[haematologica reports]
2005;1(9):2-4

Occult cancer and idiopathic venous thromboembolism

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The existence of a two-way clinical correlation between cancer and venous thromboembolism (VTE) has been recognized since Trousseau's time and has been overtime confirmed and documented. In fact it has been clearly demonstrated that cancer patients are at higher risk of developing a thrombotic event when compared to non cancer patients. Moreover, VTE, especially in its idiopathic presentation, sometimes may act as an epiphenomenon of yet undisclosed cancer, offering possible chances for anticipated diagnosis of the pathology.

It has been in fact demonstrated by studies addressing the topic, that the incidence of newly diagnosed cancer during follow-up of patients with VTE is higher when compared to general population. In particular the risk of newly diagnosed cancer following a thrombotic event is higher among patients with idiopathic VTE when compared with secondary ones. Newly discovered malignancies involve virtually all body systems. Part of these malignancies can be identified by routine assessments at the time of the diagnosis of the thrombotic event. However in patients with idiopathic VTE, who are apparently cancer free at baseline, there remains an approximate 10% incidence of clinically overt malignant disease during the follow-up period after the thrombotic event.[1]

Risk of cancer in patients with venous thromboembolism

Because of the well known association between cancer and VTE, researchers have become interested in assessing the prevalence of either cancer diagnosed concomitantly to VTE or malignancy disclosed during the follow-up of these patients.

In patients presenting with VTE, the presence of concomitant cancer, defined as cancer not known before the thrombotic event and discovered by routine exams at the time of VTE diagnosis, varies between available studies. This variation might be related to the depth of routine examinations performed and to the characteristics of the included patients. It has been noted that the risk of concomitant cancer was increased among patients with idiopathic VTE by a factor 3-19, whereas the prevalence of concomitant cancer in patients with secondary VTE was low and fully comparable to that obsereved in general population after middle age.[2]

Moreover, studies performed in the last two decades have clearly shown that the incidence of newly discovered malignancies among patients with idiopathic VTE, in whom a routine initial screening for cancer identification is negative, is higher than in those with secondary ones (Table 1)[3-9] and is consistently around 10%.[1]

In the case of bilateral idiopathic DVT presentation the risk is even higher[10] as well as in patients recurrent episodes of VTE.[4] The above mentioned findings are fully consistent with the observations reported in three large population-based studies conducted in Denmark, Sweden and Scotland.[11-13] All three studies reported data from cancer and thromboembolic disease national registries. All the studies found a significantly increased risk of developing cancer in patients discharged with thromboembolism, particularly in the first year after the thrombotic event. The risk is higher in patients with idiopathic VTE.

Prognosis of patients with concomitant diagnosis of cancer and VTE

Although a strict relationship has been demostrated between cancer and VTE, little is known about the prognosis of patients in whom cancer is discovered at the time or following the thrombotic event. This is not an academic distinction but encounters practical implications on the need or not to screen for occult malignancy this catogory of patients. In fact, since an extensive screening battery is associated with high costs and carry itself some morbidity and disconfort for the patient, it is acceptable only if it is proved to be cost-effective and have an impact on cancer-related mortali-

Table 1. Incidence of occult cancer after diagnosis of VTE.

Authors	All VTE	Cancer Secondary VTE	Idiopathic VTE
Aderka 1986 (3)	11/83 (13.3%)	2/48 (4.2%)	9/35 (25.7%)
Prandoni 1992 (4)	13/250 (5.2%)	2/105 (1.9%)	11/145 (7.6%)
Ahmed 1996 (5)	3/196 (1.5%)	0/83 (0%)	3/113 (2.7%)
Monreal 1997 (6)	8/659 (1.2%)	4/563 (0.7%)	4/96 (4.2%)
Hettiarachchi 1998 (7)	13/326 (4.0%)	3/171 (1.8%)	10/155 (6.5%)
Rajan 1998 (8)	21/264 (8.0%)	8/112 (7.1%)	13/152 (8.6%)
Schulman 2000 (9)	111/854 (13.0%)	18/320 (5.6%)	93/534 (17.4%)

Table 2. Estensive screening battery according to the SOMIT Study.

