Anticoagulantes orais diretos no tratamento do tromboembolismo venoso em pacientes com câncer

Direct oral anticoagulants for treatment of venous thromboembolism in cancer patients

Winston Bonetti Yoshida[1]

Os novos anticoagulantes orais (NOACs) vêm sendo chamados mais recentemente de anticoagulantes orais diretos (DOACs), tendo em vista o foco de ação direto em sítios específicos da cascata de coagulação, como o fator Xa (rivaroxabana, apixabana e edoxabana) e o fator IIa (dabigatrana). Já a antivitamina K (AVK) age de forma indireta, assim como a heparina e seus derivados. Além disso, as pesquisas com os DOACs se iniciaram por volta do ano 2000 e, assim, estes já não são considerados tão novos[1].

Essas drogas vêm sendo prescritas com frequência crescente para o tratamento do tromboembolismo venoso (TEV), tendo em vista fatores como via de administração oral em doses fixas, boa biodisponibilidade, meia-vida variando de 8 a 15 horas, sem necessidade de monitoramento[2]. A via de excreção renal varia conforme a droga, com 25% para apixabana, 33% para rivaroxabana, 50% para edoxabana e 80% para dabigatrana[2]. Em todas elas, o metabolismo é feito pela p-glicoproteína, sendo que para rivaroxabana e apixabana há envolvimento do citocromo P450-3A4. Em função disso, há uma série de interações medicamentosas com medicamentos que também utilizam essas vias metabólicas[3]. Como limitações, destacam-se a falta de antídotos e os preços em nosso meio. Nos casos de sangramento, a conduta recomendada é a suspensão das drogas (todas com meia-vida inferior à das AVKs), transfusões de sangue e concentrados de fatores da coagulação[4]. Para a dabigatrana, a diálise é uma opção devido à predominância de excreção renal; para a apixabana e a rivaroxabana, o uso de carvão ativado pode ser útil para a redução da absorção dessas drogas[2,5].

Os DOACs foram licenciados para profilaxia do TEV em pacientes submetidos a cirurgias ortopédicas de grande porte[6], prevenção de acidente vascular cerebral em pacientes com fibrilação atrial e tratamento do TEV[7]. Uma metanálise de estudos de fase III de tratamento do TEV com os DOACs mostrou eficácia e segurança similares ao tratamento convencional[8].

O câncer é um fator de risco importante para o TEV, uma vez que está presente em todos os elementos da tríade de Virchow[9]. Pode interferir no fluxo sanguíneo através da possibilidade de aumento da viscosidade sanguínea e compressão tumoral. Com relação à lesão endotelial, pode invadir a parede vascular, aumentar o fator de von Willebrand e ativar a trombomodulina e interleucinas. Com relação à hipercoagulabilidade, pode promover aumento do fator tissular, do fibrinogênio e do inibidor da ativação da plasmina, além de diminuição da antitrombina e das proteínas C e S[9].

Nos pacientes com TEV não provocado, cerca de 20 a 25% têm câncer associado. Por outro lado, nos pacientes com câncer, o risco de TEV aumenta de 6 a 7 vezes. Nos pacientes com metástases, o risco aumenta 3,2 vezes[10,11].

As diretrizes para o tratamento de TEV associado ao câncer (CAT) recomendam que ele seja feito com heparina de baixo peso molecular (HBPM)[12,13]. Para os casos em que esse tratamento não é possível, as opções secundárias são AVK ou DOAC, sem preferência entre os dois[13]. Essa recomendação se deve à superioridade da HBPM em relação à AVK quanto à recorrência de TEV e pela similaridade de sangramento[12,14-16]. Além disso, ainda não foi feito nenhum estudo específico de CAT com os DOACs em comparação com as HBPMs. As informações disponíveis derivam de análises de subgrupos de tratamento de TEV dos estudos de Fase III com os DOACs, em que o comparador foi a AVK[17].

Essas análises mostraram, em geral, similaridade de eficácia e segurança dos DOACs em relação à AVK nos subgrupos de pacientes com CAT e sem diferença entre os DOACs[18]. As limitações desses estudos incluem: ausência de comparação com as HBPMs (padrão-ouro), heterogeneidade entre as

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bases de dados dos estudos-fonte – sem estratificação dos tipos de TEV e de câncer – e a atividade ou não desta última doença no momento do tratamento. Portanto, os subgrupos avaliados podem não ser totalmente representativos do universo de pacientes com ambas as doenças (CAT)[18]. Finalmente, o tamanho da amostra dos subgrupos com câncer é inferior ao necessário para conclusões mais definitivas sobre eficácia e segurança[19].

