Future perspective of clinical trials of antithrombotics and cancer survival

Er O

Erciyes University Medical Faculty, MK Dedeman Oncology Hospital, Kayseri, Turkey

One of the most exciting issue related to anticoagulant therapy is its potential for an antineoplastic effect. The notion that anticoagulants have an antineoplastic effect is provocative.

A strong association between cancer and thrombosis has been demonstrated consistently in experimental and clinical studies. Randomized controlled trials and meta-analyses of studies that compared low molecular weight heparins (LMWH) with unfractionated heparin for the initial treatment of venous thromboembolism have reported a reduction in the overall mortality of patients with cancer who were randomly assigned to receive a LMWH.[1] The reduction in mortality has been consistent across studies and could not be attributed to differences in fatal pulmonary embolism or bleeding. It is more likely that the mechanism of this long-term benefit can be explained through effects on tumor cell biology. Inhibiton of fibrin formation, modulation of growth factor activity and inhibition of selectin activity are important factors in understanding the mechanism of heparin anticancer activity. In this regard, there has been extensive evaluation of the potential role that the coagulation proteases play in tumor stromal interactions at a molecular level. Tissue factor is frequently overexpressed as a result of progression from benign to malignant phenotype. Tissue factor is the physiological initiator of blood coagulation. Experimental manipulation of tissue factor is associated with enhanced tumor growth, invasion, and metastasis. The evidence also suggests that tissue factor might have a fundamental role in tumor angiogenesis. Low molecular weight heparins can inhibit angiogenesis, a process that is critical for tumor growth and metastasis. Additionally, there are observations that suggest that heparins have direct effects that may influence tumor cell behavior.

Clinical evidence in support of anticoagulants having an antineoplastic effect was first reported in a multicenter, randomized, controlled trial in 1981. In the Veterans Affairs Research Service Cooperative Study, warfarin was found to be associated with an improvement in median survival in patients with small-cell lung cancer who were receiving chemotherapy.[2] In a recent study conducted by our group, again in patients with small-cell lung cancer who were randomly assigned to standard care with combination chemotherapy alone versus LMWH plus combination chemotherapy, advantages in terms of progression-free and overall survival for patients who received LMWH for 18 weeks were shown.[3]

Recently, two randomized clinical trials testing LMWHs for survival in malignant patients who don't have thromboembolism and one large study in cancer patients who also have thromboembolism have been published.[4-6]

Fragmin for Advanced Malignancy Outcome Study (FAMOUS) is a large randomized, double-blind, placebo controlled trial to assess the efficacy and safety of chronic administration of LMWH –dalteparin- in cancer patients without underlying thrombosis.[4] The primary objective was to determine the effect on survival. Survival estimates for the dalteparin- and placebo group patients at 1 year after randomization were 46% and 41%, respectively (p=0.19). This trial has failed to detect a difference, in terms of survival at 1 year from randomization. However, a posthoc analysis was undertaken in a group of patients with a better prognosis who survived beyond 17 months from randomization. In this subgroup of patients with a good prognosis disease, there was a statistically significant difference in survival in favor of those patients randomly assigned to receive LMWH.

A second study, by Klerk et al, showed the value of up to 6 weeks of LMWH therapy compared with placebo in patients with advanced malignant disease.[5] A variety of tumor types were included in this study and for both the overall trial population and for a subgroup of patients with better progno-

sis at the time of random assignment, LMWH therapy was associated with a significant survival advantage. In the intention-to-treat population, the median survival was 8.0 months in the nadroparin group and 6.6 months in the placebo group.

The hazard ratio of mortality was 0.75 (p=0.021) in favor of the nadroparin group. When adjusted for life expectancy, performance status, concomitant treatment, and type and histology of cancer, the treatment effect remained statistically significant (hazard ratio, 0.76). *Lee et al.,* performed a posthoc analysis of the mortality data in patients with solid tumors who participated in the Comparison of Low Molecular Weight Heparin Versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients With Venous Thromboembolism (CLOT) trial.[6] In this subgroup analysis of the CLOT trial, the effect of a low molecular weight heparin –dalteparin- on the survival of patients with cancer and venous thromboembolism were examined and the hypothesis that low molecular weight heparins have a greater impact on survival in cancer patients with limited disease than in those with disseminated cancer were investigated. Although a difference in survival at 12 months was not observed for the entire study population and patients with known metastases, a statistically significant improvement in overall survival associated with dalteparin, relative to oral anticoagulant therapy were demonstrated in patients with solid tumors who were not known to have metastatic disease at the time of their thromboembolic event. The 50% relative risk reduction in the 12 month mortality remained significant after adjusting for known prognostic factors.

Several studies have demonstrated positive impact of LMWH on survival in patients with advanced solid malignancy. The potential role of LMWH in cancer patients deserves additional clinical evaluation. The types and stage of cancer that are most likely to respond to this form of therapy should be identified in well designed clinical trials and also the dose and duration of treatment needs to be optimized.

References

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