Abstract #: 281

M-ONC 402-a non anticoagulant low molecular weight heparin inhibits tumor metastasis

He Zhou, Nancy Dussault, Edward Cochran, Rain Kwan, Juliane Karlgen, Marińska Barnes, Sucharita Roy, Radouane Zouaoui, Jay Duffner, Chia Lin Chu, Sean Smith, Chris Honan, Zoya Galcheva-Gargova, Yi Wei Qi, Tanmoy Ganguly, Birgit Schultes, Kei Kishimoto.

Momena Pharmaceuticals, Inc., Cambridge, MA

Abstract

The major cause of death in cancer patients is due to metastases that are resistant to conventional therapy. Heparin, a complex glycosaminoglycan commonly used as an anticoagulant, has been reported to have anti-metastatic properties. In addition to inhibiting coagulation proteases, heparin is known to interact with a number of growth and angiogenic and pro-metastatic molecules. In vivo anti-tumor efficacy was initially screened in the B16F10 murine melanoma experimental metastasis model. A single dose of M-ONC 402, administered subcutaneously prior to tumor inoculation, significantly reduced tumor colonization in the lung in a dose-dependent manner. Next, the anti-tumor efficacy of M-ONC 402 was further tested for the ability to inhibit spontaneous metastasis in an orthotropic mouse breast cancer model utilizing syngeneic 4T1 breast carcinoma cells. This model mimics human stage IV breast carcinoma. Briefly, mice orthotopically implanted with 4T1 tumor cells were treated either with M-ONC 402, cisplatin, or the combination of M-ONC 402 and cisplatin. Primary tumors were removed between day 9 to day 15, and tumor metastases to the lung were quantified by lung weight, lung nodular counting, lung tumor size and volume quantification 30-35 days after tumor inoculation. M-ONC 402 in combination with cisplatin significantly inhibited 4T1 tumor cell metastasis to the lung compared to the saline control, M-ONC 402 or cisplatin monotherapy groups. Immunohistological analyses demonstrated a decrease in microvessel density in both primary tumors and lung metastases in M-ONC 402 treated groups, suggesting anti-angiogenesis to be one of the anti-tumor mechanisms of the compound. Tumor burden and treatment effect correlated with myeloid-derived suppressor cell population and plasma levels of G-CSF and MMP-9. These data, taken together, suggest the potential of M-ONC 402 in the treatment of cancers.

Introduction

Heparin

• Neutralizes growth factors and cytokines that are essential for angiogenesis and metastasis: VEGF, FGF, HB-EGF, HGF, PDGF, TGF-β, TNF-α, P-IL-1, IL-6, IL-8, IL-10, IL-12, TNF-α

• Heparin or LMWH (low molecular weight heparin) was able to inhibit experimental metastasis in animal models

• The anti-tumor effect of heparins appears to be unrelated to the anti-coagulant activity.

• Retrospective analyses of clinical trials in which LMWHs were used to treat hyper-coagulability in cancer patients have suggested a survival benefit for the treated groups

• However, full exploitation of anti-tumor effect of heparins or LMWH is limited by its anti-coagulant activity

M-ONCs

• Naturally angiogenically LMWHs generated at Momena Pharmaceuticals, Inc
• M-ONC 402: lead compound with greatly reduced anti-coagulant activity
• M-ONC 202: compound with no detectable anti-coagulant activity

4T1 murine mammary carcinoma model

• Tumor growth and metastasis closely mimics Stage IV human breast cancer
• Metastasis through hematogenous route to lymph nodes, lung, liver, bone and brain
• 100% animal death and site of lethal metastases (98% pulmonary)

