

Orthomolecular Therapy

6.1. Introduction

Fundamentally, orthomolecular therapy is a supplementation of essential vitamins, trace elements, minerals, amino acids and polyunsaturated fatty acids. Often, in cancer patients, because of life style, their underlying disease, or because of the effects of chemotherapy and radiation, there is a depletion or unbalance of many of these elements.

It is estimated that 60% of all cancer patients have an unbalanced diet and are lacking essential vitamins, trace elements, and alike.[i],[ii],[iii]

Usually, in healthy individuals with a balanced diet, a short course of a conventional medication will not have a negative effect on the nutritional status. However, in the case of a long-term application of a conventional medication or in polypharmacotherapy, there can be an interaction with absorption of nutrients from the gut and/or the metabolism of these substances. Xenobiotica, as an example, can alter the metabolism of essential nutrients through affecting the Cytochrome P450 system in the liver, inhibit or accelerate the excretion, inhibit absorption by changing the pH in the gastrointestinal tract, or change the intestinal flora, etc.

6.2. Therapeutic interventions

From birth on, the development of the gastrointestinal tract and the immune system (GALT) depends, to a large extent, on the intake of nutrition and the colonisation with appropriate intestinal flora (see chapter 7. Improvement of Intestinal Mucosa and Flora).

A healthy diet is universally recognized as the main prophylaxis of tumor growth and inhibition of metastatic disease. But what is a healthy diet? A regular diet in industrialized countries usually contains more than enough calories, protein and fats. But, after more than a century of monoculture and the use of artificial fertilizers and pesticides, common food stuffs are usually loaded with pesticides and antifungal agents and depleted from most trace elements, like zinc, selen, cobalt, essential amino acids, and vitamins.

In addition, many products are refined and thus have lost part of their nutritional value. Even in a mixed and varied diet, a deficiency of trace elements and other nutrients can develop easily over time.

Therefore, in the *Cologne Model*, a screening of the blood for main trace elements, antioxidants and vitamins is conducted. If deficiencies are found, supplementation will be recommended.

Phytoestrogens, phenols and flavonoids inhibit growth of (pre-) cancerous cells.[iv],[v]

Therefore, in the *Cologne Model*, patients will be advised how to guarantee a sufficient intake of all these nutrients. Supplementation of phytoestrogens, flavonoids and phenols are usually suggested.

Since the initiation of tumor growth is correlated with an increased burden of endogenous and exogenous oxygen radicals,[vi] supportive therapeutic interventions with strong antioxidants, like the combination of vitamin C and E, beta-carotene and marine fatty acids, are part of the *Cologne Model*.

[i] Doll R, Peto R: The causes of cancer; quantitative estimates of avoidable risk of cancer in the United States. *J Natl Cancer Inst* (1981) 66: 1191-1308.

[ii] Bertram HP.: *Spurenelemente*, Urban & Schwarzenberg (1992).

[iii] Zhang L, Blot WJ, You W, Chang Y, Liu X, Kneller RW: Serum micronutrients relation to precancerous gastric lesions. *Int J Cancer* (1994) 56: 650-654.

[iv] Trock B, Lanza E, Greenwald P: Dietary fiber, vegetables, and colon cancer: critical review and metaanalyses of the epidemiological evidence. *J Natl Cancer Inst* (1992) 82: 650-661.

[v] Sala N, Miller HJ, Paganga P, Tijburg L, Bollwell GP, Rice-Evans C: Polyphenolic flavonols as scavengers of aqueous phase radicals and as chain breaking antioxidants. *Arch Biochem Biophys* (1995) 332(2): 339-346.

[vi] Prasad KN, Edwards –Prasad J: Expressions of some molecular cancer risk factors and their modifications by vitamins. *J Amer Coll Nutr* (1990) 9: 28-34.

6.2.1 The use of vitamin C in oncological practice

Vitamin C (ascorbic acid) is one of the most extensively investigated vitamins. In 1928 the Hungarian scientist Albert Szent-Györgi managed to isolate pure vitamin C. The American researchers Waugh and King were the first to recognise that the substance discovered by Szent-Györgi was vitamin C. Vitamin C became widely known in the 20th century, at the end of the 70s, through the work of double Nobel prize winner Linus Pauling who recognised the therapeutic qualities of this versatile vitamin.

Since the beginning of the 90s intensive research has been done in the therapeutic use of vitamin C. Since 1990 more than 5 000 works concerned with vitamin C have been entered alone in Medline (the most important medical data bank).

Vitamin C belongs to the group of water-soluble vitamins and is an essential micronutrient. This means that the human needs to obtain vitamin C from nutrition and cannot, like many animals, produce it.

