



Breaking the exclusiveness of LMWH for treating cancer-associated VTE

Malignancy is substantially related to a high risk of venous thromboembolism (VTE) as the second leading cause of death in cancer patients after death from cancer itself [1]. Recommended standard treatment of acute cancer-associated thrombosis is low molecular weight heparin (LMWH), since proven more effective than oral coumarin [2, 3]. So far, there was little evidence supporting direct oral anticoagulants (DOACs) in cancer patients with VTE [4].

Now, the SELECT-D study [5] and the Hokusai-trial [6] throw new light on this topic. Both open label, randomised pilot trials investigated rivaroxaban [5] and edoxaban [6] each versus dalteparin for recurrence of VTE and bleeding complications.

The multicenter SELECT-D study included 406 patients with primary VTE, defined as deep venous thrombosis (DVT), pulmonary embolism either symptomatic or incidental as confirmed by ultrasound or CT. Anticoagulant standard dosages were used for dalteparin (200 IE/kg for four weeks followed by 150 IE/kg for five months) and rivaroxaban (2x15 mg for three weeks followed by 20 mg/day for total six months). Cumulative recurrency rate for VTE as the primary endpoint during six months observation occurred in 11% of patients on dalteparin (95%-CI, 7%–16%) vs. 4% on rivaroxaban (95%-CI, 2%–9%) (HR 0.43; 95%-CI 0.19–0.99). On the other hand, secondary bleeding complication rate was lower under dalteparin (4%; 95%-CI, 2%–8%) compared to rivaroxaban (6%; 95%-CI, 3%–11%) but did not reach statistical significance (HR 1.83; 95%-CI 0.68–4.96) except for clinically significant non-major bleeding (4% dalteparin vs. 13% rivaroxaban; HR 3.76; 95%-CI 1.63–8.69).

The Hokusai trial randomised $n = 1.050$ patients: $n = 522$ were treated with dalteparin for 5 days followed by edoxaban for 12 months total, $n = 524$ patients received only dalteparin in standard dosage. The primary endpoint was a composite of VTE recurrence and major bleeding and occurred in 13.5% ($n = 71$) of dalteparin only treated patients during the first year compared to 12.8% ($n = 67$) under dalteparin/edoxaban (HR 0.97; 95%-CI 0.70–1.36; p for superiority $p = n.s.$; p for non-inferiority of edoxaban $p = 0.0006$). Whereas the composite endpoint under dalteparin was driven by VTE recurrence however at non-significant level (11.3% VTE, 7.9% major bleeding; HR 0.71; 95%-CI 0.48–1.06; $p = 0.09$), it masked edoxaban/dalteparin treatment to achieve lower VTE recurrence at the cost of higher rate of major bleeding events (6.9% VTE, 4.0% major bleeding; HR 1.77; 95%-CI 1.03–3.04; $p = 0.04$). Both studies were potentially biased due to a

lack of blinding, which is ethically comprehensible. In summary, a non-inferiority of DOACs in preventing recurrent VTE as compared to standard treatment with LMWH could be observed in both studies.

Despite a trend towards a higher bleeding risk under DOACs, none of these bleedings occurred intracranial nor ended up fatally in these subgroups. In addition, the type of cancer had a profound impact on bleeding risk; in both studies, gastrointestinal cancer was with statistical significance connected to higher rate of major and not major bleeding under DOACs. There was a similar tendency observed in case of bladder cancer, however, by small amount of patients the significance could not be confirmed. Therefore, further studies on subgroups of cancer patients are needed to fully expose those who may not benefit, just as those who may benefit in particular from the use of DOACs.

References

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