Haemophilia and cancer: a personal perspective

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Introduction

Since the early 1970s there have been dramatic improvements in the availability and quality of treatment for people with haemophilia[1]. As a result of these improvements, excluding the consequences of the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) epidemics in the 1970s and 1980s, the life span of haemophiliacs has progressively approached that of males in the general population, at least in more developed countries[2]. However, with ageing, people with haemophilia develop medical and surgical diseases (e.g. cardiovascular diseases, prostatic hypertrophy, cancer, renal disease) not previously seen in this group. These diseases represent a new challenge for physicians working in haemophilia centres[3,4]. As a consequence, in the last few years the interest of investigators has been focused on the management of age-related clinical conditions in patients with inherited haemorrhagic disorders.

The issue of malignancies in haemophiliacs is particularly intriguing, although the published information on the epidemiology, clinical presentation and treatment options for this combination of conditions is limited[5-9]. In this paper, I shall focus not only on the correlation between haemophilia and cancer but shall also consider this issue from a broader point of view, i.e. the relationship between haemostasis and cancer.

Haemostasis and cancer: the molecular basis

The existence of a correlation between haemostasis and cancer was known nearly 150 years, as it was reported for the first time in 1865 by the French doctor, Armand Trousseau[10]. Since then, various investigators have analysed this relationship, focusing in particular on endogenous thrombin, which has been identified as a major contributor to tumour implantation, seeding and metastatisation[11]. However, tumour cells are able to use all the different components of the haemostatic system. Indeed, activated coagulation factors may in turn activate endothelial cells and/or platelets leading to growth factor release and tumour proliferation. The mechanism leading to the formation of a cancer cell-platelet-fibrin complex is particularly interesting; this complex protects cancer cells against mechanical stress and the host immune system, especially natural killer cells. In addition, the formation of this complex favours cancer-cell adhesion to the vascular endothelium and provides a matrix for tumour-associated angiogenesis[12].

As regards experimental studies using haemophilia models, the most important published so far are those by Langer and colleagues[13] and Bruggemann and colleagues[14]. In both studies, a murine model of haemophilia A was used together with a melanoma cell line able to produce lung metastases. In the first study[13], it was demonstrated that replacement therapy with factor VIII in the haemophilic mice enhanced formation of lung metastases while lepirudin, a direct thrombin inhibitor, inhibited lung seeding, suggesting that thrombin generation contributed to pulmonary metastasis even in the absence of factor VIII. In the second study[14], it was documented that while factor VIII deficiency reduced metastatic spread, mice with factor V Leiden developed more metastases than wild-type controls, thus identifying endogenous thrombin as a major contributor to tumour dissemination.

Haemostasis and cancer: clinical studies in non-haemophilic patients

Following these observations derived from *in vitro* studies, a number of investigators have evaluated the anti-neoplastic effect of antiplatelet and anticoagulant agents. For instance, from a systematic review of studies published over 40 years (1966-2006), Dubé and colleagues[15] concluded that acetylsalicylic acid reduced the risk of developing colorectal cancer by 22%, being especially effective

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when used at high doses (325 mg on alternate days) for more than 10 years.

As regards oral anticoagulants, randomised clinical trials of warfarin in patients with various types of cancer have provided conflicting results[16-21], and a pooled analysis of five of the warfarin trials, conducted by Smorenburg and colleagues[22], found that the addition of warfarin to chemotherapy did not significantly influence 1-year mortality rates in patients with a variety of types of cancer (odds ratio [OR] 0.89; 95% confidence interval [CI] 0.70-1.13) or in patients with small cell lung cancer only (OR 0.75; 95% CI 0.44-1.16). Furthermore, a recently published Cochrane review[23] of randomised clinical trials evaluating oral anticoagulation in patients with cancer who had no therapeutic or prophylactic indication for anticoagulation also found no evidence of a significant reduction in mortality although it did reveal that the risk of bleeding was increased.

