Non-vitamin K antagonist oral anticoagulants in cancer patients with atrial fibrillation

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Abstract

To the best of our knowledge, non-vitamin K antagonist oral anticoagulants (NOACs), or direct oral anticoagulants, have not been tested in randomized trials conducted in patients with atrial fibrillation (AF), affected by malignant disease. However, their use in patients with cancer is increasing, while real-life evidence for their effectiveness and safety in this vulnerable subset of patients is growing. The challenges of the use of NOACs in cancer patients with AF and current expert opinion on this subject have been summarized in this review article. *(Anatol J Cardiol 2020; 23: 10-8)*
Keywords: anticoagulation, atrial fibrillation, bleeding, cancer, direct oral anticoagulants

Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs), or direct oral anticoagulants, are approved for treatment of stroke prevention in patients with nonvalvular atrial fibrillation (AF) and therapy of venous thromboembolism (VTE) encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE) (1-3). The NOACs currently available in Europe include three direct factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban, and one direct thrombin inhibitor, dabigatran. NOACs offer a number of important advantages over vitamin K antagonists (VKAs), such as a predictable dose response, fewer drug and food interactions, and no need for laboratory monitoring of the international normalized ratio (INR) or other coagulation tests (3–6). Long-term VKA therapy is fraught with several inconveniences, including multiple food and drug interactions, need for INR monitoring, frequent bleeding complications, and difficulties in the optimal INR maintenance (7–9).

When 71,000 patients with AF treated with NOACs were compared to those using warfarin, there was a 19% reduction in the occurrence of stroke or systemic embolism (SE), a 10% reduction in all-cause mortality, and a 50% reduction in both hemorrhagic stroke and intracranial bleeding (1). However, in contrast to the patients with VTE, NOACs used in patients with AF were associated with a 25% relative increase in major gastrointestinal bleeding, which is likely due to different patient characteristics (in particular concomitantly used antiplatelet drugs) and treatment duration (1).

The current European guidelines published in 2016 stated that NOACs should be preferred over VKA in most AF patients, except for individuals with severe or moderate mitral stenosis, and those following implantation of mechanical prosthetic heart valve (10). Evidence on the safety and effectiveness of NOAC in cancer patients is rather weak and largely observational as compared to high-quality data from randomized controlled trials (RCTs) supporting the use of NOAC in AF patients without active cancer.

Epidemiology of atrial fibrillation in cancer patients

It is estimated that the percentage of patients with diagnosed cancer, who had paroxysmal, persistent, or chronic AF is approximately 2.5%. Moreover, 2% of cancer patients experience AF for the first time in the first months following the cancer diagnosis (11–15). Of note, in the registries of patients with AF, e.g., ORBIT-AF, up to 20% of the subjects had a history of malignant disease (16). Based on the clinical practice in noncancer AF patients, about 80% of cancer cases with AF have indications for chronic anticoagulation, given the stroke risk estimation based on the CHA_2DS_2-VASc scoring system. However, despite the recognized pro-thrombotic state during its duration, the tumor is not

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included in this scale, and it has not been validated in cancer patients (11). Patell et al. (17) showed that in cancer patients with AF, the $CHADS_2$ score had a higher predictive value for ischemic stroke than the CHA_2DS_2-VASc score, and that it also predicted an increased risk of death [relative hazard (HR) 1.24; 95% confidence interval (CI) 1.17–1.32]. Hu et al. (18) made similar observations in cancer patients with previously diagnosed AF, and they reported that the risk of a thromboembolic event reaches 27% when the patient has 4–6 points on the $CHADS_2$ scale, at 0–1 point of 6.7%, and at 2–3 points of 15.8%, but without affecting mortality in this group of patients. A large Danish observational study (19) involving 122,053 patients without oral anticoagulation or heparins, hospitalized due to AF between 2000 and 2015 and followed for 2 years, showed that in cancer patients with AF (10%, n=12.014), the risk of stroke and peripheral embolism was increased compared to patients not affected by cancer. One point in the CHA_2DS_2-VASc score was associated with a risk of such thromboembolic incidents four times higher in AF patients with cancer compared to those free of cancer. In addition, it was demonstrated in this study that the highest risk of bleeding occurs in patients with AF and concomitant cancer at 0–1 points in the CHA_2DS_2-VASc score, with up to two times higher risk of bleeding when cancer is present (19).

