

# Humlegaarden



## **Metronomic Chemotherapy (MCT)**

Within the world of music a metronome is a rhythm device , that emits a fast regular rhythm.

In the same way with chemotherapy of cancer you can use either a frequent dose , that is to say each day or every second day with a small amount of the chemo drug, or the usual amount in the maximal tolerable dose (MTD) every second or third week.

The advantage of MCT is that is usually is given in tablet form, and so small doses are used that there are only few side effects. MCT does not attack the cancer cells, but the endothelial cells, that make up the walls of the blood vessels in the cancer, so that a regeneration of bloodvessels (angiogenesis) stops or is reduced. This therapy also attacks the already existing bloodvessels in the cancer, whereby the nourishment of the tumor is made difficult, which leads to shrinkage of tumor size or total destruction of the tumor in many cases.

The good thing about this therapy is, that it can also be used for patients who earlier have received one or more kinds of chemotherapy, and have stopped treatment because the cancer cells have become resistant. In the MCT it does not matter if the cells have become resistant, since it is not the cancer cells that are targeted.

MCT should always be combined with other therapies like cox-2-inhibitors, antiangiogenic drugs or other chemosubstances in metronomic dosage.

Usually it is an inexpensive treatment, because it is normally given in tablet form and in a low dosage.

Apparently all kind of tumors can be treated with MCT, and actually over time you can reach the same or even a higher total dose of chemotherapy , than if one dispenses it the usual way every third week.

## **What Happens During Chemotherapy ?**

The usual chemotherapy every 2nd or 3rd week (MTD) :

Cancer cells and endothelial cells suffer death of apoptosis (programmed cell death). In the necessary pause because of the side effects in the bone marrow and bowel mucosa, the microvasculature and the endothelial cells regenerate. After some time the cancer cells usually get resistant, and the treatment is stopped or changed into another kind of chemotherapy.

During the MCT the endothelial cells start to die after 5-6 days, while the cancer cells first start to die 4-5 days later because of the lacking blood-, oxygen- and nutrition supply.

In this situation resistance is rarely developed, because the endothelial cells are more genetically stable.

In the case of large tumors it might be a good idea to start with usual chemotherapy in order to reduce the size of the tumor quickly, and then immediately follow up with MCT.

During MCT alone however even large tumors can be stopped or reduced in size.

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We are facing a new and exciting treatment principle within cancertherapy, which is far more patientfriendly, because sideeffects are much more rare.

From the already existing research, it seems that the effect of MCT can be enhanced greatly, if it is combined with other antiangiogenic drugs.

There are many remedies with an antiangiogenic effect among which we can mention: Avastin, Angiostatin and Endostatin ( or the Chinese version Endostar). Remedies that are antiangiogenic but also have other beneficial effects are : Celebrex, Iressa, Herceptin, Rosiglitazone (peroral antidiabetic), Taxol (in ultralow dosage) Zometa (biphosfonate) as well as Erbitux, Tarveca, Thalidomide and interferon-alpha ( in low dosage) and green tea.

Low dose interferon-alpha was the first antiangiogenic drug used on human beings. This happened in 1988 by the world famous antiangiogenesis researcher Judah Folkman in Boston .

These first treatments were based on the ability of interferon to diminish the motility of the endothelial cells in the lab as well as in experiments with mice.

Furthermore it was discovered that interferon diminished the production of the important growth factor FGF, which is necessary for the growth of many different tumors. For example lifethreatening hemangiomas and giantcell tumors in the jaws and in the pelvic region as well as angioblastomas. These tumors are seen to disappear completely, even though it may take some years. In such patients you usually monitor the FGF in the urine, and if it is too high, treatment with interferon is recommended. A lot of tumors for example breastcancer do not only produce FGF, but up to 5-6 different growthfactors and in this situation interferon is of no use. Here MCT is a good choice because it has a wider spectrum.

Through many years of experience with interferon-alpha it has been found that daily application is better than every second day, and that low doses are more effective than high doses. The tumorcells do not develop resistance toward interferon-alpha in this situation.

MCT should also be combined with Cox-2-inhibitors.

The Cox-2 enzyme is being produced in almost all tumours and its main function in the human body is to convert arachidonic acid into prostaglandin no. 2, which is a strong angiogenic promoter.

Well known Cox-2-inhibitors are aspirin, celebrex, ginger, flax oil and garlic.

## **Length of Treatment**

Metronomic chemotherapy can be given for a long time, actually for many years if it is working and if no side effects occur. But if progression of the tumor takes place then you can change to a higher dose or another metronomic chemo substance or another metronomic schedule

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## Side- effects

As any kind of effective medicine MCT can have side-effects, but these are far less and more seldom than with conventional chemotherapy.

