Cancer associated thrombosis (CAT). New evidence

Trombosis asociada a cáncer (TrAC). Nuevas evidencias

Trombose associada ao câncer (TrAC). Nova evidência

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For years, cancer has shown a systematic increase in frequency all over the world, international data show that from 1998 to 2012, incidence trends for all cancers (excluding nonmelanoma skin cancer) have increased in most countries across all age groups, with the greatest increase observed in adults aged > 75 years old in Ecuador with an average annual percentage change (AAPC) = +3%. Colorectal cancer incidence rates increased in most countries, across all age groups. Lung cancer rates among females have increased but decreased a little for males. Prostate cancer rates have sharply increased in men aged 50-64 with AAPC between 5% and 15% in 24 countries, while decreasing in the 75+ age group in 21 countries, by up to -7% in Bahrain. Female breast cancer rates have increased across all age groups in most countries, especially in the 65-74 age group and in Asia with AAPC increasing to 7% in the Republic of Korea.

Just in the USA, there were in 2019 around 1'752,735 new cancer cases reported and 599,589 people died of cancer, being the second cause of death. For every 100,000 people, 439 new cancer cases were reported and 146 people died of cancer. In Mexico, cancer is the third cause of death, 14 out of every 100 Mexicans die from this disease and the life expectancy of those who suffer it is around 63 years. In 2019, a total of 747,784 deaths were recorded in our country, of which 12% were due to malignant tumors (88,683), 51% in women. Therefore, it has been considered that Mexico is facing another pandemic, that of cancer, which highlights the social inequalities that unfortunately affect the country.

Over the past two decades, huge advances in cancer diagnosis and treatment have been made, including the use of high-dose chemotherapy, stem cell transplantation, targeted therapies and immunotherapy with a resultant increase in the number of people around the world living with a tumor, about two-thirds of patients diagnosed with malignancy survive more than five years after diagnosis, and soon almost 20 millions of American citizens will be living with a cancer diagnosis, and many more worldwide.

That is why the epidemiology of critically ill patients admitted to ICU's has changed in recent decades, including increasing numbers of cancer patients with a variety of problems. In recent years, patients with malignancy have been reported to account for 10% to 15% of all ICU admissions, and it is expected that this figure will increase in the following years. Intensive care for cancer patients is not only relatively new and fascinating, but also complex and full of future as advances are made in understanding their biology and new therapies are developed.

There are many reasons why a cancer patient may require admission to the ICU, either due to the disease per se or as a consequence of the treatment. The most frequent indications for cancer patients ICU admission include acute respiratory failure from infectious and noninfectious causes; neutropenic sepsis, oncologic emergencies such as tumor lysis syndrome, leukostasis and hypercalcemia, and postoperative monitoring and management of complications from high-risk cancer surgery, acute kidney injury, neurologic, cardiovascular and pulmonary complications, specially thrombosis in the form of venous thromboembolism (VTE), which classically includes both deep vein thrombosis of the lower extremities and pulmonary thromboembolism, without forgetting the possibility of tumoral pulmonary embolism resulting from the accumulation of circulating tumor cells at the level of the pulmonary microvasculature, producing flow obstruction without changes in the vascular architecture.

The association between cancer and thrombosis is so important that Khorana created a specific VTE risk score to estimate the risk in this population, useful in general cancer cases (solid tumors and lymphomas), but not in patients with brain tumors or myelomas). It consists in different variables such as the cancer type (stomach and pancreas: 2 points each, lung, lymphoma, gynecologic, bladder or testicular: 1 point each, (others: 0 points), prechemotherapy platelet count > 350,000 (plus 1 point), Hb level < 10 gm/dL or using RBC growth factors (plus 1 point), prechemotherapy leukocyte count > 11,000 (plus 1 point), and BMI > 35 kg/m^2 (plus 1 point).

CAT is therefore of interest to all medical specialties, including Critical Care Medicine; all contemporary textbooks in the specialty include a chapter on the cancer patient in the ICU and surely, we will read in the

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future a greater number of works on all these aspects around CAT in our journal.

It is considered in general that there are inherited and acquired thrombophilias, malignancy together with pregnancy, some medications, antiphospholipid antibody syndrome, some chronic diseases, obesity, smoking and COVID-19 belong to the last group.

Malignancy is present in up to 20% of VTE patients. The most common are lung, pancreas, colon, kidney and prostate, although the risk is higher in pancreatic cancer, so we must consider administering prophylaxis in high-risk patients (lung, pancreas) receiving chemotherapy. In CAT patients there is also a higher risk for recurrence as well as a higher risk for major bleeding than in similar patients with VTE but without a cancerous disease. It is known that active cancer like other factors as one or more previous episodes of VTE in the absence of a major transient or reversible factor and the antiphospholipid syndrome, is considered a high risk for long-term recurrence (> 8% por year).