Key evidence regarding the use of NOACs in patients with cancer came from studies performed in patients with VTE. Two randomized controlled trials in which edoxaban and rivaroxaban were evaluated, namely the Hokusai VTE Cancer trial and SELECT-D trial, respectively, showed a significant increase in the risk of gastrointestinal bleeding in patients with acute VTE who were treated with these anticoagulants compared to dalteparin therapy, and they should also be taken into account in patients with AF, who are usually 10 years older and have more comorbidities (20, 21). Although edoxaban 60 mg once daily (q.d.) was not inferior to subcutaneous dalteparin with respect to the composite outcome (recurrent VTE and major bleeding), in the secondary analysis, its use was associated with a lower risk of recurrent VTE (HR, 0.71; 95% CI 0.48–1.06) and a higher risk of major bleeding (HR, 1.77; 95% CI 1.03–3.04), especially among patients with gastrointestinal cancer (20). In the SELECT-D study on cancer patients with symptomatic DVT or PE, the population was characterized by a high prevalence of colorectal and lung cancer (25% and 12%, respectively), advanced neoplastic disease with metastases (58%), and anticancer treatment (69%), mainly chemotherapy. In this group, rivaroxaban 15 mg bid for 3 weeks followed by 20 mg q.d. for 6 months showed a 57% reduction in the recurrence rate of VTE and almost a double risk of clinically relevant non-major bleeding (HR, 1.83; 95% CI 0.68–4.96) compared to the dalteparin group. The bleeding risk was the highest in the patients with esophageal/gastroesophageal and urologic cancer (21). Registry data suggest an increase in the NOAC/VKA-associated bleeding in cancer patients with recent bleeding (<30 days), metastatic disease, advanced chronic kidney failure, and immobility longer than 4 days compared to other patients with cancer (22). It might be speculated based on data for VTE that the safety of NOACs might be similar in AF patients without lower efficacy.

Current data indicate that the risk of thromboembolism in patients with AF and cancer differ among different types of cancer. The greatest thromboembolic risk has been observed in pancreatic, ovarian, brain, and lung cancer, and in some hematological diseases, especially multiple myeloma. Disseminated disease obviously increases the risk of thromboembolism in the venous and arterial system. Other factors increasing the risk of stroke or peripheral embolism in patients with cancer include the prothrombotic action of several anticancer drugs, especially cisplatin, gemcitabine, 5-fluorouracil, and erythropoietin (2, 23).

Cancer during treatment may increase the risk of AF or increase the incidence of paroxysmal AF through chest surgery (including lung cancer) and the specific effects of some drugs, among which ibrutinib used in chronic leukemia is the best example of this effect.

There is consensus that cancer is associated with an increased risk of bleeding (12, 14), which implies a higher rate of severe bleeding during anticoagulant therapy to prevent ischemic cerebrovascular events, also among patients with cancer. Among bleeding scoring systems validated in patients with AF, only the $HEMORR_2HAGES$ bleeding risk assessment scale includes cancer as a risk factor for bleeding in AF, and data on the relationship of this disease as a whole to bleeding in AF still remain unclear (24, 25). The main risk factors for bleeding in cancer patients are;

- Thrombocytopenia with or without impairment of platelet function,
- Liver damage (usually through liver metastases),
- Kidney damage (e.g., cisplatin, contrast agents, and non-steroidal anti-inflammatory drugs are nephrotoxic),
- Damage to the vessel by a tumor infiltrating its wall (especially in the case of kidney cancer and malignant melanoma at the dissemination stage),
- Invasive procedures including surgical procedures and radiation therapy (2, 14).

NOACs in patients with cancer in seminal trials

European and American experts do not recommend a specific strategy for the prevention of thromboembolic events in cancer patients with AF. The rationale is that there is the lack of high-quality evidence.

