in vivo *25*: 983-990 (2011)

Intravenous Vitamin C Administration Improves Quality of Life in Breast Cancer Patients during Chemo-/Radiotherapy and Aftercare: Results of a Retrospective, Multicentre, Epidemiological Cohort Study in Germany

CLAUDIA VOLLBRACHT[1], BERTHOLD SCHNEIDER[2], VAN LEENDERT[4], GABRIELE WEISS[1], LEO AUERBACH[3] and JOSEF BEUTH[4]

[1]*Pascoe pharmazeutische Präparate GmbH, Giessen, Germany;*
[2]*Institute for Biometrics, Medical University Hannover, Germany;*
[3]*Department of Obstetrics and Gynecology, Senology, Vienna Medical University, Austria;*
[4]*Institute for Naturopathy, University of Cologne, Germany*

Abstract. *Aim: The aim of the study was to evaluate under praxis conditions the safety and efficacy of intravenous (i.v.) vitamin C administration in the first postoperative year of women with breast cancer. Patients and Methods: Epidemiological multicentre cohort study, including 15 gynaecologists and general practitioners representatively distributed in Germany. Data from 125 breast cancer patients in UICC stages IIa to IIIb were selected for the study. A total of 53 of these patients were treated with i.v. vitamin C (supplied as Pascorbin® 7.5 g) additional to standard tumour therapy for at least 4 weeks (study group) and 72 without this additional therapy (control group). Main outcome measures were efficacy in regard to outcome and severity of disease- or therapy-induced complaints during adjuvant chemo- and radiotherapy and aftercare. Results: Comparison of control and study groups revealed that i.v. vitamin C administration resulted in a significant reduction of complaints induced by the disease and chemo-/radiotherapy, in particular of nausea, loss of appetite, fatigue, depression, sleep disorders, dizziness and haemorrhagic diathesis. After adjustment for age and baseline conditions (intensity score before adjuvant therapy, chemotherapy, radiotherapy), the overall intensity score of symptoms during adjuvant therapy and aftercare was nearly twice as high in the control group compared to the study group. No side-effects of the i.v. vitamin C administration were documented. Discussion: Oxidative stress and vitamin C deficiency play an important role in the etiology of adverse effects of guideline-based adjuvant chemo-/radiotherapy. Restoring antioxidative capacity by complementary i.v. vitamin C administration helps to prevent or reduce disease-, or therapy-induced complaints in breast cancer patients. Conclusion: Complementary treatment of breast cancer patients with i.v. vitamin C was shown to be a well tolerated optimization of standard tumour-destructive therapies, reducing quality of life-related side-effects.*

Correspondence to: Professor Dr. med Josef Beuth, Institute for Naturopathy, University of Cologne, Joseph-Stelzmann-Str. 9/Building 35a, D-50931 Cologne, Germany. Tel: +49 2214786414, Fax.: +49 2214787017, e-mail: hans.beuth@uk-koeln.de and Claudia Vollbracht, Pascoe pharmazeutische Präparate GmbH, D-35383 Giessen, Germany. Tel: +49 64179600, Fax: +49 6417960123, e-mail: claudia.vollbracht@pascoe.de

Key Words: Ascorbic acid, breast neoplasm, intravenous vitamin C, tumour pain, side-effects, depression, fatigue, surgery.

Breast cancer is the most common cause of cancer death in women. The use of complementary medicine to improve quality of life (QoL) during treatment is common. Women with early-stage breast cancer, especially those with lower QoL, are highly likely to use complementary therapies(1). The American Cancer Society defines complementary medicine or methods as those that are used in conjunction with regular medical care. If these treatments are carefully chosen and managed, they may add to enhanced comfort and well-being (2).

Vitamin C (ascorbate) is an essential nutrient. It is an important antioxidant and co-factor for various enzymes. In particular, immune, nerve, and bone cells have a high need for vitamin C for optimal function. It is involved in synthesizing collagen, carnitine, neurotransmitters and neuropeptides and thus critically affects woundhealing, energy metabolism, and function of the nervous system.

Intravenous (*i.v.*) administration of vitamin C is part of complementary therapies in anticipation of improving QoL, protecting against side-effects of chemotherapy and radiation, increasing the immune system's defence and inducing antiproliferative effects. The administration of high dose *i.v.* vitamin C is currently debated by the oncologic community because the requirements for scientific proof of safety and effectiveness for vitamin C, as for many other complementary therapeutic approaches, has not yet been met (3-6). In the past, basic research and clinical evaluation of *i.v.* vitamin C in oncology have been intensified in an attempt to integrate this therapy into evidence-based medicine. Basic research shows that vitamin C in high concentration has an antiproliferative effect towards different cancer cells, including breast cancer cells (7-9), sensitizes cancer cells towards some cytostatic drugs (10, 11) and protects from chemotherapy related side-effects (12-14). It is important to keep in mind that orally administered vitamin C produces concentrations in plasma and tissue which are tightly controlled (<0.2 mM) and that pharmacologic concentrations of vitamin C in plasma (>0.2 mM) can only be achieved by parenteral administration (15).

Although preclinical data in animal models showed a significant reduction of tumour growth, the use of pharmacological vitamin C as a single agent was not curative (16-19). This emphasizes that a future trend may lie in a combination of vitamin C and chemotherapeutics (20). The efficacy of vitamin C as a chemotherapeutic agent has not been clinically investigated, although well-documented case reports are available (21, 22). Clinical data regarding the safety and efficacy of *i.v.* vitamin C in order to enhance QoL are also limited. In 1991, Cameron published clinical experiences with *i.v.* vitamin C (~10 g/d) and in 2007 (23), a Korean study investigated the efficacy of one week high-dose *i.v.* vitamin C (20 g/d with a 3-day interval) on health-related QoL in terminally ill cancer patients (24).

