e-Update SEOM clinical guideline of venous thromboembolism (VTE) and cancer

Treatment

Anticoagulation is the cornerstone of VTE treatment. The goals of anticoagulant therapy in patients with cancer-associated thrombosis (CAT) are to improve symptoms, reduce risk of recurrent VTE, and decrease the risk of post-thrombotic syndrome (PTS). Cancer patients present a higher risk of recurrent VTE and anticoagulant treatment-related bleeding compared to those without malignancy.

Initial treatment of VTE in cancer patients (5–10 days)

Since our previous recommendation of 2014 two Cochrane reviews have been published[1,2]. Hakoum et al.[1] showed a trend to a decrease in mortality at 3 months (RR 0.66, 95% CI 0.40–1.10) and VTE recurrence (RR 0.69, 95% CI 0.27–1.76) with LMWH compared to unfractionated heparin (UFH). Compared to LMWH or UFH, fondaparinux was not statistically different in all endpoints including mortality, recurrence VTE, and bleeding. In the second meta-analysis[2], a subgroup analysis of cancer patients reported a significant reduction in mortality with LMWH compared to UFH (OR 0.53, 95% CI 0.33–0.85; p = 0.009). Upfront treatment with direct oral anticoagulants (DOAC) showed similar efficacy compared to LMWH in the initial treatment period of SELECT-D (rivaroxaban)[3], Caravaggio[4] and ADAM[5] (both with apixaban) trials. Rivaroxaban was associated to a higher incidence of major bleeding and clinically relevant non-major bleeding, particularly described in gastrointestinal (GI) and genitourinary (GU) cancers. However, apixaban showed a safer profile with similar bleeding rates compared to LMWH, even in the gastrointestinal tract, in both trials.

Recommendations

LMWH at a body weight-adjusted dose and DOAC (apixaban and rivaroxaban) are the drugs of choice for the initial treatment of CAT (level of evidence: grade 1A). Rivaroxaban should be considered only in low-risk bleeding patients. It should be used with caution due to a higher risk of bleeding mainly in GI and GU tract. Specific drug-drug interaction assessment should be performed prior to using DOAC.

UFH and fondaparinux can be considered alternative agents to LMWH or DOAC (level of evidence: grade 1B).

Long-term treatment of VTE in cancer patients

Since the previous update of the SEOM guideline in 2014, five randomized clinical trials have been published, four with DOAC[3,4,5,6] and one with LMWH[7] (Table 1).

Multiple meta-analyses have shown that LMWH is more effective than VKAs at reducing the risk of recurrent VTE in patients with cancer[8]. The CATCH trial randomized 900 patients with active cancer and compared tinzaparin 175 IU/ kg once daily versus warfarin for 6 months. At 6 months, it showed a non-significantly lower incidence of recurrent VTE with tinzaparin (7.2 vs. 10.5%, HR 0.65, 95% CI 0.41–1.03; p = 0.07). No differences in major bleeding (HR 0.89, 95% CI 0.40–1.99; p = 0.77) and mortality (HR 1.08, 95% CI 0.85–1.36; p = 0.54) were observed, though a significant reduction in clinically relevant non-major bleeding (CRNMB) was described in the tinzaparin arm (10.9 vs. 15.3%, HR 0.58, 95% CI 0.40–0.84; p = 0.004).

