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Risk of Arterial Thrombosis in Cancer Patients

Which Role for Cancer Therapies Vascular Toxicities?

We read with great interest the paper by Navi et al. (1) in a recent issue of the *Journal*. In their work, the authors highlight that patients with incident cancer face a substantially increased short-term risk of myocardial infarction and ischemic stroke, depending on cancer type and stage, which was confined to the first year (1).

Whereas the risk for venous thromboembolism and the benefit/safety of anticoagulants in cancer patients were extensively investigated (2), the association between cancer and arterial thromboembolism was scarcely studied in the published reports. The study by Navi et al. (1) is the largest to raise this important concern, and the authors are to be congratulated for their work.

However, a main limitation of their work is that they neither address nor discuss the role of the vascular toxicities of cancer therapies. The broadly used vascular endothelial growth factor inhibitors were previously demonstrated to be associated with a 3.5-fold increased risk of myocardial infarction and a 1.8-fold increased risk of arterial thrombosis (3), these hazard ratios being consistent with the findings from Navi et al. (1). Vascular endothelial growth factor inhibitors induce an endothelial dysfunction that decreases nitrite oxide and prostacyclin levels, resulting in platelet activation (4). In patients with pre-existing coronary or cerebral artery disease, these mechanisms might contribute to promote thrombosis. Moreover, an increased risk of arterial thromboembolism has been suggested with several other cancer therapies such as lenalidomide or carfilzomib.

The major strengths of this work are to clearly establish the association between cancer and arterial thromboembolism and to highlight the urgent need for coordinated efforts of oncologists and cardiologists in managing patients with cancer. From this perspective, a better knowledge of the risk attributable to cancer therapies constitutes a major outstanding issue.

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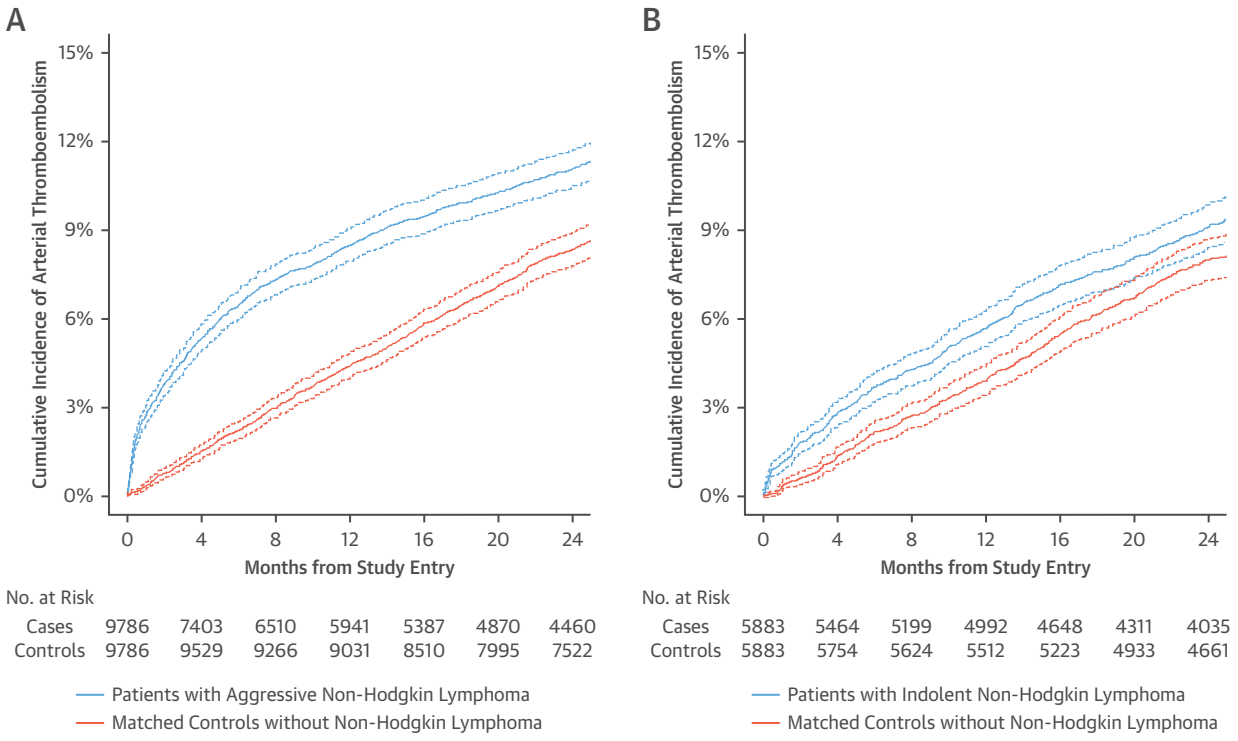
REPLY: Arterial Thromboembolism in Non-Hodgkin Lymphoma, as the Presentation of Occult Cancer, and With Cancer Therapies

