OTHER NOVEL AGENTS: RATIONALE AND CURRENT STATUS AS CHEMOPREVENTIVE AGENTS

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ABSTRACT

Several novel targets are currently being evaluated both preclinically and clinically for the prevention of prostate cancer. Four divergent and novel approaches were discussed at the National Cancer Institute–sponsored workshop entitled, "New Clinical Strategies in Prostate Cancer Prevention." These interventions are further categorized into soy protein–based serine-protease inhibitors that reduce superoxide-induced DNA damage, and molecularly targeted approaches that are directed toward endothelin-1 expression/overexpression, peroxisome proliferator–activated receptor ligands, and insulinlike growth factors. Understanding each of these approaches has offered insights into the process of malignant transformation of prostatic epithelium, and further illustrates the difficulties of developing new agents in the treatment and prevention of prostate cancer. Close scrutiny of the clinical data emerging with these approaches, including validation of biologic endpoints, is required before large-scale prevention studies with these novel agents and targets can be considered.

Several novel agents that are currently undergoing clinical evaluation were discussed at the recent National Cancer Institute workshop on "New Clinical Trials: Strategies in Prostate Cancer Chemoprevention." This overview of the agents highlights both the strengths and weaknesses associated with their application to prostate cancer chemoprevention.

BOWMAN-BIRK INHIBITOR

The Bowman-Birk Inhibitor (BBI) is an 8-kDa soybean-derived protease inhibitor with both anticarcinogenic and anti-inflammatory properties.[1,2] BBI has two functional inhibitory domains: one domain inhibits trypsinlike serine proteases, and the other inhibits chymotrypsinlike serine proteases. In some experimental systems, exposure to BBI suppresses the production and release of superoxide anion radicals from both purified polymorphonuclear leukocytes and HL-60 cells in vitro, which may reduce the likelihood for free radical DNA damage and transformation to malignant phenotypes.[1,3] BBI demonstrates growth-inhibitory properties to some malignant cells and suppresses carcinogen-induced malignant transformation in several animal model systems.[1]

Kennedy *et al.* have hypothesized that the consumption of soybean-derived protease inhibitors (such as BBI) in traditional Japanese diets may be responsible for the lower incidence of a number of malignancies in this population. A concentrate of BBI, BBI concentrate (BBIC), was developed for practical use in human clinical trials and is comparable to BBI in both in vitro transformation assays and in vivo carcinogenesis assay systems.[4–6]

BBI is an orally administered agent that has undergone preliminary pharmacokinetic evaluation. Animal data using ^{125}I-labeled BBI suggests that BBI does reach the systemic circulation; however, 40% to50% is excreted unchanged in the feces.[2,7] The properties of BBI must be considered somewhat extraordinary for this protein to survive the digestive process and reach the colon and bloodstream in an active form.[7]

Currently BBIC has achieved Investigational New Drug Status. Trials to evaluate its potential anticarcinogenic and chemopreventive properties are underway in cohorts with prostatic disease.

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ENDOTHELIN-1 INHIBITOR ATRASENTAN

Endothelin-1 (ET-1) is a potent vasoconstrictor found normally in high concentrations in the human ejaculate.[8] Human seminal fluid contains the highest concentrations of ET-1, with concentrations approximately 500-fold greater than plasma. ET-1 acts as an autocrine/paracrine growth factor that has growth stimulatory properties in several cell lines.[9] Exogenous ET-1 induces prostate cancer proliferation in vitro and enhances the mitogenic effects of insulinlike growth factor (IGF)-I, IGF-II, platelet-derived growth factor, basic fibroblast growth factor, and epidermal growth factor.[10] There is tissue selectivity for the expression of receptors to ET-1. The ET-1 receptors are subclassified into ET_A and ET_B, with evidence that ET_A receptors are highly expressed in prostate carcinomas.[8,11] Physiologically, ET_A receptors appear to mediate vasoconstriction and cell proliferation, whereas ET_B receptors mediate vasomotor tone and clearance of ET.[12,13]

ET-1 may be operative in the stepwise progression from normal prostate epithelium to prostate cancer. Normal prostate epithelium contains both ET receptors, but primarily ET_B, and produces low levels of ET-1. In prostate cancer, ET-1 protein is highly expressed, and has been detected in 14 of 14 primary prostatic carcinomas and 14 of 16 metastatic prostate tumor biopsies.[8] Furthermore, ET-1 is known to be nociceptive and may therefore mediate a component of pain associated with metastatic bone lesions.[14]

Atrasentan(ABT 627) is an orally active, selective ET_A receptor antagonist that inhibits ET-1–stimulated growth. In the initial phase 1 dose-finding study in normal male volunteers, headache was dose limiting. A subsequent dose escalation study using a continuous dosing schedule demonstrated PSA responses in some patients with hormone-refractory prostate cancer (HRPC) without identification of a dose-limiting toxicity.[15] Several phase 2 studies examining the antitumor activity of Atrasentan in HRPC are nearing completion.