4T1 tumor burden and metastasis

• Tumor volume: Day 32
• Lung weight/g
• Lung tumor microvessel density

Methods and Results

Abstract

The major cause of death in cancer patients is due to metastases that are resistant to conventional therapy. Heparin, a complex glycosaminoglycan commonly used as an anticoagulant, has been reported to have anti-metastatic properties. In addition to inhibiting coagulation proteases, heparin is known to interact with a number of growth and angiogenic and pro-metastatic molecules. In vivo anti-tumor efficacy was initially screened in the B16F10 murine melanoma experimental metastasis model. A single dose of M-ONC 402, administered subcutaneously prior to tumor inoculation, significantly reduced tumor colonization in the lung in a dose-dependent manner. Next, the anti-tumor efficacy of M-ONC 402 was further tested for the ability to inhibit spontaneous metastasis in an orthotropic mouse breast cancer model utilizing syngeneic 4T1 breast carcinoma cells. This model mimics human stage IV breast carcinoma. Briefly, mice orthotopically implanted with 4T1 tumor cells were treated either with M-ONC 402, cisplatin, or the combination of M-ONC 402 and cisplatin. Primary tumors were removed between day 9 to day 15, and tumor metastases to the lung were quantified by lung weight, lung nodular counting, lung tumor size and volume quantification 30-35 days after tumor inoculation. M-ONC 402 in combination with cisplatin significantly inhibited 4T1 tumor cell metastasis to the lung compared to the saline control, M-ONC 402 or cisplatin monotherapy groups. Immunohistological analyses demonstrated a decrease in microvessel density in both primary tumors and lung metastases in M-ONC 402 treated groups, suggesting anti-angiogenesis to be one of the anti-tumor mechanisms of the compound. Tumor burden and treatment effect correlated with myeloid-derived suppressor cell population and plasma levels of G-CSF and MMP-9. These data, taken together, suggest the potential of M-ONC 402 in the treatment of cancers.

Introduction

Heparin

• Neutralizes growth factors and cytokines that are essential for angiogenesis and metastasis: VEGF, FGF, HB-EGF, HGF, PDGF, TGF-β, TNF-α, P-IL-1, IL-6, IL-8, IL-10, IL-12, TNF-α

• Heparin or LMWH (low molecular weight heparin) was able to inhibit experimental metastasis in animal models

• The anti-tumor effect of heparins appears to be unrelated to the anti-coagulant activity.

• Retrospective analyses of clinical trials in which LMWHs were used to treat hyper-coagulability in cancer patients have suggested a survival benefit for the treated groups

• However, full exploitation of anti-tumor effect of heparins or LMWH is limited by its anti-coagulant activity

M-ONCs

• Naturally angiogenically LMWHs generated at Momena Pharmaceuticals, Inc
• M-ONC 402: lead compound with greatly reduced anti-coagulant activity
• M-ONC 202: compound with no detectable anti-coagulant activity

4T1 murine mammary carcinoma model

• Tumor growth and metastasis closely mimics Stage IV human breast cancer
• Metastasis through hematogenous route to lymph nodes, lung, liver, bone and brain
• 100% animal death and site of lethal metastases (98% pulmonary)

4T1 tumor burden and metastasis

• Tumor volume: Day 32
• Lung weight/g
• Lung tumor microvessel density

Methods and Results

Abstract

The major cause of death in cancer patients is due to metastases that are resistant to conventional therapy. Heparin, a complex glycosaminoglycan commonly used as an anticoagulant, has been reported to have anti-metastatic properties. In addition to inhibiting coagulation proteases, heparin is known to interact with a number of growth and angiogenic and pro-metastatic molecules. In vivo anti-tumor efficacy was initially screened in the B16F10 murine melanoma experimental metastasis model. A single dose of M-ONC 402, administered subcutaneously prior to tumor inoculation, significantly reduced tumor colonization in the lung in a dose-dependent manner. Next, the anti-tumor efficacy of M-ONC 402 was further tested for the ability to inhibit spontaneous metastasis in an orthotropic mouse breast cancer model utilizing syngeneic 4T1 breast carcinoma cells. This model mimics human stage IV breast carcinoma. Briefly, mice orthotopically implanted with 4T1 tumor cells were treated either with M-ONC 402, cisplatin, or the combination of M-ONC 402 and cisplatin. Primary tumors were removed between day 9 to day 15, and tumor metastases to the lung were quantified by lung weight, lung nodular counting, lung tumor size and volume quantification 30-35 days after tumor inoculation. M-ONC 402 in combination with cisplatin significantly inhibited 4T1 tumor cell metastasis to the lung compared to the saline control, M-ONC 402 or cisplatin monotherapy groups. Immunohistological analyses demonstrated a decrease in microvessel density in both primary tumors and lung metastases in M-ONC 402 treated groups, suggesting anti-angiogenesis to be one of the anti-tumor mechanisms of the compound. Tumor burden and treatment effect correlated with myeloid-derived suppressor cell population and plasma levels of G-CSF and MMP-9. These data, taken together, suggest the potential of M-ONC 402 in the treatment of cancers.

Conclusion

• M-ONC 402 has lower anti-coagulant activity while maintained binding to key molecules
• M-ONC 402 inhibits tumor colonization to the lung in B16F10 experimental metastasis model
• M-ONC 402 inhibits spontaneous metastasis of orthotopically implanted 4T1 breast carcinoma
• M-ONC 402 inhibits microvessel density in 4T1 primary tumors
• M-ONC 402 treatment normalizes MDSC, plasma MMP-9 and G-CSF levels in 4T1 model