M-ONC 402, a novel non-anticoagulant heparin, inhibits P-Selectin function and metastatic seeding of tumor cells in mice

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Introduction and Rationale

Heparin, widely used in the clinic as an anticoagulant for thromboembolic conditions, has been shown to potentially increase survival in cancer patients. Its use as a potential anti-metastatic agent has been limited by its intrinsic anti-coagulant properties. M-ONC 402 is an engineered LMWH with significantly reduced anti-coagulant activity.

Heparin is believed to inhibit cancer progression through multiple mechanisms and selective targets:
1) Heparin-binding factors modulating angiogenesis and malignant growth of tumors
2) Selectin interactions mediating tumor cell adhesion and metastasis
3) Heparanases regulating tumor invasion and migration
4) Blood coagulation proteases

We have previously shown that M-ONC 402 retains specific binding activity to several major tumor factors. This results in reduced tumor growth factors that regulate tumor angiogenesis (including PDGF-β, VEGF, HGF, and EGF) and heparanases. We have further demonstrated that a novel molecular weight heparin derivative, M-ONC 402, with substantially reduced anti-coagulant activity.

During cancer metastasis, interaction of tumor cells with platelets is thought to facilitate P-Selectin-mediated adhesion to endothelial cells that can be modulated by LMWH. Through surface plasmon resonance (SPR), we measured how M-ONC 402 affected P-Selectin and ligand binding affinities and kinetics. We evaluated the effect of M-ONC 402 on tumor cell adhesion with P-Selectin-Fc fusion binding assays in several tumor cell lines (B16F10, 4T1, WEHI-3). To examine the effect of M-ONC 402 on platelet-tumor cell interactions, we tested M-ONC 402 in platelet-aggregation studies. Using the 4T1 murine breast cancer model and blockage imaging, we also conducted a series of in vivo studies to investigate the effect of M-ONC 402 on early metastatic events, tumor progression and ultimately survival, either as a monotherapy or in combination therapy with cisplatin and taxanes. The results show that, in vitro, M-ONC 402 inhibited tumor cell adhesion mediated by either P-Selectin or platelets. In murine models, M-ONC 402 reduced initial tumor seeding in the lung and yielded survival benefit when used in combination therapy with cisplatin and taxanes. These results provide a rationale for the clinical investigation of M-ONC 402 as a potential anti-metastatic agent in cancer patients.

Results

Through surface plasmon resonance (SPR), we measured how M-ONC 402 affected P-Selectin and ligand binding affinities and kinetics. We evaluated the effect of M-ONC 402 on tumor cell adhesion with P-Selectin-Fc fusion binding assays in several tumor cell lines (B16F10, 4T1, WEHI-3). To examine the effect of M-ONC 402 on platelet-tumor cell interactions, we tested M-ONC 402 in platelet-aggregation studies. Using the 4T1 murine breast cancer model and blockage imaging, we also conducted a series of in vivo studies to investigate the effect of M-ONC 402 on early metastatic events, tumor progression and ultimately survival, either as a monotherapy or in combination therapy with cisplatin and taxanes. The results show that, in vitro, M-ONC 402 inhibited tumor cell adhesion mediated by either P-Selectin or platelets. In murine models, M-ONC 402 reduced initial tumor seeding in the lung and yielded survival benefit when used in combination therapy with cisplatin and taxanes. These results provide a rationale for the clinical investigation of M-ONC 402 as a potential anti-metastatic agent in cancer patients.

Conclusion

In the non-clinical models described in this poster:
> M-ONC 402, a novel LMWH derivative with reduced anti-coagulant activity, inhibited P-Selectin-mediated binding on tumor cells.
> M-ONC 402 prevented formation of platelet-tumor cell rosettes.
> In vivo, M-ONC 402 reduced tumor seeding at early metastatic timepoints and tumor growth.
> M-ONC 402 in combination with cisplatin decreased lung tumor burden.
> M-ONC 402 may inhibit tumor metastasis through modulation of P-Selectin adhesive interactions between platelets and tumor cells.

These results provide a rationale for clinical investigation of M-ONC 402 as a potential anti-metastatic agent in cancer patients.

References