As regards parenteral anticoagulation, a large number of retrospective and prospective studies have assessed the effect of heparin on overall survival in cancer patients[24]. However, a systematic review of all clinical studies comparing unfractionated heparin (UFH) *vs* placebo or no treatment in patients with cancer without venous thromboembolism found no convincing evidence of beneficial effects of UFH on survival of patients with neoplasia[25]. More convincing data have emerged from studies using low molecular weight heparin (LMWH). For instance, a clinical trial conducted by Altinbas and colleagues[26] on 84 patients with small cell lung cancer randomised to receive standard chemotherapy alone or in combination with dalteparin at a dose of 5,000 anti-Xa units once daily for up to 18 weeks showed that LMWH was associated with improved tumour response rate, median disease-free survival and overall survival. The Fragmin for Advanced Malignancy OUtcome Study (FAMOUS) was a large, randomised, placebo-controlled trial designed to examine the effect of a low dose of LMWH on survival in patients with cancer[27]. In this study, 385 patients with advanced solid tumours were randomised to receive LMWH dalteparin 5,000 anti-Xa units or placebo once daily for 1 year. According to an intention-to-treat analysis, survival advantages, albeit not statistically significant, were observed at 1, 2 and 3 years in the patients who received dalteparin. However, in a post-hoc analysis in the subgroup of patients with a relatively good prognosis at randomisation (expected life span >17 months), the improvement in survival at 2 and 3 years in favour of the group treated with the LMWH was statistically significant (P =0.04), suggesting that this drug had a greater impact on survival in patients with early limited disease. Similarly, the Malignancy and Low molecular weight heparin Therapy (MALT) trial randomised 302 patients with advanced cancer to 6 weeks of nadroparin (9,500 anti-Xa units twice daily) or placebo[28]. The median survival was improved from 6.6 months in the placebo group to 8.0 months in the group of patients receiving LMWH therapy (P =0.02). Again, the beneficial effect was more evident in patients with a better prognosis at the time of enrolment (expected life span >6 months) (median survival 15.4 months in the LMWH group *vs* 9.4 months in the placebo group, P =0.01). Recently, Lazo-Lagner and colleagues conducted a systematic review of randomised trials evaluating the impact of LMWH compared to placebo or no anticoagulant treatment on the survival of cancer patients[29]. Among the four studies included in the final review, the pooled hazard ratio in all patients was 0.83 (95% CI, 0.70-0.99; P =0.03) and 0.86 (95% CI, 0.74-0.99; P =0.04), both in favour of the LMWH group. Thus, the authors concluded that LMWH improves overall survival in cancer patients, even in those with advanced disease. Finally, a recent Cochrane review of randomised controlled trials assessing the benefits and harm of parenteral anticoagulation (UFH or LMWH) in patients with cancer but no therapeutic or prophylactic indication for anticoagulation found that heparin was associated with a significant reduction of death at 24 months and of venous thromboembolism without significantly increasing the risk of bleeding[30].

Other studies have compared the influence of warfarin and LMWH on survival in cancer patients[31] and a recent meta-analysis of 11 such studies demonstrated that although LMWH increased survival (RR 0.88; 95% CI: 0.79-0.97; P =0.01) warfarin did not (RR 0.94; 95% CI: 0.85-1.04; P =0.24)[32]. Furthermore, patients receiving warfarin therapy had a significant increase in the risk of major bleeding (RR 2.98; 95% CI: 2.13-4.16; P <0.0001) whereas those receiving LMWH did not (RR 1.68; 95% CI: 0.86-2.27, P =0.13). Table I summarises

Table I - Results of the most important studies on the antineoplastic effect of anticoagulants.

