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Bleeding risk and major adverse events in patients with cancer on oral anticoagulation therapy

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ABSTRACT

Background: The efficacy of oral anticoagulation therapy (OAT) has not been revealed in atrial fibrillation (AF) patients with newly diagnosed cancers. This study evaluated the thromboembolic and bleeding events in AF patients with malignancies according to OAT.

Methods and results: In 2168 consecutive non-valvular AF patients with newly diagnosed malignancies, we analyzed the composite endpoints including major adverse cardiac events (MACEs) and major bleeding. Based on a propensity score matching, two groups with 690 matched pairs were created.

Patient baseline characteristics were comparable between the matched groups. During a follow-up period of 3.9 ± 2.8 years, 72 (10%) and 65 (9%) patients had MACEs in the propensity score-matched OAT+ and OAT− groups, respectively ($p = 0.461$). There was no significant difference in the major bleeding (10% vs. 8%, $p = 0.300$) and composite endpoints (18% vs. 16%, $p = 0.181$) between OAT+ and OAT− patients. During the first year after the cancer diagnosis, 66 (48%) MACEs, 52 (41%) major bleedings, and 116 (49%) composite end points of all events occurred. The optimal international normalized ratio (2.0 to 3.0) level was achieved in only 85 (12%) patients. However, 1 year after cancer diagnosis, OAT+ patients with the target therapeutic range of ≥60% demonstrated better cumulative survival free of composite end point than OAT− patients ($p = 0.026$).

Conclusion: During the first year after the cancer diagnosis, OAT did not improve the composite end point because of poor INR control caused by cancer treatment. However, after 1 year after diagnosis of cancer, optimal anticoagulation significantly reduced the composite end point.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population [1,2]. AF confers a 5-fold risk of a stroke, and one in five of all strokes are attributed to this arrhythmia. Multiple clinical trials have demonstrated the superior therapeutic effect of vitamin K antagonists (VKAs) compared to a placebo in the prevention of thromboembolic events among patients with non-valvular AF [3]. However, AF patients with comorbidities such as end stage renal disease, bleeding, and malignancy have the concomitant risk of fatal bleeding, which causes clinicians to be reluctant to use VKAs in spite of the high stroke risk [4].

AF is common in patients with life-threatening cancer and those undergoing active cancer treatments [5]. The development of AF after cancer surgery is well known [6–8]. Several studies have suggested that the association between cancer and AF is not limited to the postoperative period [9–13]. Despite the excellent effect of VKAs in the prevention of thromboembolisms, OAT might result in an elevated bleeding risk in patients with cancer and a history of non-valvular AF [14]. Moreover, the effect of the OAT according to the time duration, and treatment modalities of cancer has not been revealed.

We hypothesized that OAT in patients with newly diagnosed cancer and previous AF would result in an increase in major bleeding and a decrease of thromboembolic events. The aim of this study was to evaluate the clinical course, including thromboembolic and bleeding events, in patients with cancer and a history of AF according to whether or not they received OAT.

2. Methods

2.1. Patients

The study protocol was approved by the Institutional Review Board of Severance Cardiovascular Hospital, Seoul, Korea and complied with the Declaration of Helsinki. From November 2005 to January 2015, using the International Classification of Disease, Ninth Revision, codes, we identified 2168 consecutive patients with non-valvular AF and

Abbreviations: OAT, oral anticoagulation therapy; AF, atrial fibrillation; MACE, major adverse cardiac event; INR, international normalized ratio; VKA, vitamin K antagonist; RFCA, radiofrequency catheter ablation; TTR, target therapeutic range; NOACs, new oral anticoagulants.

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cancer. Patients who underwent radiofrequency catheter ablation (RFCA) or cardioversion (n = 7) and who had insufficient clinical data (n = 43) were excluded (Fig. 1). Finally, we enrolled 2118 patients in this study and they were divided into two groups. Those receiving OAT (OAT +, n = 1182) and those not receiving OAT (OAT −, n = 936).

