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Treatment of cancer-associated thrombosis: perspectives on the use of novel oral anticoagulants

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ABSTRACT

Therapeutic options for the management of venous thromboembolism have expanded with the introduction of novel oral anticoagulants (NOACs). These agents offer significant advantages in convenience and simplicity, and large, well-designed clinical trials have shown that NOACs are comparable in efficacy and safety to traditional therapy using low molecular weight heparin (LMWH) followed by a vitamin K antagonist in most patients with deep vein thrombosis or pulmonary embolism. However, these results cannot be extrapolated to the general oncology population because randomized clinical trials have included very few and highly selected patients with cancer. Furthermore, how well these agents perform in comparison to LMWH, the drug of choice for both initial and long-term treatment of cancer-associated thrombosis, has not been evaluated. Other limitations of particular importance to patients with cancer, such as chemotherapy interaction, renal impairment, or hepatic involvement with metastases also need to be carefully considered because these patients have higher risks of recurrent thrombosis and bleeding. The use of NOACs is currently not recommended by international consensus guidelines but is now being explored in ongoing clinical trials. The results are eagerly awaited.

Introduction

Patients living with cancer have a high risk of clinically significant thrombotic events [1]. While deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most frequent presentations, thrombosis in other vascular territories, such as the splanchnic veins and upper extremity venous system, are also common. With the increasing age and cancer prevalence of our population, more frequent detection of incidental thrombosis, and the thrombogenecity of targeted therapy and multi-agent chemotherapeutic regimens, the incidence of cancer-associated thrombosis is expected to climb [2]. Furthermore, oncology patients who develop thrombosis have a 2- to 6-fold higher risk of death and the thrombotic event might trigger a delay or discontinuation of their cancer treatment [3,4]. Undoubtedly, having simple, effective and affordable anticoagulant regimens for the prevention and treatment of venous thromboembolism (VTE) in cancer patients is an urgent, unmet clinical need.

But despite the well-recognized problem of VTE in oncology patients, there has been little advancement in the management of cancer-associated thrombosis since the introduction of low molecular weight heparin (LMWH) for long-term therapy. Also, anticoagulant therapy with LMWH or warfarin in patients with cancer remains burdensome and is viewed as having a negative impact on patient quality of life. Consequently, novel oral anticoagulants (NOACs) that target thrombin or activated factor X offer a tempting opportunity to improve the convenience and comfort of anticoagulant therapy in oncology patients. The evidence on the efficacy and safety of these agents for the prevention and treatment of cancer-associated thrombosis is summarized in this review.

Prevention of VTE

Routine pharmacological thromboprophylaxis is recommended in patients with cancer admitted to hospital for medical or surgical reasons [5-7]. This is largely based on the presence of multiple risk factors for VTE in these patients and the proven efficacy of pharmacological prophylaxis in the general medical and surgical populations [8,9]. The evidence is strong in the oncology surgical literature, with risk reductions of at least 50% reported for prophylaxis using LMWH or fondaparinux, but the evidence is weak in cancer patients admitted with acute medical illnesses. In this setting, level I evidence showing efficacy and safety is lacking [10]. In a recent meta-analysis of the three placebo-controlled trials studying a LMWH or fondaparinux, anticoagulant prophylaxis failed to demonstrate a significant reduction in VTE [11]. The relative risk was 0.91 (95% CI 0.21 to 4.0) in a combined sample size of 307 patients with cancer.

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Although this post-hoc observation is limited because of the small sample size, this relative risk reduction in the cancer subgroup appears dramatically lower than the risk reduction of 50 – 60% in medically ill patients reported in meta-analyses of randomized trials [12,13].

Medical Patients

The evidence for the efficacy and safety of NOACs to prevent VTE in cancer patients admitted to hospital for medical illnesses is even weaker. Only two studies have been conducted and only one study has reported its cancer-specific data. Both of these placebo-controlled, randomized trials were designed to examine extended prophylaxis with NOAC beyond hospitalization, not in-hospital prophylaxis.

The ADOPT study randomized 6528 patients to receive apixaban 2.5 mg twice daily for 30 days or enoxaparin 40 mg once daily for 6 – 14 days; 113 patients (3.5%) and 98 patients (3.0%) with active cancer (defined as those who had been receiving treatment for cancer within the previous year) were included, respectively [14]. The primary efficacy outcome was a 30-day composite of death related to VTE, fatal or nonfatal PE, symptomatic DVT, or asymptomatic proximal leg DVT as detected with systematic bilateral compression ultrasonography at the time of hospital discharge and at day 30. Overall, there was no difference in the incidence of the primary efficacy outcome: 2.71% in the apixaban group versus 3.06% in the enoxaparin group (relative risk with apixaban 0.87; 95% CI 0.62 to 1.23; p=0.44). However, by day 30, major bleeding had occurred in 0.47% of the patients in the apixaban group and in 0.19% of the patients in the enoxaparin group (relative risk with apixaban 2.58; 95% CI 1.02 to 7.24; P=0.04). There was also no observed difference in the efficacy between apixaban and enoxaparin at the end of the parenteral-treatment period (relative risk 1.06; 95% CI 0.69 to 1.63) but there was a non significant trend of fewer symptomatic DVT during the extended prophylaxis period in those who received apixaban than among those who received enoxaparin. Results of the 211 cancer patients have not been published.

