

A vitamin with a history

- The use of vitamin C in the treatment of solid tumours -

A useful treatment for improving quality of life

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I. A vitamin with a history

Vitamin C is one of the most interesting vitamins, not only from a therapeutic viewpoint but also from a historical viewpoint. There have been reports on scurvy epidemics during expeditions at sea, journeys of exploration, and military conflicts since the Middle Ages. In the 16th century it was slowly realized that the onset of this disease could be prevented by eating citrus fruits and fresh vegetables. However, it took two centuries for this to be widely accepted, and in 1795 the British Admiralty commanded that all sailors should receive a ration of fresh lemon juice daily. In-depth testing of numerous foodstuffs for their effectiveness against scurvy and the search for evidence of a causal connection with a deficiency of vitamin C has only taken place since the 20th century. In 1928 Albert Szent Györgyi managed to isolate pure vitamin C. But only in 1932 did Waugh and King recognize that the substance discovered by Szent Györgyi was vitamin C. Vitamin C became well-known primarily through the work of Linus Pauling, the winner of two Nobel prizes, in the late 1970s. In the 1970s Pauling recognized the therapeutic benefits of this versatile vitamin. At the beginning of the 1980s the Linus Pauling Institute in the United States conducted seminal studies which established the use of vitamin C in the prevention and treatment of solid tumours.

Since the beginning of the 1990s intensive research has been carried out in the area of vitamin C therapy. In MEDLINE alone there have been more than 4000 studies focussing on vitamin C since 1990.

II. What contribution does vitamin C make to cancer therapy?

Many cancer patients exhibit a considerable deficiency of this vitamin. It is very important to replenish the body's own reserves.

Many causes contribute to a deficiency of vitamin C in the cancer patient: cancer cachexia, chemotherapy and radiotherapy, parenteral feeding, depression, loss of appetite, gastrointestinal pain, dysphagia, malabsorption following radiation therapy, increased energy consumption, and poor energy utilization.

Under chemotherapy and radiotherapy in particular the level of vitamin C can fall to minimal values. During these treatments not only is enteral feeding disturbed in relation to the quantity and absorption of the vitamin, but there is also an increase in free radicals and, as a result of this, higher vitamin C consumption. In immunotherapy with IL-2, for example, the ascorbic acid level falls by around 80%. In a combination of IL-2 and lymphokine-activated TK cells, vitamin C levels fall to plasma values of under 0.049 mg/dl (Marcus 1991). Scurvy has been found to manifest itself at plasma levels of 0.021 mg/dl of vitamin C.

Scurvy in cancer patients

The first signs of scurvy can be seen from a loss of physical strength, depression, restlessness, and rapidly occurring states of exhaustion on physical effort. The patient complains of muscle pain and the skin is sallow and dark grey. In the next stage there are ulcers on the palate, bleeding from the gums, and tooth loss as signs of the weakness of the connective tissue. Haemorrhaging occurs in the muscles and other tissues. The final stages of the disease are characterized by severe states of exhaustion, diarrhoea, and damage to the lungs and kidneys, which ultimately lead to death.

In many places it is assumed that scurvy hardly ever occurs in industrialized countries. A vitamin C deficit or the first signs of scurvy do, however, occur in people with unbalanced dietary habits and predominantly in people with chronic diseases with an increased level of radicals. A massive vitamin C deficit can, for example, be seen in patients with

rheumatoid arthritis and in asthmatics. Cancer patients generally display a deficiency of antioxidative vitamins, which is further worsened by radiotherapy and chemotherapy (Clemens 1994).

Olivier Fain et al. at the Jean Verdier Hospital in Bondy, France, studied the onset of scurvy in cancer patients and in patients with other diseases and published their observations in 1998 in the BMJ (British Medical Journal). In 219 cancer patients observed, they found six cases of scurvy. This means that every 37th patient suffered from scurvy. In 3723 patients with another underlying disease, only every 621th patient exhibited signs of scurvy. In this study not only was there evidence of reduced levels of vitamin C in the plasma, but clear signs of scurvy such as exhaustion, bleeding gums, gingivitis, etc. were also seen.

