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Kuwait Emir HH Sheikh Nawaf Al-Ahmad Al-Jaber Al-Sabah and Crown prince HH Sheikh Meshal Al-Ahmad Al-Jaber Al-Sabah

Late Emir HH Sheikh Sabah Al-Ahmad Al-Jaber Al-Sabah headed a meeting for Kuwait Foundation for the Advancement of Sciences (KFAS)

R.I.P. SHEIKH SABAH AL-AHMAD AL-JABER AL-SABAH
THE EMIR OF KUWAIT
1929-2020

Late Emir HH Sheikh Sabah Al-Ahmad Al-Jaber Al-Sabah.
Late Dr. Abdulrahman Abdullah Al-Awadi, Dr. Rasheed Hamad Al-Hamad and Dr. Khaled Ahmed Al-Saleh

Late Emir His Highness welcomes the Minister of Health and members of the Gulf Federation for Cancer Control (GFFCC).
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Abstract

Background: The objective of this study was to clarify the onset of arterial and venous thrombosis and the safety of antithrombic therapy in patients with gastrointestinal cancer.

Patients and Methods: In a retrospective cohort study of adults aged ≥18 years, 1187 patients with gastrointestinal cancer were admitted to our hospital between January 1, 2015 and December 31, 2017. We investigated the incidence of arterial thromboembolism (ATE) and venous thromboembolism (VTE) and serious bleeding following antithrombotic therapy.

Results: In the 1187 patients diagnosed with gastrointestinal cancer, VTE occurred in 4.5% of cases and ATE in 2.8% of cases, and in 7.2% of cases overall. Among 239 patients who received antithrombotic therapy, the combination antithrombotic therapy group (n = 43), such as dual antiplatelet therapy, had more major bleeding events than the monotherapy group (n = 196; 49% vs. 17%, p < 0.01).

Discussion: In our gastroesophageal cancer patients, arterial thrombosis occurred more frequently than venous thrombosis (17/393, 4.3% vs. 9/393, 2.3%, respectively). This result may be affected by chemotherapy or radiation therapy and needs further analysis.

Conclusion: The risk of ATE also needs to be considered in gastrointestinal cancer patients. Combination therapy with antithrombotics increases bleeding events, so it is necessary to determine the risk of thrombosis as well as bleeding.

Keywords: Arterial thromboembolism, Venous thromboembolism, Thromboembolism, Cancer, Anticoagulant, Bleeding

Introduction

Cancer is itself a prothrombotic state, and the second leading cause of death among cancer patients is thromboembolic disease [1]. Cancer is associated with an increased incidence of venous thromboembolism (VTE; 4%–20%) and an increased incidence of arterial thromboembolism (ATE; 2%–5%) [2–6]. In contrast to the large number of studies on VTE, comparatively few have focused on ATE. In addition, cancer patients have a two-fold increased risk of major hemorrhage compared with non–cancer patients, and therefore bleeding risk must be considered when antithrombotic therapy is administered [7–8].

Current national guidelines, including those of the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network, all recommend at least 6 months of low molecular weight heparin as the standard treatment for cancer–related VTE [9–11]. In recent years, oral edoxaban was found to be non–inferior to subcutaneous dalteparin with regards to an outcome of recurrent VTE or serious bleeding, despite reports of a higher rate of gastrointestinal bleeding [12].

For non–cancer patients, most studies report that major gastrointestinal bleeding (MGIB) is more common with direct oral anticoagulants (DOACs) than with vitamin K antagonists, and that MGIB occurs at a rate of
approximately 1%–2% per year (13-14). So far, there have been few DOAC clinical trials in cancer patients. In this study, we investigated the incidence of ATE, VTE, MGIB, and other major bleeding events in gastrointestinal cancer patients receiving antithrombotic therapy.

Patients and Methods

1. Patients

Patients were included if they had received a diagnosis of gastrointestinal cancer (intestine, stomach, esophagus, liver, bile duct and pancreas) between January 1, 2015 and December 31, 2017. Patients were excluded if they were under 18 years of age, had diagnosed disease other than carcinoma (including difficulty in distinguishing benign from malignant lesions without cytodiagnosis), and were hospitalized for examination only. The study protocol was approved by the Institutional Review Board of our institution, and informed consent was obtained via the opt-out method.

The incidence of ATE and VTE and the safety of oral antithrombotic therapy in patients with gastrointestinal cancer (including colorectal, stomach, esophageal, liver, bile duct, and pancreatic cancer) was retrospectively analyzed among a total of 1187 patients diagnosed with gastrointestinal cancer between January 1, 2015 and December 31, 2017 at our hospital. As target drugs, warfarin and DOACs (apixaban, edoxaban, rivaroxaban, dabigatran) were used as anticoagulant agents, while aspirin, clopidogrel, and cilostazol were used as antiplatelet agents in this study. The average observation period was 487 (14–1343) days. The end of the observation was the last visit day or the date of death.

