Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and roughly 75% of cases are attributed to viral infections with hepatitis B or C [1]. Furthermore, HCC is the second leading cause of cancer death surpassed only by lung malignancies [2], and is often unresectable at diagnosis. The most commonly used tumour marker for HCC is alpha-fetoprotein (AFP) but its diagnostic efficiency is poor, especially in hepatitis infected individuals [3]. Hence, better diagnostic and prognostic markers would aid in early detection and treatment of HCC.

Vitamin K is best known for its involvement in haemostasis, where it functions as a cofactor in γ-carboxylation of hepatic clotting factors II, VII, IX and X as well as protein C, S, Z and M. This post-translational modification induces a conformational change which allows the protein to bind calcium ions, a crucial step for their involvement in haemostasis [4]. In addition to aforementioned clotting factors several vitamin K dependent proteins originating from extra hepatic tissues have been identified and are collectively referred to as Gla proteins. Accumulating evidence from pre-clinical studies suggest that vitamin K and the Gla proteins are involved in a wide range of diseases, such as cardiovascular disease, osteoporosis and cancer [5].

Proteins induced by vitamin K absence for factor II (PIVKA-II, or des-gamma-carboxy prothrombin, DCP) is a measure of hypocoagulated prothrombin and has been suggested to function as a tumour marker for HCC. In the following sections, the efficacy of PIVKA-II as a tumour marker and the role of vitamin K in HCC treatment are discussed.
vein thrombosis [17] and microvascular invasion, which is a major prognostic factor in HCC [18]. In addition to PIVKA–II and AFP, several other HCC biomarkers have been proposed. Due to the heterogeneity of HCC it seems that a combination of biomarkers is favorable, but currently no large scale studies investigating the optimal biomarker combination have been performed [19].

In addition to viral hepatitis, alcohol–induced liver damage is a major risk factor for developing HCC [20]. In a study investigating PIVKA–II levels in patients with benign alcoholic liver disease (ALD), 21% of cases had PIVKA–II levels above the cut–off value commonly used for the tumour marker [21]. Similar results were demonstrated in a more recent study [22]. The causative mechanism of the PIVKA–II increase is unknown. Vitamin K deficiency has been suggested [23], but no correlation between plasma vitamin K levels and PIVKA–II has been demonstrated [21, 24]. The confounding effect of ALD on PIVKA–II levels should be taken into account when interpreting PIVKA–II levels, and a different cut–off value might be needed to avoid false–positive results in ALD 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 K2, which is further subdivided depending on the length and saturation of its side chain [26]. In addition, synthetic forms vitamin K3–K5 exist. Vitamin K2 subspecies MK–4 is a ligand to the steroid and xenobiotics receptor (SXR) which regulates cell growth. In vitro studies have demonstrated vitamin K2–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 K3 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 administrating 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 K2 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 K2 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.

Vitamin K3 has been investigated in several studies due to its reported ability to generate ROS. In a clinical trial where vitamin K3 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 K3 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 K3 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 K3 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.

**Figure 1:**

**References**