The MAGELLAN study included 8101 medically ill patients admitted to hospital and randomized them to receive rivaroxaban 10 mg once daily for 35 days or enoxaparin 40 mg once daily for 10 days [15]. Active cancer patients represented 7.3% of the total sample size, with 296 randomized to each of the two study treatments. The primary efficacy outcome was the composite of asymptomatic proximal or symptomatic VTE, including death related to VTE up to day 10 (for non-inferiority test) and up to day 35 (superiority test). The principal safety outcome was major or clinically relevant non-major bleeding. At day 10, 2.7% of patients receiving rivaroxaban and 2.7% of patients receiving enoxaparin had a primary efficacy outcome event (relative risk with rivaroxaban 0.97; 95% CI 0.71 to 1.31; P=0.003 for non-inferiority). At day 35, 4.4% randomized to rivaroxaban and 5.7% randomized to enoxaparin had a primary efficacy outcome event (relative risk 0.77; 95% CI 0.62 to 0.96; P=0.02 for superiority). This benefit of VTE reduction, however, occurred at a significantly increased risk of major or clinically relevant bleeding at both day 10 and day 35. Overall, 2.8% of patients in the rivaroxaban group had a primary safety outcome event compared with 1.2% of the patients in the enoxaparin group at day 10 (P<0.0001); 4.1% and 1.7% in the respective groups had a major or clinically relevant non major bleeding event at day 35 (P<0.001). In the subgroup of 405 evaluable patients with active cancer, there was no significant difference in the primary efficacy outcome at day 35 between the study treatments. Among this high risk group, 9.9% (20/202) who received rivaroxaban and 7.4% (15/203) who received enoxaparin had a thrombotic event. The subgroup analysis also found that rivaroxaban was associated with a statistically significantly higher risk of major and clinically relevant non-major bleeding in cancer patients (5.4% versus 1.7%). Overall, these unfavorable safety results along with the lack of improved efficacy despite a longer duration of active drug do raise concerns about the use of rivaroxaban in cancer patients and should prompt further investigation. Of note, the incidence of VTE in cancer patients is much higher than in the non-cancer patients in both treatment groups but the risk of major and clinically relevant non-major bleeding appear similar. Together, these findings are a good reminder that results from patients without cancer should not be extrapolated to patients with cancer.

Only one randomized trial has examined the use of a NOAC in ambulatory patients with cancer who are receiving chemotherapy. The study was designed to evaluate the acceptability and tolerability of apixaban in patients with advanced or metastatic malignancies without thrombosis [16]. Unfortunately, it was terminated prematurely because of the slow rate of accrual and it did not reach the planned sample size of 40 patients per group. In this phase II, double-blind, randomized trial, apixaban or placebo was given to 125 patients receiving first- or second-line chemotherapy for cancer of the lung, breast, gastrointestinal, bladder, ovarian, or prostate, cancer of unknown origin, myeloma, or selected lymphoma. Patients were randomized to placebo or apixaban 5 mg, 10 mg, or 20 mg once daily beginning within 4 weeks of the start of chemotherapy and for the duration of 12 weeks. The primary outcome of major or clinically relevant non-major bleeding occurred in 6.5% of the 93 patients in the apixaban group. The rate of major bleeding in patients given apixaban was low at 2.2% (95% CI 0.26% to 0.75%) and most of these events occurred in the 20 mg group. There were no fatal bleeding events. Three patients (10.3%) in the placebo group and none in the apixaban groups developed symptomatic DVT or PE. One patient in the apixaban 20 mg group and one patient in the placebo group developed catheter-related thrombosis. Median duration of study drug exposure was 84 days. Percentages of patients in each group completing the full 12 weeks of study drug were 63% for placebo, and 78%, 80%, 76%, for the apixaban 5 mg, 10 mg, and 20 mg groups, respectively. Biomarkers of thrombin generation were also examined in this study. Apixaban decreased markers of thrombin generation compared with placebo but no statistically significant dose-response effect was observed in the levels of D-dimer, TAT, or IL-6. F_{1+2} levels did show a dose-response effect but the small sample size and heterogeneous population preclude any conclusions.

Overall, the evidence on the use of NOACs for the prevention of cancer-associated thrombosis in medical patients is very limited in the number of patients studied, is highly selective in the types of patients included, and is inadequate in the duration of exposure and follow-up. The results from prevention studies conducted in largely non-cancer patients should not be extrapolated to the oncology population. Cancer-specific clinical trials are essential to determine if NOACs have any role in primary prophylaxis.

Surgical Patients

Randomized trials have not been conducted to study the use of NOAC for primary thromboprophylaxis in oncological surgical settings. The convenience of an oral regimen is less important in the post-operative setting where many patients are unable to tolerate oral medication in the first few days after surgery. Alterations in absorption, gastrointestinal motility, renal clearance, and hepatic function, can affect the achieved plasma levels of NOACs and potentially have negative impact on efficacy and safety. Results from the medical prophylaxis or treatment