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The Role of Copper in the Angiogenesis Process and Chelating Copper As A Nutritional Anti-angiogenic Strategy + Other Available Anti-angiogenic Agents Useful in the Control of Cancer
By Dwight L. McKee M.D.

Copper:
Copper is believed to be the switch that turns on the angiogenesis process in tumor cells. It has been observed that abnormally high serum copper levels are found in patients with many types of progressive tumors.

According to the University of Michigan Oncology Journal, many studies have shown copper to be an obligatory cofactor in the process of angiogenesis. Growth factors in angiogenesis require binding to copper in order to function properly. As stated in Steven Brem's research at the Moffitt Cancer Center, "**copper-binding molecules (ceruloplasmin, heparin, and the tripeptide glycyl-histadyl-lysine) are non-angiogenic when free of copper, but they become angiogenic when bound to copper**."

On January 21, 2000, the University of Michigan reported that researchers had successfully stopped the growth and spread of cancer by depriving the tumors of the copper supply they need to form new blood vessels. This study was done with a small group of patients with advanced cancer. Researchers are using an inexpensive compound called tetrathiomolybdate, a molecule combining 4 sulfur-hydrogen groups bound to an atom of the mineral molybdenum, to lower the ceruloplasmin (Cp) levels (the major copper binding protein in blood) in patients with cancer. Because TM is not patentable, and it became available through compounding pharmacies in 2001, it has not been further developed by the cancer pharmaceutical industry, although a small pharmaceutical company is trying to develop a patented pro-drug that releases TM in the body, its progress has been slow. I have used Wayne Loveland's Prescription Center in Lacrosse Wisconsin, (Rxcentermed@gmail.com) since 2001 and consider his pharmacy the most knowledgeable about obtaining, storing, and compounding TM, as well as advising physicians and patients regarding TM therapy.

TM therapy:
The goal of copper chelation with Tetrathiomolybdate (TM) as an antiangiogenic strategy is to **lower ceruloplasmin levels to the target level, which is 15-20% percent of the**

baseline level, and remain at that level for at least 90 days, to see if the strategy will halt tumor growth. At this point, if any stabilization of tumor growth has occurred it should become apparent from scans taken at the 90 day point after reaching the target ceruloplasmin and compared to scans done after another 2-3 months (longer for tumors that have historically been slow growing). This is a long-term strategy, though, and these levels should remain low to prevent new blood vessels from growing. I have found the **TM is MOST effective when applied in the NED setting (no evidence of disease).** If Cp can be maintained in the target range (I now **generally aim for 10 mg/dl,** with a range of 7-12 mg/dl if the blood counts tolerate that, if not, the lowest level that does maintain acceptable blood counts). When tumors that can be seen on scans are present, these colonies are already angiogenic. Depriving them of the copper dependent angiogenesis growth factors slows them down for a while, but eventually most of them progress—presumably by learning to use angiogenesis growth factors that are not copper dependent.
However, with very small tumor cell colonies (<2 cubic mm), it is much more difficult for them to develop angiogenesis, which they must have to grow larger than this size, without the function of the **half dozen copper dependent angiogenesis growth factors**.

My clinical experience has been that **if these sub-angiogenic tumor colonies (which we can't see with scans, but can only presume the presence of) are deprived of the copper dependent angiogenesis growth factors, by maintaining a subclinical level of copper deficiency with TM for more than 3 years, that subsequent relapse is rare, even after TM is discontinued.** I do recommend continuing substantial supplementation with zinc—enough to **keep the serum zinc level in the upper range of normal**, which also helps keep the ceruloplasmin in the lower range of normal, without the presence of TM. Be sure to keep zinc supplements at least 2 hours away from TM doses.

Chelating Dosage
TM is currently available by a physician's prescription through a number of compounding pharmacies. T**he serum copper levels in the body will lower with the ceruloplasmin levels,** although in the first few weeks of TM therapy they may appear higher because TM chelates copper and then is bound to blood proteins and circulates before being eliminated from the body. **Serum copper levels are useful to measure prior to starting chelation with TM** and **after at least a month on TM**, after which point they will usually correlate with the ceruloplasmin level. **When ceruloplasmin has been reduced to 20% of its baseline, serum copper will usually be below the lower limit of the range of normal, although it may read higher due to some TM bound copper.** In contrast, zinc levels ideally should be at the high range of normal or even slightly above (though they are usually low when first measured in most cancer patients). **A ratio of serum zinc levels approximately two times higher than copper levels appears to be optimal for immune function and angiogenesis blockade.** The dose of TM used in the first phase of the University of Michigan study was one capsule **(20mg of TM each) with meals and three capsules (60 mg) on an empty stomach**. Taking the three "empty stomach" capsules in the middle of the night if one awakens to go to the bathroom seems to be the most effective in lowering ceruloplasmin levels. In a second phase of the U of M study the **dose was increased to two capsules (40 mg TM) with meals and 3**

capsules (60 mg) on an empty stomach. The higher dose was associated with more rapid drop in the ceruloplasmin level and showed no greater side effects (generally limited to sulfur smelling burps and occasional stomach upset, usually associated with taking the capsules on an empty stomach, and generally offset by eating a small amount of low copper food, such as rice crackers).

