

Are heparins anti-neoplastic agents?

Czy heparyny są lekami przeciwnowotworowymi?

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How are anticoagulants used in patients with cancer?

In patients with cancer, there are 3 clinical scenarios in which treatment with an anticoagulant may be considered. The first is in patients who develop acute deep vein thrombosis, pulmonary embolism or venous thrombosis at another location (e.g., portal vein, arm) in whom a low-molecular-weight heparin (LMWH), administered in a therapeutic-dose, is the treatment of choice and a vitamin K antagonist such as warfarin, administered to attain an international normalized ratio range of 2.0–3.0, is an alternative but slightly less efficacious option [1]. In our practice we routinely use long-term LMWH for the treatment of cancer-associated venous thrombosis and reserve warfarin for patients who cannot tolerate daily LMWH injections or in whom the costs of LMWH are prohibitive. The second scenario is patients with cancer but without acute venous thromboembolism in whom anticoagulants might be given in a low-dose regimen to prevent venous thrombosis [2]. This is the subject of another editorial reported in this issue [3]. Such patients typically are receiving chemotherapy through a central venous catheter and are at risk for line-associated venous thrombosis. In our practice, we do not routinely administer anticoagulants for primary prevention and if catheter-associated venous thrombosis develops, patients are treated with therapeutic-doses of LMWH and, whenever possible, the central catheter is retained to facilitate chemotherapy and blood product administration. The third, and perhaps most interesting, scenario is the potential use of LMWHs as an anti-neoplastic treatment in patients who have no indication for anticoagulant therapy to prevent or treat venous thromboembolism.

What is the rationale for anticoagulants as anti-neoplastic agents?

In recent years, researchers have hypothesized that heparin may improve survival in cancer patients through an anti-neo-

plastic effect that is independent of its antithrombotic effect [4]. This suggestion is grounded in evidence from basic science which has demonstrated that heparin blocks the expression of oncogenes, the formation of thrombin and fibrin, and inhibits cancer metastases by anti-angiogenic mechanisms [5]. Further evidence from a subgroup analysis of a clinical trial has shown that the LMWH nadroparin reduces mortality in cancer patients [6]. Given the increased bleeding risk, particularly in cancer patients, Akl et al. [7] sought to determine a) the potential benefits of heparins to improve survival in patients with cancer, and b) whether these potential benefits are outweighed by an increased bleeding risk, which is the main drawback to long-term anticoagulant therapy with LMWHs.

What did this meta-analysis aim to achieve?

Akl et al. conducted a systematic review of randomized controlled trials comparing unfractionated heparin (UFH) or LMWH with placebo or no intervention. Of these agents, LMWHs are the principal agents that would be considered for everyday practice because UFH requires twice-daily subcutaneous or intravenous administration and is associated with a higher risk for heparin-induced thrombocytopenia than LMWHs [1]. The study population included cancer patients who had no indication for prophylactic or therapeutic anticoagulation. The primary outcomes of interest were: mortality, deep vein thrombosis, pulmonary embolism, and bleeding (major and minor).

What is the quality of this meta-analysis and that of included studies?

The methods of this meta-analysis were sound, thereby supporting the validity of the authors' findings. Trial validity was assessed independently and in duplicate whereby allocation concealment, blinding (of patients, providers, outcome assessors, and analysts), follow up, whether an intention-to-treat analysis was performed, and whether the trial was stopped early was assessed. A sensitivity analysis excluding poor quality trials was planned *a priori*. Akl et al. also planned subgroup analyses based on type of intervention, type and stage of disease, and whether patients were on cancer treatment or not to explore heterogeneity if detected. The authors appropriately chose to pool outcomes using the random effects model, a more conservative estimate of overall treatment effect.

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Five randomized trials involving a total of 1,189 patients were eligible and included in the review. Four studies compared LMWHs vs. placebo [8-11] while one study compared UFH vs. placebo [12]. In all studies, the doses of UFH and LMWHs assessed were those that we would use for the prevention of venous thrombosis (except in one study the dose of LMWH used for the first 2 weeks was higher [10]). Two studies included only patients with limited or extensive small cell lung cancer (SCLC) and with good performance status [8,12]. The other three studies included patients with various types of advanced malignancy [9-11]. The duration of treatment varied substantially between trials and ranged from 5 weeks [12] to 6 weeks [10], to 18 weeks [8], to 12 months [9]. Akl et al. report that the treatment duration was not clearly reported in the trial by Sideras et al. [11]. Mortality outcomes were obtained at similar time points for all 5 trials, at 12 and 24 months, but the maximum duration of follow up ranged from 24 months [11] to 84 months [10]. The methodological quality of the trials was adequate, with only one trial failing to report whether treatment allocation was properly concealed [8]. Only one of the four studies did not perform an intention-to-treat analysis and this study was stopped early due to insufficient patient accrual [11].

What are the principal findings of this meta-analysis?

Akl et al. found that subcutaneous administration of a heparin conferred a statistically and clinically significant reduction in overall mortality (hazard ratio [HR] 0.77, 95% CI 0.65–0.91, $p = 0.003$). Akl et al. also concluded that heparin therapy conferred a significant reduction in mortality in patients with *limited* SCLC (HR 0.56, 95% CI 0.38–0.83, $p = 0.004$) but no benefit in patients with *advanced* SCLC (HR 0.80, 95% CI 0.60–1.06, $p = 0.1$) or patients with advanced cancer (HR 0.84, 95% CI 0.68–1.03, $p = 0.09$). No significant differences between groups were reported for venous thromboembolism, or bleeding (major or minor).