Vitamin C is especially actively resorbed in the duodenum and proximal jejunum. The resorption is dependent on the presence of calcium- and sodium. With an increase in single dosages, resorption rates drop and saturation is reached. After 180mg resorption lies between 80% and 90%, but after 12g at only 16%.

In the case of high dosage vitamin C therapy, it therefore makes sense to choose parenteral administration.

The importance of ascorbic acid lies in its character as a strong reducing agent. The most well known functions of vitamin C in the body are its participation in the transfer of electrons in hydroxylation reactions and its radical capturing properties.

Deficiencies or an increased need for vitamin C occur mostly in illnesses which have an increased level of radicals (oxidative stress), such as cancer, chronic viral infections, allergies, chronic degenerative diseases, etc. In the case of tumour patients there are many causes that contribute to a vitamin C deficiency: tumour cachexia, chemo- and radiation therapy, parenteral nutrition, depression, nausea and loss of appetite, stomach and intestinal pain, dysphagia, malabsorption due to radiation, increased use of energy and poor energy utilisation. The reestablishment of reserves in the body is therefore very important. The peroral intake of vitamin C is however very limited due to poor resorption ability and stomach tolerance. The oral substitution of vitamin C is therefore often not justifiable and vitamin C should be administered parenterally.

Vitamin C in itself has both *in vitro* and *in vivo* tumorstatische effects in concentrations which are easily achievable with intravenous administration (10,11).

6.2.1.a Vitamin C in non-lymphocytic and myeloid leukaemia cells

An investigation of the bone marrow cells of patients with *acute non-lymphocytic* leukaemia shows the differentiated cytotoxic effect of ascorbic acid on neoplastic cells. Even in concentrations which are easily achievable *in vivo*, there was a suppression of cell growth in leukaemia cells, whereas normal myeloid cell colonies (myeloblasts) were not affected (1,2).

6.2.1.b Vitamin C in lymphocytic tumour cells

Differences in the sensitivity of lymphocytic tumour cells have been observed by Kao *et al.* About half the patients responded and were successfully treated with high doses of intravenous vitamin C (3).

6.2.1.c Vitamin C in colon cancer (colon carcinoma)

The proliferation of mucous membrane cells in the intestinal glands of the colon and rectum are seen as the first step in a series of events, at the end of which stands the colon carcinoma. The administration of 750mg vitamin C per day results in a reduction of cell proliferation in all parts of the intestinal glands. In patients with preceding polypectomy the recurrence of adenoma can be decreased from 35,9% to 5,7% by means of the administration of vitamin C (4,5).

6.2.1.d Vitamin C in stomach cancer

The formation of nitrosamines is seen as the main reason for the start of stomach cancers. As vitamin C cuts off the formation of nitrosamines, it is not surprising that an optimal vitamin C level reduces the risk of the contraction of stomach cancer (6).

Vitamin C is also *actively* secreted from the blood plasma in the stomach lumen. Vitamin C thus reduces, not only the risk of formation of stomach carcinoma, but already existing stomach carcinomas can also be treated with high-dosage vitamin C infusions (7).

6.2.1.e Vitamin C in mammary (breast) and lung cancer

Vitamin C can also prevent the appearance of breast and lung cancer (2). Sufficient vitamin C in nutrition is a *sine qua non* for every person. Vitamin C in high dosages and administered intravenously also has a positive influence on already existing mammary (breast) and lung carcinomas (8,9).

6.2.1.f Vitamin C during chemotherapy and radiation

The vitamin C plasma level is severely reduced during chemotherapy and radiation. *In vitro* investigation of human tumour cell lines shows that vitamin C synergistically supports the cytotoxic characteristics of a number of different chemotherapies. The inhibiting nature of the combination of chemotherapy and vitamin administration is greater than the sum of the effects of each on their own.

Similar indications are found in *in vivo* investigations in humans and animals. High dosage intravenous vitamin C administration increases the inhibiting effects of chemotherapy and leads to a reduction of side effects, which in part are very severe (2,12).

- (1) Park CH, Amare M, Savin MA, Hoogstraaten. *British Cancer Research* (1980) 40: 1062-1065.
- (2) Pauling L, Nixon JC, Stitt F, Marcuson R, *et al.* *Proc Natl Acad Sci USA* (1985) 82: 5185-5189.
- (3) Kao TL, Meyer WJ, Post JF. *Cancer Letter* (1993) Jun 15, 70 (1-2) : 101-106.
- (4) Cahill RJ, OSullivan KR, Mathias PM. *C Gut* (1993) 34: 963-967.
- (5) Roncucci L, Di-Donato P, Carati L, Ferrari A. *Dis Colon Rectum* (1993) 36(3): 227-234.
- (6) Weissburger JH. *Am Soc Clin Nutr* (1991) 53: 226-237.
- (7) Sobola GM, Schorah CJ, Pignatelli B, Crabtree JE, Martin IG, Scott N. *Carcinogenesis* (1993) 14(2): 291-292.
- (8) Leung PY, Dunham WB, Tsao CS. *In Vivo* (1993) 6: 33-40.
- (9) Leung PY, Miyashita K, Young M, Tsao CS. *Anticancer Res* (1993) 13(2): 475-480.
- (10) Cameron E. *Medical Hypotheses* (1991) 36: 190-194.
- (11) Cameron E, Pauling L. *Proc Natl Acad Sci USA* (1978) 75: 4538-4542.
- (12) Okunieff P. *Am J Clin Nutr* (1991) 54: 1281-1283.