We agree with Dr. Sorigue and colleagues that besides cancer stage, cancer histology might also affect arterial thromboembolism risk, particularly in patients with non-Hodgkin lymphoma (NHL). To

FIGURE 1 Cumulative Incidence of Arterial Thromboembolism



(A) Cumulative incidence of arterial thromboembolism (composite of myocardial infarction and ischemic stroke) in patients with aggressive non-Hodgkin lymphoma histologies compared with matched control subjects without non-Hodgkin lymphoma. **(B)** Cumulative incidence of arterial thromboembolism (composite of myocardial infarction and ischemic stroke) in patients with indolent non-Hodgkin lymphoma histologies compared with matched control subjects without non-Hodgkin lymphoma. Competing risk survival statistics were used to calculate incidence. **Dashed lines** are used to indicate 95% confidence intervals.

investigate this hypothesis, we performed the subgroup analyses suggested by the correspondents. Using the International Classification of Diseases for Oncology, 3rd edition scheme outlined in their letter, we categorized patients with new diagnoses of NHL from 2002 to 2011 in the Surveillance Epidemiology and End Results-Medicare database into aggressive or indolent subgroups. As in our original study, patients with NHL were matched individually by demographics and comorbidities to a Medicare enrollee without cancer, and each pair was followed through 2012 for an arterial thromboembolism outcome, defined as myocardial infarction or ischemic stroke (1). Cumulative incidence rates accounting for the competing risk of death were calculated. Cox regression was used to compare rates between groups at discrete time points.

We identified 15,669 pairs of patients with NHL and matched control subjects without NHL. Aggressive histologies were diagnosed in 9,786 patients with NHL (62%), and indolent histologies were diagnosed in 5,883 (38%). Forty-nine percent of patients with aggressive histologies and 50% of patients with indolent histologies were Ann Arbor Stages 3 or 4 at diagnosis. Patients with aggressive histologies had substantially higher absolute and relative risks of arterial thromboembolism than those with indolent histologies, although even patients with indolent histologies had significantly increased risks of arterial thromboembolism as compared with control subjects without NHL (**Figure 1**). The 6-month cumulative incidence of arterial thromboembolism was 6.5% (95% confidence interval [CI]: 6.0% to 6.9%) in patients with aggressive NHL histologies compared with 2.2% (95% CI: 1.9% to 2.5%) in control patients (hazard ratio: 3.0; 95% CI: 2.6 to 3.5). Meanwhile, the 6-month cumulative incidence of arterial thromboembolism was 3.7% (95% CI: 3.2% to 4.2%) in patients with indolent NHL histologies compared with 2.2% (95% CI: 1.8% to 2.5%) in control patients

(hazard ratio: 1.8; 95% CI: 1.4 to 2.2). For all histologies, patients with NHL had higher incidences of ischemic stroke than myocardial infarction, but their relative risks for myocardial infarction were consistently higher than for ischemic stroke. Excess risks attenuated in all patients with NHL over time, although less so in those with aggressive histologies, and at 2 years from diagnosis, aggressive NHLs were still associated with a roughly 40% increased cumulative incidence of arterial thromboembolism as compared with matched control subjects. The association between aggressive NHL histologies and arterial thromboembolism risk was materially unchanged in a sensitivity analysis (n = 7,398) that excluded patients with nonspecific International Classification of Diseases for Oncology, 3rd edition histology codes of 9590, 9591, and 9596 from the aggressive NHL subgroup (6-month hazard ratio: 3.1; 95% CI: 2.6 to 3.7).

Dr. Leening and colleagues astutely point out that recurrent arterial thromboembolism despite antithrombotic therapy can sometimes serve as a clue to occult cancer. This phenomenon, although reported previously (2), requires more investigation, particularly surrounding risk markers and optimal screening strategies for occult cancer.

We agree with Frere and colleagues that cancer therapies might contribute to the heightened short-term risk of arterial thromboembolism in newly diagnosed patients with cancer, especially platinum-based and anti-angiogenesis chemotherapies (3,4). Although this hypothesis was beyond the scope of our initial study (1), which intended to define the risk of arterial thromboembolism in patients with incident cancer according to cancer type and stage, we are planning future large-scale studies to delineate the effects of commonly used cancer treatments on arterial thromboembolism risk.

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