

mammography. Those are the goals that should occupy our efforts in breast cancer screening.

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Suramin, an Active Nonhormonal Cytotoxic Drug for Treatment of Prostate Cancer: Compelling Reasons for Testing in Patients With Hormone-Refractory Breast Cancer

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Suramin, a polysulfonated naphthylurea, represents a novel antitumor compound with unique biological properties (1). It was initially used for the treatment of African trypanosomiasis and onchocerciasis. Subsequently, investigators have found other uses for suramin because of its potential effectiveness in the treatment of human immunodeficiency virus (HIV)-associated neoplasms and because of *in vitro* data suggesting that it could effectively protect T cells against HIV infections (2).

Suramin has a wide range of biological properties. Many are related to its structural characteristics, which include three sulfonic acid groups on each side of the molecule coupled to naphthalene rings (six sulfonic groups in total). These structures make suramin a highly charged polyanionic compound similar to other naturally occurring polymers (3). The structural analogies between suramin and other molecules result in a pattern of agonistic activity with various compounds, some of which have a well-established role in cell growth and differentiation.

Among the important functional properties of this substance are its agonistic effect on glycosaminoglycans (4); its effect on accumulation of glycosaminoglycans (largely due to inhibition of iduronate transferase) (4); its anticoagulation ability (4,5); and its inhibition of various enzymes (6), of DNA polymerases (including reverse transcriptase and protein kinase C) (6-8), and, perhaps most important, of growth factor activity (1,6).

Although the primary mechanism of antitumor activity remains elusive, it is believed that inhibition of various growth

factors represent the drug's major mechanism of action. The ability of suramin to tightly associate with a number of growth factors may result in the disassociation of the growth factor from its receptor and, hypothetically, the subsequent loss of the mitogenic signal and inhibition of cellular proliferation (9). The following factors are inhibited by suramin: platelet-derived growth factor (PDGF) (10); fibroblast growth factor (FGF), especially basic FGF (11); transforming growth factors β and α (TGF- β and TGF- α , respectively) (12); epidermal growth factor (EGF) (6); insulin-like growth factor I (IGF-I) (13).

The potential usefulness of suramin for the treatment of solid tumors was first documented in preliminary studies conducted at the National Cancer Institute (NCI) (1,6). In initial phase I and broad phase II trials, in which a short course of suramin was given by continuous intravenous infusion, NCI investigators reported that suramin had promising antitumor activity, especially in patients with hormone-refractory prostate cancer. They also reported substantial toxicity, however, especially neurotoxicity, directly related to suramin plasma concentration and duration of exposure (1,6).

Protein growth factors are thought to be important in the growth of prostate cancer (14,15). Among those growth factors that have been identified within the malignant prostatic tissue are β -FGF (14-16), EGF (17), and TGF- β (18). In this issue of the *Journal*, Vignon et al. (19) report interesting findings with suramin in breast carcinoma cell lines—whether hormone insensitive (estrogen receptor negative) or hormone responsive (estrogen receptor positive). Similar observations have been made with prostatic cancer cell lines both *in vitro* and *in vivo* (12,20). While clinical experience with suramin in breast cancer has not been reported, promising data are evolving in treatment of patients with hormone-refractory prostate cancer.

At the University of Maryland Cancer Center, we have been conducting a phase I trial using a pharmacologically guided regimen which relies on careful monitoring of levels of suramin in the blood (21,22). Contrary to the short-term treatment initially used by the NCI, our program was designed to reach and maintain levels of suramin in plasma within a predefined range with the administration of intermittent outpatient bolus injections individually projected using the Maximum-A-Posteriori Bayesian pharmacokinetic parameter value estimator (22).

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Treatment was continued until dose-limiting toxic effects or progression of disease occurred. This treatment provided the opportunity for a much longer exposure to the drug (at least 3 months) which, as supported by the experiments reported by Vignon et al., may enhance the efficacy of this agent. This careful, pharmacologically guided treatment program was associated with moderately severe but reversible dose-limiting toxic effects (fatigue, anorexia, malaise, and decrease in creatinine clearance). A delayed neuropathy, however, remains an important side effect which deserves careful study. These toxic effects were significantly less severe than those reported in earlier studies by the NCI, which did not use such intensive and careful prospective monitoring of blood levels. Similarly, because of the significant individual variability in the pharmacokinetics and pharmacodynamics of suramin, this "customized" program has proved indispensable for the administration of this drug in our study.