AF was documented by the 12 lead electrocardiography or 24-h Holter recordings. The patients' medical records were reviewed for information on the age, sex, weight, height, drug therapy, and AF duration. The patient databases were searched to identify any known or putative risk factors for ischemic strokes, including previous ischemic strokes/transient ischemic attacks, heart failure or an ejection fraction <40%, hypertension, diabetes mellitus, hyperlipidemia, tobacco use, or coronary heart disease [15]. Heart failure was defined when hospitalized patients had appropriate symptoms (shortness of breath, fatigue, fluid retention, or any combination of these symptoms) and clinical signs of fluid retention (pulmonary or peripheral) with explainable abnormalities of the cardiac structures and function [16]. The CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years ⟨doubled⟩, diabetes mellitus, previous stroke or transient ischemic attack ⟨doubled⟩, vascular disease, age 65–74 years, and gender category ⟨female⟩), and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly ⟨age >65 years⟩, drugs/alcohol concomitantly) scores were evaluated.

2.2. Follow-up

We evaluated the major adverse cardiac events (MACEs) and major bleeding events during the follow-up. MACEs included ischemic strokes, myocardial infarctions, and pulmonary thromboembolisms. Ischemic strokes were defined as a neurological deficit of a sudden onset that persisted for >24 h corresponding to a vascular territory in the absence of a primary hemorrhage and was not explained by other causes, including trauma, infection, or vasculitis [17]. Myocardial infarctions were diagnosed according to the 2007 universal definition of the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation [18]. Pulmonary embolisms were diagnosed if there were at least two segmental defects without a ventilation defect on a ventilation-perfusion scan, a positive angiogram finding, or documented evidence on computed tomography or magnetic resonance imaging of the chest [19]. Major bleeding was defined as any central nervous system (CNS) bleeding, including intracranial bleeding, subdural hemorrhages, subarachnoid hemorrhages, epidural hemorrhages, any bleeding requiring a transfusion of at least two units of red blood cells or the equivalent of whole blood over 24 h, bleeding events that caused hypotension (systolic blood pressure <90 mm Hg), multi-organ failure, or death. When a patient experienced both MACEs and major bleeding events during the follow-up period, each event was counted respectively. However, when analyzing the Kaplan–Meier cumulative event-free survival, we counted the first event only.

2.3. Intensity and quality of anticoagulation

The intensity of anticoagulation was determined by the international normalized ratio (INR) value at each outpatient clinic visit, emergency department visit, and during the hospital admission. Data on the first 4 weeks after the initiation of OAT were excluded from the analysis. All INR testing was performed in the same laboratory using the same reagents. To calculate target therapeutic range (TTR), INRs between the actual tests were estimated using the linear interpolation method as proposed by Rosendaal et al. [20] This method assumes that the INRs between two consecutive measurements vary linearly. Patients with intervals ≥56 days between INR tests were excluded from the analysis.

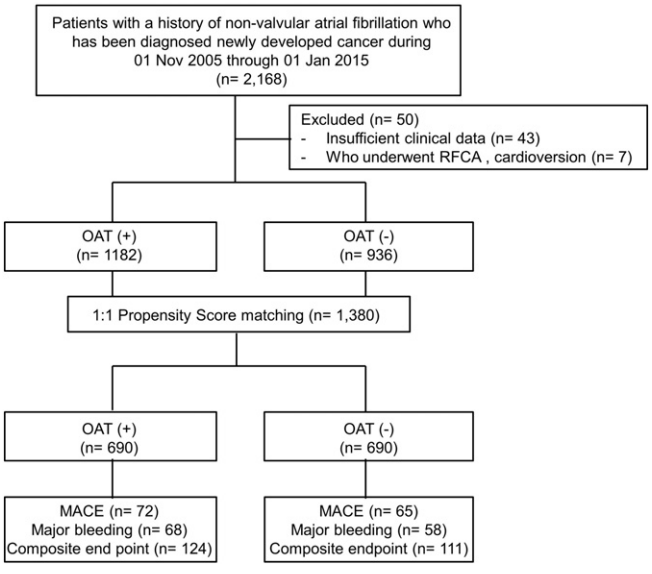

Fig. 1. Flowchart for patients participating in the trial. OAT = oral anticoagulation therapy; RFCA = radiofrequency catheter ablation; MACE = major advance cardiac events.

