580 POSTER

Selective antimetastatic effect of low molecular weight heparin on human melanoma xenograft

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Background: The common use of heparin-derivatives in oncology revealed that anti-coagulant therapies have a beneficiary side-effect: delaying tumor progression. In this study we have used experimental metastasis models of human melanoma in SCID mice to analyse the effect of heparin and its low molecular weight derivative on tumor progression.

Materials and Methods: Two models have been used: lung colonization following i.v. injection of tumor cells and spontaneous liver metastasis model following intrasplenic injection of tumor cells. Heparin (Richter, Budapest) or its low molecular weight derivative (Fragmin, Pharmacia) were administered i.p. one day before tumor cell inoculation into the circulation and for 3 consecutive days (lung colonization) or one week after tumor cell inoculation into the spleen for 10 consecutive days (liver metastasis).

Results: Neither heparin nor its low molecular weight derivative influenced in vitro growth of human melanoma cells, HT168-M1, in the concentration range of 0.01-10 IU/ml. In the lung metastasis model low molecular weight heparin significantly inhibited lung colony formation from the concentration of 0.4 IU/animal, whereas heparin was proved to be much less effective even at 40 IU/ml dose. In case of the liver metastasis model neither heparin nor its derivative was able to influence the growth of the primary spleen tumor. However, low molecular weight heparin significantly inhibited the formation of liver metastases from the dose of 20 IU/animal which effect was achieved by heparin at a log higher concentration. There was no bleeding disorders detected throughout these experiments at the heparin concentrations applied. Hirudin treatment of SCID mice with metastatic human melanoma did not affect the process of metastatization suggesting that the effect of low molecular weight heparin is not mediated by thrombin.

Conclusion: The presented experimental data further support the clinical observations that low molecular weight heparin has specific antimetastatic effect in case of human melanoma, which is independent from the coagulation cascade. Studies are on the way to identify the molecular target of low molecular weight heparin in the metastatic cascade.

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Treatment with epoetin beta corrects anaemia and decreases transfusion use in patients with solid tumours or haematological malignancies

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Background: Anaemia is common in patients with cancer, affecting their quality of life and possibly impacting on long-term outcomes. The current study was performed to assess whether response to epoetin beta varied according to underlying disease.

Materials and methods: This was a 24-week multicentre, open-label study in which anaemic patients with solid tumours or haematological malignancies were enrolled. Patients were treated with subcutaneous epoetin beta (NeoRecormon®) at a starting dose of 2000 IU daily; this was increased to 5000 IU daily in patients with insufficient haematopoietic response after 4 weeks and to a maximum dose of 10000 IU daily after 8 weeks if necessary. Efficacy variables assessed included proportion of patients with haematopoietic response (increase in Hb from baseline of ≥2 g/dl, maintained without transfusion for 4 weeks before and after Hb increase), anaemia correction (Hb increase to ≥10 g/dl), and transfusion need as well as mean increase in Hb level.

Results: The per-protocol population included 259 patients with solid tumours (32% breast, 12% ovarian, 9% lung, 8% prostate, 39% others), and 361 patients with haematological malignancies (47% multiple myeloma, 45% malignant lymphoma, 8% acute or chronic myeloproliferative diseases). Mean baseline Hb was higher in patients with solid tumours (9.2 g/dl [range = 6-14 g/dl]) compared with patients with haematological diseases (8.8 g/dl [range = 4-13 g/dl]). The numbers of Hb responders (≥2 g/dl increase) at study end were 57% and 55% in the solid tumour and haematological disease groups, respectively. Mean Hb increases were 1.6 and 1.7 g/dl in the solid and haematological disease groups, respectively, and the proportions of patients with anaemia corrected to ≥10 g/dl at study end were 64% and 59%, respectively. Patients with solid tumours experienced a greater reduction in transfusion use compared with patients with haematological malignancy (82% vs 64%, baseline to study end). Epoetin beta was well tolerated. The presence of anti-erythropoietin antibodies was assessed in 503 patients after a median interval of 23 weeks from start of treatment. No antibodies were detected in any of the patients.

Conclusions: Epoetin beta increased and maintained Hb both in patients with solid tumours and haematological malignancies, thus reducing the need for blood transfusions and the associated risks.

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A phase I study of day 1 and 8 every three weeks docetaxel infusion.

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Docetaxel has demonstred activity in the treatment of patients with advanced cancers (breast, lung, head and neck, prostate, ovary and stomach). The conventional administration (75-100 mg/m^2 every three weeks) produces substantial myelosoppression and mucositis while a weekly docetaxel dosage of 36-40 mg/m^2 is less myelotoxic and has similar activity. However the weekly schedule is not very convenient in some patient and is associated with increased fatigue and pheripheral neuropathy. To develop a new convenient outpatient schedule with a favourable toxicity profile, we have designed a phase I study to determine the maximum tolerated dose (MTD) of docetaxel given as one hour infusion on day 1 and 8 every 3 weeks in patients with advanced cancer. The starting dose of docetaxel was 40 mg/m^2, in the first three patients, and was escalated by increments of 5 mg/m^2 on both days of administration, up to determine the MTD. In this study, MTD was defined as the dose level associated with the same dose limiting toxicity in at least 33% of treated patients. Sixteen patients entered the study and their characteristics were the following: 8 breast, 4 lung, 2 gastric, 1 esophageal cancer, 1 mesothelioma, median age 58 years (range 36-71), median ECOG PS 1 (range 0-2), M/F 6/10, twelve patients pretreated with chemotherapy for metastatic disease.

Dose level	Pts	DLT
40	3	–
45	6	1 pt. dermatitis G3/ 1 pt. diarrhea G3
50	6	1 pt. mucositis G3 / 1 pt. diarrhea G3
55	1	–

Patients accrual is continuing, at the dose level of 55 mg/m^2.

Up today MTD has not been reached and dose limiting toxicities (DLT) are summarized in the table.

Tumour biology

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Increased effect in hypoxic tumors and blocking of hypoxic upregulation of vascular endothelial growth factor by topotecan.

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The angiogenic factor VEGF is induced during hypoxia through stabilisation of the transcription factor Hypoxia Inducible Factor 1 (HIF 1). Camptothecin-analogues have been shown to inhibit HIF-1 transcriptional activity (Rapisarda *et al.*, Cancer Research, 62, 2002).

Here we examined how topotecan treatment interacts with hypoxia in modulation of the expression of VEGF and HIF-1alpha, and whether the effect of topotecan treatment is dependent on the oxygen partial pressure. Lewis Lung carcinoma (LLC) cells *in vitro* and grown as subcutaneous tumors in C57/bl mice were used.

Cell cultures were exposed to hypoxia (1.5% or 0.7% O) or normoxia for 24h. Media containing 0, 6, 30, 60 or 120nM topotecan was added immediately before exposure to hypoxia. The expression of cellular protein was measured by densitometry of western blots, and VEGF protein in culture media was measured by ELISA.

Four groups of mice with LLC tumors were treated with saline or 20mg/kg topotecan i.p, immediately followed by 72h exposure to hypoxic environment (10% O) or normal air. After 72h all mice were placed in normoxia until termination of the study at a tumor size of 1000mm^3. We found that the hypoxic upregulation of VEGF secretion to the culture medium could be completely abolished by the addition of topotecan at a dose of 30nM ($p=0.000$), while doses up to 120nM had no effect on VEGF secretion under normoxia.