

Commentary on the DALTECAN study

The aim of the DALTECAN study was to determine the safety of dalteparin between 6 and 12 months in cancer-associated venous thromboembolism (VTE). Of 334 patients enrolled, 185 and 109 completed 6 and 12 months of therapy, respectively. The overall frequency of major bleeding was 10.2% and occurred in 3.6% of patients in the first month. Recurrent VTE occurred in 11.1% of patients, with the highest incidence rate for month 1 (5.7%), followed by the incidence of 3.4% during months 2 to 6, and 4.1% during months 7 to 12. In conclusion, major bleeding was less frequent during dalteparin therapy beyond 6 months. The risk of developing major bleeding complications or VTE recurrence was the highest in the first month of therapy and decreased over the subsequent 11 months.¹

The outcomes of the DALTECAN study (Dalteparin sodium for the long-term management of venous thromboembolism in cancer patients) were especially awaited by physicians treating patients with cancer-associated VTE. This was reflected, among others, in a published position of the Group of Experts on the off-label use of low-molecular-weight heparins (LMWHs).²

The aim of VTE treatment is to prevent recurrences and propagation of deep vein thrombosis and pulmonary embolism. The risk of recurrences and anticoagulant-associated bleeding during the treatment of cancer-associated thrombosis (CAT) is higher.³ Currently, the survival of cancer patients (CPs) is longer than the survival associated with VTE treatment regimens. However, the extension of therapy duration means an increase in the costs for patients and health care system as well as the risk of anticoagulation complications. Studies involving the population of CPs are hindered by a high, nearly 40% in-study mortality.^{4,5}

Three randomized controlled trials (RCTs) whose primary endpoints were similar to those of the DALTECAN study (ie, VTE recurrence and/or major bleeding during follow-up) provided the most significant outcomes so far with reference to the prolonged (6-month) use of LMWHs in CAT patients.^{4,6,7}

In the Venous Thromboembolism in Patients with Cancer (CLOT) study, enrolling 672 patients, a long-term dalteparin treatment regimen was used for the first time and compared with warfarin therapy (200 IU/kg of body weight daily for 1

month, then 150 IU/kg of body weight for another 5 months). During this period, 8% of patients in the dalteparin group developed thrombosis recurrences, compared with 15.8% in the vitamin K antagonist (VKA) group ($P = 0.002$). No significant difference between the groups with respect to major bleeding (6% and 4%, respectively) or any bleeding (14% and 19%, respectively) was observed. A 6-month mortality rate was 39% in the dalteparin group and 41% in the VKA group.⁴

In the Secondary Prevention Trial of Venous Thrombosis with Enoxaparin (ONCENOX) study, 122 CPs were randomized to a group receiving enoxaparin (1 mg/kg/12 h for 5 days, then 1 mg/kg or 1.5 mg/kg daily) and to a group initially treated with enoxaparin and then with warfarin. No significant differences between the groups as regards endpoints were demonstrated.⁶

In the Comparison of Acute Treatments in Cancer Hemostasis (CATCH) study, 900 patients were randomized to a group receiving tinzaparin at a dose of 175 IU/kg daily for 6 months or a group initially treated with tinzaparin at a dose of 175 IU/kg daily for 5 to 10 days and then with warfarin for 6 months. The VTE recurrence rate was not statistically significantly lower in tinzaparin-treated patients (7% vs 11%); in addition, no differences as regards mortality and major bleeding rates were observed.⁷ The above analyses indicate that despite the importance of the CAT issue, no treatment regimen has been established so far. The determination of LMWH dosing in long-term therapy (approx. 10% of patients develop CAT recurrences despite treatment) and the duration of anticoagulant treatment are problematic.

At present, the CLOT study and the recommendation of LMWH monotherapy for 3 to 6 months form the basis of the guidelines for the treatment of VTE in CPs, developed, among others, by the American College of Chest Physicians or the American Society of Clinical Oncology. The National Comprehensive Cancer Network recommends indefinite anticoagulation in CPs or patients with persistent risk factors.⁸⁻¹⁰ The LMWH monotherapy regimen used in the DALTECAN study was identical to the one used in the heparin arm in the CLOT study, which significantly increases the population of patients receiving the same treatment and followed-up for 6 months. In the CLOT study, the number of patients in the

heparin group was 336, and in DALTECAN—334. Early study termination before the lapse of the 6-month period was recorded in the case of 40% of patients in the CLOT study and 45.3% of patients in the DALTECAN study. The similar characteristics of subjects in both studies as regards age, sex, and Eastern Cooperative Oncology Group performance status are of note.^{1,4}

