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Novel Mechanisms in the Future of Cancer Treatment: Angiogenesis & Signal Transduction

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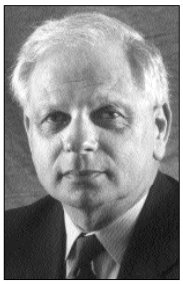
ABSTRACT

While progress has been made in the adjuvant setting, metastatic breast, lung, and gastrointestinal cancers remain very nearly as deadly now as they were in the beginning of the 20th century. Clearly, we need a new paradigm from which to approach cancer treatment. The explosion in knowledge about the basic biology of the cancer cell has laid the groundwork for this needed shift. The emerging "targeted therapies"—that grew out of the increased understanding of the processes whereby a malignant cell lives, dies, or metastasizes—utilize compounds aimed at modifying the cell's behavior. The process of angiogenesis is oriented to the growth of metastasis as well as to the initiation of cancer development in a primary area of the body. Breakthroughs in the development of new agents in signal transduction portend bringing new targets to the clinic in the near future.

Can cancer be converted from an acute to a chronic disease with the employment of these new "targeted therapies?" Many significant scientific questions, as well as economic questions, remain. While it is tempting to use the shift toward cytostasis to view cancer as we viewed diabetes after the discovery of insulin, this may be a perilous vision. We must not forget that the complications of even well-controlled diabetes can be lethal. A long road needs to be traveled before a cancer patient will be assured a normal life span despite the presence of malignancy.

Style Note:

This teaching monograph is intended to replicate a scientific symposium in which experts in a particular field advise their colleagues about new developments. While ***Oncology Spectrums*** uses generic drug names throughout, this work references trade names to ease the give-and-take between discussants, and make the advice herein more palatable to specialists or generalists, both of whom treat patients who might benefit from the advances described herein.—The Editors



Michael A. Goldstein, MD, is a medical oncologist in Brookline, Massachusetts, and assistant clinical professor of medicine at Harvard Medical School. Currently, Dr. Goldstein is a member of the Executive Subcommittee of the Clinical Practice Committee of the American Society of Clinical Oncology and has participated in the formation of the Guidelines for Chemotherapy Administration as well as in the reorganization of the State/Regional Affiliates program.

Introductory Remarks

The Evolution of Cancer Treatment

Until very recently, the guiding principle of cancer treatment has been total eradication of the last malignant cell. The observation that mustard gas poisoning resulted in the destruction of lymphocytes and atrophy of nodal tissue led to the use of nitrogen mustard to treat malignant lymphomas. For many, this was the dawn of the modern era of chemotherapy. Since then, physicians have developed more radical surgical procedures and techniques to deliver higher doses of radiation and strategies for the administration of high dose chemotherapy.

The advent of better anesthesia, improved techniques of supportive care, and the use of bone marrow or stem cell support has allowed us to deliver even more aggressive cancer treatment. Unfortunately, with only certain exceptions, this path has not led to winning what President Nixon termed "the war on cancer." Perhaps we were lulled into a false sense of security by our early successes with lymphomas, trophoblastic tumors, testicular cancer, and certain forms of leukemia. These advances led to the feeling that if we only developed the right drugs and learned to administer them properly, we could duplicate those successes when faced with the more common lung, gastrointestinal, and breast cancers. While progress has been made in the adjuvant setting, metastatic breast, lung, and gastrointestinal cancers remained just as deadly at the end of the 20th century as they were in the beginning. This failure reinforces the need for a new paradigm from which to approach cancer treatment.