In RCTs testing NOAC versus warfarin in nonvalvular AF studies, subjects with active cancer were not enrolled (26). The direct exclusion criteria included malignancy or radiation therapy within 6 months (for dabigatran in the RE-LY study), active malignancy or anticancer therapy within 5 years (edoxaban, ENGAGE-AF TIMI 48 study), and intracranial neoplasms (rivaroxaban, ROCKET-AF study). Two RCTs (ARISTOTLE with apixaban and ROCKET-AF with rivaroxaban) indirectly excluded numerous cancer patients by listing the exclusion criteria such as life ex-

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pectancy <1 or 2 years (27). In the seminal trials of NOACs for patients with AF, the number of patients with cancer was small, between 4.5% and 6.8%. In addition, in many trials, information on the type of cancer, the stage, and anticancer treatment were not collected. A retrospective analysis of these trials and a low number of AF patients with cancer hampered drawing firm conclusions on the NOACs use.

In the ARISTOTLE study comparing apixaban with warfarin, a total of 1236 patients (6.8%) had a history of cancer, including 157 (12.7%) with active disease or receiving anticancer treatment within the past year. The majority of cancers groups were solid tumors, including prostate (42%), breast (11%), colon (8%), and bladder cancer (9%) in the active cancer group. Patients with gastric and lung cancer, leukemia, and lymphoma constituted less than 3% of the study population. This study showed similar benefits of apixaban 5 mg bid in both groups, i.e., with and without cancer, and a combined analysis of death, stroke, peripheral embolism, and myocardial infarction showed a lower risk of this endpoint in patients with AF and active cancer during apixaban use (vs. warfarin, HR 0.30; 95% CI 0.11–0.83) compared to those not affected by this disease (HR 0.86; 95% CI 0.78–0.95). In the subgroup analysis, patients with non-active (remote) cancer receiving apixaban had higher rates of death from any cause (vs. warfarin, HR, 1.63; 95% CI, 1.04–2.56), driven mainly by non-cardiovascular deaths, although this group was highly heterogeneous (13, 28). In the ROCKET-AF study comparing rivaroxaban with warfarin, 640 patients (4.5%) had a history of cancer, with the highest prevalence of solid locally advanced tumors, i.e., prostate (28.6%), colorectal (16.1%), breast (14.7%), and genitourinary cancer (12.2%) (29). The risk of ischemic stroke per year was approximately 1.4% in patients with AF and cancer, and the risk of clinically significant bleeding was two times higher compared to patients with AF not affected by cancer (22.6 vs. 14.3%) (13). There were no significant differences in the rates of stroke or SE, or clinically relevant bleeding between patients treated with rivaroxaban compared to warfarin. A trend toward a lower risk of hemorrhagic stroke, critical organ bleeding, and fatal bleeding was observed in the rivaroxaban group. A total of 50 patients (0.4%) underwent active anticancer treatment, with the majority receiving hormonal therapy: leuprolide acetate and bicalutamide for prostate cancer, or anastrozole and tamoxifen for breast cancer. During the follow-up, two deaths, one ischemic stroke, and seven bleeding events were reported in the rivaroxaban group, whereas among those treated with warfarin, three deaths, one hemorrhagic stroke, and eight bleeding events were observed (29).

In the subgroup analysis of the RE-LY trial, the risk of bleeding in AF patients with cancer was two to six times higher than in patients without cancer (13).