A total of 239 patients received monotherapy or combination therapy: anticoagulant alone (n = 84), antiplatelet alone (n = 112), dual antiplatelet therapy (DAPT; n = 23), or anticoagulant + antiplatelet agents (n = 20). This included patients who had originally taken antithrombotic therapy with a history of atrial fibrillation, cerebral infarction, or percutaneous coronary intervention before a diagnosis of cancer. A flow diagram of patient selection and treatment allocation is shown in Figure 1.

Clinical parameters were obtained from the medical records of each patient at our hospital. These included age, sex, underlying disease (hypertension, diabetes, hyperlipidemia), smoking, drinking, body mass index, anticoagulant use, antiplatelet use, and cancer stage.

Major bleeding was defined based on the International Society of Thrombosis and Hemostasis (ISTH) bleeding criteria (15) as a decrease in hemoglobin by ≥ 2.0 g/dL, bleeding requiring erythrocyte transfusions of ≥ 2 units, intracranial hemorrhage, intrathecal hemorrhage, intraocular hemorrhage, epicardial hemorrhage, intrarticular bleeding, intramuscular hemorrhage with compartment syndrome, retroperitoneal bleeding, and exsanguination.

2. Thromboembolism

Deep vein thrombosis was diagnosed using Doppler ultrasound sonography of the lower limb (iliac vein to peroneal vein). Pulmonary embolism, portal vein thrombosis, and other arterial or venous thromboses were diagnosed using contrast-enhanced computed tomography (CT). Cerebral infarction was diagnosed using magnetic resonance imaging or CT. Myocardial infarction was diagnosed using electrocardiography or angiography. These medical examinations were carried out as preoperative routine tests or were based on clinical
features or a high index of suspicion from clinical findings such as elevated D–dimer levels.

3. Statistical analysis

Continuous variables are presented as the median and range. Proportions were compared with Fisher’s exact test. Analyses were performed with JMP, version 10 (SAS Institute, Cary, NC). Statistical significance was set at p < 0.05.

Results

Baseline clinical characteristics of the 239 patients are shown in Table 1.

1. Thromboembolism

There were 86 events in 68 patients with thromboembolic disorder: 53 cases of VTE and 33 of ATE (Figure 2). Among all 1187 patients diagnosed with gastrointestinal cancer, VTE occurred in 4.5% of cases and ATE in 2.8%, for a total of 7.2% cases.

In terms of the site of onset, VTE occurred as deep vein thrombosis in 22 cases, pulmonary embolism in 12 cases, portal vein thrombosis in 12 cases, and other venous thromboses (iliac vein, renal vein) in 7 cases. ATE occurred as cerebral infarction in 13 cases, myocardial infarction in 4 cases, and other arterial thromboses (iliac artery, common carotid artery) in 16 cases (Figure 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male = 188 (79%) Female = 51 (21%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>75 (38–91)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>193 (81%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>101 (42%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>105 (44%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>108 (45%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>94 (39%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21 (13.1–33.3)</td>
</tr>
<tr>
<td>Stage</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>I</td>
<td>54 (23%)</td>
</tr>
<tr>
<td>II</td>
<td>55 (23%)</td>
</tr>
<tr>
<td>III</td>
<td>68 (29%)</td>
</tr>
<tr>
<td>IV</td>
<td>55 (23%)</td>
</tr>
</tbody>
</table>

Variables are number (%) or median (range)

Table 1. Characteristics of the 239 patients receiving antithrombic therapy

Figure 2. Proportion of arterial thrombosis cases to venous thrombosis cases. Variables are number (%).

Figure 3. Thromboembolic site Variables are number (%). DVT: Deep vein thrombosis, PE: Pulmonary embolism, PVT: Portal vein thrombosis, MI: Myocardial infarction, Other venous thrombosis: iliac vein, renal vein. Other arterial thrombosis: iliac artery, common carotid artery.
Thrombosis onset according to gastrointestinal organ (Figure 4) occurred in the colorectum in 41/557 cases (7%), stomach in 18/258 cases (7%), esophagus in 8/135 cases (6%), liver in 7/51 cases (14%), bile duct in 4/70 cases (6%), and pancreas in 6/105 cases (6%).

