Magnesium and Other Biominerals in Breast and Ovarian Cancer Patients Receiving Antitumoral Chemotherapy

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Zusammenfassung

Die Behandlung mit Zytostatika geht gewöhnlich mit schweren Nebenwirkungen einher, wie kardio- und nephrotoxischen Effekten, Störungen der zellulären Immunität, Alopezie und Reduktion des Allgemeinzustandes. Die meisten dieser Nebenwirkungen werden durch Defizite von Biometallen wie Mg, Zn, Se und Cu verstärkt. Wir bestimmten vor und während zytostatischer Behandlung die Serumkonzentrationen von K, Na, Ca, Mg, Se, Fe, Cu und Zn zusätzlich zu den üblichen Laborparametern. Es wurden 3 Gruppen gebildet zu je 7 Frauen, die wegen fortgeschrittenen Mamma- bzw. Ovarialkarzinoms mit Cyclophosphamid/cis-Platin (CP), Cyclophosphamid/Methotrexat/Fluorouracil (CMF) oder Mitoxantron behandelt wurden.

Obwohl die Nierenfunktion leicht eingeschränkt war, verblieben Na, K, Ca sowie Fe und Cu im Normalbereich während des gesamten Untersuchungszeitraums. Demgegenüber wiesen mit zunehmender Behandlungsdauer Mg, Zn und Se einen progredienten Konzentrationsabfall auf. Dabei waren die Selenkonzentrationen bereits vor Behandlung weit unter dem Normalbereich. Diese progredienten Defizite bedürfen aus den o. g. Gründen weiterer diagnostischer und therapeutischer Beachtung.

Summary

Cytostatic therapy is usually coupled with severe side effects, such as cardio- and nephrotoxicity, derangements of cellular immunity, alopecia and reduction of general state. Most of these are aggravated by deficiencies of the elements Mg, Zn, Se and Cu. We determined before and during antitumoral chemotherapy the serum concentrations of various electrolytes and trace elements (K, Na, Ca, Mg, Se, Fe, Cu, Zn) in addition to the usual laboratory parameters. The study included three groups with seven women suffering from advanced breast or ovarian carcinoma. The cytostatic therapy schemes were cyclophosphamide / cisplatinum (CP), cyclophosphamide/methotrexate/fluorouracil (CMF) or mitoxantrone monotherapy.

Although renal function was slightly affected, the electrolytes Na, K and Ca and the microelements Fe and Cu remained in the normal range during the whole observation period. Marked decreases progressing with the number of cytostatic cycles were recorded in the serum levels of Mg, Zn and Se. Moreover, serum Se concentrations were already far below the normal range before cytostatic treatment. Thus, progressive deficiency of Se, Mg and Zn demands further attention.

Résumé

La thérapie cytostatique est souvent associée à de graves réactions secondaires, par exemple à la toxicité cardiale et rénale, aux dérangements de l'immunité cellulaire, à l'allopecia et à la réduction de l'état général. La plupart des ces problemes s'aggravent par la déficience des éléments comme le Mg, le Zn, le Se et le Ca. Nous avons analysé les concentrations de serum de K, Na, Ca, Mg, Se, Fe Cu et Zn avant et après la chimiothérapie antitumoral, ainsi que les paramètres de laboratoire courants.

L'examen a compris trois groups à sept femmes souffrant de cancer du sein ou de l'ovoir. Les schémas de thérapie cytostatique comprenaient: Cyclophosphamid et Cisplatinum (CP), Cyclophosphamid, Methotrexate et Fluorouracil (CMF) ou Mitoxantrone monothérapie.

Bien que la fonction rénale fût légèrement réduite, les électrolytes Na, K et Ca et les microéléments Fe et Cu restaient normaux pendant la période totale d'observation. Parcontre les taux du Mg, Zn et du Se ont sensiblement baissé avec chaque cycle du chimiothérapie. En plus les concentrations de Se étaient déjà en dessous du taux normal avant le début de la thérapie cytostatique. Donc la baisse progressive de Se, Mg et Zn demande une attention constante.

Introduction

It is well known, that tumor chemotherapy is associated with derangements of water and mineral balance due to nephrotoxic but also gastrointestinal side-effects of those drugs. This is especially true for cis-platinum (see *Bjornson* and *Stephenson* (1983), *Giaccone* and cow. (1985), *Kurtzberg* and cow. (1984), but also for cyclophosphamide, methotrexate, vincristine and anthracyclins. Main concern in diagnosis and therapy of electrolyte disorders induced by cytostatic drugs has been directed towards items as Na, K, Cl and Ca (e.g. v. *Matthiessen* and *Seeber* (1984)). More recently, some publications began to deal with magnesium loss during cisplatinum administration (*Bell* and cow. (1985), *Gomez-Campdera* and cow. (1986), *Lam* and *Adelstein* (1986)) as well as during vincristine, adriamycine and cyclophosphamide therapy (*Araskiewicz* and cow. (1987)). Almost no attention has been attributed up to now towards disorders of other essential inorganic elements and possible clinical implications of such disorders. The present study has been aimed to investigate serum electrolyte and micro element variations during common chemotherapeutic schemes in gynecological oncology.