Investigators from the ENGAGE-AF TIMI 48 study reported a total of 1153 patients (5.5%) who developed new or recurrent malignancy after randomization, including cancer involving the gastrointestinal tract (20.6%), prostate (13.6%), and lung (11.1%) (28). The risk of death and major bleeding was (+8.4% and +4.9% per year) higher in patients with AF and cancer compared to patients with AF not affected by cancer, with no difference in the risk of stroke and SE (2.0 vs. 1.8%/year). Solid tumors (93.8%) compared to other malignancies (hematologic or skin) were associated with a higher risk of stroke and SE (HR, 3.92; 95% CI, 1.21–12.69), but not bleedings (HR, 1.56; 95% CI, 0.96–2.53). Edoxaban 60 mg q.d. demonstrated a 46% risk reduction of the composite ischemic end-point (ischemic stroke/systemic embolism/myocardial infarction) in the group with AF and malignancy (HR, 0.54; 95% CI, 0.31–0.93), without difference in major bleeding and deaths compared to warfarin. Edoxaban 30 mg q.d. was as effective and safe as warfarin in the AF and malignancy group (28).

Observational studies and real-life evidence for NOACs

An observational, retrospective study involving 16,096 patients from the MarketScan database with AF and cancer treated with VKA (62.3%) and NOACs [rivaroxaban (17.4%), dabigatran (13.6%), apixaban (6.7%)] showed that treatment with apixaban is associated with a significantly lower risk of major bleeding (HR, 0.37; 95% CI, 0.317–0.79) compared to VKA, rivaroxaban, or dabigatran. Rates of ischemic stroke did not differ in head-to-head comparisons among NOACs and VKA. In addition, all NOACs were associated with a 50%–85% reductions in the rate of VTE compared with warfarin with the lowest rates of VTE and severe bleeding for apixaban. This real-life population observed for a mean follow-up of 12 months was characterized by a high prevalence of breast cancer (19.3%); followed by lung cancer (12.4%), genitourinary (29.3%), and gastrointestinal (12.7%) cancers; and intensive treatment, including chemotherapy (22.0%), and hormonal (12.7%) and radiation therapy (11.4%) (30, 31). To the best of our knowledge, no other specific clinical trials have been conducted comparing the use of NOAC versus VKA in cancer patients.

Heparins in patients with cancer

Low-molecular-weight heparin (LMWH) is not recommended for the chronic prevention of stroke in patients with AF. This class of drugs is even contraindicated in the secondary prevention of ischemic stroke in patients with acute stroke, and this also applies to patients with cancer. Malavasi et al. (32) reported over 4,500 patients admitted to the oncology ward and showed that 8.4% of patients have AF (partially recently detected AF, secondary to acute condition), and only 41% received full anticoagulation, of which 78.1% used LMWH (a similar percentage of therapeutic and prophylactic doses of LMWH), 20% VKA, and 1.9% NOACs. There was no relationship between the type of cancer, its severity, or the CHA_2DS_2-VASc score and the use of anticoagulant therapy, or a lower risk of death in patients receiving some form of anticoagulation. However, no thromboembolic or hemorrhagic risk was reported in this study. Critics of the use of LMWH in AF patients with indications other than bridging therapy, e.g., in the perioperative period, or the use of chemotherapy

with strong side effects including vomiting, provided the following arguments;

- Prophylactic dosing of LMWH in patients with AF is not effective since AF is not a risk factor for VTE for which such a strategy has been evaluated and recommended.
- The risk of bleeding is similar in patients with cancer receiving LMWH or VKA.
- If the use of LMWH at different doses does not affect survival, it would be cheaper, safer, and less burdensome to refrain from administering LMWH at all in cancer patients with AF (12).

It has been shown that cardiac care in the first months after the diagnosis of cancer in a patient with AF results in a significantly higher percentage of patients treated with anticoagulants (HR, 1.48; 95% CI, 1.45–1.52) with a reduction in ischemic strokes (HR, 0.89; 95% CI, 0.81–0.99) and without an increase in bleeding (HR, 1.04; 95% CI, 0.95–1.13) (33). The crucial role of patient education about anticoagulant therapy with VKA or NOAC in a high-risk population is underlined by the European Heart Rhythm Association guidelines (2, 34). The involvement of a cardiologist in cancer care also resulted in a more frequent treatment to control heart rhythm in patients with AF. The effects were greatest in patients with the most thrombogenic tumors, e.g., colorectal, stomach, lung, or pancreatic cancer. The support of cardiologists for oncologists in the case of patients with AF seems to be deliberate and beneficial for this group of patients in the light of available data, often with other cardiac diseases, encouraging integrated care.