Based on the evidence that ET-1 may have a role in prostate cancer progression and the encouraging, although preliminary, anticancer activity of Atrasentan in HRPC, the combination of the ET-1/ET_A pathway and Atrasentan represents a potential therapeutic strategy for prostate cancer chemoprevention.

PEROXISOME PROLIFERATOR–ACTIVATED RECEPTOR γ LIGANDS

The peroxisome proliferator–activated receptor γ (PPAR γ) is a member of the nuclear receptor superfamily that functions to regulate adipogenesis.[16,17] In response to binding of an appropriate ligand, PPAR γ forms a heterodimer with another member of the nuclear receptor superfamily (RXR-α), binds to DNA, and regulates the expression of several target genes. PPAR γ appears to be activated by prostaglandins, prostaglandinlike molecules, arachidonic acid metabolites, some nonsteroidal anti-inflammatory agents, and the thiazolidinedione oral hypoglycemic agents troglitazone and pioglitazone. Kantoff *et al.* (unpublished data) have conducted a pilot phase 2 trial with troglitazone in subjects with rising prostate-specific antigen (PSA) after surgery. The agent was well tolerated in this study and appeared to stabilize PSA levels.

PPAR γ activation by troglitazone has demonstrated potent antitumor effect both in vitro and in vivo against several human tumor cell lines, including a prostate cancer (PC 3), gastric (MKN 45), several colon, and breast cancer cell lines (MCF-7).[18,19] High levels of PPAR γ were also found in colorectal carcinoma specimens.[20] Treatment with troglitazone induced both morphologic and gene expression changes consistent with differentiation.[20,21]

Before adopting this target for chemoprevention, an increased understanding of the role of PPAR γ in tumor cell growth and carcinogenesis will be required. In some experimental mouse models of familial adenosis polyposis coli (APC^{Min}), an increased incidence of colonic polyp formation occurred in mice treated with troglitazone.[22,23] These results suggest that PPAR γ activation may actually enhance neoplastic growth in animals genetically predisposed to developing tumors.

Troglitazone therapy has also been associated with a small but clinically significant risk of fatal hepatic necrosis in patients with non-insulin-dependent diabetes.[24] Because of this complication, the manufacturer has voluntarily withdrawn troglitazone and there are no plans by the manufacturer to develop troglitazone as a chemoprevention agent. The pursuit of chemoprevention studies targeting PPAR γ will require the use of other thiazolidinedione agents (eg, pioglitazone) or new candidate compounds.

INSULIN GROWTH FACTORS: MOLECULAR TARGETS FOR PROSTATE CANCER PREVENTION STRATEGIES AND RISK ASSESSMENT

The IGFs and their binding proteins (IGFBPs) are involved in the regulation of cellular proliferation, differentiation, and apoptosis. Emerging data suggest that IGF-I, IGF-II, the IGF receptor, and the IGFBPs play roles in the development and progression of prostate cancer.[25,26] In the transgenic adenocarcinoma mouse prostate (TRAMP) cancer model, a temporal relation exists between the ex-

pression of proteins in the IGF axis and the development of prostate tumors.[27] Epidemiologic evidence suggests that plasma IGF-I is higher in subjects who subsequently develop prostate cancer compared with those who do not.[28–30] IGF physiology may therefore be relevant to the identification of populations at high risk for prostate cancer and to the identification of novel molecular targets for interventions to prevent or treat the disease.[31]

Therapeutic or prevention strategies could focus on compounds that downregulate IGF ligands or upregulate their BPs. With respect to the former concept, somatostatin analogs,[32] growth hormone antagonists, or growth hormone-releasing hormone antagonists[33–35] are reasonable drug candidates. Antiestrogens (tamoxifen) and 4HPR have been associated with decreased levels of plasma IGF-I. In terms of upregulating IGFBPs, it is of interest that classic androgen ablation upregulates IGFBP expression, an effect that may be important in the mechanism of action of castration and antiandrogens.[36,37] Furthermore, finasteride, which is currently being evaluated in a Prostate Cancer Prevention Trial, also upregulates IGFBP expression.[37,38] Novel compounds, such as vitamin D analogs, that cause regression of normal prostate and also have antiproliferative action on prostate cancer cells also upregulate IGFBP expression.[39–41] Ongoing research is exploring other inducers of IGFBP expression as well as tyrosine kinase inhibitors that target the IGF-I receptor itself.

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