Most VTE recurrences occur within several months after an acute thrombosis, which was also confirmed in DALTECAN. Extending the treatment beyond 6 months should be considered in patients with recurrent VTE despite treatment or at a high risk of recurrence (patients with present thrombotic material despite appropriate therapy, immobilized for a prolonged period, with massive thrombosis and active cancer). A decision on the extension of treatment beyond 6 months should be taken based on the benefit (prevention of death or VTE recurrence) and risk (bleeding) analysis, patient's preferences, and expected survival. The answer to the questions about the optimal treatment duration, the type of treatment, the type or stage of cancer in the context of obtaining the maximum benefit from extended treatment remains unknown. It seems that DALTECAN provides answers to at least some of these questions. In the study, active cancer was defined as a diagnosis of cancer (excluding basal cell or squamous cell carcinoma of the skin) within 6 months before enrollment, or documented recurrent or metastatic cancer.¹

Risk factors for recurrent VTE and bleeding in CPs are similar to the ones observed in patients not diagnosed with cancer. In addition, the low compliance rate for anticoagulation and treatment discontinuation due to bleeding or heparin-induced thrombocytopenia are issues specific to CPs. The risk of bleeding is higher in CPs at an advanced age (>65 years), immobilized, with metastatic disease, a history of bleeding and creatinine clearance (CrCl) of less than 30 ml/min.¹¹

The anticoagulant therapy principles applied in DALTECAN were nearly perfect, which adds a significant credibility to its results. The compliance rate was 96%, and 95% of patients received at least 80% of the study drug. Major bleeding between treatment months 7 and 12 was the primary endpoint. Secondary endpoints included symptomatic, recurrent VTE, onset of VTE, minor bleeding, time to the first bleeding episode, and overall safety and tolerance during dalteparin treatment.

Currently, LMWHs are undoubtedly the preferred anticoagulant in the long-term treatment of CPs, including outpatient CPs.⁸⁻¹⁰ The incidence of major bleeding during the first 6 months was 7.8% (1.7% a month) and was comparable to the CLOT study (6%), with most episodes occurring during the first month of the study duration (3.6%). This means that the initiation of CAT treatment with the use of LMWHs is the most dangerous stage in terms of the risk of bleeding and recurrences, which should be taken into

consideration not only by physicians but also by patients. The recurrence rate in DALTECAN in months 7 to 12 was low (4.1%) and similar to that in months 2 to 6 (3.4%); however, it was 2 times lower than during the first 6 months (8.7%).^{1,4} From the patients' perspective, both good treatment tolerance and the absence of the effect of food or vomiting are important.

There are no data on the safety of use of LMWHs in the treatment of CAT in patients with renal failure (RF), which was a common study exclusion criterion. Out of patients enrolled to DALTECAN, 6.0% were initially diagnosed with moderate renal failure (CrCl, 30–50 ml/min) and 1.3%—with severe renal failure (CrCl <30 ml/min); 11.8% of patients with moderate or severe RF developed VTE recurrences, and major bleeding was recorded in 2.9% of them. In 19 patients with severe RF in whom anti-Xa activity was determined, a safe average level of anti-Xa activity (0.3 IU/ml) was demonstrated.¹² Only in 3 patients from DALTECAN, at least 1 measurement of anti-Xa activity yielded a result above 1.0 IU/ml. This indicates that dalteparin demonstrates a low bioaccumulation capacity in patients with RF, and consequently, the need for anti-Xa level monitoring is significantly reduced. This fact is especially important in CPs, where blood drawing often can be problematic and excessive additional laboratory testing should be avoided. A relatively small number of CPs with CAT enrolled in RCTs is interesting. The largest meta-analysis taking into account the assessed population (1908 patients) demonstrated that, as opposed to VKAs, LMWHs were associated with a reduction in the VTE recurrence rate (hazard ratio, 0.47), with no improvement as regards survival.¹³ In other meta-analyses comparing long-term LMWH and VKA treatment, a significant, nearly 50% reduction in the risk of VTE recurrences in the group treated with LMWH was observed, with a comparable risk of major and minor bleeding complications.^{14,15}

In conclusion, it should be stated that the DALTECAN study demonstrated safety and efficacy of the use of dalteparin in long-term treatment of CAT. The described studies may demonstrate that their results cannot be translated into treatment with other LMWHs and the existence of the group effect should not be assumed. Optimum CAT treatment requires further studies. A relatively large number of patients with recurrence despite appropriate treatment is still a problem. However, the suggested issue of excessive costs associated with long-term LMWH therapy seems exaggerated. As demonstrated in the CLOT and DALTECAN studies, a lower number of recurrences and bleeding episodes, as well as the lack of the need for treatment monitoring, except for a small group of patients with severe RF, seems to fully justify the costs. It is still unknown whether, and if so, in what manner the location of cancer and cancer treatment impact therapy effects. There is no answer to the question of whether in CPs dosing should be adjusted to the changing body

weight, similarly to the recommendations to be followed during pregnancy. The most important practical conclusion from the DALTECAN study is the demonstration of dalteparin safety in CPs and RF patients and of the necessity to pay particular attention to patients during the first month of treatment, as it is the most dangerous period in terms of the risk of bleeding and CAT recurrences.

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