[S2-1] [10/19/2001(Fri) 10:30-11:00 / Hall B]

Clinical Application of Molecular Targets in Angiogenesis

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Angiogenesis as a physiologic process is tightly regulated by a family of pro- and anti-angiogenic factors. Recent information has demonstrated that the "dormancy" of micrometastasis is similarly dependent on angiogenesis and that a balanced rate of proliferation and apoptosis can be tipped in favor of cell growth when the tumor evolves an angiogenic phenotype. The angiogenic process is characterized by a number of independent but interlinked process. These include the dissolution of the basement membrane, the induction of endothelial cell proliferation and migration, and the resolution of the process with microtubular formation. Moreover, the extent of angiogenic heterogeneity in malignant neoplasm is regulated by the organ microenvironment. This biological environment specificity can be translated into the biological sub-stage. We found organ specific expression of MMP subtypes, eg. MMP-2 in breast cancer and MMP-9 in gastric cancer. In gastric cancer, different biological phenotypes were found with cancer progression; MMPs in early cancer, uPA/PAI-1 system in advanced cancer and adhesion molecules with liver metastasis. As a result of this stepwise progression, anti-angiogenic therapy can be developed against a specific aspect of the process.

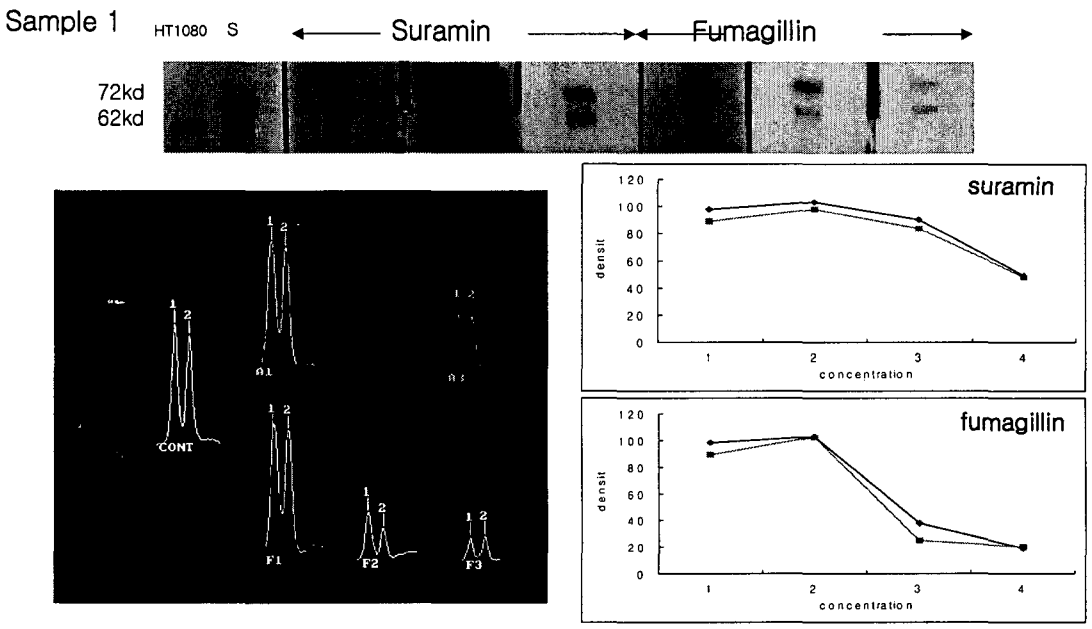
The value of anti-angiogenic therapy, targeting young, newly developed vessels as opposed to the more longstanding tumor vessels, is as yet unclear. In gastric cancer cell lines which expressed both angiogenic factor, MK, and a resistance to the conventional chemotherapeutic agent, adriamycin, a synergistic activity was found with a combination of MK inhibitor and adriamycin. Hence, the principal use of the agents may be best envisioned to be in combination with standard therapy as opposed to single-agent therapy.

Cytostatic agents may offer clinical benefits for patients in the absence of tumor shrinkage. Because of this factor, the sequence and design of traditional phase I, II, and III trials may not be appropriate for cytostatic agents. Concerns have been expressed that these differences between cytotoxic and cytostatic agents may lead to rejecting a

clinically useful cytostatic agent because it is tested using standard cytotoxic trial designs. The initial phase III matrixmetalloproteinase inhibitor(MMPI) clinical trials targeted advanced stage cancers with MMPI either as monotherapy or in combination with cytotoxic agents. The results of these trials have been disappointing. For example, treatment with the MMPI marimastat (British Biotech) provided no benefit to patients with advanced pancreatic cancer. Patients with advanced small cell lung cancer treated with tanomastat (Bayer Corp.) fared worse than placebo controls, resulting in the cessation of all clinical trials with this agent. However, although clinical trial with marimastat in gastric cancer patients did not meet its primary end point, there was a significant benefit of marimastat treatment in a subset of patients with node negative disease.

For a cytostatic agent directed as a particular molecular target, it may be appropriate to restrict eligibility in efficacy trials with any of designs to patients whose tumors have the target and at the appropriate level, eg. HER-2/neu. We found that the anti-MMP activity of the MMPI was higher against the cell lines which expressed more MMPs. Target specificity of the agents was also found that suramin affected preferentially inactive MMP-2 whereas fumagillin affected active form of MMP-2 (Fig. 1). IC_{50} of the agents against MMP showed a possible impact as a prognostic marker as well as a predictive marker. Biological activity for some biological end points would be viewed as a necessary but not sufficient condition for proceeding. Therefore even when recruiting patients on a targeted biological activity, both the changes of biological end-point and object tumor response or a progression-free survival at a designed time point can be an evaluable outcome.

If a targeted biological endpoint is known and has a reproducible *ex vivo* assay system for measurement before treatment, then it is advisable to ensure that the end point is sufficiently affected by the selected agents with a given dose in that model system.



	marker	control	suramin3	suramin30	suramin300	fumagillin 10^{-6}	fumagillin 10^{-5}	fumagillin 10^{-4}
peak1(72KD)	5	98	103	90	49	103	38	19
peak2(62KD)	101	89	98	84	48	102	25	20

Fig. 1. Selective activity of MMPI against different MMPs with *ex vivo* model