The rationale behind the use of vitamin C complementary in oncology is to combat oxidative stress, which is a major factor in chemotherapy and radiation-related side-effects that is often overlooked. Tumour cells metabolism, surgery, chemotherapy and radiation lead to an increase in reactive oxygen species (ROS), which stresses the antioxidant defense system and induces oxidative stress. QoL of tumour patients is impaired by oxidative stress-related effects such as mucosa dysfunction causing gastrointestinal ailments, anemia, fatigue, mental disorders and lipid abnormalities. Therefore, there is a strong consensus among scientists that the recommendations of antioxidants for cancer patients should be reinvestigated (25). Additionally, oxidative stress has emerged as a major aetiological factor for breast cancer. Although, a recent case–control study based on the dietary intake of antioxidant vitamins did not find any meaningful association with breast cancer risk (26), studies based on blood examinations of vitamin status found that increasing levels of vitamin C were significantly associated with a reduced risk of breast cancer (27, 28).

Taking into account the important role of oxidative stress in the development and progression of cancer and in the aetiology of adverse effects, the present clinical investigation was performed to evaluate the safety and efficacy of complementary *i.v.* vitamin C administration to reduce side-effects of guideline-based adjuvant chemo-/radiotherapy in breast cancer patients.

Patients and Methods

Study design. This was an epidemiological, retrospective cohort study with parallel groups. Design and conduct of the study were performed in accordance with current standards for observational studies (29, 30). For this type of study, a representative sample of individuals is selected out of a well-defined population (breast cancer patients in UICC stages IIa to IIIb) and the applied therapies (which are deliberately decided by the treating physician or patient and not by the study protocol) and patient's responses are observed and documented. With this design the utilization of the therapies in the population can be investigated. But as the therapies are not assigned by randomization, the decision for a certain therapy may be influenced by patient's preferences or condition, which may also influence the response. Therefore an immediate response comparison between different therapies may be biased. To obtain unbiased comparisons, the responses in all therapy groups must be adjusted to common conditions. This can be done by covariance techniques, where with the data of all treatment groups a functional relation (regression function) between response and relevant conditions (so-called covariables) is estimated and the observed responses are adjusted with this function to common conditions. This technique was applied for the analysis of this study. In addition, patients are stratified in homogenous covariable subgroups (*e.g.*, chemotherapy yes/no, radiotherapy yes/no), treatment comparisons are performed within the strata and pooled over all strata, if there is no interaction between covariables and treatments. As significance level for statistical tests $p=0.05$ was used. The analysis was performd with the statistical package SPSS 17.

Study population. A total of 15 gynaecologists and general practitioners representatively distributed across Germany, including gynaecologists and general practitioners supplied data on 125 elegible patients with breast cancer, of whom 53 formed the study group and 72 the control group. The patients of the study group were treated complementarily to basic tumour therapy with *i.v.* vitamin C (Vitamin C-Injektopas®, renamed to Pascorbin® in 2006, containing 7.5 g ascorbate for infusion; Pascoe pharmazeutische Präparate GmbH, Giessen, Germany). The patients of the control group did not receive vitamin C therapy. The criteria for inclusion in the cohort study were: primary non-metastasized breast cancer UICC levels IIa-IIIb, treatment 1/2000-12/2006 with *i.v.* vitamin C (study group) or without *i.v.* vitamin C (control group), in addition to guideline conforming antineoplastic treatment (primary surgical treatment, adjuvant chemo-, radio-, hormone therapy). Vitamin C was administered at a dosage of 7.5 g once a week during adjuvant therapies, for a minimum of 4 weeks to fulfil the inclusion criteria. According to the study protocol, no *i.v.* vitamin C was administered on the days of chemo- and radiotherapy. Baseline and treatment data

concerning characteristics of covariates that could have influenced the treatment are presented in Table I. Significantly more patients of the control group underwent chemo-, radio and hormone therapy than patients of the study group. Concerning age, overall intensity of complaints before adjuvant therapy and UICC stage, there are no significant differences between the groups.

Data collection. Prior to data collection the data elements required for the study were identified and defined in the study protocol and a case report form (CRF). Data were retrieved by the investigators from the patients' medical records at the study centres and transferred to the standardized CRFs. Data collected included patients' demographic details, characteristics of the tumour disease, treatments, signs, symptoms and side-effects experienced by the patients. A clinical quality assurance audit was carried out by an independent institution which confirmed that the data were acceptable for the purpose of a clinical trial.