A Shifting Paradigm

A veritable explosion of knowledge regarding the basic biology of the cancer cell has laid the groundwork for such a paradigm shift. From a better understanding of the processes whereby a malignant cell lives, dies, or metastasizes, compounds have been developed which modify the cell's behavior. With these new so-called targeted therapies, oncologists hope to make the next major advance in the treatment of malignant disease. Preclinical evidence has shown these agents to be cytostatic or antiproliferative rather than cytotoxic. However, the advent of this new class of antitumor agents raises many questions, such as how to evaluate what promises to be an avalanche of new compounds. Traditionally, we have utilized advanced disease in which conventional therapy had been exhausted to test new agents. Also, we have demanded a certain predetermined shrinkage in tumor volume to declare an agent suitable for further evaluation. Is it reasonable to apply these criteria to this new class of compounds? If treatment is aimed at cytostasis rather than cytotoxity, then new parameters of treatment success need to be established, or many potentially useful agents will be lost in the testing procedure. Should we expect these targeted therapies to control tumors when used as the sole form of therapy or will they, by necessity, be combined with traditional radiation surgery or chemotherapy? When in the course of a patient's illness is the opportune time for their use? If they are truly cytostatic, then we can envision a targeted therapy being administered not only during the acute phase of treatment but perhaps for years after diagnosis. How do we ascertain toxicity of compounds that may be consumed over a long period of time?

Economic Issues

In addition to scientific, there are economic issues to consider. These new treatments will almost certainly be administered orally and just as certainly will be expensive. Today, Medicare precludes reimbursement for most orally administered drugs. Thus, the segment of the population with the highest cancer incidence would be barred from the use of these new agents. I am confident that if these new treatments are highly successful, their cost will eventually be reimbursed. However, if a treatment is marginally effective, but expensive, society will have difficult decisions to make.

Cancer: From Acute to Chronic?

We are offered the proposal that cancer can be converted from an acute to a chronic disease with the employment of new therapies. While it is tempting to view cancer as we viewed diabetes after the discovery of insulin, this may be a perilous vision. Insulin did indeed convert diabetes from a rapidly fatal condition to a chronic disease. However, we must not forget that the complications of even well-controlled diabetes can be lethal. A long road needs to be traveled before a cancer patient will be assured a normal life span despite the presence of malignancy. There are a number of issues here, but what we'll be dealing with is the concept of more targeted therapies, therapies that target specific receptors and specific signal transfection pathways. Roy Herbst will be talking about agents that block—signal transduction inhibitors, specifically the epidermal growth factor receptor and its inhibitors. Michael Gordon will be discussing angiogenesis: how it works, and how it can be inhibited.

Roy S. Herbst, MD, is the assistant professor of medicine and the assistant professor of cancer biology at the University of Texas M.D. Anderson Cancer Center. As a highly regarded physician/scientist in the Department of Thoracic/Head and Neck Medical Oncology, Dr. Herbst has furthered his reputation as one of the leading researchers in the exciting field of new drug development.

Cell Surface Receptors

The agents that we are very interested in are those that block the epidermal growth factor receptor, which is a member of a superfamily of receptors. This includes epidermal growth factor-1, (EGFR-1); epidermal growth factor 2 or ER-B2, EGFR-3; and EGFR-4. These receptors are cell surface receptors. When these receptors bind ligand, they dimerize, and the dimerized receptor is unable to activate the tyrosine kinase to autophosphorylate the receptor. The phosphorylated receptor can then set off a chain of signal transduction events working through a number of pathways including the RAS and the MAP kinase pathway. This results in a cell cycle progression, which can have an effect both on cell growth and proliferation, as well as effects on angiogenesis and subsequently tumor metastasis and growth.

This target has been known for a long time to portend poor prognosis in certain malignancies. For example, focusing on EGFR-1, it is known that patients with higher receptor levels in their tumors do worse in a number of tumor types, mostly the epithelial tumors, including lung, colon, breast, and pancreas. This receptor is up-regulated in a large number of different tumors, many of which are common. For example, over 90% of head and neck tumors, about 50–60% of non–small-cell lung cancers (NSCLC), and about 60% of colon cancer, to name just a few. It's a target that is overexpressed in certain malignancies, and which is involved in single transfection pathways resulting in cell growth, and certainly a very able target for blockage.

