

Anti-Angiogenesis and Metronomic Chemotherapy

Anti-Angiogenic Principles

- * Normally, in adults, new vessel growth only occurs during the menstrual cycle, pregnancy and wound healing.
- * Abnormal angiogenesis contributes to diabetic retinopathy, psoriasis, rheumatoid arthritis and of course, cancer.
- * Regulation of angiogenesis is controlled by natural stimulatory and inhibitory factors in the body.

Anti-angiogenesis and Cancer

- * For tumors to grow larger than 2 mm, new blood vessels must form. These vessels are also necessary for metastatic spread.
- * Therefore anti-angiogenic agents may be more effective in early cancer or after substantial debulking with surgery, chemo or IPT.

In Vivo Angiogenesis Stimulators and Inhibitors

VEGF	IL-12
aFGF	endostatin
bFGF	angiostatin
IGF-1	Interferon-2a
Angiogenin	Platelet factor-4
HB-EGF	Thrombospondin
IL-8	TIMP-1 and -2
Thymidinephosphorylase (PD-ECGF)	Angiostatic steroids
HGF	16 kD prolactin
proliferin	

Possible Treatment Advantages

- * All solid tumors seem to require angiogenesis to grow and metastasize so the treatment may be able to be generalized to all tumor types.
- * Further, it may be possible to discover specific aspects of tumor vs. "normal" angiogenesis and target the therapy to tumors only.

Treatment Strategies

- * Angiogenesis stimulators can be blocked.
- * Angiogenesis inhibitors can be added (targeted agents, natural bodily inhibitors, herbs, etc.).

Anti-Angiogenic Agents

- * Those already in conventional clinical use including Bevacizumab, Thalidomide, celecoxib, interferon alpha, tagamet, catopril, lovostatin, etc.
- * Natural agents include artemesinin, sea cucumber, bindweed extract, curcumin, quercetin, omega 3 and 6 fatty acids, green tea extract, licorice, shark cartilage, squalamine, vitamin D3, NAC, CoQ10, Acetyl, L carnitine, milk thistle, shark liver oil, Se, Zinc and Tetra TM (by lowering copper).
- * Some of these natural agents are already in clinical trials (Neovastat (shark cartilage extract), squalamine, etc)

Metronomic Chemotherapy

- * Conventional chemotherapy focuses on "MTD" (maximum tolerated dose).
- * This requires infrequent doses to allow the body to recover from side effects (which of course can be serious).
- * There has been a trend in oncology to give lower dose, fractionated therapy in an attempt to reduce side effects and improve outcomes. In fact, "dose-dense" chemotherapy (using more frequent lower doses with an ultimately higher total dose) has been shown to be clearly superior in phase II clinical trials.

Metronomic Chemotherapy cont'd

- * Metronomic chemotherapy is the use of very low dose chemotherapy on a daily basis.
- * These low doses are not directly toxic to the cancer cells but they do kill endothelial cells and therefore inhibit angiogenesis.
- * They can be used with other anti-angiogenic agents (both conventional and natural) and their toxicity is generally low.

Metronomic Chemotherapy

Mechanisms of Action

- * As mentioned above it may act directly to kill or inhibit endothelial cells.
- * Cyclophosphamide, in metronomic dosages, has been shown to induce thrombospondin (TSP-1), which inhibits VEGF.
- * It may inhibit or kill circulating endothelial progenitor cells (formed in the bone marrow and circulates to various sites to stimulate angiogenesis. It has been shown that this mechanism is responsible for up to 50% of all angiogenic effects.