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Material and Methods

A total of 21 women with advanced ovarian and breast cancer formed

three groups receiving chemotherapy either according to the CP (patients with ovarian cancer), CMF scheme or mitoxantrone monotherapy (patients with breast cancer). For dosages and therapy course intervals see table 1. Blood samples were taken before the 1st, 2nd and 3rd cycle and the day after termination of the infusions (in the CMF patients the day after termination of the second branch of this cycle). Blood sampling was performed according to the recommendations of the trace element working group at the Hahn-Meitner-Institute (Berlin). After centrifugation at 3500 U/min serum samples were stored at –22 °C. Na, Mg, Ca and K were determined by means of of flame atomic absorption photometry (AAS), Cu and Fe by graphite tube cuvette AAS, Se and Zn by neutron activation analysis. The other parameters have been determined with conventional methods. Results have been plotted as mean values and standard error of the mean, statistical analysis has been carried out with the Wilcoxon test.

Tab. 1: Dosages, administration routes and intervals of cytostatic schemes.

CP-SCHEME	
Cyclophosphamide	1000 mg/sqm body surface i.v.
cis-Platinum	100 mg/sqm body surface i.v.
to be repeated in 3–4 weeks intervals	
CMF-SCHEME	
Cyclophosphamide	500 mg/sqm body surface i.v.
Methotrexate	40 mg/sqm body surface i.v.
Fluoruracile	600 mg/sqm body surface i.v.
Administration at the 1st and 8th day of each cycle to be repeated in 4 week intervals	
MITOXANTRONE	
Mitoxantrone	10–14 mg/sqm body surface i.v.
to be repeated in 3–4 week intervals	

Results

There seems to be some derangement of renal function reflected by a rise in blood urea concentration in all three groups and in creatinine concentration in the mitoxantrone group. Except for a slight, but not significant decline of the hematocrit in the mitoxantrone group, no evidence for derangements in water balance could be found (tab. 2). Accordingly, serum K-concentration shows a very slight, insignificant decrease during the three cycles in all groups but does never abandon the normal range (tab. 2). Serum-Na-concentration fell slightly after the first cycle in the CP-group and also in the three cycles in the CMF and mitoxantrone group. A similar tendency can be found in serum Ca-concentrations although changes never reach significance and values are well within the normal range (fig. 1). Mg (fig. 1) and Zn (fig. 2) start from the middle (Mg) or lower (Zn) part of the normal range and decrease significantly to the subnormal range. Mg decreases rather continuously while Zn shows a decline in the average with an improvement in the pre-cycle values.
Even more impressive are the findings in Se-concentrations (fig. 2): pretherapeutic values are far below the normal range and show a continuous and significant decrease with cycle number II in all three groups. Here, too, the precycle values seem to show a small sign of recovery. The behaviour of serum Cu shows only one surprising peak in the CMF group after the 1st cycle. Regarding serum Fe we find also one significantly increased value after the 1st cycle only in the CP group.

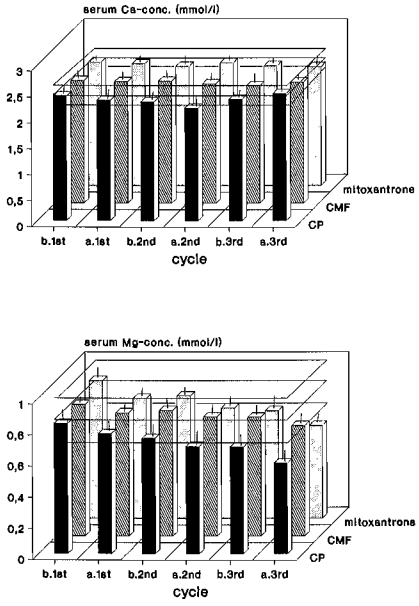

Fig. 1: Serum Ca- and Mg-concentration before and after the first three cycles of CP/CMF and mitoxantrone therapy (mean, standard error of the mean, the three levels indicate lower and upper border and mean of normal range).

