Biological and Clinical Aspects of Anticancer Effects of Antithrombotics

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Key Words

Cancer · Antithrombotics · Low molecular weight heparin · Vitamin K antagonists

Abstract

Hemostatic mechanisms play a role not only in cancer-associated thrombotic diathesis, but also in tumor growth and dissemination. Hence, inhibition of fibrin formation has been considered a possible tool against the progression of malignant disease. An antineoplastic effect of antithrombotic agents in various experimental models (i.e. tumor cell in culture, experimental animals, and cancer patients) has often been suggested. Anticoagulant drugs such as heparins and vitamin K antagonists have been repeatedly tested in this context. However, heparins have been more extensively studied. Several reports in animal models demonstrate that heparin can reduce the primary tumor growth or its metastatic spread. Clinical studies of thrombosis in cancer patients show that, besides their role as antithrombotics, heparins may have beneficial effects on survival in these patients, with a major role for low-molecular-weight heparin (LMWHs) compared to unfractionated heparin (UFH). More recently a number of prospective randomized clinical trials of LMWH for survival as a primary end-point in cancer patients have

been conducted, showing favourable results.

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Cancer and Thrombosis

The association between cancer and thrombosis has been known for more than a century. The occurrence of venous thromboembolism as a common complication of malignant disease was first reported by Armand Trousseau in 1865. After few years, the possibility that a relation between the clotting mechanisms and the development of metastasis might exist was postulated by Billroth, who described cancer cells within a thrombus and interpreted his finding as an evidence of the spread of tumor cells by thromboemboli. In the recent years a considerable progress has been made in our knowledge of the mechanisms and the significance of coagulation activation in human malignancy. Basic research studies have indicated that: 1. tumor cells possess the capacity to activate blood coagulation by various mechanisms, 2. this capacity increases with tumor cell malignant transformation, and 3. fibrin formation in tumor tissues, as a final product of the clotting cascade activation, is involved in tumor growth and dissemination [1].

At present the dual role played by haemostatic proteins (i.e. tissue factor, thrombin, fibrin, fibrin split products) in

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both thrombus formation and cancer progression is being increasingly elucidated [2].

Following these observations, over the past three to four decades several investigators have tested the hypothesis that inhibiting blood coagulation may interfere with the progression of malignancy, and an anti-cancer effect of anticoagulant agents (i.e. heparins and vitamin K antagonists VKA) has often been suggested. A number of experimental studies 'in vitro' or in animal models and clinical observations have contributed to raise the interest in this field [3, 4], even though sometimes the results of these studies were conflicting.

Vitamin K Antagonists and Cancer

The first report on a beneficial effect of VKA on mortality in patients with cancer dates back to 1964 [5]. In 1981, Zacharski et al. published the first prospective randomised clinical trial testing warfarin for cancer survival [6]. This study showed that survival of patients with small cell carcinoma of the lung (SCLC) was prolonged on addition of warfarin sodium to combination chemotherapy plus radiation therapy. Median survival for control patients was 24 weeks and for warfarin-treated patients was 50 weeks. The survival advantage associated with warfarin administration was observed both in patients with extensive disease and in those who failed to achieve complete or partial remission. The warfarin-treated group also demonstrated a significantly increased time to first evidence of disease progression.

Another multicenter randomized clinical trial conducted in the same type of cancer patients did not confirm this observation [7]. A systematic review of clinical studies on VKA and cancer mortality was performed by Smorenburg et al [8]. The analysis of level 1 studies did not prove a significant differences in 1 year mortality rates among patients treated with VKA compared to untreated patients (OR 0.89; 95% CI 0.70-1.13). Differently, in level 2 studies, the mortality rates were lower in VKA-treated patients. The authors concluded that there was not enough evidence to support long-term therapy with VKA to prolong survival in patients with established cancer.

More recently, in patients with venous thromboembolism (VTE) and no apparent cancer, a clinical randomized study designed to evaluate the duration of VKA therapy of VTE for 6 weeks versus 6 months (DURAC I trial), showed a lower incidence of newly diagnosed cancers among patients who received the prolonged treatment with VKA in the subsequent 6 years of follow-up [9]. This effect was evident after 2 years and became significant in the subsequent years: at 6 years of follow-up there were 50% more patients diagnosed with cancer in the 6-week group than in the 6-

months group. The multivariate analysis suggested that the duration of VKA therapy could be considered an independent risk factor.

Biological Mechanisms of Antitumor Effect of Vitamin K Antagonists

The results of clinical trials indicate that VKA do not possess a clear effect on manifest neoplastic disease, but rather that they could play a role in the initial phases of malignant transformation. The biological mechanisms of this effect are speculative and refer mainly to the inhibition of blood coagulation and fibrin formation: i.e. inhibition of tissue factor-FVII complex, the reduction of urokinase receptor expression, inhibition of thrombin generation. Other mechanisms include the release of metalloproteinase-2 from subendothelial matrix and the inhibition of other vitamin K- dependent proteins.