Outcome analysis. Typical disease/therapy-induced signs and symptoms were assessed based on the data collected from the patient records after operation, reflecting values at baseline (before start of adjuvant treatment), during 6 months' adjuvant chemo-/radiotherapy (period of 6 months postoperative) and during 6 months of aftercare (period from 6 to 12 months postoperative). Signs and symptoms were allocated intensity scores of 0 (no symptoms), 1 (mild symptoms) or 2 (severe symptoms). The following symptoms were recorded: gastrointestinal tract symptoms (nausea, vomiting, loss of appetite, diarrhoea), mental conditions (tiredness/lassitude/fatigue, depression), sleep disturbances, dizziness, headache, tumour pain, cachexia, skin irritation, mucositis, haemorrhagic diathesis and infections. For a specific symptom, a patient was included in the analysis if the symptom was present either at the beginning and/or during the standard treatment (operation, chemo-/ radiotherapy) or during 6 months of aftercare, but only if an assessment was available for both time points. In efficacy analysis, the symptom intensity scores were considered as quantitative variables and their distribution was characterized by its mean. The primary efficacy criterion was the overall intensity score: *i.e.* the average of the symptom intensity scores reported by a patient during adjuvant therapy and aftercare, adjusted for equal baseline conditions. Further efficacy endpoints were the comparison of the Karnofsky index and the Everyday Cognition (ECOG) score between the test group and the control group during adjuvant chemo-, radiotherapy and during the subsequent 6 months of after care. Adjustment of the overall intensity score to equal baseline conditions was performed by the analysis of covariance for age, overall intensity score before adjuvant therapy, chemo-, radio- and hormone-therapy.

Safety. Analysis of the safety of the treatment with *i.v.* vitamin C included analysis of the number and severity of side-effects, their duration, treatment and outcome as documented in patient's files.

Results

Data from the medical records of 125 patients with breast cancer were documented from 15 centres/practices. All women underwent guideline conforming treatment during 1/2000-12/2006 with or without *i.v.* vitamin C administration complementary to adjuvant chemo-, radio- and hormone therapy. Main chemotherapy regimens were epirubicin/ cyclophosphamide (56%), cyclophosphamide/ methotrexate/ fluorouracil (20%) and fluorouracil/epirubicin/ cyclophosphamide (15.2%).

Table I. *Demographic and disease-relevant parameters.*

	Study group n=53	Control group n=72	*p*-Value
Mean age (years)	56.1	53.9	0.314
Mean overall intensity score before adjuvant therapy	0.87	0.77	0.243
UICC stage (%)			0.584
IIa	62.3	55.6	
IIb	22.6	25.0	
IIIa	13.2	12.5	
IIIb	1.9	6.9	
All stages	100.0	100.0	
Chemotherapy (%)	67.9	83.3	0.044
Radiotherapy (%)	34.0	61.1	0.003
Hormone therapy (%)	0	11.1	0.012

Covariate. The baseline characteristics and patient data of the study and control groups were comparable except for basic therapy. Significant differences between the two groups were seen for radiotherapy (p=0.003), for chemotherapy (p=0.044) and hormone therapy (p=0.012). Concerning UICC stage and other tumour-relevant parameters, no statistically significant differences were documented between the study and control groups (Table I).

Complaints. Response criteria for effectiveness are the intensity of the complaints (0=no complaints, 1=mild complaints, 2=severe complaints) during the adjuvant therapy phase (up to 6 months after operation) and aftercare phase (6-12 months after operation) as documented in the patients' records. As the study and control group differed in use of chemo- and radiotherapy, the documented intensities were adjusted to common values (total means) of age, baseline overall intensity score, chemotherapy, radiotherapy and hormone therapy. The means of the adjusted intensities in the adjuvant therapy phase are shown in Figure 1, those in the aftercare phase in Figure 2. The means of the study group for all complaints and phases are lower than those of the control group. The differences are statistically significant at the 0.05 level for loss of appetite (p=0.046), fatigue (p=0.004), depression (p=0.017) and sleep disorders (p=0.005) in the adjuvant therapy phase, and for nausea (p=0.022), loss of appetite (p=0.005), fatigue (p=0.023), sleep disorders (p=0.044), dizziness (p=0.004) and haemorrhagic diathesis (p=0.032) in the aftercare phase. The primary effect criterion was the overall intensity score (*i.e.* the average over the

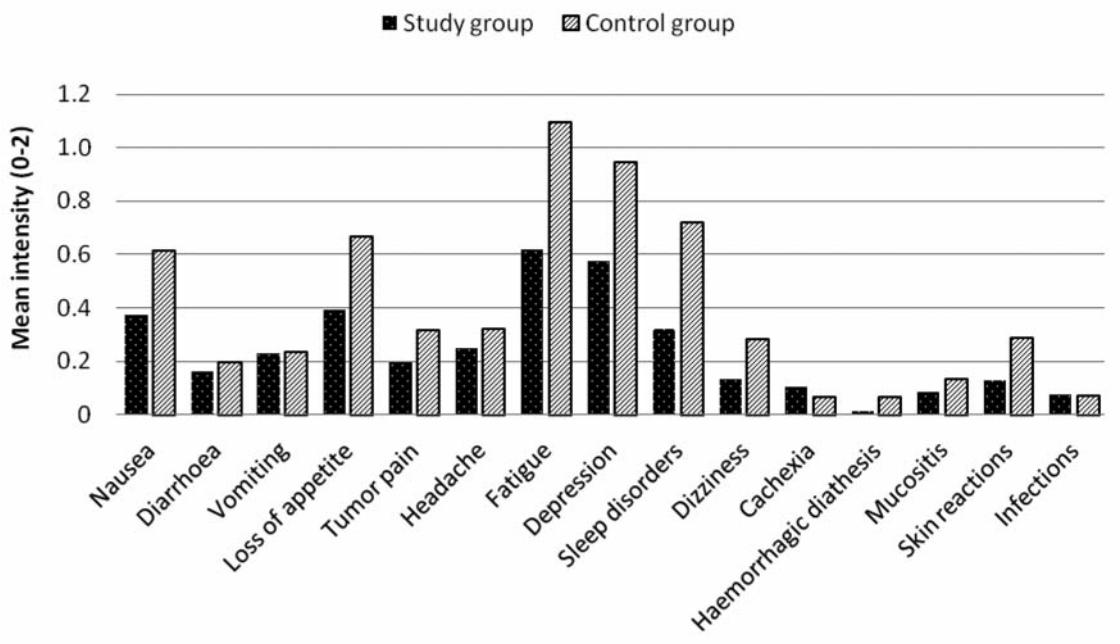

Figure 1. *Mean intensity of complaints during adjuvant therapy, adjusted for age, baseline overall intensity, chemotherapy, radiotherapy and hormone therapy.*