Metronomic Chemotherapy

Mechanisms of Action cont'd

- * M.C. can, paradoxically, stimulate the immune system.
(Ben-Efraim, S. Immunomodulating anticancer alkylating drugs: targets and mechanisms of activity. *Curr. Drug Targets* 2, 197-212 (2001).
Matar, P., Guillermo, G., Celoria, C., Font, M. T. & Scharovsky, O. G. Antimetastatic effect of a single-low dose of cyclophosphamide on a rat lymphoma. *J. Exp. Clin. Cancer Res.* 14, 59-63 (1995).
Hermans, I. F., Chong, T. W., Palmowski, M. J., Harris, A. L. & Cerundolo, V. Synergistic effect of metronomic dosing of cyclophosphamide combined with specific antitumor immunotherapy in a murine melanoma model. *Cancer Res.* 63, 8408-8413 (2003). ***An important study illustrating the potential benefits of combining a non-immunosuppressive metronomic weekly cyclophosphamide regimen with an immunotherapeutic approach to treat cancer. This circumvents the contra-indicated use of immunosuppressive MTD cytotoxic drug regimens with immunotherapy.***
- * M.C. can induce differentiation in tumor cells (at this time an unproven hypothesis).

Metronomic Chemotherapy

Advantages

- * Low toxicity (as described above). Most common side effect is lymphocytopenia.
- * Unlikely to induce chemoresistance because the target cells are the relatively genetically stable host endothelial cells and not the genetically unstable cancer cells expressing MDR and other resistance factors described.
- * They can be used with targeted and natural agents to enhance their benefit.
- * It is a relatively inexpensive treatment.

Metronomic Chemotherapy Disadvantages

- * It is unlikely to work as well with large tumor burden. It's best use would be in early cancers, after IPT, and/or after debulking surgery.
- * It is probably not going to be curative. Cancerous tumors of <2mm don't need angiogenesis to survive. It is rather perhaps a means of turning cancer into a manageable chronic condition.
- * Side effects include lymphocytopenia, and delayed or impaired wound healing.

Metronomic Chemotherapy Regimens

- * Cyclophosphamide: 50 mgs/day p.o. without interruption for two to three years.
- * Etoposide (VP-16): 50 mgs/day p.o. 2-3 yrs.
- * May alternate the above two drugs: cyclophosphamide for 21 days and VP-16 for 7-14 days.
- * Other regimens could include low dose capecitabine, UFT (uracil plus tegafur, a fluoropyrimidine antimetabolite), or MTX.

Anti-Angiogenesis Regimens: Basic Regimen for Prevention or When in Remission

- * Acetyl Carnitine 500 mgs BID
- * Alpha Lipoic Acid 300 mgs BID
- * Aspirin 325 mgs Qd or Celebrex
- * Mixed Carotenoids 75,000 IU/day
- * CoQ10 100 mgs TID
- * Curcumin 600 mgs TID
- * Quercetin 1000 mgs TID

Basic Regimen cont'd

- * Flax seed oil or fish oil or shark liver oil at least a tsp/day
- * Genestine 2800 mgs TID (not with estrogen sensitive tumors)
- * Green Tea extract 1000 mgs TID
- * Milk Thistle extract (Sylimarin) 500mg Qd
- * NAC 1000 mgs 5X/day
- * Se 200 mcg Qd

Basic Regimen cont'd

- * Vit B 100 Qd
- * Vit C 4 gms BID
- * Vit E (mixed tocopherols) 400 IU/day
- * Zinc Gluconate up to 250 mgs/day (with great care if also using Tetrathiomolybdate). Excessive zinc may be contraindicated in prostate cancer and melanoma.

Active Disease Regimen

- * Continue basic regimen and add the following:
- * Biaxin 500 mgs, BID (or minocycline 100 BID or doxycycline 250 BID or azithromycin 500 BID).
- * Thalidomide 50mgs ½ hr before h.s.
- * Lovostatin (may turn on tumor suppressor genes) 80 mgs/day X 3 wks, then 2 wks off then repeat.
- * Squalamine 650 mgs. TID,
- * Tamoxifen (EGF inhibitor) 20 mgs TID (not in uterine cancers).

Active Disease Regimen cont'd

- * Tagamet 800-1000mgs/day.
- * Retinoic acid 0.5-4.0 mg/kg/day.
- * Vit D 5000 IU/day
- * Cytosan or Etoposide 50 mg/day or MTX 2.5 mgs/day
- * Interferon alpha 500,000 U BID.
- * Tetrathiomolybdate 30 mgs QID (caution when using with zinc-must measure copper levels).

References Upon Request

Linchitz Medical Wellness

Glen Cove, NY

LinchitzWellness.com