6.3. Vitamin C and cancer cells

Padayatty, *et al.* found that vitamin C at high concentrations is toxic to cancer cells *in vitro*. And they determine whether plasma vitamin C concentrations vary substantially with the route of administration. Peak plasma vitamin C concentrations were higher

after administration of intravenous doses than after administration of oral doses and the difference increased according to dose. They concluded that oral vitamin C produces plasma concentrations that are tightly controlled. Only *intravenous* administration of vitamin C produces high plasma and urine concentrations that might have antitumor activity. Because efficacy of vitamin C treatment cannot be judged from clinical trials that use only oral dosing, the role of vitamin C in cancer treatment should be re-evaluated.⁽¹⁾

Stanner, *et al* did an independent review of the scientific literature on the role of antioxidants in chronic disease prevention. There is consistent evidence that diets rich in fruit and vegetables and other plant foods are associated with moderately lower overall mortality rates and lower death rates from cardiovascular disease and some types of cancer. The 'antioxidant hypothesis' proposes that vitamin C, vitamin E, carotenoids and other antioxidant nutrients afford protection against chronic diseases by decreasing oxidative damage. The suggestion that antioxidant supplements can prevent chronic diseases has not been proved or consistently supported by the findings of published intervention trials. Further evidence regarding the efficacy, safety and appropriate dosage of antioxidants in relation to chronic disease is needed. The most prudent public health advice remains to increase the consumption of plant foods, as such dietary patterns are associated with reduced risk of chronic disease, and cancer.⁽²⁾

Gunawardena, *et al.* postulated that combinations of C and E vitamins modulate the antioxidant network and blocks surviving gene expression in androgen-responsive and non-responsive human prostate cancer cell (HPCC) lines. They found that all the tested combinations of vitamins C and E reduced cell growth (4-83%). Vitamin C enhanced the growth suppressive effect of vitamin E. Apoptosis was enhanced (25-45%) (vitamins = 100 microM, 24 hr). Survivin mRNA was decreased (26-29%) (vitamins = 250 microM, 24 hr), and survivin protein was decreased (>90%) (vitamins = 100 microM, 72 hr). NF-kappaB and AP-1 activities were increased (vitamins = 100 microM, 24 hr). They concluded that the combinations of vitamins C and E are potent inducers of apoptosis in HPCC.⁽³⁾

Ascorbic acid is the single-nutrient supplement most commonly used by cancerous cells. A comprehensive review was done by Block, *et al*, of the literature presenting the impact of ascorbic acid on cancer survival. Findings from 6 uncontrolled studies suggest that ascorbic acid may increase survival, whereas 2 controlled trials have yielded null results. Controversy about these trials still persists, however, in the alternative cancer community it is necessary the development of more controlled studies.⁽⁴⁾

Oxidative DNA damage in humans could arise also from incorrect nutritional habit and life style. DNA strand breaks + oxidized purines are significantly reduced in vegetarians, DNA strand breaks are nonsignificantly decreased. The sufficient antioxidative status is crucial in free radical defense. Intake of protective food commodities (fruit, vegetables, dark grain products, grain sprouts, oil seeds) is significantly higher in vegetarians. Alternative nutrition subjects have a significantly increased plasma levels of vitamin C, vitamin E, beta-carotene with high incidence of overthreshold values (92% vs. 42% - vitamin C, 67% vs. 33% - vitamin E, 67% vs. 17% - beta-carotene). There is recorded a significant inverse linear correlation

between values of DNA strand breaks + oxidized purines and vitamin C or beta-carotene levels). Vegetarian diet is significantly more rich source of antioxidants. The results of reduced endogenous DNA damage and higher antioxidative status in vegetarians document that a correct vegetarian nutrition might represent an effective cancer prevention.⁽⁵⁾