intensities of all complaints). The means of the adjusted overall intensity score are shown in Figure 3 for both study groups and phases. The means of the study group in both phases were significantly lower than those of the control group (p=0.013 in adjuvant therapy phase and p=0.021 in aftercare phase) and for both groups, lower in the aftercare phase than in the adjuvant therapy phase. This means that under comparable conditions, disease-or therapy-induced complaints during adjuvant therapy and aftercare were significantly reduced for patients with additional vitamin C therapy.

To determine whether the influence of vitamin C therapy differed for patients with and without chemo- or radiotherapy, patients were stratified according their adjuvant therapy (with/without chemotherapy, with/without radiotherapy) and a 2-factorial analysis of variance was performed with the overall intensity score in the adjuvant therapy phase as response variable and vitamin C treatment and chemotherapy and radiotherapy as influencing factors. The means of the overall intensity for both groups and all strata are shown in Figure 4. The mean overall intensity in the study group for all strata was remarkably lower than in the control group. The difference was particularly pronounced for the stratum without chemotherapy. As there was no significant interaction between vitamin C therapy and adjuvant therapy (p=0.255 for chemotherapy and p=0.905 for radiotherapy), the effect sizes (*i.e.* the differences in means between study and control groups) can be pooled over the strata with and without adjuvant therapy to a common estimate. This estimate is –0.195 for the strata with/without chemotherapy and –0.171 for strata with/without radiotherapy, and in both cases, statistically significant (p=0.008 and 0.009 respectively). This indicates that additional therapy with vitamin C has a significant effect on reduction of complaints during the adjuvant therapy phase and that this effect is independent of the applied adjuvant therapy.

Performance status. Women who received vitamin C intravenously had a markedly higher performance status during adjuvant therapy and the aftercare phase. During the 6 months of adjuvant treatment the mean index in the study group (80%) was significantly higher (p<0.001) than that in the control group (71%). The performance during the aftercare improved to 87% in the study group and was significantly better (p<0.001) than in the control group (78%) (Figure 5). The results of performance status as indicated by the ECOG are comparable to that of the Karnofsky index. During adjuvant therapy, the mean scores of ECOG (which can range from 1=normal performance to 5=constantly bedridden) were 1.596 in the study group and 2.067 in the control group (p=0.002) and, during aftercare, 1.11 in the study group and 1.71 in the control group (p<0.001) (Figure 6).

Safety. The safety of complementary *i.v.* vitamin C administration was assessed using a panel of adverse reactions. However, no *i.v.* vitamin C-induced side-effect was documented. Patient assessment during adjuvant therapy of the tolerability of complementary *i.v.* vitamin C administration was excellent (86.8%) and good (13.2%).

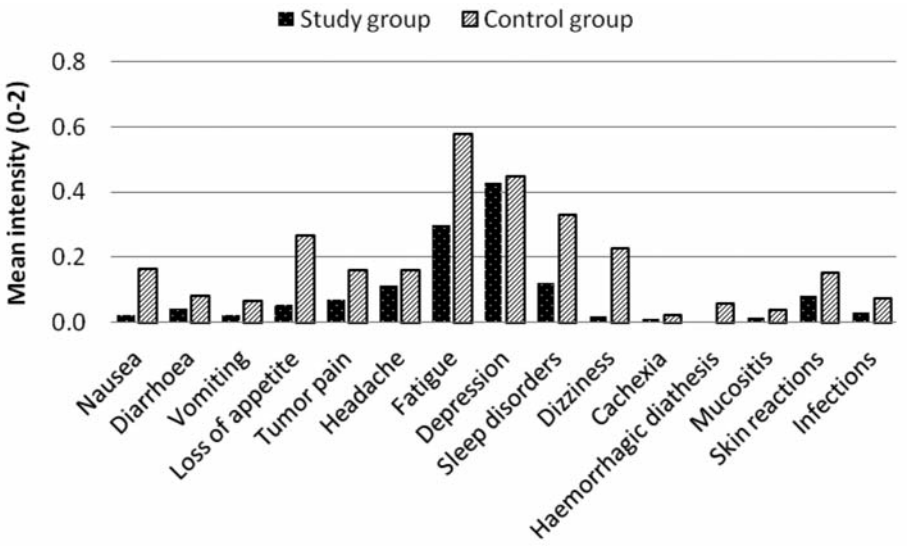

Figure 2. *Mean intensity of complaints during aftercare, adjusted for age, baseline overall intensity, chemotherapy, radiotherapy and hormone therapy.*

Discussion

The aim of the study was to evaluate the efficacy in terms of QoL and tolerability of Vitamin C-Injektopas® 7.5 g/Pascorbin® 7.5 g in the first postoperative year of women with breast cancer. The amelioration of QoL is an important optimization of standard therapy, because chemotherapy and radiation-related side-effects often cause a reduction in dosage or even abortion of guideline conforming therapy. To carry out optimal tumour-destructive therapy, the reduction or prevention of therapy-related side-effects is important.