Heparins and Cancer

Heparins. First unfractionated heparin (UFH) and then low molecular weight heparin (LMWH) have been the subject of more extensive investigation than VKA. Indeed, a quite large number of studies have focused on the impact of heparins on mortality in patients with cancer. Several retrospective analyses of cohorts of cancer patients enrolled in randomized clinical trials of peri-operative thromboprophylaxis with UFH versus no prophylaxis, reported a beneficial effect of UFH on the overall survival [3]. A prospective randomized multicentre clinical trial by Lebeau et al. demonstrated a significant improvement in survival in patients with SCLC receiving chemotherapy in combination with UFH versus chemotherapy alone [10]. However, a systematic review of all methodologically sound clinical studies that compared UFH versus placebo or no treatment in patients with cancer without VTE found no convincing evidence of either positive or negative effects of UFH on survival of patients with malignancy [11]. Differently, a meta-analysis published in 1999 of clinical trials testing the efficacy of LMWH versus UFH for the initial treatment of VTE, showed a reduced mortality among cancer patients receiving LMWH for initial treatment [12]. Interestingly, an early prospective study of LMWH versus UFH prophylaxis for 7 days following surgery for breast or pelvic cancer suggested a benefit of LMWH prophylaxis on survival in the setting of pelvic cancer [13]. The mortality rate at day 650 after surgery was 28.6% in the UFH-treated group versus 8.1% in the LMWH-treated group ($p < 0.01$). The advantages of LMWH administration (i.e. no need for laboratory moni-

toring, favourable safety profile, little effects on osteoporosis), and the feasibility of long-term administration [14], have much attracted the interest of clinical investigators on this type of anticoagulant, and has encouraged the designs of prospective randomized clinical trials of LMWHs for survival, as a primary end-point, in patients with cancer. Recently, the results of a randomised, placebo-controlled trial named FAMOUS [Fragmin (LMWH) for Advanced Malignancy Outcome Study] have been published [15]. In this study 382 patients with advanced solid malignant tumors of various types, without any sign of VTE, were randomised to receive prophylactic dose LMWH dalteparin (5,000 IU/d) for one year or until death. The overall effect on survival was not statistically significant ($p=0.29$), but in patients with a good prognosis (surviving more than 17 months after randomisation), the survival at 2- and 3- year was significantly in favour of LMWH versus placebo ($p=0.04$).

Another randomised, placebo-controlled trial is the MALT study (Malignancy and Low molecular weight-heparin Therapy), which enrolled 302 patients with various solid malignant tumors, without evidence of VTE. Patients were randomized to receive a therapeutic dose of LMWH nadroparin for 2 weeks followed by half a dose for other 4 weeks, whereas the control group received placebo for 6 weeks. An increased survival in patients treated with nadroparin versus controls was observed, but again the beneficial effect was statistically significant in patients with a better prognosis at time of enrolment (expected life span of more than 6 months) [16].

Finally a randomized clinical trial in patients with SCLC evaluated the effect on mortality of a prophylactic dose of LMWH dalteparin (5,000 IU/d) given in combination with chemotherapy versus chemotherapy alone [17]. The results show an increased response rate to chemotherapy in patients receiving LMWH, which is statistically significant in those patients with limited disease. In addition, the same group of

patients receiving LMWH showed a significant improvement in the median progression free survival and median overall survival, as compared to the chemotherapy alone group. The advantage in survival is similar between patients with limited and extensive disease.

Interestingly, the advantage in survival for the subjects receiving long-term LMWH, appears also from the analyses of data from two recent randomized clinical trials [14, 18], designed to evaluate the efficacy of long-term LMWH versus conventional oral anticoagulation for VTE treatment in patients with cancer [19].

All these findings provide solid ground to future trials assessing the role of anticoagulants in the therapy of the tumor. The heparins, particularly LMWH, seem the most promising drugs in this setting.

Mechanisms for Antineoplastic Effect of Heparins

Biological mechanisms for antineoplastic effect of heparins include not only the inhibition of clotting activation and thrombin / fibrin formation, but also numerous coagulation-independent antimalignant properties [3]. They include: 1. inhibition of thrombin and fibrin formation, 2. immune system modulation, 3. block of tumor cell adhesion to host cells (endothelial cells, platelets, leukocytes), 4. inhibition of neo-angiogenesis, 5. inhibition of endothelial cell proliferation, 6. induction of apoptosis, 7. inhibition of tumor cell-derived heparanase activity, 8. interference with tumor cell glycosaminoglycans. However, the relative weight of each of these antitumor features, with regard to the survival in cancer, has to be clarified yet. This information could be valuable and help to identify the most effective polysaccharidic molecules based on the selective interference with specific patterns of malignancy progression in specific tumor types.

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