HOKUSAI VTE Cancer trial randomized 1050 patients to edoxaban, after an initial course of at least 5 days of LMWH ,or dalteparin based on the CLOT regimen. It was designed as a non-inferiority trial. Edoxaban was administered at a fixed dose of 60 mg daily except in patients with creatinine clearance of 30–50 ml per minute, body weight of 60 kg or less, or in those receiving concomitant treatment with potent P-glycoprotein inhibitors that all received a reduced dose of 30 mg daily. The duration of the study was at least 6 months and up to 12 months. The primary endpoint was a composite of recurrent VTE or major bleeding up to 12 months after randomization. The median drug exposure was higher with edoxaban than dalteparin, 211 vs. 84 days. It should be noted that inconvenience dosing (patient decision) was the reason for permanent study drug discontinuation in 1 in 7 patients in the dalteparin arm compared to 1 in 25 patients in the edoxaban arm. Around one-fourth of the study population met the criteria to received edoxaban 30 mg. All types of cancer were represented in the trial including metastatic or primary brain tumors, and all systemic anticancer therapies were allowed. The primary endpoint was achieved; edoxaban was not inferior to dalteparin for the composite of recurrent VTE and major bleeding (edoxaban 12.8% vs. dalteparin 13.5%, HR 0.97, 95% CI 0.70–1.36; p = 0.006 for non-inferiority). In the secondary endpoints, a trend to a reduced recurrent VTE was observed for edoxaban (7.9% vs. 11.3%, HR 0.71, 95% CI 0.48–1.06; p = 0.09) with a significant increase in major bleeding (6.9% vs. 4.0%, HR 1.77, 95% CI 1.03–3.04; p = 0.04). The most common bleeding location with edoxaban was the gastrointestinal (GI) tract, in particular in the upper GI tract. In addition to, genitourinary (GU) bleedings were more frequent with the oral anticoagulation. In a post hoc analysis, Kraaijpoel et al.[9] published later showed that tumors associated with major bleeding were predominantly GI cancers (major bleeding in GI cancers treated with edoxaban 12.5% vs. dalteparin 3.5%, HR 4.0, 95% CI 1.5–10.6, p = 0.005). The event-free survival and mortality rate were similar in the two arms, and must be pointed out that the main cause of death was cancer related (34.7% in the experimental arm and 32.8% with dalteparin) and only a minority of deaths were VTE related (1.1% with edoxaban and 0.8 in the LMWH arm).

SELECT-D trial is a pilot study that randomized 406 patients to rivaroxaban versus dalteparin (CLOT regimen). Rivaroxaban was administered orally 15 mg twice daily for 3 weeks, then 20 mg once daily up to 6 months. The primary endpoint was VTE recurrence, though no formal hypothesis was established. It was planned a second randomization after 6 months to continue rivaroxaban versus placebo, but it was closed due to poor recruitment based on data and safety monitoring committee recommendation and also the sample size was reduced to 406 patients. After an interim analysis, esophageal and gastric cancer were excluded because of a higher incidence of major bleeding with rivaroxaban compared to LMWH (36% vs. 11%). The VTE recurrence rate at 6 months was significantly lower with rivaroxaban compared to LMWH (4 vs. 11%, HR 0.43 95% CI 0.19–0.99). Again, as observed in the HOKUSAI trial, more major bleeding was described with DOAC compared to subcutaneous treatment (6-month cumulative rate of major bleeding for rivaroxaban 6% vs. 4% for dalteparin, HR 1.83, 95% CI 0.68–4.96). Also, a significant increase in the rate of CRNMB was associated to rivaroxaban (13 vs. 4%, HR 3.76, 95% CI 1.63–8.69). Most major bleeding and CRNMB occurred in the GI and GU tract.

Despite the fact that initial data with DOAC were associated with significantly increased risk of bleeding, as evident from the Caravaggio and ADAM studies, apixaban is the only DOAC that demonstrated similar efficacy compared to LMWH without increasing the risk of major bleeding even in patient with GI cancers.

The ADAM VTE trial randomized 300 patients to apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily or dalteparin (CLOT trial regimen) for 6 months. The primary endpoint was major bleeding. Major bleeding rate was similar in both arms (apixaban 0.0 vs. 1.4% dalteparin; HR not estimable; p = 0.138) and a significant reduction in VTE recurrent rate was described with apixaban (0.7 vs. 6.3%, HR 0.099, 95% CI 0.013–0.780; p = 0.0218). The secondary safety composite endpoint, major bleeding or CRNMB, was comparable in both arms (6% in both groups). The quality of life showed globally better results for apixaban including concern for excess bruising, stress, irritation, burden of delivery, and overall satisfaction with anticoagulant therapy. The mortality rate at 6 months was similar comparing apixaban with dalteparin (15.9 vs. 10.6%, HR 1.36, 95% CI 0.79–2.35).