Cancer prevention

Vitamin C protects the body from carcinogenic and mutagenic substances. Free radicals have been found to play a part at all stages of the development of cancer. Vitamin C is the most effective anti-oxidant in the human blood plasma (Frei 1989). In addition vitamin C regenerates oxidated, i.e. radical, vitamin E and, as a result of this, protects the lipid membrane (Niki et al. 1991), with the cooperation of glutathione peroxidase.

Epidemiological studies show a close correlation between the vitamin C status and the frequency of the occurrence of certain types of cancer. Low vitamin C plasma levels are closely correlated to the risk of cancer in the oesophagus, larynx, oral cavity, pancreas, stomach, rectum, breast, and cervix (Block 1991). It is noticeable here that the correlation is strongest for tumours in the digestive organs. The reason for this is most likely the inhibition of the formation of nitrosamine by vitamin C (Weisburger 1991, Tannenbaum 1991). The effect on *Helicobacter pylori* infections is also significant. People with high intakes of vitamin C more rarely contract a helicobacter infection.

A vitamin C deficit also leads to an increase in mutagens in the faeces and to increased oxidative damage to the DNA of the sperm (Jakob 1991).

III. Oral versus parenteral therapy

The absorption of vitamin C takes place mainly through Na⁺-dependent active transport in the duodenum and in the proximal jejunum, but the oral mucosa are also capable of absorption. Absorption falls with increasing individual doses and reaches saturation.

- i. In addition, high oral administrations of vitamin C are often poorly tolerated in the gastrointestinal tract.
- ii. Oral absorption of ascorbic acid is therefore limited by its ability to be absorbed and by gastrointestinal tolerability.
- iii. On high-dose treatment with vitamin C, intravenous administration therefore proves to be superior to oral administration.

IV. The bioavailability of ascorbic acid after high-dose infusion therapy

In a pilot study carried out in 1998, data were collected on the pharmacokinetics and pharmacology after intravenous administrations of high doses of ascorbic acid in healthy patients.

Bioavailability of ascorbic acid after high-dose infusion therapy

The biological functions of ascorbic acid take many forms. In particular its antioxidative properties have increasingly been receiving attention.

Free radicals occur, for example, as side-effects of therapeutic measures such as radiotherapy, chemotherapy with cytostatics, and in operations. The administration of antioxidants in the form of high-dosed vitamin C preparations has been able to limit the harmful side-effects. A precondition for this is that the ascorbic acid is readily available at the time of the increased attack from free radicals.

Plasma concentrations of ascorbic acid and elimination in the urine

The bioavailability determines the rate and the extent at which the therapeutic proportion of a drug is released from the medicinal forms in question or is available at the site of action. It can be determined by measurements of the level of the medicinal product in the body fluids and gives information about the acute pharmacological effect.

In a study in line with GCP on the pharmacokinetics and pharmacology after intravenous administration of high doses of ascorbic acid, the levels of the medicinal product in the blood plasma and in the urine were determined at intervals over a period of 24 hours. A validated normal phase HPLC testing method was used for the quantitative determination of the L-ascorbic acid in the human plasma and urine samples. It was validated before and during the processing of the clinical samples in the concentration range of the HPLC measuring samples from 1 to 250 µg/ml L-ascorbic acid. The plasma levels of ascorbic acid found after infusions of Vitamin C-Injektapas® after administrations of 7.5 g showed an effective plasma concentration over the physiological values for a period of action of approx. six hours and after administrations of 15 g of ascorbic acid for a period of action of 12 hours.

This period of action is particularly useful for the targeted removal of after-effects after therapeutically-induced radical formation and has proved to be helpful in practice. These include in particular radiotherapy and chemotherapy which lead to the formation of free radicals during cellular breakdown, as well as all inflammatory processes, in which free radicals are released (e.g. inflammatory rheumatic diseases).