Women who received vitamin C suffered significantly less from side-effects due to the tumour itself and the standard therapy. Similar effects were achieved for the aftercare period, where women in the vitamin C group were nearly free of complaints. After adjustment to the same baseline and treatment conditions, the confirmatory analysis also showed significant differences in the groups. During chemo- and radiotherapy, as well as during the aftercare period, the overall intensity of symptoms was reduced by one-third and one-half, respectively in the study group as compared to the control group (Figures 1 and 2). Clearly, the reduction of side-effects in the study group cannot be explained by inhomogeneities in covariates between both groups, but is due to the effect of complementary *i.v.* vitamin C therapy.

In particular, symptoms regarding the intestines, such as nausea and poor appetite, as well as neurodegenerative symptoms, such as loss of motivation and depression, were less severe in the vitamin C-treated group. Noteworthy as well is the outcome of scores for fatigue and sleeping disorders in the vitamin C-treated group, as sleeping disorders are a key step in the pathology of depression. As

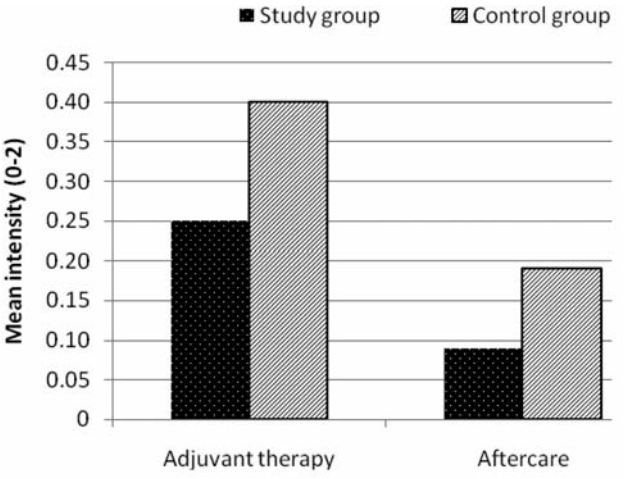

Figure 3. *Means of overall intensity of complaints, adjusted for age, baseline overall intensity, chemotherapy, radiotherapy and hormone therapy.*

expected during the aftercare period, fewer side-effects occurred, however, symptoms affecting the gut such as nausea and poor appetite, or the nervous system, such as fatigue, depression and sleeping disorders, were still less significant in the study group. Similar results have been observed after treatment of terminally ill cancer patients with 10 g vitamin C twice a day with a 3-day interval. After one week, the symptom scores for fatigue, nausea, vomiting, appetite loss and pain were significantly lower (24).

As known from the literature, tumour patients generally have a deficiency of vitamin C. This has also been confirmed for breast cancer patients (27). Low serum levels of vitamin C, in

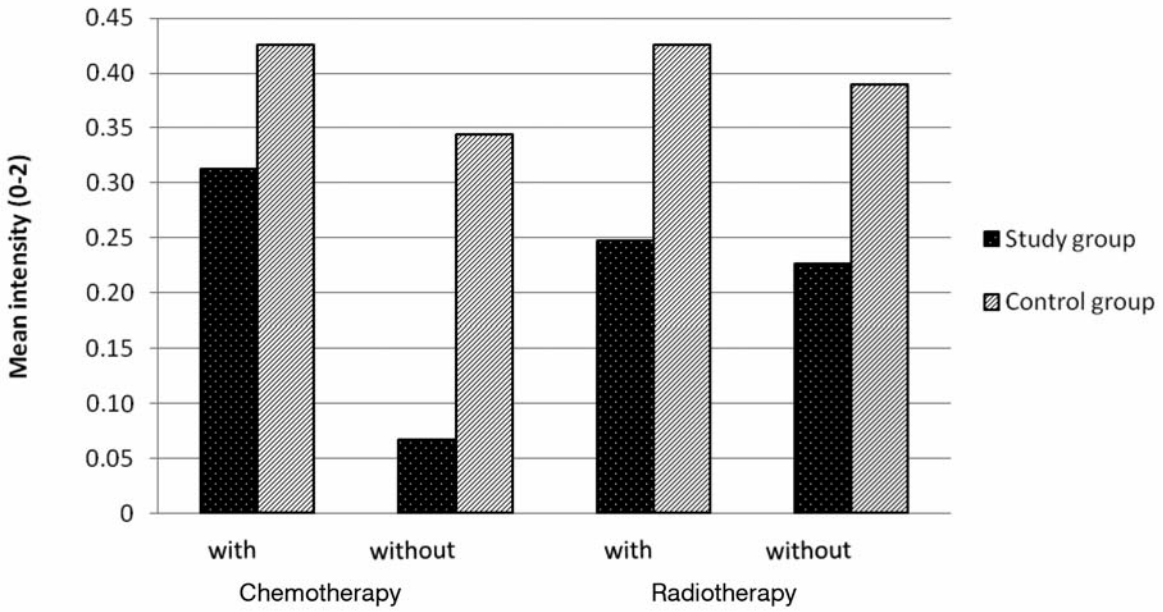

Figure 4. *Means of overall intensity of complaints during adjuvant therapy in strata with/without chemotherapy and with/without radiotherapy.*

spite of adequate daily intake, may be due to increased utilization of vitamin C for detoxification of ROS during surgery, chemo- and radiotherapy, as well as vitamin C sequestration by tumour cells. It is known that tissue trauma and surgical procedures reduce the antioxidant capacity, particularly that of vitamin C (31, 32), because of high metabolic turnover due to oxidative stress and wound healing. To prevent this deficit, at least 3 g *i.v.* vitamin C daily are required (33, 34). If surgery-related vitamin C loss is not sufficiently corrected, tumour patients experience severely reduced systemic antioxidant capacity even before starting chemo- and radiotherapy. Non-cancerous tissue is not adequately protected from ROS, which accumulate even more due to the therapy. Vitamin C deficiency or a generally depleted antioxidant capacity is a frequently underestimated problem in tumour patients. Noteworthy is an inverse relationship between vitamin C concentration and tumour markers (35), progression of disease (36, 37) and survival time (38). The deficiency scenario becomes worse after administration of chemotherapy or radiation (39-42).