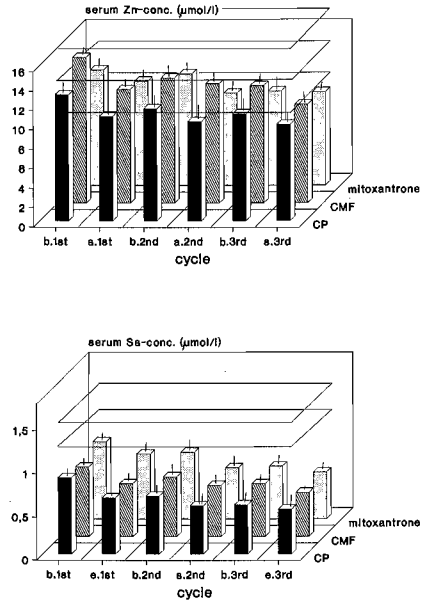

Fig. 2: Serum Zn- and Se-concentrations. Presentation as in Fig. 1 (normal ranges for Se according to *Iyengar, Kollmer* and *Bowen* (1978)).

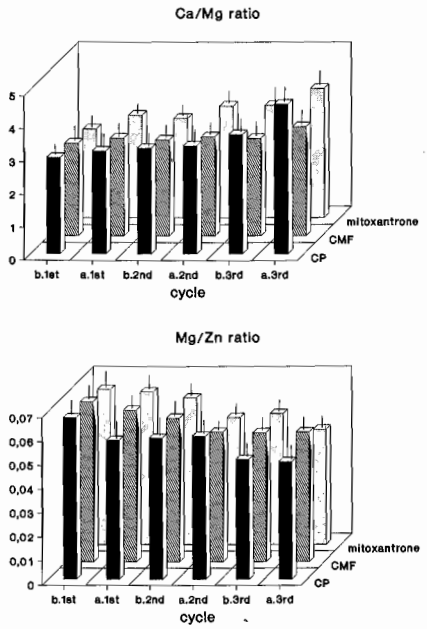

Fig. 3: Ca/Mg and Mg/Zn-ratio.

Fig. 3 illustrates, how these derangements change the symmetry of macro- and microelement patterns. While the Cu/Fe ratio is quite unaffected, Ca/Mg ratio shows a marked shift in favour of Ca. Relative decline is most impressive in Zn. Serum Cu- and Fe-concentrations failed to reveal any changes throughout the three cycles in all three groups, nor did the values ever leave the normal range. This might also be due to the fact, that hematologic parameters remained almost stable throughout the therapy (tab. 2).

Discussion

The reason, why oncologist's interest should be directed also to these parameters when administering cytostatics is, that severe side effects of them are enhanced by biomineral deficiencies.

The marked decrease of serum magnesium, zinc and selenium concentrations, the latter starting from by far subnormal levels, at first has to be interpreted in view of the fact, that these ions are present intracellularly in much higher concentrations than in serum. The serum concentrations are often kept constant at the expense of the intracellular concentrations leading up to a quite severe degree of intracellular depletion, as could be shown for Mg by *Wischnik* and cow. (1983). This, on the other hand means, that, from the decrease in serum concentration shown above an even more pronounced intracellular deficiency has to be calculated.

Besides enterohepatic dermatitis, which is induced by zinc deficiency alone, zinc is involved in many dermatologic problems, part of which arises also in antitumor chemotherapy such as decubital and other cutaneous ulcera, alopecia, stomatitis and wound healing derangements (*Heinitz* (1983)).

As Zn stimulates the blastogenesis of lymphocytes and Zn-deficiency impedes blastic transformation of lymphocytes (*Schmidt* (1983)), thus intensifying a lack in immunologic competence and counteracting efforts for possible immunologic treatment of gynecologic malignant tumours. Among others, *Taguchi* (1978) could show, that immunologic potentiation leads to a significant augmentation of survival and remission interval respectively.

DNA- and RNA polymerases are Zn-dependent enzymes; thus Zn-de-

Tab. 2: Laboratory parameters without significant variations throughout the three analyzed cycles.

