

## How to Anticoagulate Patients with Heart Failure and Cancer?

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Patients with cancer have a high risk of deep vein thrombosis and pulmonary embolism, as well as a risk of developing atrial fibrillation (AF) secondary to antineoplastic treatment. These events have a poor prognosis and depend on factors related to the tumor and the ongoing therapy. They are usually elevated during the first 6 months of treatment.<sup>1</sup>

Many neoplasms may be associated with paroxysmal, persistent, or permanent AF in patients with cancer, and AF may arise as a direct effect of the cancer (extracardiac or intracardiac compression) or more frequently after surgery, as a complication of thoracic (postoperative thoracic or esophageal surgery) or abdominal (colon surgery) surgery. AF can also arise during or after chemotherapy or radiation therapy. This latter condition is underestimated, since information on drug-related AF is derived from case reports.<sup>2</sup>

Antineoplastic drugs can produce non-valvular AF by several mechanisms, and the most common are the release of pro-inflammatory proteins (cytokines), calcium homeostasis changes, and direct damage to the myocardium. Anthracyclines, for example, reduce the antioxidant effect of cardiomyocytes, and they increase vagal and adrenergic tonus, due to hypotension, myocardial ischemia, and hydroelectrolytic disturbances. These mechanisms are also induced by alkylating agents, gencitabine, fluorouracil, antimetabolic agents, docetaxel, rituximab, paclitaxel, and alemtuzumab.<sup>3</sup>

AF poses a challenge to managing antineoplastic therapy and predicting prognosis of cancer patients.<sup>4</sup> Anticoagulation in patients with AF becomes a major problem due to imbalance between the thromboembolic and bleeding risks that are high, due to both the cancer itself and the adverse effects of its treatment.<sup>2</sup>

New anticoagulant drugs have emerged. In 2009, dabigatran was the first direct oral anticoagulant (DOAC), a direct thrombin inhibitor as an anticoagulant alternative. Later came the factor Xa inhibitors, rivaroxaban, edoxaban, and apixaban that brought clinical studies of efficacy and safety, with the benefits that they do not need monitoring, and they have fewer drug interactions and better safety profile. Anti-

Xa DOACs have presented studies in the oncology patient population (SELECT-D, Hokusai Cancer, and Caravaggio), which have made their use in anticoagulation therapy in cancer patients feasible and safe.<sup>5-7</sup>

Apixaban has a dosage of 2 daily doses, a half-life of 12 hours, a maximum plasma concentration of 4 hours, and a renal clearance of 27%. It is mainly metabolized by CYP3A4.<sup>5</sup> Edoxaban has a dosage of 1 dose per day; its absorption and clearance depend on P-gp, and in cases of possible interactions, a 50% dose reduction is advocated. It is eliminated mainly by the kidneys (50%).<sup>6</sup> Rivaroxaban is the DOAC with the highest oral bioavailability ( $\geq 80\%$ ). Unlike other DOACs, its absorption requires food intake. Like apixaban, it is also metabolized mainly by CYP3A4/5 ( $\sim 18\%$ ). Its renal excretion is about 36%.<sup>7</sup> Knowing the metabolism of DOACs is important, because most antineoplastic drugs are metabolized by CYP, and their interaction can lead to a higher hemorrhagic or thrombotic risk depending on whether these drugs act as inducers (increase the risk of recurrence) or inhibitors (bleeders). Similar effects occur with P-gp inhibitor drugs.<sup>8</sup>

Heart failure and AF are closely related. These patients have even worse symptoms and poorer prognosis. When considering the cardiotoxic effects of antineoplastic therapies, this association in cancer patients adds an additional risk and a challenge to anticoagulant therapy.<sup>9</sup> We must evaluate not only the antineoplastic therapies, but also those that are used for heart failure. For example, amiodarone increases bleeding risk due to changes in plasma concentrations in concomitant use with apixaban and edoxaban; antiplatelet aggregating drugs increase bleeding risk.<sup>8,10,11</sup>

There is still discussion regarding prospects of widespread use among patients with AF or venous thromboembolism and cancer in addition to chronic kidney disease with creatinine clearance below 15 mL/min and/or undergoing hemodialysis. Apixaban, edoxaban, and rivaroxaban, through small clinical and pharmacokinetic studies, are the oral anticoagulants that have already been approved by the United States Food and Drug Administration for use in this patient profile.<sup>12</sup>

When establishing an anticoagulant therapy for these patients, we should consider their primary neoplasm, cardiovascular risks, the therapies that are being administered, the moment in their oncologic therapy, surgeries, chemotherapies, hemorrhagic and thromboembolic risk, and especially the drugs that are involved. Only after studying those coefficients, we propose an anticoagulant therapy that is more effective, safer, and individualized.

Unfortunately, we still do not have a specific risk score for cardioembolic events in patients with cancer and AF who require anticoagulation, such as the one used in the general population, CHADSVASC. Some small studies reinforce, however, that even patients with a CHADSVASC of 1 may

### Keywords

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be at increased risk of these phenomena, underscoring the importance of not failing anticoagulation for this cancer population.<sup>13</sup>

Considering the pharmacological characteristics of anti-Xa drugs, we observed that edoxaban has a safer profile during antineoplastic therapy due to the lower risk of bleeding and great applicability in the elderly. Apixaban is safer, with respect to bleeding risk, and rivaroxaban has more studies regarding extended anticoagulation therapies. However, the professional's experience in handling anticoagulant drugs is extremely important when prescribing them.

## Conclusion

Anticoagulation in oncologic patients is a huge challenge, and we must always consider the risks and benefits of this management. However, with the prescription of DOACs, it becomes easier, safer, and more effective. When we individualize a patient's therapy, according to the oncologic treatment, we can purpose the most appropriated strategy. We reinforce that, because of a high complex profile with several treatments, patients must be reevaluated periodically. In this way, we will further good medical practice.

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## Author Contributions

Conception and design of the research: Renni MJP; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Renni MJP, Marinho TAS.

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This study is not associated with any thesis or dissertation work.

## Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.



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