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Inhibitory effects of Pazopanib during the metastatic formation in mice undifferentiated pleomorphic sarcoma and osteosarcoma

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Introduction: Pazopanib is a multi-kinase inhibitor which potently inhibits the activity of several receptor tyrosine kinases, including vascular endothelial growth factor receptor 1 (VEGFR1), VEGFR2, VEGFR3, platelet-derived growth factor receptor (PDGFR), and c-Kit. Although it is reported that pazopanib inhibits cell proliferation and survival by the regulation of tumor neoangiogenesis, there are a few reports about influences of the metastatic formation. In the present study, we investigated the anti-metastatic potential of pazopanib against undifferentiated pleomorphic sarcoma (UPS) and osteosarcoma (OS).

Methods: Tumor Cells: RCT cell: mouse spontaneous UPS and Dunn/LM8 cell: mouse spontaneous OS were used. As UPS model, high-metastatic RCT+ and low-metastatic RCT– cell clones of RCT sarcoma were obtained. As OS model, high-metastatic LM8 and low-metastatic Dunn cell clones of osteosarcoma were obtained. Endothelial Cells: Murine lung microvascular endothelial cell (MLE) was used. Reverse-transcription polymerase chain reaction (RT-PCR): Expressions of VEGFA, VEGFR1, and VEGFR2 were assessed using RT-PCR. Cell growth: To determine effect of Pazopanib, tumor cell growth was measured using MTT assay. Invasion Assay: The ability of tumor cells to invade through the MLE monolayer was measured by using a Transcell chamber with a microporous filter (pore size: 8.0 μm). The upper compartment was coated with fibronectin, and MLE monolayer was cultured. The number of tumor cells penetrating the MLE monolayer was counted by useing fluorescence microscope.

Results: In all 4 tumor cells, VEGFA was expressed, but VEGFR1 was expressed only in RCT cells, and VEGFR2 were not expressed. In RCT and Dunn cell lines, the proliferation potency was inhibited by additional pazopanib in a concentration-dependent manner. In addition, invasion ability was inhibited by additional pazopanib. The invasion ability in the high metastatic clones (RCT+ and LM8) was inhibited stronger than those in the low metastatic clones (RCT– and Dunn).

Conclusions: Metastasis is a complex process, including attachment to endothelial cells, extracellular matrix components at distant sites, and invasion into the endothelial cell monolayer and extracellular matrix components. During these processes, pazopanib inhibited the growth of tumor cells and invasiveness to the endothelial cell monolayer and extracellular matrix component.