	CP-Scheme						CMF-Scheme						Mitoxantrone					
	before 1st cycle	after 1st cycle	before 2nd cycle	after 2nd cycle	before 3rd cycle	after 3rd cycle	before 1st cycle	after 1st cycle	before 2nd cycle	after 2nd cycle	before 3rd cycle	after 3rd cycle	before 1st cycle	after 1st cycle	before 2nd cycle	after 2nd cycle	before 3rd cycle	after 3rd cycle
Cu	20.49	21.73	21.25	18.76	19.10	19.01	18.58	29.21	19.19	20.29	21.84	20.56	21.39	17.90	17.39	18.36	19.05	20.47
(µmol/l)	2.95	1.88	1.68	1.12	1.48	1.07	2.55	3.56	2.97	1.56	2.33	2.45	3.23	2.75	1.48	2.10	2.31	1.57
Fe	23.29	37.02	22.96	22.04	29.61	29.02	25.31	19.28	22.91	24.85	19.94	27.97	21.93	22.58	22.29	22.65	16.82	20.12
(µmol/l)	3.21	12.98	5.36	6.73	5.93	5.83	4.90	1.63	3.55	5.37	4.71	3.50	4.97	3.09	7.61	4.02	2.61	3.70
K	4.53	4.36	4.40	4.13	4.38	4.37	4.53	4.05	4.09	4.17	4.19	4.07	4.50	4.40	4.17	4.21	4.27	4.11
(µmol/l)	0.11	1.46	0.10	0.06	0.22	0.12	0.17	0.12	0.20	0.09	0.24	115.81	0.16	0.24	0.17	0.04	0.12	0.12
Na	132.85		125.87	130.53	134.57	132.45	135.25	130.34	133.64	128.13	271.24	17.31	135.56	133.39	135.13	132.83	134.26	119.22
(mmol/l)	1.71		5.91	1.67	2.13	1.62	1.62	1.79	0.80	2.06	139.96		1.18	0.97	1.13	1.31	2.41	14.11
leucoc	8.90		7.70		8.77		6.40		7.95		6.50		6.26		5.80		5.90	
(10^3/mm^3)	0.76		0.79		1.50		0.87		1.89		1.79		1.12		0.99		1.14	
erythr.	4.33		4.07		3.92		3.98		108.14		4.00		3.90		3.49		3.37	
(10^6/mm^3)	1.74		0.10		0.11		0.33		103.95		0.41		0.12		0.26		0.21	
hemogl.	12.95		12.11		12.18		12.07		17.70		12.35		11.68		10.62		10.24	
(g/loo ml)	0.33		0.23		0.34		0.43		5.04		0.92		0.34		0.42		0.32	
thromboc	377.57		347.57		360.42		316.00		288.25		271.25		310.60		285.20		260.00	
(10^3/mm^3)	29.13		31.04		34.55		19.90		106.65		41.22		54.26		32.79		42.21	
hematocrit	39.28		37.18		36.60		36.82		33.42		36.97		35.40		32.32		31.14	
(%)	1.58		0.67		0.82		1.74		4.98		3.05		0.89		1.36		1.12	
GOT	8.57		7.42		7.28		15.25		17.50		17.00		14.60		20.80		10.00	
(mU/ml)	1.08		0.99		1.26		7.98		5.42		7.11		5.90		4.99		1.30	
GPT	8.42		7.57		5.14		20.50		14.02		20.25		27.40		40.20		13.00	
(mU/ml)	2.12		1.04		0.82		14.55		4.96		5.97		16.08		14.92		6.86	
urea	25.14		32.85		34.85		25.00		77.50		34.00		24.20		32.60		35.00	
(mg/100 ml)	3.18		4.02		5.21		2.67		51.50		3.71		3.42		7.68		6.73	
creatinine	0.82		0.81		0.84		0.75		0.77		0.80		0.84		0.98		1.00	
(mg 100 ml)	0.07		0.11		0.12		0.06		0.08		0.11		0.09		0.22		0.28	

ficiency can lead to disturbances in amino acid utilisation, aggravating the effect of reduced intestinal amino acid absorption of cancer patients (*Casado* (1986)). Consequences of magnesium deficiencies are complex, so they have been described as "magnesium deficiency syndrome" by *Holtmaier* (1985). Its manifestations for the tumour patient are:

- cerebral: vertigo, anxiety, depression, psychotic disorders, as have also been described by *Matzen* and *Martin* (1985) as consequence of cancer therapy.
- visceral: Nausea, vomiting, diarrhea.
- the neuromuscular manifestation: Polyneuropathy (*Göldner* an cow. (1987), *Walker* and cow. (1986)).
- cardiovascular: essentially, Mg is a calcium antagonist. Derangements in the Ca/Mg-balance, as they occured in our patients in all groups, are leading to a hyperexcitability of the myocardial cell with hazardous hemodynamic consequences and uneconomically high consumption of oxygen and high energy substrates (*Wischnik* and cow. 1982, 83). This is of special interest when using anthracyclins as cardiovascular manifestations of anthracyclin toxicity and magnesium deficiency resemble each other to a great extent and both of them affect the mitochondria as the centre of energy metabolism.