Authors/Study, years	Study design	Patients	Main results
Duration of Anticoagulation Trial, 2000[20]	Prospective randomised	854 VTE patients treated with VKA for 6 weeks or 6 months	The incidence of cancers in patients receiving 6 months of VKA therapy was lower than that in patients receiving 6 weeks of VKA therapy. The duration of therapy was an independent risk factor in a multivariate analysis
Tagalakis, 2007[21]	Case-control	19,412 cases of urogenital cancers and 116,470 controls	The prolonged use of VKA (4 years) was associated with a decreased incidence rate (0.80, 95% CI 0.65-0.99) of prostate cancer
Altinbas, 2004[26]	Prospective randomised	84 patients with SCLC treated with CT alone or with CT + LMWH	Overall tumour response rate (69.2% *vs* 42.5%, P =0.07) was higher and median progression-free survival (10.0 *vs* 6.0 months, P =0.01) and median overall survival (13.0 *vs* 8.0 months, P =0.001) were longer in patients treated with CT + LMWH than in those treated with CT alone
FAMOUS, 2004[27]	Prospective randomised	385 patients with advanced cancer treated with LMWH or placebo	The use of LMWH was associated with a survival advantage at 1, 2 and 3 years, especially in patients with early limited disease (P =0.04)
MALT, 2005[28]	Prospective randomised	302 patients with advanced cancer treated with LMWH or placebo	The use of LMWH was associated with an improvement of median survival (8.0 *vs* 6.6 months, P =0.02), especially in patients with a better prognosis at enrolment (15.4 *vs* 9.4 months, P =0.01)
CLOT, 2005[31]	Prospective randomised	676 VTE cancer patients treated with VKA or LMWH for months	A survival benefit for LMWH over VKA was observed in patients with non-metastatic cancer, with a 20% mortality rate in the LMWH group compared with 36% with VKA (HR 0.50; 95% CI: 0.27-0.95; P =0.03).

Legend VTE: venous thromboembolism; VKA: vitamin K antagonists; SCLC: small cell lung cancer; CT: chemotherapy; LMWH: low molecular weight heparin.

the results of the most important studies. Overall, the analysis of the data available in the literature suggests that, of the various anticoagulants, only LMWH improve overall survival in cancer patients.

Haemostasis and cancer: epidemiological studies in haemophiliacs

The distance between studies on cancers in pharmacologically anticoagulated patients and studies in naturally anticoagulated patients (i.e., haemophiliacs) is very short. Human immunodeficiency virus (HIV)-associated non-Hodgkin's lymphomas and hepatitis C virus (HCV)-associated hepatocellular carcinomas (HCC) are important causes of death among the virus-infected ageing haemophilia population[33,34]. For instance, in a study conducted in the Netherlands between 1992-2001, the death rate due to neoplasms, including HCC, was 1.5-times higher in haemophiliacs than in the general population[35]. Similarly, a multicentre study on cancer in more than 3,000 haemophiliacs published in 1993 found a 36.5-fold higher incidence of non-Hodgkin's lymphoma in HIV-positive haemophiliacs than in HIV-negative ones[36]. However, the widespread use of highly active antiretroviral treatment (HAART) since 1997 has resulted in a substantial reduction in the incidence of lymphomas among HIV-positive haemophiliacs, as documented in a study conducted by Wilde *et al.* in which the observed to expected ratio of non-Hodgkin's lymphomas among HIV-positive haemophiliacs fell from 84 to 42 during the periods 1985-1996 and 1997-1999[37].

Unfortunately, only a few studies have specifically analysed this issue after excluding virus infection-related malignancies and the majority of literature data published on this topic regard the epidemiology of cancer-related mortality in haemophiliacs as compared to that in the general population (i.e. the standardised mortality ratio [SMR]). For instance, on behalf of the Association of Haemophilia Clinic Directors of Canada, Walker and Julian analysed the causes of death among 2,450 haemophiliacs during the years 1980-1995 and found an unexpectedly lower (0.3) SMR for cancer in HIV-negative patients[38]. More recently, on behalf the United Kingdom Haemophilia Centre Doctor's Organization, Darby and colleagues

analysed mortality rates and causes of death in 6018 HIV-uninfected haemophiliacs during the period 1977-1998 and noted that while mortality from liver cancer and Hodgkin's disease in these subjects was increased compared to that in the general population (SMR of 13.51 and 4.95, respectively), for other cancers there was no evidence of increased mortality (SMR 0.90). Interestingly, the authors observed a progressive reduction of cancer-related mortality with increasing severity of haemophilia[39]. Indeed, while the SMR for malignancies other than liver cancers or lymphomas was 0.95 in patients with mild/moderate haemophilia, it decreased to 0.65 in patients with severe haemophilia. On behalf of the Italian Association of Haemophilia Centres (AICE), we have recently published the results of mortality and causes of death among Italian haemophiliacs during the period 1990-2007[2]. An increasing SMR for non-HCC cancers was observed during the study periods (0.34 during the years 1990-1999 *vs* 0.67 during the years 2000-2007). A low SMR (0.3) due to non-HCC/HIV-related cancers was also found in another recent study conducted by the same group which analysed 127 cancers in 122 Italian haemophiliacs during the period 1980-2010[40]. Contrasting with these findings, other studies have found a similar or even higher rate of non-HIV/HCV-related cancers in haemophilic subjects compared with in non-haemophilic people[35,41]. In a recent review on epidemiological studies regarding cancer in haemophilia, Miesbach and Seifried[9] found that non-HIV/HCV-related cancers accounted for 8-16% of all deaths in haemophiliacs, with a SMR lower than 1 in all studies, indicating a lower cancer mortality in the virally unaffected haemophilia population than in the matched general male population.