Coronary interventions in anticoagulated cancer patients

Aspirin (ASA) and/or clopidogrel with an anticoagulant should be combined in patients with cancer previously treated with anticoagulants, who have been diagnosed with acute coronary syndrome (ACS) (35). The use of ticagrelor or prasugrel in patients with cancer is not recommended. The administration of NOAC and antiplatelet agents may be considered with caution if the patient is not within the first months following the cancer diagnosis when the risk of bleeding is the highest. In practice, regardless of the current anticoagulant treatment, the diagnosis of ACS in anticoagulated cancer patients begins the administration of LMWH or, more rarely, unfractionated heparin. The premises for such a strategy, in addition to a wide availability of LMWH, are long-term experience and easy strategy of interruption of anticoagulant treatment due to invasive diagnostic or therapeutic procedures in relation to cancer. It has been suggested that LMWH is more effective than VKA in patients with cancer (27).

As cancer patients with ACS and AF are the high-bleeding risk group, triple anticoagulation therapy is rarely administered, i.e., ASA+clopidogrel+LMWH/VKA, except when the outpatient is in a good or fairly good condition without thrombocytopenia in the chronic phase of treatment, and the prognosis is optimistic (36). Most of the centers for cancer patients with AF and ACS, especially those transferred from wards where they undergo intensive cancer treatment in the first weeks of the cancer diagnosis, prefer dual antithrombotic therapy, i.e., clopidogrel+LMWH/VKA (37). The duration of such therapy for chronic anticoagulation is up to 12 months and depends on the cancer stage and bleeding risk or cardiac ischemia during therapy. In the event of unacceptable bleeding, therapy is shortened to 1 month or even the first few days following the symptom onset.

If urgent oncological surgery is required in patients in the first weeks (especially the first six) after ACS, clopidogrel should be discontinued 5 days before surgery, continuing ASA therapy, or ASA should be introduced if previously only clopidogrel with an anticoagulant was used (except for patients with gastric or esophageal cancer, etc.). After surgery, clopidogrel should be started again, initially at a loading dose (300 mg), followed by a maintenance dose (75 mg) 24–72 hours after surgery with preserved hemostasis. In patients with high thrombotic risk, bridging therapy with tirofiban or eptifibatid intravenously 3 days before and discontinuation 4–6 hours before surgery may be considered after clopidogrel discontinuation (38).

If the clinical situation requires urgent surgery in patients receiving antiplatelet agents and NOACs, the risk of excessive bleeding in the perioperative period should be taken into account, but the anticoagulant effect of NOACs should be reversed or at least minimized. In this situation, an optimal four-factor prothrombin factor concentrate at a dose of 30–50 U/kg intravenously (e.g., Beriplex, Octaplex) is recommended in patients treated with rivaroxaban or apixaban. Andeksanet alfa, a specific reversal drug of these two NOACs was registered for use in the European Union in 2019, but its use is currently very limited due to high costs. Idarucizumab was approved at the end of 2015 and now is widely available for patients with AF treated with dabigatran in case of life-threatening bleeding, which is of utmost importance in patients with cancer (39).

The occurrence or higher initial risk of bleeding in patients with ACS increases in-hospital mortality (40). The occurrence of severe bleeding in cancer patients with AF following ACS often results in discontinuation of anticoagulants with potentially lethal thrombotic episodes, in particular, ischemic stroke. In the case of clinically significant nonmajor bleeding (e.g., epistaxis, hemoptysis, hematuria), combined therapy with a NOAC and an antiplatelet agent should be continued for at least a month. The anticoagulant can be discontinued for 1–3 days if bleeding symptoms are unacceptable to the patient or require invasive diagnostic procedure. In the event of major bleeding (decrease in hemoglobin >2 g/dL and hospitalization with or without blood transfusion), anticoagulation should be discontinued, and recovery after a minimum of 4–7 days with a subsequent shorter duration should be considered.