2.4. Statistical analysis

Continuous variables that were normally distributed were reported as the mean ± SD and were compared by use of a Student's *t*-test for parametric data and Mann–Whitney test for nonparametric data. Categorical variables were reported as the count (percentage) and were compared using a Chi-square or Fisher's exact test. The matched patient groups were compared using the paired *t*-test for continuous variables and the McNemar test for categorical variables.

To reduce the effect of selection bias and potential confounding in this retrospective cohort study, estimated propensity scores were used to match the patients who had OAT to patients who had no OAT. Propensity scores were estimated using a non-parsimonious multiple logistic regression model for OAT + and OAT − groups. The following variables were entered: age, sex, CHA_2DS_2-VASc and HAS-BLED scores. Cases then were matched, without replacement, with controls 1:1 based on the closest possible value of the propensity score (nearest neighbor matching). A matching caliper of 0.2 standard deviations of the logit of the estimated propensity score was enforced to ensure that matches of poor fit were excluded. The matching procedure was performed using R packages, including Matchit, RItools, and CEM (version 1.0, by Felix Thoemmes). Kaplan–Meier survival curves were plotted for the OAT + and OAT − groups and compared by means of the log-rank test. The SPSS statistical package (SSPS Inc., Chicago, Illinois) version 19.0 was used to perform all statistical evaluations. A p value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The clinical characteristics of the OAT + and OAT − groups are presented in Table 1. Compared with the OAT − group, the OAT + group was composed of more female patients (64% vs. 73%, $p < 0.001$), had a higher prevalence of hypertension (75% vs. 57%, $p < 0.001$), diabetes (38% vs. 30%, $p < 0.001$), a history of a stroke/transient ischemic attacks (12% vs. 3%, $p < 0.001$), and a history of brain hemorrhages (2% vs. 1%, $p < 0.001$). The CHA_2DS_2-VASc (3.5 ± 1.5 vs. 2.7 ± 1.4, $p < 0.001$) and HAS-BLED (4.1 ± 1.4 vs. 2.5 ± 1.5, $p < 0.001$) scores were higher in the OAT + group. After one-to-one propensity-score matching, baseline characteristics were well matched, except for the prevalence of hypertension (60% vs. 71%, $p = 0.012$), diabetes (28% vs. 35%, $p = 0.014$), liver disease (18% vs. 39%, $p < 0.001$), and alcohol use (40% vs. 51%, $p < 0.001$) (Table 1).

3.2. Incidence of MACEs and major bleeding

The incidence rates of MACEs and major bleeding for the matched population are presented in Table 2. During the follow-up period of 3.9 ± 2.8 years, there was no significant difference in MACEs between the OAT + and OAT − group. (10% vs. 9%, $p = 0.461$). While 55 (8%) patients developed strokes in the OAT + group, 47 (7%) patients developed strokes in the OAT − group ($p = 0.361$). Fig. 2A shows the Kaplan–Meier cumulative survival free of MACEs according to OAT + and OAT − in propensity score-matched patients. There was no significant difference between the 2 groups ($p = 0.505$). Furthermore, there was no significant difference in major bleeding between the OAT + and OAT − group (10% vs. 8%, $p = 0.300$). While 18 (3%) patients developed CNS bleeding in the OAT + group, 14 (2%) patients developed CNS bleeding in the OAT − group ($p = 0.444$). Different from MACEs, a generous portion of major bleeding events was gastrointestinal bleeding in both OAT + and OAT − group (45/68 [66%], 43/58 [74%]). Fig. 2B shows the Kaplan–Meier cumulative survival free of major bleeding according to OAT + and OAT − in propensity score-matched patients. There was no significant difference between the 2 groups ($p = 0.397$).

The incidence rates of MACEs and major bleeding for the total population are presented in supplemental Table 1. The Kaplan–Meier cumulative survival free of MACEs and major bleeding according to OAT + and OAT − in total patients are presented in supplemental Fig. 1.