It must be assumed that the administration of 7.5 g intravenous vitamin C in the study group restored vitamin C plasma levels and boosted the antioxidative capacity. This would explain the strong protection from gastrointestinal and neurodegenerative symptoms because both mucosa and nerves are very vulnerable to oxidative stress. For example, vitamin C is highly concentrated in the brain to protect it from ROS which accumulate during oxygen utilization. Oxidative stress correlates with the severity of depression because ROS degrade neurotransmitter (43-45) and animal studies with parenteral application of vitamin C observed antidepressant-like effects (46).

Besides efficacy, the evaluation of the safety of *i.v.* vitamin C in addition to guideline conforming antineoplastic treatment was a strong motivation for the present study. No adverse effects were documented that were associated with intake of Vitamin C-Injektopas® 7.5 g/Pascorbin® 7.5 g. Clinical studies affirm the tolerability of high-dose intravenous vitamin C in dosages up to 1.5 g per kg body weight, if known and accepted contraindications such as oxalate calculus, renal failure, haemochromatosis and glucose-6-phosphate-dehydrogenase deficiency, are kept in mind (20). In the present study, *i.v.* administration of vitamin C had no effect on tumour status after 6 or 12 months. This is noteworthy with respect to concerns that a strong antioxidant such as vitamin C may reduce the efficacy of chemo- or radiotherapy (4). So far no clinical studies have evaluated possible interactions between standard therapy and adjuvant *i.v.* vitamin C application. A benefit of complementary high-dosage vitamin C injections has been observed in case reports and animal experiments (12-14, 47, 48). *In vitro* experiments showed that pretreatment of tumour cells with ascorbate, which acts extracellularly as a pro-oxidant toward tumour cells, leads to increased sensitivity towards several antineoplastic drugs, such as epirubicin, and 5-fluorouracil (10, 11, 49), two drugs frequently used in breast cancer treatment.

But because of the absence of clinical studies, a safety margin between chemo-/radiotherapy and the administration of *i.v.* vitamin C is strictly recommended. This recommendation was explicitly followed by the present study protocol.

Complementary treatment of breast cancer patients with high-dosage *i.v.* vitamin C (Pascorbin® 7.5 g) was shown to be a well-tolerated optimization of standard tumour-destructive therapies, mainly reducing QoL related side-effects.

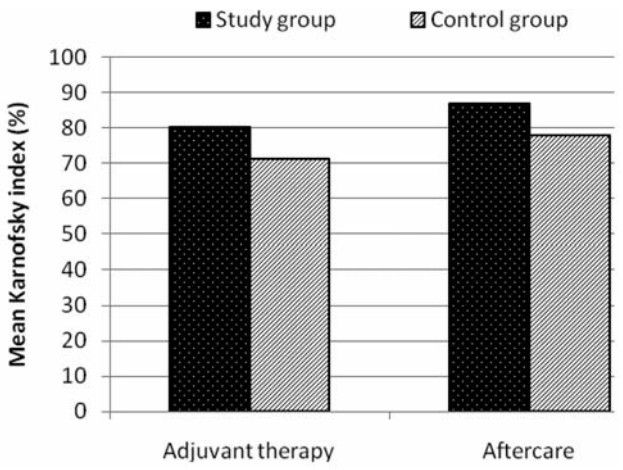

Figure 5. *Mean Karnofsky index, adjusted for age, baseline overall intensity, chemotherapy, radiotherapy and hormone therapy.*

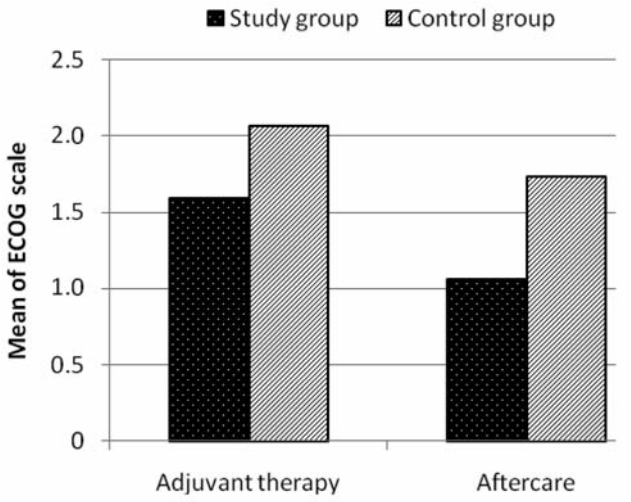

Figure 6. *Mean ECOG scale, adjusted for age, baseline overall intensity, chemotherapy, radiotherapy and hormone therapy.*

References

1 Wyatt G, Sikorskii A, Wills CE and Su H: Complementary and alternative medicine use, spending, and quality of life in early stage breast cancer. Nurs Res *59(1)*: 58-66, 2010.