Interactions of NOACs with anticancer drugs

Several anticancer drugs that are inhibitors or inducers of P-glycoprotein or CYP3A4 also interfere with the anticoagulant effect of NOACs, although most data on this topic are given as expected effects from molecular mechanisms described *in vitro*.

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Usually, when these drugs are combined, the anticoagulant effect is enhanced by inhibiting CYP3A4 (no such effect in dabigatran, and approximately 20% for apixaban and rivaroxaban) and/or P-glycoprotein, which is responsible for reverse NOAC secretion (applies to all NOACs) (Table 1). Strong NOAC interactions that significantly reduce their anticoagulant effect are rare with oncological drugs (Table 2). However, several NOACs do not interact significantly with anticancer drugs and can be used at typical doses. It should be highlighted that there are no published or ongoing randomized trials assessing NOAC in patients with AF and cancer with uncertain conclusions about their efficacy and safety based on observational studies. When using anticoagulants to prevent stroke in cancer patients, it is important to remember that there are possible interactions with chemotherapeutic agents, which implies the need for more frequent visits to the clinic and an assessment of the often dynamically varying risk of bleeding and stroke.

It is unclear whether a laboratory assessment of anticoagulant effects of NOACs can optimize their use among patients with cancer in whom the renal function impairment or drug–drug interactions are likely to alter such effects (41, 42).

NOACs in cancer patients with thrombocytopenia

It is estimated that 10%–25% of patients with cancer have thrombocytopenia, defined as a platelet count T<100,000/μL (37, 43, 44). The presence of thrombocytopenia as a consequence of chemotherapy increases the risk of hemorrhagic complications and other cardiovascular incidents (45). While NOACs have been tested in the general population, no specific randomized trials have been conducted evaluating NOACs use in cancer patients with AF and thrombocytopenia. The platelet count <90,000 or 100,000/μL was an exclusion criterion in the ARISTOTLE, ENGAGE-AF TIMI 48, RE-LY, and ROCKET-AF trials (27). Our research showed that in 62 AF patients with mild thrombocytopenia, a reduced dose of NOACs could be effective and safe when compared to the use of recommended dose in AF patients with a normal platelet count during a median follow-up of 55 months (46). A recent analysis of patients with AF from Taiwan (4.4%) with thrombocytopenia showed that in 181 who used NOACs, there was a tendency for lower risk of major bleeding (HR, 0.45; 95% CI, 0.16–1.14) and a similar risk of ischemic stroke (HR, 0.94, 95% CI, 0.29–2.91) or death (HR 0.95; 95% CI, 0.46–1.95) when compared with warfarin therapy (n=186), and authors concluded that "NOAC therapy is a reasonable choice for stroke prevention in AF patients with thrombocytopenia" (47).

However, in AF patients with a platelet count <50,000/μL, an individualized approach to anticoagulant therapy with a frequent bleeding risk assessment is required. No NOACs are used in patients with severe thrombocytopenia. Especially if bleeding symptoms occur.

Nausea and vomiting in cancer patients and the use of NOACs

Because oncological treatment often has nausea and vomiting, specialists have developed recommendations for the use of

Table 1. Characteristics of most commonly used NOACs (50)

	Dabigatran bid	Rivaroxaban q.d.	Apixaban bid
Action	Direct thrombin inhibition	Direct inhibition of active factor X	Direct inhibition of active factor X
The onset of the anticoagulant effect	0.5-2 h	2-4 h	1-4 h
Anticoagulation effect (half-life)	12-14 h	5-9 h (young) 11-13 h (>65 y.o.)	8-13 h
P-glycoprotein transporter substrate	Yes	Yes	Yes
CYP enzyme substrate	No	Yes (CYP3A/5, CYP2J2)	Yes (CYP3A4, CYP2C9)
Elimination	80% renal	33% renal	25% renal
Protein binding	35%	90%	90%
The basic daily dose in AF	2x150 mg	1x20 mg	2x5 mg
Reduced dose in AF *considered to be at high risk of gastrointestinal bleeding in patients with atrial fibrillation	2x110 mg*	1x15 mg*	2x2.5 mg
Indications for dose reduction	-age ≥80 years -co-administration of verapamil	-CrCl, 15–49 ml/min	-creatinine ≥133 μM -age ≥80 years -weight ≤60 kg 2 or 3 criteria met