To assess the levels of erythrocyte glutathione peroxidase (GSH-Px), and the serum levels of antioxidant vitamins (A, E and C), selenium and malondialdehyde (MDA) in patients with transitional cell carcinoma (TCC) of the bladder. Yalcin O, et al found the serum levels of vitamin A, E and C, and selenium were significantly lower in patients with TCC than in controls. However, erythrocyte GSH-Px activities and serum MDA levels were significantly higher in patients with TCC than in the controls. In conclusion the levels of free oxygen species were higher, and antioxidant vitamin and selenium levels lower, in patients with bladder TCC than in controls. These findings, with the results of previous animal studies, suggest that giving vitamin A, C, E and selenium may be beneficial in preventing and treating human bladder cancer.⁽⁶⁾

To examine the role of six flavonoid classes (flavanones, flavan-3-ols, flavonols, flavones, anthocyanidins and isoflavones) and vitamin C in the aetiology of stomach cancer Lagiou studied models including sociodemographic variables, energy intake, vegetables, fruits and, alternatively, vitamin C the six flavonoid classes, only flavanones and vegetables remained significantly inversely associated with stomach cancer risk. The odds ratio (95% confidence intervals) per one standard deviation increase of intake of flavanones was 0.55 (0.31-0.96) whereas for vitamin C it was 1.05 (0.46-2.41). When fruits and vegetables were not adjusted for, both vitamin C and several flavonoid categories were inversely associated with stomach cancer risk, but these associations could be attributed to other compounds in these foods. Lagiou concluded that among the major flavonoid classes studied, only flavanone intake is inversely associated with stomach cancer risk and could account for the apparent protective effect of fruit intake against this form of cancer. Additional factors, however, are likely to be involved in the consistent protection conveyed by vegetables.⁽⁷⁾

1. Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA, Levine M: Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med.* 2004 Apr 6;140(7):533-7.
2. Stanner S, Hughes J, Kelly C, Buttriss J: A review of the epidemiological evidence for the 'antioxidant hypothesis' *Public Health Nutr.* 2004 May;7(3):407-422.
3. Gunawardena K, Campbell LD, Meikle AW: Combination therapy with vitamins C plus E inhibits survivin and human prostate cancer cell growth. *Prostate.* 2004 May 15;59(3):319-27.
4. Block KI, Mead MN: Vitamin C in alternative cancer treatment: historical background. *Integr Cancer Ther.* 2003 Jun;2(2):147-54.
5. Krajcovicova-Kudlackova M, Dusinska M: Oxidative DNA damage in relation to nutrition. *Neoplasma.* 2004;51(1):30-3
6. Yalcin O, Karatas F, Erulas FA, Ozdemir E: The levels of glutathione peroxidase, vitamin A, E, C and lipid peroxidation in patients with transitional cell carcinoma of the bladder. *BJU Int.* 2004 Apr;93(6):863-6.
7. Lagiou P, Samoli E, Lagiou A, Peterson J, Tzonou A, Dwyer J, Trichopoulos D: Flavonoids, vitamin C and adenocarcinoma of the stomach. *Cancer Causes Control.* 2004 Feb;15(1):67-72.

8. Selvendiran K, Senthilnathan P, Magesh V, Sakthisekaran D: Modulatory effect of Piperine on mitochondrial antioxidant system in Benzo(a)pyrene-induced experimental lung carcinogenesis. *Phytomedicine*. 2004 Jan;11(1):85-9.

6.4. Dietary omega-3 polyunsaturated fatty acids and Cancer

Malnutrition appears to be an important predictor of survival for patients with end stage malignant disease. Omega-3 polyunsaturated fatty acids had a significant immunomodulating effect and seemed to prolong the survival of malnourished patients with generalized malignancy.

Gogos et al. (1) randomized sixty patients with generalized solid tumors in two groups: one group received dietary supplementation with either fish oil (18 g of omega-3 polyunsaturated fatty acids, PUFA), the other group placebo daily until death. Each group included 15 well-nourished and 15 malnourished patients. The authors measured total T cells, T-helper cells, T-suppressor cells, natural killer cells, and the synthesis of interleukin-1, interleukin-6, and tumor necrosis factor by peripheral blood mononuclear cells before and on Day 40 of fish oil supplementation. Karnofsky performance status, nutritional state, and survival were also estimated.

The ratio of T-helper cells to T-suppressor cells was significantly lower in malnourished patients. Omega-3 PUFA had a considerable immunomodulating effect by increasing this ratio in the subgroup of malnourished patients. There were no significant differences in cytokine production among the various groups, except for a decrease in tumor necrosis factor production in malnourished cancer patients, which was restored by omega-3 fatty acids. The mean survival was significantly higher for the subgroup of well-nourished patients in both groups, whereas omega-3 fatty acids prolonged the survival of all the patients.

1. Gogos CA, Ginopoulos P, Salsa B, Apostolidou E, Zoumbos NC, Kalfarentzos F. : Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial. *Cancer*. 1998 Jan 15;82(2):395-402.