The other member of this family that has had a great deal of research is the EGFR-2 or the ER-B2 receptor. This is the receptor that is the target for the licensed drug Herceptin. This receptor, again, binds in response to the ligand, which is not known for this receptor, but dimerizes and results in the same autophosphorylation and signal transduction.

Agents in Development

The problem with studying this type of agent is that as single agents, with a few exceptions, they do not cause advanced tumors to shrink, which is the usual setting for our Phase I studies. As a target, EGFR is quite important for these cancer cells, and is a very active area of cancer investigation. Preclinical studies have shown that a group of agents can work against tumor cells of the types already mentioned in cell culture and in animal models also. Combinations with chemotherapy have been known to be synergistic and have been seen with many of these new biologic agents. Hence, these agents are heading towards clinical trial, in most cases, in combination with chemotherapy. Rather, at their very best, they might cause stabilization of disease, and decrease time to tumor progression. However, there have been some surprises. For example, the small molecule inhibitor known as Iressa, or ZD1839, did produce about a 10% response in NSCLC patients in the Phase I trials. This was unexpected. And even with a response rate such as that, it is still going into first-line use in lung cancer in combination with chemotherapy. The question is how to study a new class of agents where we don't expect to see a standard response rate. This becomes problematic because, unlike standard clinical trials, when Phase I trials are done with these relatively non-toxic agents, observations must include an optimal biologic dose rather than for a maximum tolerated dose. In many of these trials, the new paradigm has been to do small Phase I studies for proof of concept. These studies include tumor biopsies whenever possible for evidence of inhibition of the single transduction pathway. A good example of this is antibodies that recognize activated MAP kinase or phosphorylated EGFR; investigators are now looking to see if these agents can inhibit that phosphorylation.

Outcomes and Utilization

Due to low toxicity, some of these agents are moving very quickly to Phase II and III, some as single agents in very advanced diseases but most in combination with chemotherapy, for up-front therapy. The main toxicities of the epidermal growth factor receptor inhibitors appear to be skin toxicity, producing an acne-like rash, and with the small molecules only; and diarrhea, although this effect is variable. Iressa is in two Phase III multicenter trials. Over 200 centers are looking at metastatic NSCLC using the drug in combination with Paraplatin and Taxol, or Platinol/Gemzar in a randomized placebo controlled study. The C225 antibody is in Phase I and Phase II trials, and is being studied with both platinum in refractory head and neck cancer and with CPT-11 in refractory colon cancer. CI1033 and some of the other small molecules are now in earlier stages of development, mostly Phase I/II, in clinical trials including the surrogate as discussed. Several other agents are in Phase II or Phase III clinical trials.

Signal transduction represents a very important new target for cancer therapy. In my opinion, it is as close if not closer than the angiogenesis field to bringing a drug to the clinic within the next several years. Within the next year to year-and-a-half, results from several of the agents mentioned could allow the licensing of these agents for clinical use. We're beginning to see Phase IV-type studies looking at these agents in a whole wide variety of disease types. These agents could be used in combination with chemotherapy in advanced disease, but could also clearly be used as maintenance therapy, something which doesn't exist in most of our solid tumor treatments. Perhaps they will even be used alone in high risk or early stage disease or as chemopreventative agents for suitably identified patients.

Michael S. Gordon, MD, is associate dean for research for the Phoenix Campus of the University of Arizona College of Medicine and an associate professor of medicine in the section of hematology/oncology. Dr. Gordon's interests are clinical trials development and coordinating the efforts for the development of the Arizona Cancer Center's clinical trials program.