Table I summarises the results of the most important studies on the antineoplastic effect of anticoagulants. Overall, the conflicting results arising from the analysis of the published studies are mainly due to the fact that most of the studies were retrospective with possible inaccuracy of the estimation of mortality ratios. Only the results of ongoing prospective trials, such as an Italian multicentre study, the Sixty Plus Haemophilia Registry Assessment (SPHERA), which is evaluating the health status of patients with severe haemophilia aged 60 years or over, will be able to help us to determine definitely the incidence of cancers in the haemophilia population.

The management of haemophilic patients with cancers

The hypothesis that haemophilia could be a mutation that confers some kind of protection against the diseases of our century, such as cardiovascular disorders and cancer, is quite attractive and intriguing but at present it is only a speculation that needs investigation in prospective trials with adequately large populations of patients and appropriate follow-up periods.

Nevertheless, physicians operating at haemophilia centres are faced every day with co-morbidities developed by haemophilic patients with ageing. The relationship between haemophilia and cancer raises a number of questions, most of which are still without an answer. How does haemophilia influence the clinical presentation and natural history of neoplasia? Are diagnostic/invasive procedures or chemotherapy/radiotherapy regimens in haemophiliacs hindered or complicated by adverse haemorrhagic events due to the underlying congenital bleeding disorder? Do haemophiliacs receive suboptimal anti-cancer treatment because of concerns related to the possibility of concomitant haemorrhagic risk factors (mucosal damage or thrombocytopenia following chemotherapy/radiotherapy)? Are haemophiliacs excluded from experimental anti-cancer regimens or from treatment with newer chemotherapy agents interfering with haemostatic system, such as the anti-angiogenic monoclonal antibody bevacizumab?

Unfortunately, the data available in the literature on the clinical management of cancers in haemophiliacs are very scarce, being limited mostly to anecdotal case reports with very few and fragmentary clinical data[8]. The largest study published so far is a retrospective survey conducted by the AICE, which collected information on 127 cancers in 122 patients followed at 21 Italian haemophilia centres[40]. Non-virus-related cancers were less frequent in patients with severe haemophilia than in those with milder forms of the coagulopathy (P =0.0004), in accordance with the previous findings by Darby and colleagues[39]. Interestingly, haemorrhagic complications occurred more frequently in patients receiving chemotherapy or radiotherapy than in patients undergoing invasive or surgical procedures. Thus, based on these data and in agreement with some recent practical recommendations made by a

panel of haemophilia experts[42], replacement therapy should be administered not only at the time of invasive diagnostic or therapeutic procedures, but also as continuous prophylaxis during chemotherapy or radiotherapy, especially when accompanied by severe thrombocytopenia (i.e., platelet count less than 30×10^9/L). Finally, the questionnaires returned from each haemophilia centre participating in the study documented that in all but two cases the underlying haemophilia did not preclude access to chemotherapy and/or radiotherapy regimens[40].

Conclusions

Haemophilia provides a unique model for studying the interactions between the haemostatic system and cancer. However, apart from being an interesting field of research, it is reasonable to foresee practical implications since haemophilia caregivers will encounter an increasing number of haemophiliacs with cancer because of these patients' increasing life-expectancy. Thus, prospective trials are needed to characterise the epidemiology of cancers in haemophiliacs better and to optimise the therapeutic approach to malignancies in these patients.

Keywords: haemophilia, cancer, therapy.

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