Genitourinary Hemorrhagic Complications and Malignancies in Patients Receiving Anticoagulation Therapy

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Hemorrhagic complications are a perpetual problem in any patient receiving anticoagulation therapy, not only in those with atrial fibrillation (AF). Net clinical benefit of anticoagulation therapy can be obtained when the incidence of hemorrhagic events is less than that of thromboembolism.¹ Therefore, physicians have always considered the balance of risk (i.e., hemorrhagic complications) and benefit (i.e., prevention of thromboembolism) to achieve positive results of anticoagulation therapy. Although hematuria is a common and important hemorrhagic complication, along with intracranial hemorrhage and gastrointestinal bleeding, there is little information about genitourinary tract bleeding during anticoagulation therapy in preceding studies.

In this issue of the Journal, Yu et al² focus on hematuria and genitourinary complications in patients with AF receiving oral anticoagulation therapy (OAT). The authors clearly demonstrate that the frequency of hematuria and its grade are higher in patients with OAT than in those not on OAT. The prevalence of bladder cancer was higher in patients with OAT, even in the propensity score-matched population, and the risk of bladder cancer was associated with urine red blood cell (RBC) grading. The odds ratio for genitourinary cancers in patients with urine RBC grade 3+ and gross hematuria was significantly higher compared with patients with urine RBC grade 1+ (Figure 1A).²

Considerations for Hematuria

Several possibilities for the cause of hematuria during anticoagulation therapy should be considered, as well as gastrointestinal bleeding. First, preexisting benign organic disorders or malignancies as the source of bleeding are actualized by anticoagulation therapy. Most hemorrhagic complications in the genitourinary and gastrointestinal tracts may correspond to this hypothesis. The authors also state that being on OAT can detect preexisting occult genitourinary cancer earlier, especially bladder cancer.² Indeed, the pathological grade of bladder cancer detected in patients with OAT was lower than that in those who were not, indicating that OAT had helped to detect the cancer earlier.²

Second, another consideration is whether an anticoagulant itself influences the incidence of genitourinary cancer. A few years ago, Lewis et al reported from the Kaiser Permanente Northern California diabetes registry that the

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long-term use (>2 years) of pioglitazone, an oral hypoglycemic agent for diabetes mellitus, increased the risk of bladder cancer among diabetic patients (hazard ratio, 1.4; 95% confidence interval, 1.0–2.0).³ Subsequent pooled multipopulation analysis revealed that the cumulative use of pioglitazone was not associated with the incidence of bladder cancer.^{4,5} However, the impact of the first result was larger than the beneficial effect of pioglitazone and the use of this drug has decreased worldwide, despite it being reported to reduce the risk of macrovascular events such as nonfatal myocardial infarction, stroke, and all-cause death in patients with type 2 diabetes.⁶ Therefore, the mitogenic potency and oncogenicity of drugs should be taken into account, especially in patients who are undergoing long-term drug therapy. Fortunately, there has been no evidence that warfarin itself increases the incidence of renal or bladder cancer. Conversely, an anticancer effect of warfarin can be found in some reports, in which the long-term use of warfarin was associated with a lower incidence of prostate cancer.^{7–9} These findings support the first hypothesis.

Age is a strong risk factor for the incidence of cancer. Indeed, the odds ratio for genitourinary cancers in patients

Figure 1. Odds ratios of hematuria grade (A) and age groups (B) for genitourinary cancers in patients with atrial fibrillation undergoing oral anticoagulation therapy. RBC, red blood cell. (Generated with permission from Yu HT, et al.²)

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aged ≥ 75 years was significantly higher compared with that in those aged <65 years in the study by Yu et al² (Figure 1B). Age is also a risk factor for thromboembolic and hemorrhagic complications. The risk of thromboembolism and major hemorrhage increased linearly with age in the J-RHYTHM Registry, which was a prospective observational study and followed 7,406 Japanese non-valvular AF patients, including 6,404 treated with warfarin for 2 years¹⁰ (Figure 2). However, warfarin could have beneficial effects, even in very old patients, if the international normalized ratio of prothrombin time is maintained between 1.6 and 2.6.¹⁰

Another important issue to consider is whether concomitant antiplatelet therapy affects the prevalence of genitourinary tract bleeding. Antiplatelet use generally increases the incidence of hemorrhagic complications. However, antiplatelet use did not affect the main results after propensity score matching in the study by Yu et al, despite the frequency of aspirin use being significantly different between patients with and without OAT.²

Expectation of Future Studies

Although the study by Yu et al only focused on hematuria and genitourinary complications,² it would be interesting to complete the same analyses with regard to gastrointestinal bleeding in the same population. In addition, warfarin was the sole anticoagulant in that study.² The influence of non-vitamin K antagonist oral anticoagulants (NOACs or direct oral anticoagulants [DOACs]) on genitourinary bleeding may be different from that of warfarin as for gastrointestinal bleeding. Additional studies using NOACs are expected in the future. Thus far, in recent reports of the J-RHYTHM Registry 2 from Japan, which was an extended study of the J-RHYTHM Registry for 3 years,¹¹ and an observational cohort study using Danish nationwide data-

bases with more than 60,000 patients,¹² the risk of major hemorrhage has been significantly lower in patients receiving NOACs compared with that in those receiving warfarin.

Concluding Remarks

Anticoagulation therapy is an indispensable clinical intervention for the prevention of cardiogenic thromboembolism in patients with AF. Concurrently, it can be said that anticoagulation therapy plays an important role in the early detection of genitourinary cancer, especially bladder cancer, in patients with AF. Because the early detection of occult malignancy is extremely important for all patients to obtain a true net clinical outcome, meticulous evaluation of the cause of hematuria is necessary and important when hematuria is found during anticoagulation therapy.

Disclosures

The author has no conflicts of interest to disclose.

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