Assim, como conclusão, os estudos indicam que os DOACs parecem ser igualmente eficazes e seguros em comparação com a AVK em pacientes com CAT. No entanto, estudos clínicos dedicados a esses pacientes, incluindo como comparador as HBPMs, são necessários para obtenção de melhor nível de evidência nesses casos.

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New oral anticoagulants (NOACs) have more recently come to be referred to as direct oral anticoagulants (DOACs) because of their direct focus of action on specific sites in the coagulation cascade, such as factor Xa (rivaroxaban, apixaban and edoxaban) and factor IIa (dabigatran). In contrast, antivitamin K (AVK) acts indirectly and so do heparin and it derivatives. Additionally, studies with DOACs began around the year 2000 and so they are no longer considered new.[1]

These drugs are being prescribed with increasing frequency to treat venous thromboembolism (VTE), because of factors such as oral administration in fixed doses, good bioavailability, half-lives varying from 8 to 15 hours, and no need for monitoring.[2] The proportion of renal clearance varies from drug to drug, at 25% for apixaban, 33% for rivaroxaban, 50% for edoxaban, and 80% for dabigatran.[2] In all of these, metabolism is via p-glycoprotein, while for rivaroxaban and apixaban the P450-3A4 cytochrome is also involved. This means that there is a series of drug interactions with other medications that also use these metabolic pathways.[3] The most important limitations are the lack of antidotes and the prices charged in our setting (Brazil). The recommended approach for management of cases of bleeding is suspension of the drugs (all of which have a shorter half-life than AVKs), blood transfusions, and concentrated coagulation factors.[4] Dialysis is another option in the case of dabigatran, since excretion is predominantly renal; while for apixaban and rivaroxaban, activated charcoal can be useful to reduce absorption.[2,5]

The DOACs have been licensed for VTE prophylaxis in patients undergoing major orthopedic surgery,[6] for prevention of cerebral vascular accidents in patients with atrial fibrillation, and as a treatment for VTE.[7] A meta-analysis of studies describing phase III trials of DOACs to treat VTE found that efficacy and safety are similar to conventional treatment.[8]

Cancer is an important risk factor for VTE, since it is present in all of the elements that make up Virchow's triad.[9] It can interfere in blood flow via increased blood viscosity and through compression by tumors. With regard to endothelial injury, it can invade the vessel wall, increase von Willebrand factor levels and activate thrombomodulin and interleukins. With regard to hypercoagulability, it can provoke increases in tissue factor, fibrinogen, and of plasmin activator inhibitor, and it can reduce levels of antithrombin and of C and S proteins.[9]

Around 20 to 25% of patients with unprovoked VTE have cancer. Seen from the opposite perspective, patients with cancer have a 6 to 7 times greater risk of VTE. In patients with metastases, the risk increases 3.2 times.[10,11]

The guidelines for treatment of cancer-associated thrombosis (CAT) recommend using low molecular weight heparin (LMWH).[12,13] For cases in which this option is not possible, secondary choices are AVK or DOAC, with no preference for either.[13] This recommendation is because LMWH is superior to AVK with relation to VTE recurrence and because they are similar with relation to bleeding.[12,14-16] Furthermore, no studies specific to CAT have been conducted to compare DOACs with LMWHs. The information that is available has been derived from analyses of subsets of phase III trials of DOACs for VTE treatment, in which they were compared to AVK.[17]

In general, these analyses show that DOACs have similar efficacy and safety to AVK in subsets of patients with CAT and no differences between DOACs.[18] Limitations of these studies include: lack of comparison with LMWHs (the gold standard), non-uniformity of source study databases – with

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no stratification of types of VTE or cancer – and differences in cancer activity or inactivity at the time of treatment. As a result, the subsets analyzed may not be entirely representative of the universe of patients with both diseases (CAT).[18] Finally, the sample sizes of subsets with cancer were smaller than is needed for more definitive conclusions about efficacy and safety.[19]

As such, these studies concluded that DOACs appear to be equally effective and as safe as AVK in patients with CAT, but clinical studies dedicated to these patients and including comparison with LMWHs are needed to obtain results with the best evidence level for these cases.

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