The bone marrow is less affected, but we monitor white blood cells, platelets and haemoglobin once a month to be secure. Once in a while pain in the epigastric region is observed, perhaps caused by a slight gastritis.

If disturbing symptoms should appear during treatment, you have to contact a medical doctor, who decides if the treatment has to be changed. MCT can be combined with many other treatments, such as hyperthermia, which seems to enhance the effect. On the other hand it cannot be combined with conventional chemotherapy.

Important: Pregnancy is a Contraindication for MCT.

Men and women in the fertile age must use anticonception as long as they are in treatment with MCT.

## Summary

One has to understand that the use of MTC is expanding fast in many countries and represents a genuine alternative to MTD-chemotherapy for certain cancer diseases and certain categories of patients.

Especially older patients and patients in a bad general condition, who do not tolerate MTD very well.

Also cancer forms like pancreatic cancer and cancer of the prostate where traditional chemotherapy has not yet shown to be of great value.

Patients who have developed resistance towards a given chemotherapy might also benefit, because MTC is not dependent upon this resistance, the reason being that it does not target the cancer cells but the blood vessels. The cancer cells can be as resistant as they like, because MTC attacks the endothelial cells and it is therefore possible to use the same drug, that the patient has developed resistance towards, just in a lower dosage.

By now there are already many interesting case stories with complete remissions, partial remissions and long lasting stable disease. Interesting protocols like for example KEES (The protocol from Sahlgrenska in Gothenburg for prostate cancer) and KLEIN (The protocol from Cologne for solid tumours) have been developed.

What is common for these protocols is the fact that they consist of a combination of different chemo substances, antiangiogenic substances, antifungals etc. Not just one substance.

The challenge is to find the right combination. If you find it, the results can be astounding.

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Here are 2 Case stories from Humlegaarden, where MTC is the Essential Element

## **Chondrosarcoma**

A Norwegian patient born in 1959 arrived at Humlegaarden 9<sup>th</sup> of May 2006 after having been diagnosed with a tumour in the sacral bone April 2006. A biopsy showed a highly differentiated chondrosarcoma, i.e. a connective tissue tumour with cartilage components. The size of the tumour was 8x11x16 cm, which is a big tumour. Radiation or chemotherapy could not be offered and surgical removal would be a large and lifethreatening intervention and would last 24 hours.

Besides light pain in the sacral area periodically in 10 years the patient was without symptoms. We started treatment with local hyperthermia and mistletoe (Iscador P) in increasing doses, in addition to Icelandic moss (cetraria pr.) and Celebrex . The pain in the back disappeared during the following months, and the patient was feeling very well.

The 10<sup>th</sup> of January 2007 he fell down from a roof and hurt his back on a concrete floor and was reported sick for 14 days. A CAT scan then showed a minor growth and once again he was offered an operation and was informed that he must be bedridden for a year after the operation.

At the beginning of February 2007 the patient returns to Humlegaarden and was again being treated with local hyperthermia and metronomic cyclofosfamide 50 mg daily was started. Furthermore the mistletoe treatment is changed to Helixor A in increasing dosage.

The patient once again refuses surgical intervention.

Since then the patient has been CAT scanned the 2<sup>nd</sup> of May 2007 with approximately the same result as the 21<sup>st</sup> of April 2006, and the same goes for a CAT scan in October 2007 : the tumor has not grown in size. The patient has a very good quality of life which has now lasted one and a half year.

## **Prostate Cancer**

A Danish male, J.C. born in 1953, developed haematuria September 2005 after several years with symptoms from the urogenital region and a blood sample showed a PSA over 1000. Cancer cells were found in all 6 biopsy specimens from the prostate gland and the patient had a diffusely spread infiltration of adenocarcinoma in the prostate, which was very hard. Gleasons score was 7. Bone scintigraphy showed widespread metastasis suspect foci in the spine, ribs, sternum and pelvic region.

He started Casodex treatment 150 mg daily on the 15<sup>th</sup> of September 2005.

PSA gradually decreased to 55 at the end of November, but already in January 2006 the PSA starts to increase to 149 - thereafter in March to 200 and the 6<sup>th</sup> of June 2006 to 260.

At this time the patient arrives at Humlegaarden and starts our mild treatment with mistletoe injections, Avodart ( an effective inhibitor of the transformation of testosterone to dihydrotestosterone) and continuation of Casodex in order to give a total androgene blockage. Furthermore Prostatol and our usual vitamin and mineral supplements.