2 American Cancer Society: Guidelines for using complementary and alternative medicine. www.cancer.org, 2008.

3 Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG and Gluud C: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev *(2)*: CD007176, 2008.

4 Lawenda BD, Kelly KM, Ladas EJ, Sagar SM, Vickers A and Blumberg JB: Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? J Natl Cancer Inst *100(11)*: 773-783, 2008.

5 Heaney ML, Gardner JR, Karasavvas N, Golde DW, Scheinberg DA, Smith EA and O'Connor OA: Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. Cancer Res *68(19)*: 8031-8038, 2008.

6 Espey MG, Chen Q and Levine M: Comment re: Vitamin C antagonizes the cytotoxic effects of chemotherapy. Cancer Res *69(22)*: 8830; author reply 8830-8831, 2009.

7 Chen Q, Espey MG, Krishna MC, Mitchell JB, Corpe CP, Buettner GR, Shacter E and Levine M: Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. Proc Natl Acad Sci USA *102(38)*: 13604-13609, 2005.

8 Kim KN, Pie JE, Park JH, Park YH, Kim HW and Kim MK: Retinoic acid and ascorbic acid act synergistically in inhibiting human breast cancer cell proliferation. J Nutr Biochem *17(7)*: 454-462, 2006.

9 Hong SW, Jin DH, Hahm ES, Yim SH, Lim JS, Kim KI, Yang Y, Lee SS, Kang JS, Lee WJ, Lee WK and Lee MS: Ascorbate (vitamin C) induces cell death through the apoptosis-inducing factor in human breast cancer cells. Oncol Rep *18(4)*: 811-815, 2007.

10 Kurbacher CM, Wagner U, Kolster B, Andreotti PE, Krebs D and Bruckner HW: Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells *in vitro*. Cancer Lett *103(2)*: 183-189, 1996.

11 Fromberg A, Gutsch D, Schulze D, Vollbracht C, Weiss G, Czubayko F and Aigner A: Ascorbate exerts anti-proliferative effects through cell cycle inhibition and sensitizes tumor cells towards cytostatic drugs. Cancer Chemother Pharmacol *67(5)*: 1157-1166, 2010.

12 El-Merzabani MM, El-Aaser AA, Osman AM, Ismael N and Abu el-Ela F: Potentiation of therapeutic effect of methanesulphonate and protection against its organ cytotoxicity by vitamin C in Ehrlich ascites carcinoma bearing mice. J Pharm Belg *44(2)*: 109-116, 1989.

13 Shimpo K, Nagatsu T, Yamada K, Sato T, Niimi H, Shamoto M, Takeuchi T, Umezawa H and Fujita K: Ascorbic acid and adriamycin toxicity. Am J Clin Nutr *54(6 Suppl)*: 1298S-1301S, 1991.

14 Prasad SB, Giri A and Arjun J: Use of subtherapeutical dose of cisplatin and vitamin C against murine Dalton's lymphoma. Pol J Pharmacol Pharm *44(4)*: 383-391, 1992.

15 Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA and Levine M: Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med *140(7)*: 533-537, 2004.

16 Casciari JJ, Riordan HD, Miranda-Massari JR and Gonzalez MJ: Effects of high dose ascorbate administration on L-10 tumor growth in guinea pigs. P R Health Sci J *24(2)*: 145-150, 2005.

17 Chen Q, Espey MG, Sun AY, Pooput C, Kirk KL, Krishna MC, Khosh DB, Drisko J and Levine M: Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. Proc Natl Acad Sci USA *105(32)*: 11105-11109, 2008.

18 Du J, Martin SM, Levine M, Wagner BA, Buettner GR, Wang SH, Taghiyev AF, Du C, Knudson CM and Cullen JJ: Mechanisms of ascorbate-induced cytotoxicity in pancreatic cancer. Clin Cancer Res *16(2)*: 509-520, 2010.

19 Pollard HB, Levine MA, Eidelman O and Pollard M: Pharmacological ascorbic acid suppresses syngeneic tumor growth and metastases in hormone-refractory prostate cancer. In Vivo *24(3)*: 249-255, 2010.

20 Hoffer LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, Rosadiuk K, Rousseau C, Robitaille L and Miller WH Jr.: Phase I clinical trial of *i.v.* ascorbic acid in advanced malignancy. Ann Oncol *19(11)*: 1969-1974, 2008.

21 Drisko JA, Chapman J and Hunter VJ: The use of antioxidants with first-line chemotherapy in two cases of ovarian cancer. 0J Am Coll Nutr *22(2)*: 118-123, 2003.

22 Padayatty SJ, Riordan HD, Hewitt SM, Katz A, Hoffer LJ and Levine M: Intravenously administered vitamin C as cancer therapy: three cases. Cmaj *174(7)*: 937-942, 2006.

23 Cameron E: Protocol for the use of vitamin C in the treatment of cancer. Med Hypotheses *36(3)*: 190-194, 1991.

24 Yeom CH, Jung GC and Song KJ: Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration. J Korean Med Sci *22(1)*: 7-11, 2007.

25 Kennedy DD, Tucker KL, Ladas ED, Rheingold SR, Blumberg J and Kelly KM: Low antioxidant vitamin intakes are associated with increases in adverse effects of chemotherapy in children with acute lymphoblastic leukemia. Am J Clin Nutr *79(6)*: 1029-36, 2004.

