Personalized management of cancer associated thrombosis: Actual status and perspectives
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More than 150 years after its first description by Armand Trousseau, the association between cancer and thrombosis remains a major clinical problem. Venous thromboembolism (VTE) occurs in up to 15% of cancer patients during the disease course and remains the second leading cause of death after malignancy itself. Overall, cancer accounts for an estimated 18% of the total number of VTE cases. The incidence of VTE is near 6-fold higher in patients with cancer than in patients without cancer. In addition, cancer patients developing VTE present lower survival rates, worse prognosis and higher healthcare costs compared with VTE patients without cancer. Thus, being an independent prognostic factor of both cancer progression and death, VTE occurrence has been proposed as a secondary endpoint in many oncological trials. A routine assessment to identify patients at high risk for CAT is recommended by international and national guidelines. Nevertheless, according to the European Society of Medical Oncology (ESMO), "*most oncologists underestimate the prevalence of CAT and its negative impact on their patients*". A routine assessment to identify patients at high risk for VTE is recommended. Moreover, the collaboration between oncologists and specialists of angiology/vascular medicine is still weak. During the last decade, important progress has been made in the comprehension of CAT pathogenesis and in the efficacy and safety of antithrombotic agents in prophylaxis and treatment of CAT.

The LMWHs dalteparin, enoxaparin and tinzaparin, emerge up to now as a cornerstone therapeutic strategy for primary prevention and treatment of cancer associated thrombosis (CAT). The CLOT trial, which demonstrated the superiority of the LMWH dalteparin over warfarin for recurrent VTE, established LMWH as the standard of care for cancer-associated VTE. This was further supported by the results from the CATCH trial which compared tinzaparin versus warfarin in the treatment of CAT. While more patients with CAT require long-term anticoagulant treatment, daily subcutaneous injections are associated with discomfort, reduced patient compliance and injection fatigue. The direct specific factor Xa

inhibitors rivaroxaban, apixaban and edoxaban and the direct specific thrombin inhibitor dabigatran became the first line therapeutic option for the acute phase treatment and the secondary prevention of VTE. Direct oral anticoagulants (DOACs) have a stable and predicted anticoagulant effect, do not show any food interactions and have few drug-to-drug interferences. Thus, DOACs appear as attractive alternative for CAT treatment. Meta-analysis of subgroup data from the large phase III clinical trials of DOAC in the treatment of VTE and data from small non-randomized studies indicate that the efficacy and safety profile of DOAC is similar in patients with cancer as compared to the non-cancer ones. Though, the decision to switch the antithrombotic treatment from LMWH to DOAC should not be based on the argument of the predictive pharmacokinetics and pharmacodynamics of DOAC since these properties have been studied in healthy population.

The management of CAT has not yet been paralleled with the above scientific achievements. Health authorities and expert panels in EU and USA recognize an increasing **knowledge translation gap** between the actual status of knowledge in pathogenesis and treatment of CAT and the clinical practice. The distance between fundamental and translational/clinical research and the lack of an overall structure for the management of the risk for vascular complications in cancer patients figure among the major causes of this gap. An additional major barrier for the prevention and treatment of CAT is given by the absence of reliable risk assessment tools with high positive predictive value (i.e. accurate to identify patients at high risk for CAT who should receive thromboprophylaxis). According to the most modern concept, such tools should incorporate predictors related with the cancer and its treatment, as well as patients' intrinsic risk factors and biomarkers of hypercoagulability and specific biomarkers of coagulation and vascular activation.

Personalize prevention and treatment of CAT is based on the evaluation of clinical profile of the patients (cardiovascular risk factors and comorbidities), on cancer related characteristics, on the presence of hypercoagulabiltiy of plasma or cellular origin and on the genetic profile of the patient. This strategy requires a new multidisciplinary concept in the management of oncological patients and is expected to improve the efficacy/safety profile of the antithrombotic strategies.