Anticoagulantes orales directos en pacientes con cáncer

DOACs in patients with cancer

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Venous thromboembolism (VTE) occurs in up to 15% of cancer patients during the course of the disease[1]. Patients with cancer associated thrombosis have a worst prognosis than patients with cancer without thrombosis and higher rates of recurrent thrombosis and bleeding during anticoagulation than patients with VTE without cancer[2,3].

Low molecular weight heparin (LMWH) has long represented the standard of treatment for at least the first 3 to 6 months of therapy after a number of randomized clinical trials have shown its greater efficacy as compared to vitamin K antagonists (VKA)[4-10]. In the CLOT trial, dalteparin was more effective than warfarin (recurrent VTE, 9% versus 16%, p = 0.002) with no significant difference in the rates of bleeding or mortality[4]. In the more recent CATCH trial, tinzaparin showed a non-statistically significant reduction in the composite primary efficacy outcome (recurrent DVT, fatal or nonfatal pulmonary embolism, and incidental VTE) as compared to warfarin[4]. There was no difference in major bleeding rates, but tinzaparin was associated with a significant reduction in clinically relevant non-major bleeding events. Based on the results of these trials, all major international guidelines have recommended LMWH as the first treatment option in patients with cancer associated thrombosis[11-14].

However, long-term treatment with LMWH is inconvenient and may affect patient quality of life and adherence. For this reason, alternative therapeutic strategies for these patients are needed. The direct oral anticoagulants (DOACs) have been shown to be as effective as LMWH/VKA and possibly safer for the acute and long-term treatment of patients with VTE and are now suggested by guidelines as the preferred treatment choice[13]. Based on these results, the DOACs appeared as an optimal therapeutic alternative also for patients with cancer associated VTE. Unfortunately, in the pivotal phase III clinical trials patients with cancer were scarcely represented and highly selected, thus possibly not representing the "real" cancer population. Subgroup analyses of these trials and their meta-analyses found no significant difference in terms of recurrent VTE and major bleeding between DOACs and VKAs[15,16], but no head to head comparison with LMWH, the standard of treatment, was available at the time when the DOACs entered the market. Thus, doctors have been reluctant in using the DOACs in cancer patients in routine clinical practice, in particular for patients with active cancer undergoing chemotherapy[17].

Because the DOACs have the potential to improve the quality of anticoagulation in this setting, randomized controlled trials were finally designed to address this important clinical need. The HOKUSAI-VTE cancer trial comparing edoxaban with LMWH was the first to be published[18]. In this open-label, randomized controlled trial with a PROBE design, patients with cancer who had both acute symptomatic and incidentally detected VTE were randomized to receive LMWH for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily or subcutaneous dalteparin 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin 150 IU per kilogram once daily. Edoxaban dose was reduced to 30 mg in patients with moderate renal insufficiency, a body weight of 60 Kg or less, and in patients receiving concomitant treatment with potent P-glycoprotein inhibitors. Treatment was to be continued for a minimum of 6 months and all patients were followed-up for 12 months. The study included a large sample of patients (n=1,050), 98% of whom with active cancer, 53% with metastatic disease and 72% receiving cancer therapy at the time of randomization. The primary outcome was the composite of recurrent VTE or major bleeding at 12 months, regardless of treatment duration. The primary-outcome occurred in 12.8% patients in the edoxaban arm as compared with 13.5% patients in the dalteparin arm (hazard ratio, 0.97; 95% CI 0.70 to 1.36; P = 0.006 for non-inferiority; P = 0.87 for superiority). The same results were found when comparing the two treatment arms at 6 months in a pre-specified analysis, with an incidence of 10.5% in the edoxaban group and 10.7% in the dalteparin. When efficacy and safety outcomes were separately analyzed, the rate of recurrent VTE was non-significantly lower with edoxaban than with dalteparin (7.9% and 11.3%, respectively; hazard ratio 0.71; 95% CI, 0.48 to 1.06; P = 0.09) and the rate of major bleeding was significantly higher with edoxaban than with dalteparin (6.9% and 4.0%, respectively; hazard ratio 1.77; 95% CI, 1.03 to 3.04; P = 0.04). This difference in the rate of major bleeding was primarily attributable to a higher incidence of upper gastrointestinal bleeding with edoxaban, mainly in patients with gastrointestinal cancer. The rate of severe or life-threatening major bleeding was similar between the two treatment arms (12 patients in each group, respectively), with no fatal bleedings in the edoxaban arm and two fatal bleedings in the dalteparin arm. Of interest, the median duration of the assigned treatment was longer in the edoxaban arm (211 days) than in the dalteparin arm (184 days).

The second published trial was the Select-d study[19]. In this randomized, open-label, pilot trial, 406 patients with active cancer who had symptomatic PE, incidental PE, or symptomatic lower limb DVT were allocated to dalteparin (200 IU/kg daily for 1 month, then 150 IU/kg daily for a total duration of treatment of 6 months) or rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for a total of 6 months). A total of 203 patients were randomly assigned to each group, 58% of whom had metastases, 70% were currently receiving cancer treatment. The primary outcome of the study was VTE recurrence over 6 months, secondary outcomes included major and clinically relevant non major bleeding. Recurrent VTE occurred less frequently in patients on rivaroxaban[8] than in patients treated with dalteparin[18], with 8 and 3 PE events, respectively. There was one fatal PE in each arm. The 6-month cumulative VTE recurrence rate was 4% (95% CI, 2% to

9%) in the rivaroxaban arm and 11% (95% CI, 7% to 16%) in the dalteparin arm, for an hazard ratio of 0.43; 95% CI, 0.19 to 0.99. Six patients receiving dalteparin and 11 patients treated with rivaroxaban had major bleeding events, for a 6-month cumulative rate of major bleeding of 4% (95% CI, 2% to 8%) with dalteparin and 6% (95% CI, 3% to 11%) with rivaroxaban, hazard ratio 1.83; 95% CI, 0.68 to 4.96. As in the HOKUSAI-VTE Cancer study most major bleeding events were gastrointestinal, and there were no central nervous system bleedings. Patients with esophageal or gastroesophageal cancer tended to experience more major bleedings with rivaroxaban than with dalteparin - 4 of 11 (36%) versus 1 of 19 (11%). Clinically relevant non major bleeding occurred in 7 patients receiving dalteparin and in 25 patients on rivaroxaban, with corresponding rates of 4% (95% CI, 2% to 9%) and 13% (95% CI, 9% to 19%), respectively (hazard ratio 3.76; 95% CI, 1.63 to 8.69).
Other studies comparing DOACs, in particular apixaban and rivaroxaban, with LMWH are currently underway.

Based on the results of completed studies, the DOACs appear as an important alternative to LMWH for the majority of patients with cancer associated VTE. A preference remains for the use of LMWH over DOACs in the population of patients with active gastrointestinal cancer in the light of their more favorable safety profile. Finally, because data on the clinical relevance of interactions between anticancer drugs and DOACs are lacking, caution should be exerted when administering DOACs in patients receiving potentially interacting agents.

Declaration of conflicts of interest:
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