with AFP has been reported to improve accuracy [14]. Other studies looking exclusively at hepatitis B infected individuals suggest PIVKA-II is superior to AFP, and that the combination of both measures may enhance early detection [15]. A recent study comprising roughly 2 000 participants concluded that 230 HCC cases would have been neglected if using AFP alone, and that PIVKA-II levels increased over a year before image discovery [16]. Also, high PIVKA-II levels where associated with greater risk of developing HCC within a 2-year period in high risk populations with chronic hepatitis B. Furthermore, PIVKA-II has also been associated with portal...
Vitamin K has been investigated in several studies due to its reported ability to generate ROS. In a clinical trial where vitamin K was administered to patients with advanced HCC, reduction of tumour size was demonstrated in 17% of the patient population. These patients also demonstrated increased mean survival time, but overall mortality was not affected [36]. Vitamin K has also been used as a radio-sensitizer, and older studies have demonstrated increased survival time compared to radiotherapy alone in bronchial carcinoma patients [37]. Similar potentiation have been demonstrated in animal experiments [38, 39], but whether this can be used as adjuvant therapy in humans have not been studied in recent years. Vitamin K has not been extensively studied in humans due to its hematological toxicities related to erythrocyte glutathione metabolism [40]. However, if administered concomitant with vitamin C, the necessary dose decreases due to synergistic effects. A small clinical trial investigating the effect of vitamin K and vitamin C on therapy-resistant prostate cancer demonstrated a decrease in the rate of prostate specific antigen (PSA) increase after 12 weeks [41], but the combination has not been studied on HCC patients.

HCC treatment with vitamin K

Due to the aforementioned effects of PIVKA-II on HCC tumour cells, and that PIVKA-II seems to predispose for more aggressive disease [25], studies have investigated whether vitamin K administration could affect the disease course. Vitamin K occurs naturally in two forms, vitamin K1 and vitamin K3–K5 exist. Vitamin K 2 subspecies MK-4 is a ligand to the steroid and xenobiotics receptor (SXR) which regulates saturation of its side chain [26]. In addition, synthetic forms vitamin K1–K5 exist. Vitamin K subspecies MK-4 is a ligand to the steroid and xenobiotics receptor (SXR) which regulates cell growth. In vitro studies have demonstrated vitamin K-dependent suppression of proliferation and motility of HCC cells [27]. Furthermore, administration of vitamin K to patients with HCC subsequently decreased plasma PIVKA-II levels [28]. This study also demonstrated that PIVKA-II levels were not correlated with plasma levels of vitamin K derivatives, suggesting that the increase is not due to vitamin K deficiency but rather related to tumour metabolism.

In 2004 vitamin K supplementation was reported to prevent HCC in women with viral cirrhosis [29]. Since then, several supplementation studies with MK-4 to HCC patients have been performed with mixed results. Although a few smaller studies have demonstrated a reduction of HCC recurrence when administering MK-4 [30], this effect was not confirmed in larger study populations using MK-4 [31]. In a recent meta-analysis of five randomized control trials evaluating the effect of vitamin K on HCC recurrence after resection, survival was not improved [32]. However, synergistic effects were observed when MK-4 and the multikinase inhibitor sorafenib were administered together [33]. The vitamin K derivative MK-7 has a longer half-life and better bioavailability for both hepatic and extra hepatic Gla proteins [34]. Several clinical trials investigating the effects of MK-7 on vascular disease are currently ongoing [35], but its effects on HCC has not been investigated.

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Figure 1:
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