The cumulative clearance of ascorbic acid in the urine at doses of 7.5 g and 15 g revealed an elimination of the active substance over 24 hours of approx. 73%. In other words, of 7.5 g of vitamin C administered, 5.5 g were eliminated within 24 hours; and of 15 g of vitamin C administered, 11 g were eliminated within 24 hours. The remaining 2 and 4 g of vitamin C were fully metabolized.

In this study on bioavailability the values found for the plasma levels of ascorbic acid and for the cumulative elimination of ascorbic acid in the urine after administrations of 7.5 g and 15 g of vitamin C in the form of 50 ml and 100 ml Vitamin C-Injektapas® underline the wide therapeutic range of high-dose vitamin C therapy and allow targeted deduction of the dose depending on the time of the expected increased attack by free radicals.

V. There are many reasons for using vitamin C in the treatment of solid tumours

Vitamin C

..... has tumour cytotoxic properties
(Kurbacher 1996, Riordan 1995, Metzger 1999)

Vitamin C is used as complementary therapy in the treatment of solid tumours. It is not used as a cytostatic but seen as accompanying conventional therapy (chemotherapy, radiotherapy or immunotherapy). Recent in-vitro studies do, however, also indicate that the vitamin has tumour cytotoxic properties. In this regard, vitamin C has been seen to have selective action. Vitamin C levels, which lead to a 100% inhibition of the growth of tumour cells, have no or a very slight effect on the growth characteristics of normal cell lines. So far these in-vitro studies have been carried out on a number of types of tumours, including colon cancer cells and normal colonic fibroblasts, endometrial adenocarcinoma cells, pancreatic carcinoma cells, and normal skin fibroblasts (Riordan 1995).

Two new in-vitro studies with the preparation Vitamin C-Injektapas® 7.5 g also show very promising results. In 1996 Kurbacher et al. studied the effect of different vitamin C concentrations on the growth of human breast cancer cells. In the cell lines used, MCF-7 and MDA-MB-231, vitamin C exhibits antineoplastic activity at a concentration of between 102 and 103 µM (1.76 – 17.6 mg/dl).

In 1999 Metzger et al. also carried out cytotoxicity studies with the preparation Vitamin C-Injektapas® 7.5 g. The study was carried out with a Cytosensor-Microphysiometer. In this the metabolism and the pH value changes of the tumour cell were continually 'online' over 20 hours. This in-vitro study gave the following IC50 values (the IC50 value gives the vitamin C concentration which is necessary for inhibiting the growth of the tumour cell by up to 50%; i.e. the smaller this value, the more effective the tumour cytostatic action of the vitamin C):

The stimulating and protective effects of vitamin C on the immune system have long been known (high vitamin C concentration in leukocytes). Even in the presence of carcinogens, which normally lead to a reduction in the immune response, vitamin C leads to an increase in the body's defences. Foremost is the increase in the chemotaxis of the leukocytes and the suppression of the T-suppressor lymphocytes.

...has a pain-alleviating effect and leads to an improvement in general condition
(Cameron 1991; Riordan et al. 1990; Campbell and Cameron 1991)

Based on his experiences in the Vale of Leven Hospital, Cameron describes an improvement in well-being and in the Karnofsky Index (Assessment of the activity of patients taking into account physical and social factors) within 5-7 days. The reason for this improvement is the facilitated endogenous carnitine synthesis, for which vitamin C is necessary. Carnitine is necessary for the transportation of fatty acids in the mitochondria and therefore facilitates the body's energy supply. He also observed a reduction in pain in skeletal metastases after 5-7 days. A partial reduction in the protein tumour markers is seen in the serum and in favourable cases resorption of malignant pleural effusions and a reduction in the size of lung metastases. The treatment plan begins with adjuvant high-dose intravenous vitamin C therapy (0.5-10 g/day, followed by continuous oral administration of vitamin C (10 to 30 g/day) (Cameron 1991). In the literature there are also cases in which an improvement in general condition and spontaneous remission have been described under high-dose vitamin C therapy in cancer patients (adenocarcinoma of the kidney, reticulum cell sarcoma) (Riordan et al. 1990, Campbell and Cameron 1991).

