

ANTI-ANGIOGENESIS

A GREAT IDEA WHO'S TIME HAS COME!

INTRODUCTION

Research has shown there are a number of basic anti tumour strategies. These include:

1. Direct cell death (Necrosis)
2. Anti-angiogenesis (cutting off blood supply to tumours)
3. Apoptosis induction (programmed cell death)
4. Immune therapy

This article outlines a new approach to dealing with cancer using the strategy of antiangiogenesis.

ANGIOGENESIS

Angiogenesis is the growth of new blood vessels and is needed anywhere new tissue is grown, therefore it does not only occur in benign and malignant tumours but also in wound healing, menstruation and pregnancy. Abnormal angiogenesis also takes place in other diseases involving the immune system such as rheumatoid arthritis and serositis. It is believed that if you can inhibit angiogenesis in cancer patient's tumour growth will be inhibited as well or even reversed. The factors and the environments that drive angiogenesis during cancer also drive angiogenesis in wound healing and other normal conditions in the body. Since wound healing is vital for survival, the body employs many mechanisms to ensure angiogenesis occurs when it is needed. Overriding these mechanisms to stop tumour angiogenesis has posed a significant scientific challenge. Nevertheless, a number of natural compounds have been shown to inhibit tumour angiogenesis. Some compounds have inhibited angiogenesis in animal studies and have also been shown as helpful therapies in humans. Since angiogenesis is a normal process, the goal in angiogenesis therapy is to inhibit blood vessel growth as much as possible at the tumour site while allowing it to continue as necessary elsewhere.

When looking at tumour growth studies, tumours grow very slowly and gradually before angiogenesis, but once angiogenesis has been stimulated the growth rate can increase dramatically. What we do know about angiogenesis from tumours is that:

1. Cancer cells secrete substances that stimulate angiogenic factors. The most shared of these is VEGF (Vascular Endothelial Growth Factor).
2. The membranes surrounding the capillary cells dissolve and a bud begins to grow. The bud sends out a new capillary itself allowing another capillary tributary to be formed.

Research has shown that new blood vessels or angiogenesis in tumours is rather chaotic and that the blood vessels that are formed in this way are often of poor quality, thin walled and leaky. The inability of the cancer to get a good supply of blood to its centre, because of this rather haphazard blood vessel growth, can lead to necrosis or death inside the tumour and this is often seen in large tumours.

Angiogenesis and Copper

There has been a lot of interest in anti-copper compounds and their possible ability to inhibit angiogenesis. In Western Australia we are constantly seeing high copper levels in patients' hair. However, even at normal copper levels there is evidence that cancer uses the copper to promote angiogenesis. Copper levels are often elevated in cancer tissue as well as in the plasma of cancer patients and this can contribute to the uncontrolled angiogenesis.

History of Anti-angiogenesis

The initial idea for blocking angiogenesis as a way to treat cancer was first suggested by a researcher by the name of Folkman. He had noticed in certain tumours that the development of secondaries in a particular cancer did not develop until the primary cancer had been removed. He postulated that the cancer put out an inhibitory substance that stopped small metastatic cells from gaining new blood vessels. Folkman went on to develop two antiangiogenic approaches. He initially resurrected an old and extremely controversial drug thalidomide, which is in use today as an antiangiogenic program for selected tumours such as multiple myeloma, and gliomas. This treatment has had some success but has a number of significant side effects, particularly after long term use.

Anti copper treatment and Wilson's Disease

Wilson's disease is a hereditary disease, which involves excess copper being stored in the liver. The search for a treatment had been taken up by a researcher by the name of George Brewer MD, University of Michigan USA. He looked at copper's natural antagonists and researched a number of compounds including zinc. However, he finally settled on a molybdenum compound called tetrathiomolybdate (TM). This molecule contained sulphur and the metal molybdenum. Farmers and agriculturists have known that soils high in copper were molybdenum deficient and visa versa. The problem with using plain molybdenum salts commonly available as supplements was that the doses required to lower the copper sufficiently were too toxic. Not so for TM, the dose levels of 100mg per day were well tolerated, so a new and non-toxic therapy for Wilson's disease was registered.

TM and Cancer

Brewer's success with Wilson's disease did not go unnoticed by researchers looking into the role copper played in tumour angiogenesis. Could TM lower the copper in cancer patients? Would this inhibit blood vessel growth in the tumour? Animal models supported this approach to antiangiogenesis. The next step was a human trial.

George J Brewer and his team at the University of Michigan, along with support from the University of California in San Francisco, investigated the use of TM in reducing the copper levels in the patient's plasma by 20% of their original base line to see if angiogenesis could be slowed down or stopped and the growth of tumours inhibited. .

These researchers took 18 patients with solid metastatic tumours and a life expectancy of 3 months or more, they were placed on 120mg of TM and their copper levels were monitored on a weekly basis for over a 3-6 month period. The ability to achieve the lower levels of copper, that being 20% of the normal copper level in the blood took up to three months. Once the copper level was achieved the patients were monitored. Of the 14 patients that achieved the target level for copper in the blood, 6 patients had responses. The aim of the study was not to test in this early study the effectiveness of the treatment but more to develop the technique for using this therapy and also to look at side effects.

Toxicity of Anti-copper Therapy

There were no signs of cardiac pulmonary, intestinal, kidney, liver, blood or skin reactions to the treatment. If the copper level dropped below the 20% of the base line a reversible anaemia was observed in 4 patients. This was corrected when the dose was reduced and the copper level came back to 20% of the base line. Patients sometimes noticed a sulphur burping sensation.

Study conclusion

The study concluded that 6 patients out of 14 had a significant and lasting response to the therapy. In most cases the disease remained stable for an indefinite time, however, in two cases the tumours disappeared. The low toxicity of the therapy meant that it could be continued indefinitely and the fact that this therapy was a natural substance precluded the ability to patent it. The biggest problem was the time delay between starting the therapy and its benefit taking up to three months.

Copper and Immune Evasion

It has been known for some time that the cancer cells produce enzymes, which have the ability to digest incoming immune cells. Dr Rubin, from Israel, has studied one of these enzymes extensively. This enzyme is called Tyrosinase. Tyrosinase has the ability to breakdown the amino acid Tyrosine that is found in interferon.

Degradation of tyrosine in interferon renders the interferon inactive. Interferon, which is an important part of the immune response to the cancer cell, is therefore unavailable. It turns out that the tyrosinase enzyme is a copper containing enzyme and as such, by reducing the copper available to the cancer cell the tyrosinase activity is reduced. This opens the door for new type of therapy, one where the immune evasion of the cancer can be reduced by the use of simple substances such as the TM . As a consequence the cell becomes more susceptible to the immune system attack. Early studies by the Rubin group using the copper collating agent penicillamine and interferon have shown promising results in the reduction of melanoma tumours. Dr Rubin has also studied the level of tyrosinase in many other cancer tissues and found them to be elevated in a lot of different cancers. We at **Resort to Health** are using this technique with the TM medicine to enhance our already successful immune stimulating programmes, hopefully reducing the ability of the cancer to resist the immune system response.

Natural therapy with great promise

This molybdenum product Tetrathiomolybdate therefore promises to be an important part of any therapeutic regime. Not only can it block the angiogenesis of the cancer cell, but it can also reduce the cancer cell immune evasion. TM comes in capsule form and is prescribed in a 6 capsule per day regime, giving 120mg per day. Blood levels for copper and the protein caeroplasmin need to be checked on a weekly basis and the dose of TM adjusted accordingly. As noted previously, few side effects have been noted with this therapy.

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