AF - atrial fibrillation; CYP - cytochrome P; CrCl - creatinine clearance

Table 2. Interactions of anticancer drugs with NOAC

No effect on NOAC dosage	
Antimetabolites	Methotrexate, analogues of purines and pyrimidines
Topoisomerase inhibitors	Topotecan, irinorekan, etoposide
Anthracyclines	Daunorubicin, mitoxantrone
Alkylating drugs	Busulfan, bendamustine, chlorambucil, melphalan, carmustine, pro-carbazine, dacarbazine, temozolomide
Platinum preparations	Cisplatin, carboplatin, oxaliplatin
Intercalating drugs	Bleomycin, dactinomycin, mitomycin C
Tyrosine kinase inhibitors	Erlotinib, gefitinib
Immunomodulatory drugs	Everolimus, sirolimus
Enhanced anticoagulant effects of NOAC activity. Consider dose reduction.	
Immunomodulatory drugs	Ciclosporin, tacrolimus (strongest for dabigatran–do not use in com-bination)
Hormonal drugs	Tamoxifen
Alkylating drugs	Ifesfamide, cyclophosphamide, lomustine (for rivaroxaban and apixaban)
Tyrosine kinase inhibitors	Nilotinib, dasatinib
Impaired anticoagulant effects of NOAC. Use full-dose regimen	
Antimitotic drugs	Docetaxel, vincristine, vinorelbine, paclitaxel (for rivaroxaban and apixaban)
Immunomodulatory drugs	Prednisone
Do not use; strong interaction with NOAC. Effect on NOAC	
Hormonal drugs	Abiratoren (increase of activity)
Tyrosine kinase inhibitors	Imatinib, crizotinib (potentiation)
Antimitotic drugs	Vinblastine (weakening of action)
Anthracyclines	Doxorubicin (weakening of effect)
Immunomodulatory drugs	Dexamethasone (weakening of effect)

NOAC - non-vitamin K antagonist oral anticoagulants

NOAC in such a situation (48). During oncological treatment, the following suggestions should be considered:

- Use anti-emetic drugs (they do not interact significantly with NOACs).
- Do not change treatment if vomiting occurs >2 hours after taking NOACs.
- Consider temporary transition to LMWH when anti-emetics should be used during chemotherapy >3 days.
- Consider temporary transition to LMWH when there are symptoms of oral mucositis (especially in head and neck cancer).
- Do not use NOACs for gastrointestinal obstruction, but it is possible to administer apixaban or rivaroxaban after crushing the tablet to the probe or by gastro- or jejunostomy.
- The patient should be provided with LMWH (1–2 packages) if severe nausea or vomiting is likely after discharge from the hospital.

The use of NOACs in patients with cancer undergoing chemotherapy depends on the risk of nausea or vomiting. In patients at low risk of nausea or vomiting, NOAC should be used together with anti-emetic agents (if indicated). In patients at intermediate or high risk of nausea or vomiting, an assessment of the AF risk should be performed. At the low risk of thromboembolism, NOAC should be continued along with an anti-emetic treatment; however, patients should be provided with 1–2 packages of LMWH. In case of nausea/vomiting that lasts >24 hours, the patient should stop NOAC and use an anticoagulant parenterally until symptoms subside. At the high risk of stroke, NOACs should be stopped, and a parenteral anticoagulant together with an anti-emetic should be used.

NOAC treatment in patients with cancer undergoing radiotherapy depends on the risk of vomiting. At a low risk of stroke, patients with AF should take NOAC and anti-emetic treatment (if indicated). In patients at intermediate or high risk of nausea or vomiting, an assessment of the stroke risk should be performed, and the algorithm of treatment is the same as in patients during chemotherapy at low or high risk of stroke in AF, respectively.

