

**Comment on Ferroni *et al.*: “Impact of chemotherapy on venous thromboembolism. Comment to: Regional lymph node metastases are a strong risk factor for venous thromboembolism: results from the Vienna Cancer and Thrombosis Study” HAEMATOL/2012/073338 and HAEMATOL/2013/092528**

The notion of an increased venous thromboembolism (VTE) risk in patients with distant and regional stage cancer compared to those with local stage cancer can obviously be explained by the elevated tumor burden and an already systemic interaction of tumor cells via the lymph and blood system in regional and distant stage cancer.<sup>1</sup>

Ferroni *et al.*<sup>2</sup> presented data of a cohort of ambulatory cancer patients who underwent chemotherapy and attempted to compare their results with our findings concerning VTE in regional stage cancer patients.<sup>1</sup> Interestingly, there was a similar incidence of VTE between the cohorts: 7% in the cohort of Ferroni *et al.*<sup>2</sup> and 6.9% in ours.<sup>1</sup> Also similar to the results in our Vienna Cancer And Thrombosis Study (CATS), the authors found an association between tumor stage and the occurrence of VTE. The univariate hazard ratio (HR) of progressive tumor stage (from low to regional to distant stage) for VTE was 1.61 (95% confidence interval (95%CI) 1.02-2.54;  $P=0.042$ ). However, in multivariate analyses, predictive value of progressive stage for VTE was completely lost in their study. Unfortunately, detailed results of multivariate analyses were not shown by Ferroni *et al.*<sup>2</sup>

Conversely, in CATS, patients with both regional stage and distant stage cancer had a significantly higher risk of VTE compared to local stage cancer patients in univariate and multivariate analyses. In detail, the association between progressive tumor stage and occurrence of VTE was strong and highly statistically significant (HR=1.81, 95%CI: 1.27-2.56;  $P=0.001$ ; separate HRs for regional and distant stage *versus* local stage were 3.5 (95%CI: 1.4-8.9) and 4.0 (95%CI: 1.8-9.0), respectively).

In a cross-tabulation analysis, Ferroni *et al.*<sup>2</sup> found a higher administration of prothrombotic anti-cancer drugs in patients with regional and distant disease. They conclude that a more aggressive treatment with anti-cancer drugs may contribute to the high VTE incidence in patients with regional and distant disease. We completely agree with the authors that treatment with specific anti-cancer drugs is an important risk factor for the occurrence of VTE. However, we want to stress that treatment with anti-cancer drugs is only one of many risk factors for cancer-associated VTE.<sup>2,8</sup> Naturally, there are interactions between the risk factors for cancer-associated VTE and thus not all risk factors are independent predictors of cancer-associated VTE. In our study we adjusted for multiple risk factors, including the administration of anti-cancer drugs. Moreover, the administration of anti-cancer drugs was considered as a time-dependent variable in the multivariable Cox regression analysis, to provide better weighting of the duration of treatment with anti-cancer drugs. Interestingly, in our study, chemotherapy was not independently associated with the occurrence of VTE. In contrast, regional stage and distant stage were independently associated with the occurrence of VTE.

In our opinion, the conflicting results concerning the predictive value of tumor stage and administration of anti-cancer drugs on the occurrence of VTE can be largely attributed to the different cohorts of cancer patients in CATS and the study of Ferroni *et al.* Although, the distribution of tumor entities in both studies was almost similar,

different patients' inclusion criteria were applied. While the study of Ferroni *et al.* only included ambulatory cancer patients at start of a new chemotherapy,<sup>9</sup> the CATS population was more heterogeneous, including patients who underwent cancer surgery, irradiation or even no treatment. During admission to the hospital due to intercurrent illness, patients received short-term thromboprophylaxis during follow up.<sup>10</sup>

Despite the concerns about an increased risk of VTE in advanced cancer patients by Ferroni *et al.*, we believe the tumor stage (regional and metastatic disease) is an important and independent risk factor for cancer-associated VTE. This is substantiated by studies focusing on VTE as first manifestation of cancer. In these studies, VTE occurred before administration of chemotherapy. When VTE was concurrently diagnosed with cancer, VTE patients had a significantly higher risk of advanced tumor stage.<sup>11</sup>

However, to what extent the tumor stage contributes to the occurrence of VTE independently from chemotherapy in ambulatory cancer patients is still unclear. We are looking forward to seeing more detailed results regarding this issue in future publications by Ferroni *et al.* and other groups. Furthermore, large studies in single tumor entities considering the tumor stage and treatment with anti-cancer drugs could probably provide better answers to the question about the association between lymph node metastases, chemotherapy and occurrence of VTE.

*Boris Dickmann,<sup>1,2</sup> Jonas Ahlbrecht,<sup>1,2</sup> Cihan Ay,<sup>1,2</sup> and Ingrid Pabinger<sup>1,2</sup>*

<sup>1</sup>Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna; and <sup>2</sup>Comprehensive Cancer Center Vienna, Medical University of Vienna, Austria

Correspondence: [ingrid.pabinger@medunivien.ac.at](mailto:ingrid.pabinger@medunivien.ac.at)  
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