Procedures
Ultrasound of abdomen and pelvis
CT scanning of abdomen and pelvis
Gastroscopy or double contrast barium swallowing
Flexible sigmoidoscopy or rectoscopy followed by barium enema or colonoscopy
Haemoccult, sputum citology, tumor markers (CEA, αFP, CA 125)
Mammography and pap smear in women
Transabdominal ultrasound of the prostate and PSA in men

ty. Some authors have raised some concern about the utility of screening for occult malignacy all patients with idiopathic VTE. The real benefit of early cancer identification through extensive screening seems to be compromised by the reported pending poor prognosis of these patients. In fact in a study by Sorensen and coll[14] assessing the survival rate in patients with cancer diagnosed in the first year following the thrombotic event in comparison with that of cancer patients without thrombosis, the Authors found an increased mortality in the former group. Moreover, patients in whom cancer was detected at the time of the thrombotic event experienced a poor prognosis as well. Results seems discouraging as it appears that whenever cancer is preceded by a clinical manifestation of thrombosis its prognosis is far worse. However, given the retrospective nature of the study, it is likely that considered cancer were already symptomatic at the time thrombosis occurred, hence easily detectable by routine tests. This may be the crucial point to be considered: only patients in whom no manifestation of malignancy is present at the time of VTE could really benefit from anticipated diagnosis of the pathology. The early detection of occult cancer at the time the disease is still totally asymptomatic might in fact yield a more favourable clinical outcome.[15]

Recent prospective evaluations addressing the topic

In order to shed more light to the above mentioned unsolved issues, recently two prospective evaluations have recently appeared. Monreal and coll.[16] have recently published the results of a prospective cohort follow-up study in consecutive patients with acute VTE. All patients underwent a routine clinical evaluation for malignancy and if negative they underwent a limited diagnostic work-up consisting in abdominal and pelvis ultrasound and laboratory markers for malignancy. The routine clinical evaluation was performed in 864 patients and revealed malignancy in 34 (3.9%). Among the remaining 830 patients, the limited diagnostic work up revealed 13 further malignancies. During follow-up, cancer became symptomatic in 14 patients who were negative for cancer at screening (sensitivity of the limited diagnostic work-up 48%). Malignancies that were identified by the limited diagnostic work-up were early stage in 61% of cases compared with 14% in cases occurring during follow-up. Most patients with occult cancer had idiopathic VTE and were older than 70 years. According to the results of this study a limited diagnostic work-up for occult cancer has the capacity to identify approximately one half of the malignancies. Identified malignancies were at earlier stage.

We have recently conducted a multicentre randomized trial (the SOMIT Study)[17] among apparently cancer free patients with symptomatic idiopathic venous thromboembolism. These patients were randomized to either the strategy of extensive screening for occult cancer (Table 2) or to no further testing. Patients had a two-year follow-up period. Of the 201 patients, 99 were allocated to the extensive screening group and 102 to no further testing. In 13 patients (13,1%) the extensive screening identified occult cancer (mostly

detected by CT scanning): In the extensive screening group a soingle (1,0%) malignancy became apparent during follow-up, whereas in the control group a total of 10 (9.8%) malignancies becomew symptomatic. Overall amlignancies identified in the extensive screening group were at an earlier stage and the mean delay to diagnosis was reduced from 11.6 to 1.0 months. Cancer related mortality occurred in 2 patients of the 99 patients of the extensiive screening group versus 4 (3,9%) of the 102 control patients. A selective diagnostic work-up is capable of identifying most of cancers, whose earlier detection is likely to be associated with improved treatment possibilities and thus prognosis.

Although data from either study do not conclusively demonstrate that early diagnosis ultimately prolong life, the collective observation make such a beneficial effect likely. The early discovery of cancer, which might mean identification of the disease at an attackable stage, may be crucuial in an unpredictable rate of patients, especially nowadays when continuos protocol innovations are providing growing chances of success and eradication of malignancies.

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