The Process of Angiogenesis

In addition to the development of targeted therapy based upon the identification of molecular targets within tumor cells, one of the fundamental principles of tumor biology has been the recognition that for cancer to grow, it needs to develop the ability to create new vessels, the process of angiogenesis. This is a critical process, oriented not only to the development of metastatic disease but to the initiation of cancer development in an initial primary area. Hence, angiogenesis plays a role in the evolution from a dysplastic lesion, to an early cancer, to the expansion of the tumor population. It then plays a significant role in the metastasis and micrometastasis of tumors and the subsequent development of micrometastatic disease into macroscopic or clinically relevant disease. This process is one that is tightly regulated by a variety of autocrine and paracrine factors—it is oriented, controlled, and well organized. Additionally, it's been recognized over many years that in a variety of tumors, the angiogenic process as defined by the number of blood vessels within tumors, the so-called microvessel count or density, does have a significant role or impact on the prognosis of cancers. Similar to the expression of receptors or molecular receptors on the surface of tumor cells, the tumor microenvironment, as defined by microvessel density, also has significant prognostic implications in breast cancer, lung cancer, and a variety of other solid tumor malignancies. The process of angiogenesis is actually one that is aggressively controlled not only by autocrine factors that are proangiogenic, but also by antiangiogenic endogenous factors. The development of the angiogenic phenotype, is dependent upon the level of angiogenic vs antiangiogenic factors. The process is characterized by the dissolution of the basement membrane; the first step towards the development of new blood vessels. The proliferative effects and migratory effects on endothelial cells that form new vessel tubules, the reestablishment of the blood vessels, the basement membrane integrity.

Metalloproteases

Several important metalloproteases have been identified that play a significant role in the dissolution of the basement membrane and the potential for angiogenesis, as well as the extravasation and intravasation of micrometastatic tumor cells. Two of these very important metalloproteases are MMP-2, or gelatinase A, and MMP-9, or gelatinase B. A number of drugs have been developed to inhibit the activities of these two enzymes. The tissue plasminogen activator pathway, is an alternative to the MMP path for dissolution of basement membranes and identifies the fact that in many of these pathways there are redundancies with the potential for resistance to any one single drug or mechanism. The MMP inhibitors as a family inhibit the matrix metalloproteases and are characterized by a number of agents that either inhibit protein expression or by way of chelation of the zinc moiety. Because of the effect they have on the basement membrane, matrix metalloproteases, in addition to being angiogenesis-inhibiting, may actually be antimetastatic. Many of the MMPs that have been developed have been studied in early clinical trials and have now progressed to Phase III. Similar to the cytostatic drugs that have been identified earlier, many of these agents have failed to demonstrate significant antitumor clinical activity as defined by the classical algorithm of tumor shrinkage. However, there has been some suggestion or evidence of a slowing of progression of tumors or perhaps a reduction in the development of metastases. As a result, many of these agents have been developed in their Phase II and Phase III evolution in conjunction with chemotherapy. Although a number of these Phase III trials have been completed, none to date has indicated or demonstrated an improvement in progression free or overall survival. But several Phase III trials are currently in the maturation process and may hold some potential for benefit.

Other Agents

In addition to the inhibition of the basement membrane, direct inhibition of endothelial cells activity, such as proliferation or migration, has a clinical potential. A number of agents have been developed to try and inhibit autocrine growth factors such as vascular endothelial growth factor (VEGF) or basic fibroblast growth factor (FGF). Within this family, there are both monocolonal antibodies such as the recombinant human monoclonal antibody against VEGF as well as a number of agents that have been developed to actually inhibit the signaling of VEGF. Additional agents which are nonspecifically targeting angiogenic factors, such as the low dose interferon regimens as well as the drug TNP470, appear to have some potential activity in preclinical models. Clinical trials exploring their true antitumor activity, either alone or in combination with chemotherapy or other antiangiogenics, are ongoing.