The **capsules taken with meals block the copper from absorbing into the body from food** or drink intake. **The capsules taken on an empty stomach bind and excrete residual copper from the body.** This is important to remember when titrating (adjusting) the dose of the TM as ceruloplasmin levels near the desired target.

Testing

Ceruloplasmin levels should be tested monthly to begin, then every two weeks as the target nears. Once the target is close, it should be tested weekly, continually, until the ceruloplasmin is successfully stabilized at the target. **As the ceruloplasmin levels approach the target (15-20% of the baseline), in patients with a significant tumor burden** (e.g. tumor masses visible on scans) **the ceruloplasmin may begin to rise.** This is thought to be the result of death of the most newly formed blood vessels feeding the tumors, with consequent death of the cancer cells dependent on this blood supply, and release of copper from these tumor cells (tumors concentrate copper from the body). In such patients, the copper chelation dose should not be reduced until the target has been achieved and maintained for several months. **If the ceruloplasmin level goes too low, however (usually less than 5 mg/dl), the copper needed for normal bone marrow function may be inadequate and blood cell levels (red cells, white cells, and/or platelets) may fall.** In patients being treated with chemotherapy or a lot of prior chemotherapy treatment, the bone marrow may be more sensitive to low copper levels, and low blood counts may occur with ceruloplasmin levels between 5 and 10. It is unusual for levels above 10 to affect bone marrow function. **If TM is stopped or reduced for a week or so in patients with active tumor, copper levels generally rebound quickly.**

Bone Marrow Drugs

Red blood cell growth factor (procrit) often appears to compensate for low red blood cell levels (anemia) associated with low (i.e. anti-angiogenic) levels of ceruloplasmin, white blood cell growth factors (Neupogen, Leukine) nearly always raise low white counts, if they are seriously low. Although Leukine (GMCSF) is usually slower acting than Neupogen (GCSF) there are reasons to prefer it (Leukine) in this setting, as it has shown anti-angiogenic activity in several test systems, whereas Neupogen shows angiogenic activity. **Some patients experience increased fatigue for a time after reaching target ceruloplasmin levels, but this generally resolves over a few weeks to months as the body adjusts.** No other consistent side effects have been associated with lowering ceruloplasmin levels to this range, though **some patients have reported nocturnal leg cramps and constipation, both of which appear to respond to increased magnesium supplementation**. If surgery is required it may be prudent to allow ceruloplasmin levels to elevate to the low range of normal for 6 weeks to ensure adequate angiogenesis for wound healing, and then lower them again to the target range.

Other Copper Chelators

Another copper chelating compound, widely available in health food stores, and less expensive than TM is N-acetyl cysteine (NAC). **Taken in amounts of 2-4 grams (2,000-4,000 mg), starting with 500 mg. daily and gradually increasing to 4 divided doses of 500-1000 mg. each, it can significantly lower copper levels in the body, though more slowly than TM.** It too is quite non-toxic, and also can help to raise levels of glutathione in cells, one of the body's major anti-oxidant systems. **It can be useful, along with zinc supplements in maintaining target ceruloplasmin levels after lowering them with TM, and may be used in place of TM in cases where developing angiogenesis blockade is not an urgent issue.** Also available through health food stores and compounding pharmacies is the anti-oxidant **alpha-lipoic acid (ALA**-- also known as thioctic acid). This is another non-toxic sulfhydryl containing compound that will chelate copper, as well as some other heavy metals, in doses of 100-400 mg./day; it is best absorbed on an empty stomach. A good preparation is ALA-MaxCR, which comes in **400 mg time released tablets, 1 twice daily is a good dose**. In some cases ceruloplasmin comes down very slowly or not at all, despite doses of TM up to 200 mg. per day. This is possibly related to increased hepatic need for sulfur compounds which results in use of TM as a sulfur source, not allowing it to circulate and chelate copper. In such cases it is often useful to a**dd other nutritional sources of sulfur, such as N-acetyl cysteine (NAC) and alpha-lipoic acid (ALA) as well as others, such as the amino acid l-taurine (500-1000 mg. per day) or MSM (methyl sulfonyl methane), 500 mg-2000mg daily in divided doses**.

With TM therapy, serum copper levels are not useful, as with other copper chelators, because TM binds copper and circulates as an inactive complex, which is still measured as serum copper—**only the ceruloplasmin level reflects the true copper status of the body.**

With non-TM chelators, serum copper and serum zinc levels should be tested monthly, until the zinc to copper ratio has been near 3 for several months. It is important to have blood drawn prior to taking any zinc supplements for the day, as oral intake of zinc prior to blood draw may falsely elevate the serum zinc level. The copper chelating strategy is a long-term strategy.

