ANTIVASCULAR THERAPY OF CANCER METASTASIS

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The major cause of death from prostate cancer is metastases that are resistant to conventional therapies such as androgen ablation and cytotoxic chemotherapy. To produce a metastasis, tumor cells must complete a series of sequential and highly selective steps whose outcome is determined by the interactions of tumor cells with homeostatic host mechanisms. Preferential metastasis of tumor cells to certain organs is independent of vascular anatomy, rate of blood flow, and number of tumor cells delivered to each organ. The outcome of metastasis depends on multiple continuous interactions between unique subpopulations of tumor cells and specific host factors within the organ microenvironment, such as the vasculature. The progressive growth and metastasis of prostate cancer are dependent on the induction and maintenance of angiogenesis.

Prostate cancer metastases are commonly found in bones where their growth rate exceeds that of primary tumors. We have developed relevant orthotopic models for bone metastasis by implanting human prostate cancer cells (metastatic cells) into the tibia of athymic nude mice. The implantation of these cells into the tibia produces advanced growth of tumors with lymph node metastasis.

The PDGF-R is a member of the family of PTKs that includes many oncogenes and protooncogenes. PDGF itself is a potent mitogen for both normal cells and tumor cells. PDGF and its receptor are coexpressed in many human carcinomas, including those of the ovary, pancreas, lung, and prostate. The binding of PDGF to its receptor can stimulate cell division, migration, and angiogenesis. Tumor cells that grow in bone damage the bone tissue and induce the production of various factors, such as TGF-β, by osteoblasts and osteoclasts. TGF-β in turn induces the release of PDGF by tumor cells. The PDGF can activate the PDGF-R on tumor cells (autocrine pathway) and tumor-associated endothelial cells (paracrine pathway). The activation of the PDGF-R has been shown to protect cells against apoptosis by upregulating expression (and activity) by Bcl-2, Bcl-xL, pI3 kinase and Akt, and inhibition of caspase 3 activity. Hence, inhibition of the PDGF-R activity can decrease cell proliferation and increase the susceptibility of endothelial cells to anticycling drugs.

STI571 (Imatinib mesylate, Gleevec), a derivative of 2-phenylamino-pyrimidine, was originally developed as an ATP-competitive inhibitor of the ABL tyrosine kinase. STI571, a potent tyrosine kinase inhibitor of c-KIT and the PDGF-R tyrosine kinases, inhibits cell proliferation, and increases apoptosis. Since PDGF and PDGF-R may play a critical role in the osteotropism of human prostate cancer cells and the development of bone metastases, we determined whether oral administration of STI571 alone or in combination with injectable taxol would inhibit the growth of multidrug resistant PC-3MM2 human prostate cancer cells in the bones of nude mice. In vitro STI571 treatment of PC-3MM2 cells cultured from bone lesions established in nude mice inhibited PDGF-R autophosphorylation. Oral administration of STI571 or STI571 plus injectable taxol after the implantation of multidrug resistant PC-3MM2 cells into the tibia of
male nude mice reduced the incidence and size of tumors and prevented bone lysis as measured by digital radiography. Immunohistochemical analysis of untreated bone lesions demonstrated that PC-3MM2 cells growing adjacent to the bone expressed high levels of PDGF and activated (phosphorylated) PDGF-R, whereas tumor cells growing in the adjacent musculature following lysis of the bone did not. Moreover, activated PDGF-R was abundant on the surface of endothelial cells within the bone tumor lesions but not in endothelial cells of uninvolved bone or in tumors in the muscle. Treatment with STI571 and more so with STI571 plus taxol significantly inhibited phosphorylation of PDGF-R on tumor cells and endothelial cells, decreased tumor cell proliferation, and induced significant apoptosis in tumor cells and tumor-associated endothelial cells and tumor cells.

Collectively, these data indicate that endothelial cells exposed to PDGF released by tumor cells express activated PDGF-R and that targeting PDGF-R phosphorylation can produce significant therapeutic effects against prostate cancer bone metastasis. A recent completed modular phase I trial of STI571 alone and STI571 combined with docetaxel strongly recommended that targeting PDGF-R in androgen-independent chemotherapy-insensitive prostate cancer has therapeutic benefits. To test the hypothesis that PDGF-R inhibition in combination with cytotoxic therapy is a useful strategy in patients with prostate cancer bone metastases, a randomized phase II trial of docetaxel and imatinib versus docetaxel and placebo was designed and is currently underway. The primary endpoint is detection of an improvement in time to progression. Secondary endpoints include modulation of bone markers, quality of life, and the predictive value of tumor-PDGF-R expression on response outcomes. A crossover provision for the docetaxel and placebo arm allows a test of the ability of imatinib to reverse taxane resistance. If bone micrometastases associated with high-risk localized prostate cancer are particularly dependent on induction of PDGF-R signaling networks for survival and proliferation, this neoadjuvant strategy may also target metastatic tumor populations and their vasculature.