Prophylaxis, of which the LMWH has been a standard until recently in the cancer patient for more than 20 years, as well as a correct and timely treatment is of paramount importance in patients with CAT inside and outside the ICU.

We know that warfarin is not effective in cancer patients, and that LMWH (probably bid) is no longer a standard in this population. New data supports the target specific oral anticoagulants (TSOAC's) use in cancer patients.

There are many studies, one of them by Raskob et al comparing in an open-label, non-inferiority study oral edoxaban vs SC dalteparin in cancer patients-related VTE, the Hokusai trial. The experimental arm received LMWH > 5 days, followed by edoxaban 60 mg per day (n = 522), vs the control group receiving dalteparin 200 mg/day for one month, followed by the same drug 150 mg per day (n = 524). The results were tied as the mixed outcome variable recurrent VTE or major bleeding were lesser in the edoxaban group (67, 12.8%) than in the dalteparin group (71, 13.5%), p value of 0.006 for noninferiority, and 0.87 for superiority (a difference of just 0.7 porcental points between groups). But when considering these outcomes individually, recurrent VTE was surprisingly smaller: 41 patients (7.9%) vs 59 (11.3%), p = 0.09 in the edoxaban group, but major bleeding was apparently the problem: 36 patients in the edoxaban group (6.9%) bled, against 21 patients in the dalteparin group (4.0%), p = 0.04. Non-major bleeding was around the same: 76 (14.6%) in the edoxaban group, vs 58 (11.1%), in the dalteparin one. (p-NS). Although the group size was acceptable (1,046 patients) it did not reach the necessary size to find statistical differences. It is very possible that data coming from a bigger population (GUSTO trial-like) will

show significant statistical differences if these figures could be reproduced.

In a recent systematic review and trade-off analysis of four RCT's involving 2,894 patients, TSOAC's were more effective than dalteparin in reducing the risk of recurrent VTE (RR: 0.62, 95% CI: 0.44-0.87), with a comparative risk of major bleeding (RR: 1.33, 95% CI: 0.84-2.11) and an increased risk of clinically relevant bleeding (RR: 1.45, 95% CI: 1.05-1.99). No significant difference was observed among individual anticoagulants in terms of recurrent VTE and major bleeding.

In the CASSINI study in 2019, a double-blind, thromboprophylaxis, randomized, placebo-controlled trial involving high-risk ambulatory patients with cancer (Khorana score of ≥ 2), authors randomly assigned patients without deep-vein thrombosis (DVT) at screening to receive rivaroxaban (at a dose of 10 mg) or placebo daily for up to 180 days, with screening every eight weeks. Of the 841 patients who underwent randomization, the primary end point occurred in 25 of 420 patients (6.0%) in the rivaroxaban group and in 37 of 421 (8.8%) in the placebo group (hazard ratio, 0.66; 95% CI, 0.40 to 1.09; p = 0.10) in the period up to day 180. Major bleeding occurred in 8 of 405 patients (2.0%) in the rivaroxaban group and in 4 of 404 (1.0%) in the placebo group (hazard ratio, 1.96; 95% CI, 0.59 to 6.49); is in this way that a benefit of treatment with rivaroxaban was not establish, because the between-group difference in the prespecified primary efficacy endpoint up to day 180 was not significant.

That is why in the 2019 version of the European Society of Cardiology (ESC) Guidelines, both edoxaban and rivaroxaban were equally considered as an alternative to weight-adjusted SC LMWH in patients without gastrointestinal cancer, a class IIa recommendation, with the difference in the level of evidence: B level for edoxaban and C for rivaroxaban.

The Caravaggio trial findings were presented later, at the virtual ACC 2020 Scientific Sessions; a multinational, randomized, investigator-initiated, open-label, noninferiority trial with blinded central outcome adjudication. In it apixaban therapy was as effective as LMWH therapy for the prevention of recurrence of VTE in patients with cancer, with no increase in major bleeding events. This trial included patients with symptomatic or incidental acute proximal DVT or PE who were randomly assigned to receive oral apixaban or SC LMWH (dalteparin) at standard regimens. During the 6-month treatment period, recurrent VTE (the primary efficacy endpoint) occurred in 5.6% of 576 patients in the apixaban group and in 7.9% of 579 patients in the LMWH group, which met the requirement for noninferiority (HR 0.63, 95% CI 0.37-1.07, p < 0.001). The rate of major bleeding events was similar in both