Prolonged administration was associated with major antitumor activity, despite the fact that responses are not a major end point of study in a phase I trial (21,22). At the present time, of the initial 26 assessable patients, 14 have shown evidence of a 50% or greater decrease in tumor mass if they had measurable soft-tissue disease (seven patients) or a 75% decrease in prostate-specific antigen with a major subjective improvement if they had bone disease only (seven patients). Impressive soft-tissue responses were seen in the liver, lung, and voluminous retroperitoneal and pelvic adenopathy.

In their report, Vignon et al. also have demonstrated that suramin inhibits EGF, IGF-I, and IGF-II stimulation of growth of the MCF7 breast carcinoma cell line. The growth-enhancing role of these and other polypeptide hormones in *in vivo* breast carcinoma cell proliferation has been firmly established (23). A number of these agents have been shown to act in either a paracrine or an autocrine fashion. FGF and TGF- α can be produced by a number of breast carcinoma cell lines and can enhance the proliferation of these cells by binding to specific receptors (24-28). IGF-I and IGF-II are also potent mitogens for breast carcinoma cell line proliferation (25,29). These cell lines possess a large number of IGF-I membrane receptors. Synthesis and secretion of IGF-I and IGF-II have been demonstrated in a minority of breast carcinoma cells (30); thus, IGF-I and IGF-II stimulation of breast carcinoma growth appears to function predominantly in a paracrine fashion (30,31). Cullen et al. (31) have recently demonstrated that stromal cells surrounding the breast tumor cells secrete large quantities of IGF-I or IGF-II, which in turn stimulate tumor growth through their binding and activation of the IGF-I receptor. Interestingly, these tumor cells also secrete PDGF, but they do not appear to possess PDGF receptors (32). The PDGF, in turn, binds to the surrounding stromal cells and enhances IGF-I secretion (31).

Suramin also inhibits estradiol stimulation of MCF7 cell proliferation. Estrogens have a crucial role in both normal breast epithelium and regulation of growth of a majority of neoplastic breast tissue (23). These tissues display specific nuclear estrogen receptors, which in turn bind to estrogen-responsive elements in the promoters of numerous genes and enhance their transcription (33). A number of these receptors code for polypeptide hormones which, on secretion, stimulate the pro-

liferation of the cells. The addition of estradiol to estrogen receptor-positive cells directly results in the increased transcription of the TGF- α , pS2, and cathepsin D genes and their subsequent increased secretion (27,33). TGF- α enhances breast carcinoma cell proliferation by its binding to the EGF receptor (28); the roles of the lysosomal protease cathepsin D and the pS2 protein in breast carcinoma cell proliferation are unclear. Cathepsin D may, however, enhance the ability of breast carcinoma cells to metastasize (34). We need to define the mechanism by which estradiol stimulation of MCF7 cell proliferation and basal cathepsin D synthesis and secretion is inhibited by suramin. Suramin's inhibition of estradiol stimulation of growth may be due to its ability to inhibit the growth-promoting activity of those growth factors whose synthesis and secretion are increased by estradiol.

Finally, the reversible effects of inhibition of growth with suramin and the finding that low levels of the agent actually stimulate basal and EGF-enhanced MCF7 cell growth, as demonstrated by Vignon et al., suggest that high serum levels of suramin and prolonged courses of treatment would be required for therapeutic benefit.

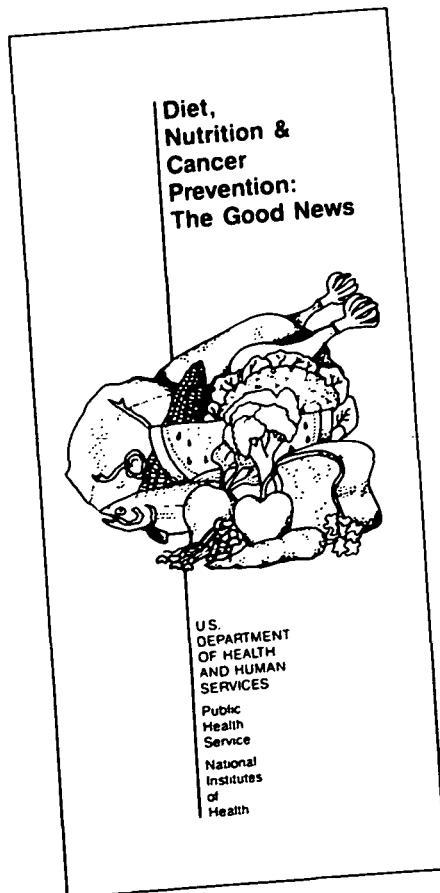
In summary, existing laboratory and clinical experience strongly indicates that suramin will likely become an important addition to the armamentarium of anticancer drugs. Perhaps as important, a better elucidation of the drug's mechanism of action may enhance our understanding of the role of growth factors in the pathogenesis of human malignancies.

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