Patient Example:

An example of titration of one patient's ceruloplasmin levels with TM is as follows: (although Cp levels were monitored weekly in this example, intervals as noted above are generally adequate) baseline Cp 42-target 8.

Began TM 40 mg three times daily with meals, 60 mg. empty stomach.
Week 1 Cp 33
Week 2 Cp 25
Week 3 Cp 16
Week 4 Cp 14
Week 5 Cp 9 -TM lowered to 20 mg with meals and 40 mg. on empty stomach.

Week 6 Cp 7.3- TM stopped
Week 7 Cp 13.9 TM restarted at 20 mg with one meal, and 20 mg. on empty stomach.
Week 8 Cp 16.3
Week 9 Cp 17.2 TM increased to 20 mg. with two meals and 20 mg on empty stomach.
Week 10 Cp 21.4 TM increased to 20 mg. with three meals and 40 mg on empty stomach.
Week 11 Cp 18.1
Week 12 Cp 12.6
Week 13 Cp 7.9
Week 14 Cp 6.6 TM decreased to 20 mg. with three meals and 20 mg. on empty stomach.
Week 16 Cp 5.7 TM decreased to 20mg with 2 meals and 20 mg on empty stomach.
Week 17 Cp 6.7 TM changed to 20 mg with each meal.
Week 18 Cp 5.2
Week 19 Cp 5.4 TM decreased to 20 mg. with two meals only.
Week 20 Cp 16 TM increased to 20 mg. with two meals and 20 mg on empty stomach.

After this point, Cp remained between 5 and 8, with no dose adjustments necessary for the next two months.
During the above time period, the patient's hemoglobin dropped from 14.8 gm at baseline to 10.1 gm at week 6. Procrit was started and hemoglobin increased to 12.9 by week 16. **WBC was 4.4 at baseline, dropped to 1.9 at week 6 and recovered to 4.1 by week 17 without growth factor support. Platelets were 100,000 at baseline, dropped to 80 by week 4, and recovered to 137 by week 17 without support**. CT scans (stage 4 lung cancers with lung, bone, and brain metastases) showed no progression between baseline and week 14, with no other treatment. This patient was also taking Celebrex 400 mg. twice daily.

Copper Foods
In addition to the TM supplement, it is also important to refrain from consuming high-copper foods and water, especially if TM is ultimately discontinued. **The only foods high enough in copper to overwhelm the chelating capacity of TM are liver and other organ meats, and some shellfish, particularly lobster** (though scallops are often low in copper). Food tables listing copper content of foods are not necessarily highly reliable however, as copper content may vary widely depending on the area of the country, seed strain, growing conditions, types of fertilizer used, etc. (For example, copper compounds are frequently used in organic agriculture for their anti-fungal effects, which may significantly elevate the copper content of the produce). The bottom line is monitoring the blood levels, and using copper binding agents such as **TM, zinc, and if needed, NAC/ALA in the diet to maintain the target level.**

Regarding diet, here are some examples of **some foods which often are high in copper:** whole grains, particularly buckwheat and whole wheat; shellfish, such as shrimp and other seafoods; liver and other organ meats; most dried peas and beans; and nuts, such as Brazil nuts, almonds, hazelnuts, walnuts, and pecans. Oysters have high amounts, about five times as much as other foods. Soybeans supply copper, as do dark leafy greens and some dried fruits, such as prunes; cocoa, black pepper, and yeast are also sources. In addition to food sources, copper can come from water pipes and cookware. For most

patients, **avoidance of shellfish and organ meats** (or supplements with freeze dried organ tissue), is all that is needed in terms of diet.

Enhancing Effectiveness

Other available prescription medications have anti-angiogenic activity as well, and may increase the effectiveness of lowered copper as an anti-angiogenesis strategy. These include the anti-inflammatory medications referred to as **COX-2 inhibitors**, Celebrex being the only currently available one. For most people without a history of ulcers or kidney problems these medications can be safely used long term at up to twice the maximum labeled dosage (i.e. **400 mg twice daily with food for Celebrex)**. People with a history of sensitivity to sulfa anti-biotics (like Septra/Bactrim) and high blood pressure should not use Celebrex. There are also a number of botanical sources of COX-2 inhibitors that do not cause GI irritation, such as turmeric, reseveratrol (from Polygonum cuspidatum), rosemary extract, boswellia, and meadowsweet. Thalidomide and its newer analogue Revlimid are also useful, and generally has few side effects up to doses of 200 mg (10 mg for Revlimid), taken at bedtime, but they are both strongly thrombogenic, and prophylaxis with LMW heparins such as Lovenox is advised (which also may contribute anti-angiogenic activity). Older patients tend to tolerate thalidomide less well, and tend to develop an irreversible peripheral neuropathy if continued too long, so sensory nerve function monitoring is important. **Alfa interferon that may be injected subcutaneously or taken sublingually, in low doses, such as one quarter to one-half million units daily, may also add to effectiveness of angiogenesis blockade, being a particularly effective inhibitor of fibroblast growth factor.**