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At the beginning of December 2006 PSA has fallen to 10,8, and the patient feels very fine.

February 2007 PSA starts increasing, and we discover that the patient has stopped the treatment, because of financial difficulties.

At the end of February he underwent a 40 day Breuss fasting cure in his home to which he himself had taken the initiative, because it was the only treatment he could afford.

The patient got worse and at last was admitted to the local hospital on the 26<sup>th</sup> of July 2007 with a PSA over 930 and a alkaline phosphatase of 2427 as a marker for his pronounced bone metastases in the ribs, spine, pelvic region, sternum, arms and thighs. At that time he is in strong pain, very constipated and barely able to stand on his feet. During the admission he gets bloodtransfusion and the Casodex treatment is stopped. He gets Zometa infusion for the bone metastases and is discharged to terminal care.

He arrives at Humlegaarden the 8<sup>th</sup> of August 2007 in a bad general condition demanding very high doses of morphine and fentanyl patches with a ferritin (a nonspecific tumormarker) at 22.228 ( normal range from 50 – 660), which is one of the highest values ever being measured here. His PSA was 435,5, CRP 3855, LDH 888, Alkaline phosphatase 2119, and he starts immediately on the metronomic KEES protocol ( from Sahlgrenska Hospital in Gothenburg ) as well as local hyperthermia on the painful bone metastases, high dose vitamin-C infusions and our usual general strengthening treatments. His condition rapidly improves, and after just one week he can put away all morphine and fentanyl. All blood values decrease toward the normal range, and at the last control on the 20<sup>th</sup> of December 2007 he is very fine, PSA is 35 and alkaline phosphatase 790, CRP less than 10. The last control of ferritin on the 12<sup>th</sup> November : 1904. The patient is now working full time like a young man and carries heavy paving stones etc. Actually we have seldom seen anything like this and are surprised that MTC can be so effective.

In the Swedish studies the PSA of 65% of hormone resistant prostate cancers was halved , some even to 0.

The protocol itself consists of Cyclofosfamide ,Etoposide ,Estracyt, all as tablet treatment in metronomic doses and furthermore 10 mg Prednisolone daily and the antifungal remedy Ketoconazol.

The Specific Effect of MTC

(Mostly for Medical Professionals)

1. The growth of endothelial cells, i.e. the squamous epithelial cells that in one layer covers the inner side of the wall of the bloodvessel, is inhibited by small concentrations of chemotherapy, and a wide spectrum of chemo drugs can be used in this regard.

A – Only tumor endothelial cells are affected in this way, not normal endothelial cells. The reason might be that the tumour endothelial cells are activated in comparison with the normal endothelial cells.

B – This activation happens through changes in the cytokine environment around the tumour

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C – The increased proliferation index in the tumour endothelial cells opens the possibility for a sufficient therapeutic index of the MTC

2. The expression of thrombospondin 1 (TSP-1) on the endothelial cells increases during MCT and this

- 1) Inhibits the angiogenesis through an inhibition of endothelial cell proliferation
- 2) Increases the apoptosis
- 3) Removes VEGF from the endothelial cells

3. Decreases the expression of HIF-1 alpha protein, which is an important checkpoint for many proangiogenic genes

4. Decreases permanently the number and the viability of circulating endothelial precursor cells (CEP's), resulting in an angiogenic inhibition of the tumour cells.

5. Makes the tumour cells go into apoptosis through an activation of Caspase-9 and a down regulation of Bcl-2.

6. Decreases the amount of regulatory T-cells (so called T-regs or T-suppressor cells) thereby resulting in a direct positive effect on the ability of the immune system to destroy tumour cells.

7. Another effect on the immune system is that the MCT causes a shift in the TH2/TH1 ratio towards more TH1 and thereby again a positive stimulating effect on the immune system.

8. A certain minor effect of MCT directly on the tumour cells cannot be ruled out, although the predominant effect is through inhibition of angiogenesis.

9. As there will always be a certain fraction of the tumour cells in the mitotic phase, ordinary chemotherapy (MTD) will also have a certain effect on those, but in the usual 2-3 weeks` pause in the MTD Chemotherapy, the tumor cells will regenerate, in the same way as the cells of the bonemarrow regenerate in the pause.

The MTC affects especially the endothelial cells in and just outside the tumours (peritumoral). The tumour cells develop often quite quickly resistance towards a given chemotherapy on account of their genetic instability and because of the selection of resistant clones, but the endothelial cells have a greater stability and are therefore less susceptible to develop resistance.