... is essential for the stability of the connective tissue and improves wound healing
(Taylor 1975, Dryburgh 1985, Vaxman 1990, Yu 1991 and Kim 1992)

One of the most important functions of vitamin C consists of the hydroxylation of the two amino acids essential for collagen synthesis, proline and lysine. Vitamin C is, however, not only important for building collagen but is also involved in the regulation of the breakdown mechanisms.

Studies carried out as early as 1947 showed that people with an inadequate supply of vitamin C (10 mg/day) display around 50-60% worse wound healing. Animal studies confirm that administrations of vitamin C lead, in a dose-related manner, to accelerated wound healing through increased collagen synthesis (Vaxman 1990, Yu 1991 and Kim 1992).

After operations on the third day post-operatively there is a drastic drop in the levels of ascorbic acid in the leukocytes. Even the administration of 500 mg of vitamin C per day cannot prevent this fall in the levels (Secondary bibliography Dryburgh 1985). Rümelin, too, (1999) speaks of reduced ascorbic acid levels in the plasma in the early post-operative phase in a patient population of 236 patients.

Interesting in this connection is a study with patients with pressure sores. By taking vitamin C daily, it was possible to reduce the pressure points within one month by 84% compared with a control group in which they were reduced by 42.7% (Taylor 1975).

Combined with chemotherapy and radiotherapy
(Shimpo 1991, Taper 1992, 1987, Prasad 1992, Meadows 1986, 1991, Pierson 1985, Kurbacher 1996, Metzger 1999)

The deficiency of antioxidative vitamins is further increased by radiotherapy and chemotherapy (Clemens 1994). Both forms of treatment lead to an accumulation of free, aggressive radicals and therefore to a reduction in antioxidative capacity. Many of the chemotherapy and radiotherapy-induced side-effects are attributable to an increase in the levels of the radicals in many tissues. Free radicals damage cell membranes, proteins and the DNA.

In animal studies the adjuvant administration of vitamin C, mostly given intraperitoneally, leads to an increase in the inhibitory effects of the chemotherapeutic agent and to a reduction in the (in some cases) very onerous side-effects. Of particular interest in this respect are three studies which describe the combined use of vitamin C with Adriamycin, Oncovin and methanesulfonate aminoglycols.

The clinical use of Adriamycin is frequently hampered by severe side-effects, in particular cardiomyopathy due to increased lipid peroxidation. Vitamin C injections prevent adriamycin-induced cardiomyopathy by reducing lipid peroxidation in the heart (Shimpo et al. 1991).

The sensitivity of a liver tumour cell line resistant to Oncovin can be considerably increased by vitamin C injections being administered beforehand. This treatment leads to an increased survival time (Taper 1992).

Improsulfan tosilate (Drug 864.T, NSC 140117), an alkylating cytostatic exhibits strong toxicity. In animal studies a dosage of 200mg/kg leads to approx. 10% of the animals dying within a very short time. The adjuvant injection of vitamin C (250 mg/kg per day for 6 days, starting on the first day after the injection of the tumour cells) in animals with Ehrlich ascites carcinoma under Improsulfan tosilate treatment prevents early mortality and increases the average survival time by 77%. The number of long-term survivors also increases with this combination from 50% (Improsulfan tosilate alone) to 80% (combining improsulfan tosilate and vitamin C). To determine the tissue toxicity, the levels of DNA, RNA, protein and certain enzymes in the liver and viscera were determined. All the parameters disturbed by improsulfan tosilate could be normalized by combining it with vitamin C (El-Merzabani et al.1989).