Another class of agents that appears to have significant potential as an inhibitor of endothelial cells are the integrin inhibitors. Small molecules such as the integrins exist on the surface of endothelial cells and, in particular, the integrins α_V-β_3 and α_V-β_5 are critical for the mobility and migration of endothelial cells. They serve an important role in terms of adhesion to vitranectin and to the exposed basement membrane. Some of the most exciting agents that are being developed are drugs for which their clear-cut antiangiogenic activity or their clear mechanism of action has not been completely defined. The drugs like endostatin and angiostatin, which function potentially through an integrin dependent pathway have completed their Phase I studies and are moving into Phase II clinical trials. These drugs have tremendous preclinical activity and hold perhaps the best potential for the true realization of antiangiogenic agents in cancer therapy. A number of other agents that have poorly defined mechanisms, such as the drug Thalomid, are being explored. In addition to its antiangiogenic activity, Thalomid has an anti-inflammatory and anticytokine activity and it is very difficult to define which of these mechanisms play the most significant role in its antitumor potential.

Question & Answer Forum

Q: What does Herceptin do?

RH: Herceptin is an antibody that blocks the HER-2 or the ER-B2 receptor. Both of these receptors now have several drugs currently available for clinical trial. For the epidermal growth factor receptor, we can block that receptor with an antibody known as CT25, initially discovered by Dr. John Mendelsohn. This antibody binds the external domain of the epidermal growth factor receptor, preventing ligand binding and preventing receptor dimerization. This agent is currently in Phase II and Phase III clinical studies. We also have several small molecules, oral tyrosine kinase inhibitors, which block the internal domain of this receptor, functioning enzymatic inhibitors of the tyrosine kinase event. Those include ZD1839, also known as Iressa, OSI774, and CI1033, which is a bit different than the others because it is a pan-ER-B blocker. Not only does it block EGFR-1 but it also blocks EGFR-2, the ER-B2 receptor as well as EGFR-3 and -4 to lesser extents. It's also an irreversible inhibitor which suggests that it might perhaps be more potent and perhaps could be given on a schedule of less frequent administration.

This is now a licensed drug, and it's certainly the paradigm for how these drugs have been developed. The Herceptin agent was initially and previously used to treat metastatic breast cancer, with response rates only in the 14–15% range. There is some evidence that if used earlier, the response rates might be higher. Based on that, it was combined with either anthracyclines or with Taxol and used in several seminal Phase III studies which showed a survival benefit of the combination over the chemotherapy alone. Currently, Herceptin is a licensed agent for breast cancer and is being used in several other tumor types. The problem with Herceptin in lung cancer or in colon cancer, for example, is that the up-regulation of that receptor is not quite as high in other tumor types as it is in breast cancer. In breast cancer, the up-regulation of the receptor is 30%, and in lung cancer it is more on the order of 10% to 15%. It's not as good a target as the epidermal growth factor receptor, which is a much more widespread target.

Q: Is there any animal data on long-term administration of these agents in signal transduction? Are they as nontoxic as people really think they are?

RH: There really isn't very much animal data, and we are concerned with this. Many of these early stage clinical trials show that something is well-tolerated in a patient who receives it every 2 or 3 months. What is going to happen is we'll give it to earlier stage patients and use it in the maintenance setting. The example of that is matrix metalloprotease inhibitors—they went into their Phase III trials, and the toxicities became quite obvious, including musculoskeletal toxicity in some trials. You can't take anything for granted. You need to do the clinical trials and show for sure that it's safe. Also, we need to reeducate the FDA on how to look at anticancer drugs, and this is being done already. I think certainly there are a great number of agents now that are being brought forward in the accelerated approval pathway, where a response rate endpoint is allowed contingent approval for a disease for which no good treatment options exist. For example, a reasonable strategy, which we'll probably hear about at the American Society of Clinical Oncology annual meeting, is to take advanced colorectal cancer patients who have failed CPT11 regimens and administer CT25 in combination with CPT11 at the same dose at which they failed. The lowest dose is always used, so this is not a dose study. The investigators then treat those patients in order to find a response rate endpoint. This is a strategy that I think the FDA might accept. Of course, quality of life is being followed, but how well you can really do that in a Phase II trial is questionable.

Q: How does the vascular endothelial growth factor (VEGF) class of agents work in angiogenesis?