groups: 3.8% versus 4.0% (hazard ratio, 0.82; 95% CI, 0.40 to 1.69; p = 0.60), including gastrointestinal bleeding events (1.9% versus 1.7%). Mortality was also similar in the two groups and was mostly related to cancer, reinforcing the efficacy data and improving the safety data compared with other TSOAC's, and expanding the proportion of patients with CAT who will be eligible for treatment with this agent, including patients with gastrointestinal cancer. Sub analyses of this trial are being performed, including the assessment of drug–drug interactions. In addition, the API-CAT study to assess the efficacy and safety of apixaban beyond six months is ongoing. The main objective of this European multicenter, international, prospective, randomized, parallel-group, double-blind non-inferiority trial with blinded adjudication of outcome events, is to determine whether a low-dose regimen of apixaban (2.5 mg bid) is non inferior to a full-dose regimen of apixaban (5 mg bid) for the prevention of VTE in patients with active cancer who have completed at least six months of anticoagulant therapy for treating a documented index event of DVT (symptomatic or incidental) or PE (symptomatic or incidental), and to demonstrate the superiority of the 2.5 mg bid regimen as compared to the 5 mg bid on the safety endpoint in a group of more than 1,700 adult CAT patients. We expect April 30, 2023 to have this study completed.

In the 2021 American College of Chest Physicians Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel, it is recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy (strong recommendation, with a moderate-certainty evidence), but also it was established that because TSOAC's have not been compared head-to-head among patients with cancer, that apixaban or LMWH may be the preferred option in patients with luminal GI malignancies who place higher value on avoiding GI major bleeding (edoxaban and rivaroxaban appear to be associated with a higher risk of GI major bleeding than LMWH in CAT patients), whereas others may elect the convenience of once-daily TSOAC's therapy (edoxaban or rivaroxaban). However, LMWH has the potential advantages of bypassing the GI system in patients with problems such as nausea, mucositis (and in the critically ill) and may be more easily dose-adjusted in patients with thrombocytopenia due to cancer therapy.

Once treatment has started, recurrence and bleeding are the two variables of interest in the follow-up at any time of patients with CAT and VTE in general, especially in the critically ill. As already pointed out, in CAT cases there is a higher risk for recurrence as well as a higher risk for major bleeding than in patients with similar VTE but without cancer.

Although existing evidence is limited, there are different forms to calculate the recurrence risk, I prefer a simple one score described by the Wells group in 2012, because it is specific and validated for cancer patients with a VTE. It consists in three variables: breast cancer (minus 1 point), tumor node metastasis stage I or II (minus 1 point) and female sex, lung cancer and a history of past VTE (plus 1 point each). If the score is negative (< 0 points), the risk for recurrence is low (< 4.5%), while if it is positive (> 1 points), it describes a high risk for VTE recurrence (> 19%) over the first six months.

Several risk scores for bleeding during anticoagulation have been developed or validated in patients with VTE. Cancer per se is a predictor in many of these models. This suggests that maybe the models also apply to the CAT population. However, as baseline risk of bleeding is higher and both cancer and treatment may have a profound impact on bleeding risk, it is unclear whether these models may indeed be generalizable to patients with CAT. Up till present, none of these models have been validated in patients with CAT.

Is in this way that the bleeding risk is in search of a specific validated score for CAT patients; in this scenario there have been some proposals. One of them, the newly derived CAT-BLEED model for clinically relevant bleeding during anticoagulation in patients with CAT highlights, it is composed by variables as genitourinary cancer with a HR (95% CI) of 2.48 (1.14-5.38), gastrointestinal cancer with edoxaban treatment 2.20 (1.07-4.53), recent use of anticancer therapies associated with gastrointestinal toxicity (< 4 weeks) 1.74 (1.03-2.92), regionally advanced or metastatic cancer 1.21 (0.82-1.80), age > 75 years 1.02 (0.98-1.08) and creatinine clearance (mL/min) 1.00 (0.99-1.00). It has been suggested a pragmatic distinction based on type of cancer and other well-established risk factors (e.g. history of bleeding, severe thrombocytopenia, anemia and frequent falls risk) as better estimates of clinically relevant bleeding risk. Further improvement may be achieved with «CAT-BLEED», but this requires external validation in practice-based settings and with other TSOAC's and its clinical usefulness is yet to be fully demonstrated.

For now, the issue of cancer associated thrombosis is rapidly generating new knowledge and evidence of great importance for a growing number of patients, so it is essential to follow the literature in this regard and provide the best prophylactic or therapeutic management to our cancer patients with VTE or high risk to develop it.

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