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ANTI-EPIDERMAL GROWTH FACTOR (EGF) RECEPTOR (R) MONOCLONAL ANTIBODIES (mAbs) AS POTENTIAL ANTI-CANCER AGENTS. John Mendelsohn, M.D., Memorial Sloan-Kettering Cancer Center, NY, NY 10021. We have produced mAbs 225 IgG1 and 528 IgG2a against the R for EGF, which can inhibit binding of EGF and TGFα, prevent activation of R tyrosine protein kinase, and inhibit growth factor-dependent proliferation of normal and malignant human cell lines, both in culture and in xenografts. We have evidence that the mechanism is related to blocking of an autocrine loop. MAb labelled with ^{111}In can selectively concentrate in and image xenografts bearing high numbers of EGF R. A phase I trial with ^{111}In-225 IgG1 was carried out in patients with advanced squamous lung cancer, which invariably expresses high levels of EGF R. 4 mg ^{111}In-225 (5 mCi) was administered by itself or co-infused with 16, 36, 116 or 296 mg of unlabelled mAb in groups of 3 patients each. No toxicity occurred at any dose level. The primary tumor was visualized in all patients receiving 20 mg or more mAb, and was optimal 3 days after injection. Significant liver visualization was also observed. At a dose of 120 mg, the distribution of ^{111}In-225 to the tumor site reached 3.4% ID at 72 hrs. All patients produced human anti-mouse antibodies. We conclude that 225-IgG1 mAb against the EGF R can be administered safely and can localize squamous lung cancer, a tumor known to express elevated levels of R. Supported by the NCI and Hybritech, Inc.

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LOCAL REGULATION OF OSTEOCLASTIC ACTIVITY IN BONE AND ITS MODULATION THROUGH BISPHOSPHONATE

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Exception made for myeloma and perhaps some instances of breast cancer, hypercalcemia as a complication of malignancy is associated with acute discomfort and a short life expectancy. It requires acute and vigorous treatment, aiming at short-term therapeutic results. Patients with metastatic bone disease on the other hand, especially those with breast cancer in whom this is frequent, experience protracted morbidity, and have a life expectancy which may be often counted in years. Treatment should not merely suppress symptoms but aim at preventing future morbidity. These two different options, therapeutic suppression and preventive modulation of secondary bone pathology, require different pharmacologic approaches.

Both hypercalcemia and metastatic disease involve excessive bone breakdown, mediated through osteoclasts. A surprising finding of the last decades was that osteoclastic resorption is regulated by osteogenic, bone forming cells and bone resorption in its turn is a source of signals affecting bone forming cells. This so called cell-cell interaction, which even involves cells from the hematopoietic but also from the supportive cell systems in bone, is mediated through cytokines, prostaglandins or growth factors. Indeed the mechanism by which tumours affect bone resorption involves disregulation at the level of these humoral factors.

Bisphosphonates adhere to bone, but contain secondary groups that modify cyclic processes leading to bone resorption, and ultimately remodelling. They can be administered in shortterm suppressive settings with dramatic results and without side effects. Prolonged administration however will not merely suppress resorption but also have consequences for remodelling of bone. Their prolonged use in secondary prevention of metastatic bone disease or even in adjuvant settings requires taking into account secondary effects on bone remodelling and -turnover and appropriate adjustment of dose and mode of administration.

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GROWTH FACTOR ANTAGONISTIC TREATMENT OF CANCER WITH SURAMIN

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Suramin is an analog of heparin and other highly sulfated glycosaminoglycans. This drug thus binds to many heparin-binding proteins and alters their action. Three of the most important tumor growth factors are known to have a high affinity for heparin and heparan sulfate: platelet-derived growth factor (PDGF), transforming growth factor ß (TGF-ß), and fibroblast growth factor (FGF). Heparin-sepharose plays an important role in the purification of these growth factors. *In vitro* suramin has been shown to bind to each of these growth factors and to inhibit their ability to act at their cell surface receptors. Thus, suramin is able to reverse transformation of fibroblasts by v-sis secondary to simian sarcoma virus infection. The drug appears to work whether the autocrine loop is internal or external. Similarly suramin has been shown to block the action of exogenously added growth factors on a range of human malignancies.

We have tested the activity of suramin in a range of human tumors including prostate ca, adrenal ca and lymphomas. In both of these diseases, we have seen significant responses to suramin as a singly agent. Because these growth factors are also important in a range of normal physiologic events, toxicities are to be expected. In practice, this drug has a range of toxicities unusual for an anticancer drug, but consistant with the known biology of these growth factors. This includes neurotoxicity, immunosuppression, skin rash, renal injury and hypoadrenalism. We have worked out a dose and schedule of suramin which controls the severity of these toxicities while preserving worthwhile antitumor activity. Prospects for future analog development will be discussed.