MSG: VEGF signals through a variety of receptors, most notably KDR and FLIT-1, and a number of agents have been developed to inhibit the signaling through these receptors. KDR in particular, which signals through the tyrosine kinase receptor, has been the target of a number of drugs such as SU-5416 and SU-6668, which have been developed in or are now progressing through their Phase I, Phase II and Phase III studies. The recombinant human monocolonal antibody against VEGF is currently in Phase III trials with some early Phase II activity demonstrating not only single agent activity in women with metastatic breast cancer but a suggestion of improved activity when administered in conjunction with chemotherapy. The Phase III trials need to be able to clearly demonstrate a benefit in that setting.

Q: How does this new advent of drugs in angiogenesis break from past treatment models?

MSG: Like the small inhibitors of molecular targets, antiangiogenic therapies are causing us to redefine our algorithms for anticancer therapy. The most critical endpoint, overall survival, tends to be the gold standard against which drugs are measured. The old algorithm of looking at antitumor responses, particularly for single agents, appears to be less valuable, particularly in comparison with drugs which in the diffuse metastatic setting may only slow overall progression. Hence, the incorporation of these drugs into early disease settings such as in the adjuvant setting or following maximal tumor regression may have their greatest potential. One of the most confounding issues relates to the preclinical models which tend to overemphasize the value of single or combination antiangiogenic agents. The realization that xenograft models of tumors in mice, where the angiogenic profile is much earlier than that of an established vascularity of existing tumors in humans, orients us to the fact that diffuse metastatic disease is unlikely to be benefitted by antiangiogenics alone. However, clearly in diseases where chemotherapy or other forms of treatment, be it biologic or pharmacologic, do have anticancer activity, the addition of an antiangiogenic, perhaps to either inhibit the regrowth of resistant cells or to improve upon the overall value of those established combination, may hold the greatest potential for this family of drugs.

The Impact of Traditional Therapies

01.3.01

- Traditional cancer therapy has aimed to cure the disease by utilizing aggressive surgery, high dose radiation, and ever more intensive chemotherapy
- With the exception of trophoblastic tumors, testicular cancer, certain leukemias, and lymphomas, this strategy has failed in the metastatic setting.
- Metastatic breast, lung, and gastrointestinal cancers have not yielded to traditional therapies

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

New Targeted Therapies

01.3.02

- Our new understanding of basic cellular growth mechanisms of the malignant cell has allowed the development of specific compounds that modify cell growth
- These new "targeted therapies" have been shown to be cytostatic or antiproliferative rather than cytotoxic

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

Problems Presented by This New Class of Anticancer Drugs

01.3.03

- How are these drugs to be evaluated? The traditional tumor shrinkage in advanced disease model may be inappropriate
- Are these cytostatic agents suitable as sole therapy or will they be additive to traditional treatments?
- If these new agents are truly cytostatic and capable of being administered over many months or years, how are we to evaluate toxicity?
- Economic issues:
  - Cost
  - Oral administration
  - Long-term physician surveillance accompanies long-term administration

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

New Treatment Approaches

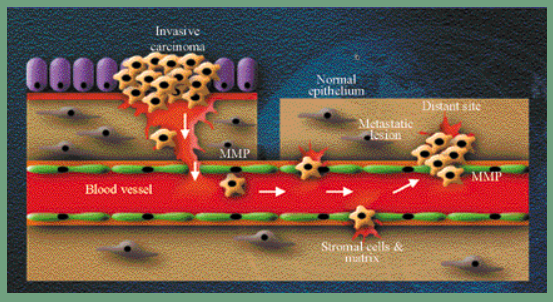
01.3.04

- Chemotherapy
  - Combinations of new cytotoxic agents (doublets/triplets)
  - Multimodality treatment of early stage disease
- Biologic therapy
  - Signal transduction
  - Growth factors (EGFR, erbB)
  - Antiangiogenesis
  - Maintenance therapy/chemoprevention
- Chemotherapy + biologic therapy