In view of these facts, magnesium supplementation seems advisable, also, as there are investigations, showing that magnesium supplementation attenuates cis-platinum side-effects without impairing the therapeutic effect (*Sasaki* and cow. (1985), *Willox* and cow. (1986)).

The importance of selenium as an essential microelement is based upon the fact, that it is part of the glutathione peroxidase (GSH-Px, see fig. 4), thus acting as antioxidant. Cellular oxidations initiate from free radicals which derive from oxidases, from the mitochondrial Krebs-cycle, from cells of the immunologic system (granulocytes, macrophages), from toxic substances (e.g. chemical carcinogens as carbon tetrachloride) or from drugs such as anthracyclins. Reacting with polyunsaturated fatty acids, which are an important cell membrane constituent, they form lipid peroxides, which cause damage to enzymes and cell membranes. Besides Vitamin E, C, catalase and superoxide dismutase, GSH-Px protects the organism from such uncontrolled free radical reactions. As mutagenic reactions take place by mediation of free radicals, those animal experimental findings become clear, showing that chemical carcinogenesis is inhibited by adding Se compounds (literature reviewed by *Seidel* (1983)). This seems to be true especially for tumors being correlated to a high fat intake (colon, breast). When screening patients with tumours of the uterus, ovaries and vulva, *Sundstroem* and cow. (1984) found significantly reduced serum concentrations of Se, GSH-Px and lipid peroxides compared to healthy controls. All these derangements could be reverted by Se supplementation.

Although the possible epidemiological impact of these findings cannot be discussed here, findings have to be cited, showing that Se influences the toxicity of cytostatics.

Naganuma and cow. (1983) administered lethal doses of cisplatinum to mice, leading to death within 4 days. When additionally giving sodium selenite, the animals did not die and BUN measurements showed that cis-platinum induced renal dysfunction was reduced significantly. Antitumoral effectiveness of cis-platinum however remained unaffected by this comedication. Analogical results were obtained by *Berry* and cow. (1984) in cis-platinum treated mice with fibrosarcoma, where the reduction of side effects by Se permitted higher doses of cis platinum. *Revis* and *Marusic* (1978) showed that anthracyclin induced cardiotoxicity is coupled with reduced myocardial Se- and GSH-Px-concentrations and *van Vleet* and *Ferrans* showed a preventive effect of Se against the cardiotoxicity of adriamycine.

In conclusion, clinical and experimental findings show convincingly, that the deficiency of Zn, Mg and Se inasmuch as it is induced by widely used cytostatic therapies, intensifies severe and also therapy limitating side effects of these therapies. Since even healthy individuals show a subnormal intake of these elements (*Wischnik* (1987)), one may suggest, that this deficitary situation is superimposed to a preexisting intracellular deficiency. As up to now there is

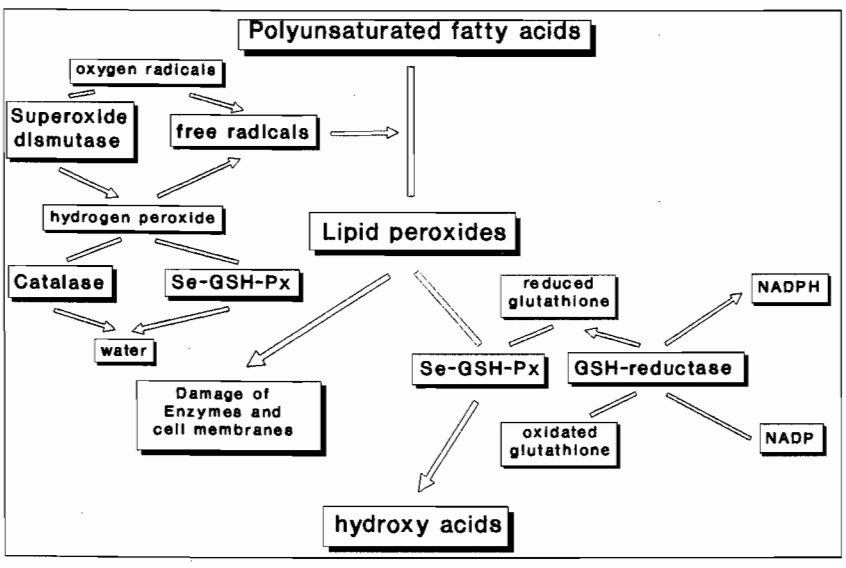

Fig. 4: Glutathione peroxidase and lipid peroxidation.

no indication of an interference with the desired effect of antitumoral chemotherapy, supplementation of these elements during cytostatic therapy should be done in order to study prospectively the necessary doses and the possible efficacy.

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