2. Bleeding

a) Monotherapy

Significant bleeding events as defined by the ISTH occurred as follows: for the anticoagulants alone group, in 11/42 cases (26%) with warfarin and in 4/42 cases (10%) with DOACs; and for the antiplatelet alone group, in 6/78 cases (8%) with aspirin, 6/22 cases (27%) with clopidogrel, and 1/12 cases (8%) with cilostazol.

In terms of bleeding site, there were 6 cases of MGIB with warfarin, 4 cases of MGIB with DOACs, 3 cases of intracranial bleeding with warfarin, and no cases of intracranial bleeding with DOACs. There was no statistically significant difference in MGIB events between warfarin monotherapy and DOAC monotherapy. The antiplatelet alone group had 5 cases of MGIB, 1 case of intracranial bleeding with aspirin and clopidogrel, 1 case of intracranial bleeding, and no cases of MGIB with cilostazol.

b) Combination therapy

In the combination therapy group, serious bleeding events occurred in 9/23 cases (39%) with DAPT and in 6/20 cases (30%) with anticoagulant and antiplatelet agent. There were 8 bleeding sites (35%) for MGIB with DAPT and 6 (30%) with antiplatelets and anticoagulants; there was 1 bleeding site (4%) for intracranial hemorrhage with DAPT and none with antithrombotic + antiplatelet.

MGIB occurred in 5/9 cases (56%) with DOAC and antiplatelet, in 1/11 cases (9%) with warfarin and antiplatelet. In monotherapy, there was no statistically significant difference in MGIB occurrence compared with warfarin; however, the combination of DOAC with antiplatelet resulted in significantly more occurrences of MGIB than warfarin with antiplatelet. (p < 0.03)

A comparison of monotherapy with combination therapy revealed 28 bleeding events (14%) in the
monotherapy group versus 15 (35%) in the combined group (p < 0.01). Severe bleeding was more common in the combination therapy group.

Discussion

VTE rates by specific type of malignancy have been reported as colorectal (3.1%–10.2%), gastroesophageal (6.9%–13.6%), hepatic (6.7%), and pancreatic (5.2%–26%) (16). Additionally, the prevalence of arterial thrombosis is in the range of 2%–5% (2–4). In the present study, occurrence rates were within these reported ranges for colorectal cancer (VTE 5.6%, ATE 2.2%), low for gastroesophageal cancer in terms of VTE (VTE 2.3%, ATE 4.3%), considerably higher for hepatic cancer for VTE (VTE 11.8%, ATE 2%), and low for pancreatic cancer (VTE 3.8%, ATE 1%). Another study reported 17%–57% of patients with pancreatic cancer may develop thrombembolism (17–18), which but the rate was low in patients with pancreatic cancer in our study. In patients with bile duct cancer, a VTE rate of 5%–19% (19) has been reported after chemotherapy. Our occurrence rate for bile duct cancer regardless of treatment (VTE 4.3%, ATE 1.4%) is newly reported. In our gastroesophageal cancer patients, arterial thrombosis occurred more frequently than venous thrombosis (17/393, 4.3% vs. 9/393, 2.3%, respectively).

Gastric cancer and esophageal cancer resulted in more occurrences of ATE than VTE. In phase III randomized controlled trials, arterial thrombosis side effects have been reported with administration of ramucirumab (20–21) and angiopathy side effects due to radiation therapy are also common (22–24). Therefore, it is necessary to analyze the effects of radiation therapy and chemotherapy in a larger population.

In this study, contrast CT follow-up was routinely performed on postoperative day 7. As a result, the probability of diagnosing portal vein thrombosis was high and thus the incidence in the liver was high in this study.

Regarding monotherapy compared with combination therapy, a prospective investigation known as the Bleeding with Antithrombotic Therapy study (25), reported that the risk of bleeding is higher with combination therapy than monotherapy, and in patients with gastrointestinal cancer, combination with anticoagulants is a high-risk factor for bleeding. Strict precautions are therefore necessary for their use.

Bleeding events often occurred after surgery or from a tumor. Advanced cancer patients tend to bleed and are also affected by chemotherapy and radiotherapy (26). Therefore, assessment of MGIB in gastrointestinal cancer patients was difficult. Furthermore, we need to consider whether primary lesion has been removed or not and the effect of myelosuppression by chemotherapy and radiation therapy.

Conclusion

This study involving patients with gastrointestinal cancer revealed that VTE and ATE occurred in 4.5% and 2.8% of cases, respectively, and that colorectal and stomach cancer tended to be complicated by thromboembolism more frequently than cancer in other organs.

In gastrointestinal cancer patients, the risk of bleeding was higher in the combined antithrombotic therapy group than in the monotherapy group. Therefore, indications for combined antithrombotic therapy should be assessed carefully in gastrointestinal cancer patients.

References