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

Matrix Metalloproteinases (MMPs) and Tissue Invasion

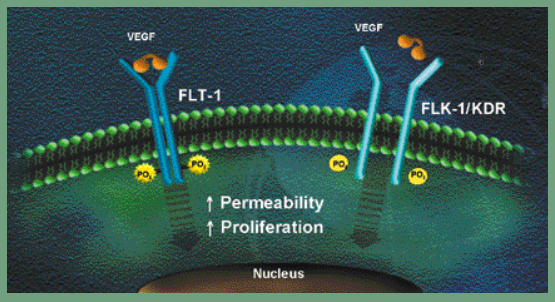
01.3.05



Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

VEGF: Vascular Permeability Factor

01.3.06



VEGF=vascular endothelial growth factor.
Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

EGFR as a Potential Clinical Target

01.3.07

Tumors showing high EGFR expression:

- NSCLC 50–80%
- Head and neck 95%
- Colorectal 25–77%
- Gastric (advanced) 33%
- Pancreatic 30–50%
- Ovarian 35–70%

High expression is generally associated with:

- Invasion
- Metastasis
- Late-stage disease
- Poor outcome

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

Inhibiting Angiogenesis—The MMPs

01.3.08

- The MMPs as a family can be inhibited by a variety of mechanisms including:
  - Chelation of zinc moiety (critical for activity)
  - Inhibition of protein expression
  - Inhibition of enzymatic activity
- Because of the critical nature of MMPs regarding the invasion of tumor cells, these agents may have additional activity
  - Prevention of metastases

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

Inhibiting Angiogenesis—EC Proliferation and Migration

01.3.09

Inhibition of VEGF as well as other factors can be accomplished by a variety of means including:

- Antibody-mediated inhibition
- Receptor inhibition (TK inhibitors or receptor specific agents)
- Post-receptors mediated inhibition
- Small molecule or drug development for selective inhibition

VEGF=vascular endothelial growth factor.

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

Inhibiting Angiogenesis and Other Issues

01.3.10

- Many "older" agents have demonstrated anti-angiogenic activity
  - Interferons (alpha and beta)
  - Chemotherapy agents (taxanes, camptothecins)
  - Cytokines (TNF-a, IL-12)
  - Others (thalidomide)
  - COX-2 inhibitors (celecoxib)
- How does one develop and apply these drugs in this new setting?

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

Drugs That Block Activators of Angiogenesis

01.3.11

Drug	Sponsor	Trial	Mechanism
Anti-VEGF Antibody	Genentech; South San Francisco, CA	Phase II/III against lung, breast, prostate, colorectal, and renal cancers	Monoclonal antibody to vascular endothelial growth factor (VEGF)
SU5416	Sugen; South San Francisco, CA	Phase I/II against Kaposi's sarcoma, Phase I/II against metastatic colorectal cancer, and Phase I/II against advanced malignancies	Blocks VEGF receptor signaling
SU6668	Sugen; South San Francisco, CA	Phase I against advanced tumors	Blocks VEGF, FGF, and EGF receptor signaling
PTK787/ZK 22584	Novartis, East Hanover, NJ	Phase I against advanced cancers (Germany and UK); Phase I against glioblastoma and Kaposi's sarcoma; Phase I/II against Von Hippel Lindau disease	Blocks VEGF receptor signaling
Interferon-alpha	Commercially available	Phase II/III	Inhibition of bFGF and VEGF production

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

Why is Angiogenesis Important?

01.3.12

- Angiogenesis represents the development and maturation of new blood vessels.
  - Characteristically involves small capillaries
- The physiologic process is involved in wound healing and embryogenesis
  - Classically tightly regulated by pro- and anti-angiogenic factors
- In cancer, angiogenesis effects neovascularization, tumor cell invasion, and metastatic development.

Goldstein M, Herbst RS, Gordon MS. *Oncology Spectrums.* Vol. 2. No. 3. 2001.

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