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Recommendations

The SSC ISTH guidance from August 2019 regarding the use of NOACs in nonvalvular AF among cancer patients receiving chemotherapy (30% of all cancer population) states the following:

1. Individualized anticoagulation is recommended based wherever possible on the risk of stroke, bleeding, and patient values. Decision making should be shared with the patients.
2. The continuation of anticoagulation started before chemotherapy is recommended, unless there are clinically relevant drug-to-drug interactions.
    a. NOACs should be considered in cancer patients on chemotherapy with clinically relevant VKA interactions or no close monitoring of VKA, if no additional drug-to-drug interactions with NOACs are expected.
    b. Parenteral anticoagulation with therapeutic dosing of LMWH with resumption of oral anticoagulation as soon as possible is suggested in patients on chemotherapy who are unable to tolerate oral administration (e.g., due to nausea and vomiting).
3. The use of a NOACs over a VKA or LMWH is suggested in patients on chemotherapy with newly diagnosed AF, with the exception of patients with luminal gastrointestinal cancers with an intact primary or patients with active gastrointestinal mucosal abnormalities, such as duodenal ulcers, gastritis, esophagitis, or colitis, if no clinically relevant drug-to-drug interactions are expected (27).

The European Heart Rhythm Association practical guide published in 2018 recommends interdisciplinary teamwork to cope with an increased thromboembolic and bleeding risk in cancer patients with AF, which includes the following:

1. Estimation of individual patient risk profile:
    a. AF-related risk factors (CHA_2DS_2-VASc, bleeding risk)
    b. Cancer-related risk factors (type, liver metastases, coagulopathy, renal/hepatic function, etc.)
    c. Treatment-related risk factors (thrombocytopenia, surgery, radiation, central lines, etc.)
2. Choosing an anticoagulant
    a. Current standard of care: VKA/LMWH. If oral therapy is not possible, reversion to LMWH is reasonable.
    b. NOACs: Available data scarce, but encouraging.
    c. Consider patient preference (VKA vs. NOAC).
3. Patient protection
    a. Gastric protection (proton-pump inhibitors/H2 blockers)
    b. Awareness of drug-to-drug interactions
    c. Dose reduction/treatment interruption (if platelets <50,000/μL, renal dysfunction, bleeding, etc.) (2, 7).

The European Society of Cardiology Position Paper from 2016 on cancer treatments and cardiovascular toxicity states the following:

- The decision on antithrombotic therapy for stroke prevention should not be based only on the risk assessment scores (e.g., CHA_2DS_2-VASc). Decisions on anticoagulation should be individualized and consider other co-morbidities, bleeding risks, and patient values and preferences
- Anticoagulation options include VKA if the INR control is stable and effective, LMWH (as a short-to-intermediate term measure), and NOAC.
- In patients with high risk (CHA_2DS_2-VASc score ≥2), anticoagulation can generally be considered if the platelet count is >50,000/μL, usually with a VKA and good anticoagulation control, with time in the therapeutic range >70%.
- In lower-risk patients with AF, prophylaxis may be considered given the risk of VTE in patients with cancer.
- The role and safety of NOACs in this patient group remains to be clarified; however, large NOAC trials suggest their safety (49).

Conclusion

Every cancer patient with AF at high risk of ischemic stroke should be treated according to current recommendations, with the use of anticoagulant agents. NOACs should be preferred unless there are strong contraindications. The strategy of long-term anticoagulation requires a multidisciplinary team involving an oncologist and a cardiologist. The benefits and risks of the use of NOACs in this specific patient group should be balanced and assessed regularly in each patient who requires anticoagulation. In cancer patients with AF, NOACs should be considered as the first choice, especially in patients with a favorable prognosis without potent drug-to-drug interactions. The effects of LMWH in stroke prevention are not certain, and therefore, heparins should not be used in patients with AF on the long-term basis. Given a growing number of cancer patients, as well as AF patients in the aging society, NOACs represent an attractive therapeutic option in the prevention of arterial thromboembolism. However, more clinical trials focused on patients with cancer are required to optimize anticoagulant therapy.

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