First studies on animals indicate that the adjuvant vitamin C injection increases the tolerance of the normal tissue (skin and marrow) to radiation, without at the same time displacing the required dose of radiation to reduce the tumour tissue (Okunieff 1991).

There are currently no studies on the effects produced on the pharmacokinetics and pharmacodynamics of certain cytostatics by adjuvant high doses of vitamin C. For this reason, the high-dose vitamin C therapy should follow after chemotherapy (1-3 days depending on the half-life of the chemotherapeutic agent).

Vitamin C can be taken orally on infusion-free days. The dosage is to be tailored to the patient's gastric tolerability. To obtain further information about the combined use of chemotherapy and vitamin C therapy, the combination of vitamin C-Injektapas® 7.5 g was tested in-vitro with various cytostatics.

The in-vitro study by Kurbacher 1996 examined the combination of Vitamin C-Injektapas® 7.5 g with doxorubicin, cisplatin, and paclitaxel on breast cancer cells. The cell lines used (MCF-7 and MDA-MB-231) are resistant to doxorubicin, MCF-7 is resistant to cisplatin and MDA-MB-231 is only moderately sensitive to cisplatin. Both cell lines are, however, very sensitive to paclitaxel. All three cytostatics had their responses increased by vitamin C concentrations of between 1 and 102 µM. The combination of vitamin C and cisplatin and paclitaxel is partly synergistic, additive or sub-additive, whereas the combination with doxorubicin is entirely synergistic.

Metzger et al. combined vitamin C with cisplatin, doxorubicin and 5-fluorouracil (5FU):

Cisplatin + vitamin C

Jurkat cells (acute leukaemia cells)

Cytotoxic effect of cisplatin is clearly increased by vitamin C.

A.375.S2 cells (skin melanoma)

Cytotoxic effect of cisplatin is slightly increased by vitamin C.

A549 cells (lung cancer)

Cytotoxic effect of cisplatin is not potentiated by vitamin C.

MCF cells (breast cancer)

Cytotoxic effect of cisplatin, at 5% PP weakened by vitamin C, at 10% increased by vitamin C.

Doxorubicin + vitamin C

A.375.S2 cells (skin melanoma)

Cytotoxic effect of small doxorubicin concentrations (1% PP) clearly increased by vitamin C; at higher doxorubicin concentrations the effect of the doxorubicin alone is already so strong that it cannot be further increased by vitamin C.

Jurkat cells (acute leukemia cells)

Cytotoxic effect of doxorubicin is clearly increased by vitamin C.

5FU + vitamin C

MCF cells (breast cancer)

5FU displays no cytotoxic effect. By being combined with vitamin C, at the highest concentration of 5FU a slight cytotoxic effect is produced. Vitamin C alone has higher cytotoxicity than the combination.

These in-vitro studies already make it clear that not only the chemotherapeutic agent used but also the type of tumour is important in the combined administration of vitamin C and chemotherapy. These results provide the first indications; the combination of cytostatics and vitamin C infusion do, however, require further clinical studies,

VI. Important for practice

1. Vitamin C therapy is not an alternative to conventional treatments such as chemotherapy, immunotherapy, or radiotherapy. Vitamin C infusions are used as adjuvant therapy in the treatment of solid tumours.
2. Currently there is insufficient experience with types of tumours which involve immunoactive cells (e.g. leukaemia cells, etc.) As vitamin C stimulates the cellular immune response, its use, similar to that of mistletoe therapy, is, however, not recommended. In addition in the literature there are contradictory in-vitro results regarding the combination of vitamin C and non-lymphocytic and myeloid leukaemia cells.
3. Vitamin C high-dose therapy should be administered after chemotherapy and radiotherapy (1-3 days according to the half-life of the chemotherapy agent), as there are no clinical data about possible interactions.
4. Vitamin C should be administered orally on the infusion-free days. The dosage of the oral medication depends on the gastric tolerability of the patient (if possible > 1 g/day).