26 Wang C, Baumgartner RN, Yang D, Slattery ML, Murtaugh MA, Byers T, Hines LM, Giuliano AR and Baumgartner KB: No evidence of association between breast cancer risk and dietary carotenoids, retinols, vitamin C and tocopherols in Southwestern Hispanic and non-Hispanic White women. Breast Cancer Res Treat *114(1)*: 137-145, 2009.

27 Shah FD, Patel JB, Shukla SN, Shah PM and Patel PS: Evaluation of plasma non-enzymatic antioxidants in breast cancer etiology. Asian Pac J Cancer Prev *10(1)*: 91-96, 2009.

28 Singh P, Kapil U, Shukla NK, Deo S and Dwivedi SN: Association between breast cancer and vitamin C, vitamin E and selenium levels: results of a case-control study in India. Asian Pac J Cancer Prev *6(2)*: 177-180, 2005.

29 Schneider B: Analysis of therapeutic efficacy in observational cohort studies. Cancer Chemother Pharmacol *47*: 35-37, 2001.

30 Beuth JH N, van Leendert R, Basten R, Noehle M and Schneider B: Safety and efficacy of local administration of contractubex to hypertrophic scars in comparison to corticoid treatment. Results of a multicenter, comparative epidemiological cohort study in Germany. In Vivo *20*: 277-284, 2006.

31 Borrelli E, Roux-Lombard P, Grau GE, Girardin E, Ricou B, Dayer J and Suter PM: Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. Crit Care Med *24(3)*: 392-397, 1996.

32 Schorah CJ, Downing C, Piripitsi A, Gallivan L, Al-Hazaa AH, Sanderson MJ and Bodenham A: Total vitamin C, ascorbic acid, and dehydroascorbic acid concentrations in plasma of critically ill patients. Am J Clin Nutr *63(5)*: 760-765, 1996.

33 Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, Radella F, Garcia I and Maier RV: Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg *236(6)*: 814-822, 2002.

34 Long CL, Maull KI, Krishnan RS, Laws HL, Geiger JW, Borghesi L, Franks W, Lawson TC and Sauberlich HE: Ascorbic acid dynamics in the seriously ill and injured. J Surg Res *109(2)*: 144-148, 2003.

35 Akinloye O, Adaramoye O and Kareem O: Changes in antioxidant status and lipid peroxidation in Nigerian patients with prostate carcinoma. Pol Arch Med Wewn *119(9)*: 526-532, 2009.

36 Esme H, Cemek M, Sezer M, Saglam H, Demir A, Melek H and Unlu M: High levels of oxidative stress in patients with advanced lung cancer. Respirology *13(1)*: 112-116, 2008.

37 Yalcin O, Karatas F, Erulas FA and 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 *93(6)*: 863-866, 2004.

38 Mayland CR, Bennett MI and Allan K: Vitamin C deficiency in cancer patients. Palliat Med *19(1)*: 17-20, 2005.

39 Sakhi AK, Russnes KM, Thoresen M, Bastani NE, Karlsen A, Smeland S and Blomhoff R: Pre-radiotherapy plasma carotenoids and markers of oxidative stress are associated with survival in head and neck squamous cell carcinoma patients: a prospective study. BMC Cancer *9*: 458, 2009.

40 Al-Gayyar MM, Eissa LA, Rabie AM and El-Gayar AM: Measurements of oxidative stress status and antioxidant activity in chronic leukaemia patients. J Pharm Pharmacol *59(3)*: 409-417, 2007.

41 Marcus SL, Petrylak DP, Dutcher JP, Paietta E, Ciobanu N, Strauman J, Wiernik PH, Hutner SH, Frank O and Baker H: Hypovitaminosis C in patients treated with high-dose interleukin 2 and lymphokine-activated killer cells. Am J Clin Nutr *54(6 Suppl)*: 1292S-1297S, 1991.

42 Chevion S, Or R and Berry EM: The antioxidant status of patients subjected to total body irradiation. Biochem Mol Biol Int *47(6)*: 1019-1027, 1999.

43 Sarandol A, Sarandol E, Eker SS, Erdinc S, Vatansever E and Kirli S: Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative-antioxidative systems. Hum Psychopharmacol *22(2)*: 67-73, 2007.

44 Khanzode SD, Dakhale GN, Khanzode SS, Saoji A and Palasodkar R: Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. Redox Rep *8(6)*: 365-370, 2003.

45 Chang CW, Chen MJ, Wang TE, Chang WH, Lin CC and Liu CY: Scurvy in a patient with depression. Dig Dis Sci *52(5)*: 1259-1261, 2007.

46 Binfare RW, Rosa AO, Lobato KR, Santos AR and Rodrigues AL: Ascorbic acid administration produces an antidepressant-like effect: evidence for the involvement of monoaminergic neurotransmission. Prog Neuropsychopharmacol Biol Psychiatry *33(3)*: 530-540, 2009.

47 Riordan HD, Riordan NH, Jackson JA, Casciari JJ, Hunninghake R, Gonzalez MJ, Mora EM, Miranda-Massari JR, Rosario N and Rivera A: Intravenous vitamin C as a chemotherapy agent: a report on clinical cases. P R Health Sci J *23(2)*: 115-118, 2004.

48 Drisko JA, Chapman J and Hunter VJ: The use of antioxidant therapies during chemotherapy. Gynecol Oncol *88(3)*: 434-439, 2003.

49 Abdel-Latif MM, Raouf AA, Sabra K, Kelleher D and Reynolds JV: Vitamin C enhances chemosensitization of esophageal cancer cells *in vitro*. J Chemother *17(5)*: 539-549, 2005.

Received June 21, 2011
Revised August 5, 2011
Accepted August 9, 2011