How does one interpret the findings of this meta-analysis?

The main conclusion reported by Akl et al. was that heparin increases survival in cancer patients overall, and particularly in those with limited SCLC. It should be noted, however, that the significant benefit reported for patients with limited SCLC comes from data from only two trials ($n = 169$), one of which was of questionable methodological quality [8]. Similarly, the non-significant pooled effect reported for the advanced SCLC patient group ($n = 192$) is also limited to evidence from only two trials that assessed different treatment agents (UFH vs. placebo and LMWH vs. placebo) and, again, one of these trials was of lower methodological quality [8]. Thus, the conclusion reached by Akl et al. that heparin is particularly bene-

ficial to patients with limited SCLC should be considered with caution. Finally, the findings should be considered in terms of the absolute survival benefits of anticoagulant therapy. Thus, the mean survival advantage of UFH or LMWH over no treatment varies according to the patient population and type of cancer but is, typically, between 3 and 6 months in patients with more advanced disease.

The main drawback of long-term anticoagulant therapy is an increased risk of bleeding, which can be further elevated in cancer patients who can develop disease- or chemotherapy-related thrombocytopenia. In this meta-analysis, heparin administration was associated with an increased risk for bleeding in four out of five trials [8-10,12]. In one trial, the control group actually had a higher incidence of bleeding [11]. The pooled analysis showed no significant difference between groups, which is probably a reflection of the use of low-dose UFH or LMWH, as this treatment is likely to confer only a modest increased risk for bleeding. Another possibility is insufficient power to detect the increased risk – in fact, another meta-analysis reported a statistically significant increase in bleeding [13]. Another potential disadvantage of anticoagulant therapy is heparin-induced thrombocytopenia. However, since most contemporary studies assessed the use of LMWH, which is associated with a very low risk for this complication, this issue is less relevant.

Overall, the finding that heparins reduce mortality in cancer patients appears valid but further research is necessary to determine whether patients with certain types of cancer or stages of disease are more likely to benefit. The authors also appropriately suggest that future research should compare the survival benefit in cancer patients receiving different types of anticoagulants with different doses and durations of treatment.

How should the clinician incorporate these findings into everyday practice?

Overall, the use of UFH or LMWH as anti-neoplastic therapy is not yet ready to be part of routine clinical practice for several reasons. First, more data are needed in larger samples of patients to confirm these findings which, though promising, are not definitive. Second, separate studies need to be done according to cancer type. To date, there are emerging data in patients with SCLC but a paucity of data in more common solid cancers, such as non-SCLC, breast, colorectal and prostate cancers. Third, LMWHs as anti-neoplastic agents should be considered within the context of other anti-angiogenic agents such as bevacizumab (Avastin®), which is currently licensed for use in patients with metastatic colon cancer [14]. Trials are needed to assess whether LMWH can be used as an adjunctive or alternative treatment to these emerging agents. Finally, the long term use of LMWH will incur a considerable cost to patients, as the “off-label” use of these drugs is unlikely to be covered by a national health system or another third party payer.

What do we do in our practice?

When we consider the “off-label” use of LMWH as an anti-neoplastic agent, this is done on a case-by-case basis and following a discussion with the patient of the rationale, costs and objectives of such treatment. For example, we might consider empiric use of LMWHs in patients with less advanced malignant disease, especially if they have SCLC, with the biological premise being that these agents may have greater anti-neoplastic efficacy to impede angiogenesis and tumor spread in the earlier stages of the disease. In another clinical scenario, we might use LMWHs in patients with more advanced stages of disease or if they are receiving chemotherapy since LMWHs may mitigate the prothrombotic effects of chemotherapy and, possibly, have modest anti-neoplastic effects. Whenever possible, we also determine whether a patient is eligible for an ongoing clinical trial that is assessing the potential anti-neoplastic effects of LMWHs. Finally, our decision to consider LMWHs as an antineoplastic agent is always done in conjunction with a patient's medical oncologist. Although these management guidelines seem rather vague, they reflect the “real world” uncertainty as to the role of LMWHs in the anti-neoplastic armamentarium.

To summarize, LMWHs show promise as potential anti-neoplastic therapy to complement existing conventional treatments. Until more definitive trials are completed, the use of LMWHs as anti-neoplastic treatment should be considered within the context of promising emerging treatments that require careful consideration before their use is recommended. Our position is consistent with guidelines by the American Society of Clinical Oncology published in December of 2007 stating that anticoagulants are not recommended to improve survival in patients with cancer without venous thromboembolism and that patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anti-neoplastic therapies [15].

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From the Editor

Synopsis: Akl EA, van Doormaal FF, Barba M, et al. Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation. *Cochrane Database Syst Rev*. 2007; 3: CD006652.

In this systematic review and meta-analysis of 5 randomized controlled trials, in which participated almost 1200 patients, the authors has checked if in cancer patients without clinical evidence of venous thromboembolism unfractionated heparin or low molecular weight heparin compared to placebo or no intervention prolongs survival and is safe. It has been shown that 5–52 weeks of using prophylactic dose of dalteparin or therapeutic dose of unfractionated heparin or prophylactic dose followed by therapeutic dose of nadroparin reduced mortality at 12 months (RRR 13%, NNT 12) and 24 months (RRR 8%, NNT 15) and did not increase significantly the risk of major and minor bleeding. The largest effect size was observed in patients with limited small cell lung cancer.

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