VII. Therapy syntheses in oncology

Cancer is a complex disease which is due to many disorders. Therefore it is not enough after the disease has been diagnosed to have the carcinoma removed from the body and/or to have chemotherapy and/or radiotherapy carried out. It is far more useful to draw up an individual treatment plan for the patient from the start and, for example, to include natural medicine in it.

The high-dose vitamin C therapy referred to above is one such alternative therapy. The Clinic St. Georg in Bad Aibling is one of the few oncology establishments which consistently follow a holistic-integrative treatment plan. 'The focus is on the individual, not the tumour or the disease' is the clinic's treatment motto.

In addition to complementary therapies such as high-dose vitamin C therapy (e.g. Vitamin C-Injektopas®), colonic cleansing, purging treatments, mistletoe therapy (e.g. Lektinol, Iscador), oxygen therapy (Ardenne oxygen multi-step therapy, intramuscular ozone administrations), enzyme therapy (e.g. Proteozyme), and pain and nutrition therapy, the so-called hyperthermia processes (on the one hand deep hyperthermia and on the other whole-body hyperthermia) play a more important role.

Heat has been used in medical treatment since ancient times. Therefore clinical hyperthermia is increasingly being used in interdisciplinary oncology treatment plans. The word hyperthermia comes from the Greek (from hyper: too much, more and thermos: heat). It is known that cancer cells react more sensitively to the effect of heat than healthy cells. Only to a limited extent do they have the ability to tailor their circulation to the external influences of heat, changed metabolic conditions, and acid value changes. Beyond a critical temperature, heat results in less circulation in the tumour tissue. Studies have shown that hyperthermia cannot be attributed only to the sensitizing effect of heat but also to the cytotoxic effects on previously damaged tumour cells and secondary triggering of immunological

processes. Due to pro-oxidatively-acting whole body hyperthermia in the case of resistance to chemotherapy, the tumour tissue can be sensitized to chemotherapy again so that patients can be treatable again

In whole-body hyperthermia treatment the whole body is heated to 41.5-42° C. This treatment is frequently combined with bacterial lysates (fever response). Bringing about an additional increase in blood sugar with 500 ml of a 20% glucose solution to approx. 300 mg/dl leads to additional over-acidification of the tumour tissue. Whole-body hyperthermia runs for over approx. 5-6 hours and is carried out under intensive medical monitoring under sedation and analgesia.

In the afternoon before the treatment a high-dose vitamin C preparation (e.g. Vitamin C-Injektapas®) is infused, and in the evening an enema is given. If chemotherapy is induced, this takes place at the plateau phase, but mostly in reduced form. If chemotherapy is not carried out, up to 50 g vitamin C and ozone are administered intravenously in the defervescence phase. In the follow-up in-house treatment lasting approx. a further two weeks, 7.5 g of vitamin C are administered intravenously 1-3 times a week. On the days when an infusion is not given, the patients are given up to 3 g ascorbic acid powder over the course of the day.

By combining hyperthermia and chemotherapy and further complementary treatment approaches, it was possible to achieve clear successes in many patients whose cancers had not responded to treatment.

In loco-regional hyperthermia the heat is only applied regionally and directly to the cancer-affected tissue or organ. The site is warmed to 42° to a maximum of 44°C, which is maintained in the tumour tissue for approx. 60-90 minutes. Here too a combination with chemotherapy is possible. During the approx. 3-week in-house stay, loco-regional hyperthermia takes place approx. 2-3 times per week, at least six times in 3 weeks. Here too a natural medicine treatment with the above-mentioned substances is indicated in parallel.

Through the treatment options of complementary medicine the doctor has procedures available which enable him/her to treat the patient holistically and to deal with the disturbed function cycle. Not only quality of life but also the response to conventional therapies and their side-effects can be improved.

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