Lastly, Caravaggio trial was presented in American College of Cardiology Congress and published in New England Journal of Medicine in March 2020. It is the largest trial published to date regarding VTE treatment in cancer patients. This trial is a multinational, investigator-initiated, open-label, non-inferiority trial with blinded central adjudication of the outcomes. It randomized 1168 patients who had symptomatic or incidental acute proximal deep-vein thrombosis or pulmonary embolism to the same regimens of apixaban and dalteparin used in ADAM trial for 6 months. The primary outcome was objectively confirmed recurrent VTE during the trial period (modified Intention-to-treat) and the principal safety outcome was major bleeding. All types of cancers were eligible to participate in the study except basal-cell or squamous-cell carcinoma of the skin, primary brain tumor, known intracerebral metastases, or acute leukemia. All anti-cancer systemic therapies were allowed including immunotherapy and biological drugs. Based on study protocol guideline only 20% of the overall trial population had incidental VTE. The drug exposure days were higher in the DOAC group, apixaban mean 143.5/median 178 (interquartile range [IQR] 106-183) and dalteparin mean 134.8/median 175 (IQR 79-183). Twelve patients withdrew consent in the apixaban arm and 41 in dalteparin group. The primary efficacy outcome occurred in 5.6% of the apixaban arm compared with 7.9% of the dalteparin arm (HR 0.63; 95% CI 0.37-1.07; p < 0.001 for noninferiority, p = 0.08 for superiority). The primary safety outcome, major bleeding based on European Medicines Agency [EMA] definition, occurred in 3.8% of the apixaban group compared with 4.0% of the dalteparin group (p = 0.60). Major gastrointestinal bleeding occurred in 11 patients (1.9%) in the apixaban group and in 10 patients (1.7%) in the dalteparin group; this endpoint was not a prespecified trial outcome). CRNMB was numerically higher in the apixaban arm compared to dalteparin arm (9.0% versus 6.0%, HR 1.42; 95% CI 0.88-2.30). There were no fatal bleeding episodes in the apixaban arm and 2 in the dalteparin arm. Similar findings in efficacy and safety were described in the per protocol analysis. Mortality rate was similar in both arms, apixaban 23.4% versus dalteparin 26.4%. As observed in HOKUSAI trial, the main cause of death was cancer related (85.2% in apixaban arm and 88.2% with dalteparin) with a minority of deaths cause by VTE (3.0% with apixaban and 2.8 with LMWH). Event free survival (EFS) was defined as the absence of recurrent venous thromboembolism, major bleeding, or

death. EFS was significantly superior for apixaban compared to dalteparin, 73.3 versus 68.6% (HR 1.36; 95% CI 1.05–1.76). All adverse events, including serious and drug-related adverse events, were numerically higher with dalteparin compared to apixaban.

Recommendations

LMWH at a body weight-adjusted dose and DOAC for 6 months are the drugs of choice for long-term treatment of VTE in cancer patients (level of evidence: grade 1A). Apixaban is the only DOAC with a similar safety profile compared to LMWH. Edoxaban and rivaroxaban increase the risk of GI and probably GU bleeding. Specific drug-drug interaction assessment should be performed prior to using DOAC. Extended duration of anticoagulation therapy after 6 months should be considered for high-risk patients such as those with active cancer and those receiving systemic therapy. Beyond 6 months, patients should be re-evaluated frequently to assess the risk–benefit ratio of continuing anticoagulant therapy (level of evidence: grade 2C).

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