Does low-molecular-weight heparin influence cancer-related mortality?

In a large multicenter prospective trial [1], in which 672 cancer patients were randomly assigned to receive LMWH or oral anticoagulant therapy (OAT) for 6 months, a statistically significant improvement in overall survival (death for any cause at 12 months) in favor of dalteparin over OAT was demonstrated in patients affected by non-metastatic disease (hazard ratio, 0.50; 95% CI, 0.27–0.95; \( P = 0.03 \)) [2]. These authors used all-cause mortality rather than cancer-related mortality. For this reason, we performed a literature-based pooled analysis to summarize the results of the randomized trials concerning cancer-related death during anticoagulant therapy and follow-up in cancer patients receiving LWMH or OAT (Table 1). Event-based relative risk (RR) ratios with 95% CIs were derived. Combined-effect estimation was computed with both random- and fixed-effect models. A heterogeneity test was applied as well.

Concerning cancer-related death, we selected eight studies [1, 3–9] to evaluate the incidence of cancer-related mortality during treatment and follow up in cancer patients by type of anticoagulant therapy. We considered only cancer patients, according to the data reported in a pooled-analysis of 1726 patients [10]. Our previously reported results [11] were based on data extracted from a prior meta-analysis [12]. No significant difference in cancer mortality was observed between the two treatment modalities: (RR 0.97; 95% CI 0.81–1.15; \( P = 0.75 \)) (Figure 1). The test for heterogeneity was not significant (\( P = 0.97 \)).

Conversely, we selected seven studies [3–8, 13] that recruited patients with and without cancer in order to evaluate the incidence of overall mortality during treatment and follow up by type of anticoagulant therapy. No significant difference was registered: a total of 15 of 495 patients (3%) in the LMWH group died versus 12 of 607 patients (1.9%) in the OAT group, with a non-significant reduction of the risk of recurrent symptomatic VTE in favor OAT (RR 1.38; 95% CI 0.63–3.00; \( P = 0.41 \)). The test for heterogeneity was not significant (\( P = 0.78 \)). No difference was observed applying both the fixed- and the random-effect model.
None of these studies was primarily designed to investigate the effect of LMWH or OAT on cancer-related mortality, because the primary question in many of them was addressing recurrent VTE. The pitfalls of this type of analysis, including the concept of combining different cancers at different stages and biologic activity, and the discrepancies among studies in anticoagulant therapy dosage and duration must be taken into account: the CLOT trial [1] reported on the mortality of patients treated for 6 months, whereas the other studies treated patients for 3–6 months [3–9, 13]. Moreover, when Lee et al. [2] separated out the good prognosis cancer patients, a statistically significant difference in mortality was seen at 1 year.

However, the absence of a significant heterogeneity \((P = 0.97)\) suggests the consistency of these results. Thus, the putative antineoplastic effect exerted by LMWH in cancer patients remains still controversial. Further large clinical trials still need to be run in order to address this fascinating issue.

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Figure 1. Cancer-related mortality during treatment and follow up in cancer patients receiving LWMH or OAT. Effect: RR; lower: 95% CI RR lower limit; upper: 95% CI RR upper limit; Ntotal: total number of patients; Fixed Combined: fixed effect model estimation; Random Combined: random effect model estimation. LMWH: low-molecular-weight heparin; OA: oral anticoagulants.


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