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Low molecular weight heparin and survival in cancer

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More recent clinical trials have evaluated the potential benefits of low molecular weight heparin therapy in prolonging survival in patients with solid tumour malignancy. The Fragmin Advance Malignancy Outcome Study (FAMOUS) randomised 385 patients to receive the low molecular weight heparin dalteparin sodium (5000 units once daily) or normal saline placebo injections for up to 1 year. Patients in this trial had advanced disease (locally advanced or disseminated). The primary endpoint of this study was mortality one year after randomisation. 46% of dalteparin patients compared to 41% of placebo group patients were alive at 1 year (p=n.s). In a post-hoc sub-group analysis of good prognosis patients (n=102) dalteparin administration was associated with an increase of median survival from 24 months in the placebo group to 43 months in the dalteparin group.

The interesting findings from the FAMOUS study have been further validated in three recent clinical trials. In the CLOT in Cancer study, 676 patients with cancer associated thromboembolic disease were randomised to receive 6 months of the LMWH dalteparin or oral anticoagulant therapy for VTE treatment. Patients in the dalteparin group received full treatment doses for one month followed by 75% of the full treatment dose for the remaining 5 months. In the oral anticoagulant group patients received dalteparin for 5-7 days in full treatment doses and thereafter the vitamin-K antagonist warfarin with a target INR of 2.5 for the remaining 6 months. There was no survival benefit for the overall trial population, but in a sub-group of patients with no metastasis at time of randomisation, dalteparin therapy was associated with an improved survival at 1 year; 64% of vitamin-K patients surviving at 1 year compared to 80% of those receiving dalteparin (p=0.03). The Malignancy and Low Molecular Weight Heparin Therapy study (MALT) randomised 302 patients to 6 weeks of the low molecular weight heparin nadroparin or placebo. In this study patients initially received full treatment doses of nadroparin and thereafter half the full treatment dose. Therapy was associated with an improvement in median survival from 6 to 8 months in favour of nadroparin therapy for the overall population and in a sub-group of patients defined as having a projected prognosis in excess of 6 months at randomisation, survival was improved from 9 to 15 months.

In a final study evaluating patients with small cell lung carcinoma, 84 patients with both limited and extensive disease, were randomised to receive the low molecular weight heparin dalteparin sodium in a dose of 5000 units once daily for 18 weeks whilst receiving standard chemotherapy or the same chemotherapeutic regimen alone. The overall trial population showed a trend towards improved survival, with the effect being more pronounced in patients with limited disease where there was a significant survival advantage associated with dalteparin therapy.

These exciting data beggar the question how low molecular weight heparin may be achieving this potential effect in prolonging survival? A number of mechanisms are proposed including the prevention of fatal but silent thromboembolic disease, coagulation protease inhibition with resultant modulation of tumour phenotype, or direct anti-cellular effects of heparins.