Limited Effects of Selenium Substitution in the Prevention of Radiation-associated Toxicities. Results of a Randomized Study in Head and Neck Cancer Patients

J. BÜNTZEL[1], D. RIESENBECK[2], M. GLATZEL[3], R. BERNDT-SKORKA[4], T. RIEDEL[5], R. MÜCKE[3], K. KISTERS[3], K.G. SCHÖNEKAES[3], U. SCHÄFER[3], F. BRUNS[6] and O. MICKE[3]

[1]*Department of Otolaryngology, Head Neck Surgery, Südharz-Krankenhaus Nordhausen, D-99734 Nordhausen, Germany;*
[2]*Department of Radiotherapy, Prosper Hospital Recklinghausen, D-45659 Recklinghausen, Germany;*
[3]*German Study Group "Trace Elements and Electrolytes in Oncology (AKTE), Germany;*
[4]*Department of Radiotherapy, Municipal Hospital Neubrandenburg, D-17036 Neubrandenburg, Germany;*
[5]*Department of Radiotherapy, University Hospital Hannover, D-30625 Hannover, Germany;*
[6]*Department of Radiotherapy, Municipal Hospital Bielefeld, D-33615 Bielefeld, Germany*

Abstract. *Objective: The substitution of selenium activates the selenium-dependent enzyme glutathione peroxidase, which is important for scavenging free radicals. To date, only limited data are available about the clinical impact of selenium regarding the toxicities due to free radical producing therapies, e.g. irradiation or chemotherapy, and therefore the objective of this study was to investigate the clinical impact of selenium in such therapies. Patients and Methods: 39 patients (8 female, 31 male) with advanced head and neck cancer were included in a randomised phase II study. The mean age was 63.52±9.31 years. Tumour localizations: oral cavity 15 patients, oropharynx 19 patients, hypopharynx 5 patients, carcinoma of unknown primary 1 patient. Group A (n=22) received 500 μg sodium selenite on the days of radiotherapy and 300 μg sodium selenite on days without radiotherapy. Group B (17) was irradiated without any selenium substitution. Both groups were well balanced according to age, gender, localization and stage of the tumour. The RTOG grade of radiation-associated toxicities was evaluated once per week. Results: The following serious toxicities were observed (group A vs. group B): dysphagia 22.7% vs. 35.3%, loss of taste 22.7% vs. 47.1%, dry mouth 22.7% vs. 23.5%, and stomatitis 36.4% vs. 23.5%. A statistical trend (Fisher's exact test) was only seen for the loss of taste (p=0.172). The weekly patient analysis (Student's t-test) showed a significant reduction of dysphagia in the selenium group (Group 1) at the last week of irradiation. Conclusion: This small randomised trial showed limited effects of selenium in the prevention of ageusia (loss of taste) and dysphagia due to radiotherapy of head and neck cancer.*

Correspondence to: PD Dr. med. Jens Büntzel, Klinik für HNO-Krankheiten, Kopf-Hals-Chirurgie, Dr.-Robert-Koch-Str. 39, D99734 Nordhausen, Germany. Tel: +49 3631412263, Fax: +49 3631412240, email: jens.buentzel@shk-ndh.de

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Selenium is well known as an essential co-factor of the enzyme glutathione peroxidase. This enzymatic system scavenges free radicals and is thus important for the endogenous detoxification of the human body (1, 2). Several investigations have shown a deficiency in endogenous selenium in cancer patients (3, 4). In a study published previously by this group, it was demonstrated that >80% of all head and neck cancer patients were characterized by decreased serum selenium levels compared to German reference values. The measurements also showed a reduced activity of the enzyme glutathione peroxidase and an increased level of free radicals (malondialdehyde, MDA) (5). The biological role of this reduced enzymatic activity is not currently well understood. The increased concentrations of free radicals and the decreased detoxifying function may have an important impact on tumour genesis as well as on the intensity of treatment-induced toxicities. In particular, irradiation is a free radical-generating therapy which is used in the majority of cancer patients (6). There are a number of observations that the grade of radiation-induced toxicity correlates with the grade of free radicals in the tumour-surrounding tissues. This was the reason for a clinical investigation program with the substance amifostine as a

radioprotector (8). As part of their participation in this program, the Authors of this study showed that the exogenous scavenger amifostine was able to reduce some typical toxicities in head and neck cancer patients (7). These supportive effects were seen without any sign of tumour protection, *e.g.* there was no influence of amifostine on the affectivity of the anti-cancer treatment.

The aim of the presented study was to evaluate the effects of selenium substituions in individuals with decreased endogenous serum-concentration of selenium during their adjuvant irradiation because of a surgically resected head and neck cancer.

Patients and Methods

Patients received single doses of 1.8 to 2.0 Gray to the primary tumours and the lymphatic neck during their daily radiation therapy. Cumulative doses ranged from 60 to 72 Gray. Treatment breaks were allowed at weekends and official holidays. Other treatment interruptions had to be registered. The patients in the selenium group (Group 1) were administered 500 μg sodium selenite two days before starting radiotherapy. They were also administered 500 μg selenite on the days of radiotherapy. During weekends and official holidays, only 300 μg selenite were given. Sodium selenite was taken as an oral fluid one hour before the radiotherapy was performed. The control subjects (Group 2) received the standardised radiotherapy without any selenium intake or other cytoprotective therapy option.

Six centres (Bielefeld, Recklinghausen, Nordhausen, Neubrandenburg, Hannover, Münster) took part in this study. The study was accepted by the International Ethics Committee Freiburg in 2000, and took place between 2001 and 2007.

The study was open to patients with squamous cell carcinoma of the head and neck region. At first a blood sample was taken from the patient. If the atom absorption spectrometry showed a deficiency in selenium and if the radiation field included 75% of the major salivary glands, the patient was refered for participation in this study. When the patient had given the informed consent, randomisation was performed and the patient received information about the treatment arm.

Primary investigation was performed in 113 patients. Overall, 93 patients (82.3%) showed a decrease in selenium concentration of the whole blood as well as the serum; 48 of these (51.6%) patients initially agreed to take part in the study, with 8 of these patients subsequently withdrawing their agreement. The remaining 40 patients were randomised, 22 to the selenium group (Group 1), and 18 to the control group (Group 2). A total of 39 out of the 40 patients received the planned therapy, and this study received information about 22 selenium patients and 17 control individuals. Demographic data of the participating patients are shown in Table I.

The laboratory investigations were performed by the sponsor (biosyn Arzneimittel GmbH, Fellbach, Germany). Atom absorption spectrometry was performed in serum and whole blood samples (Perkin Elmer Analyst 600). Selenium concentration was measured at baseline, after 4 weeks, at the end of radiotherapy, and six weeks after the last irradiation.

Each patient was investigated clinically at baseline, weekly during the radiotherapy, and six weeks after the end of radiotherapy. The evaluation of side-effects was performed by the institutional tumour board of the six participating hospitals. The toxicities were evaluated according the Radiation Therapy Oncology Group (RTOG) scale.

Table I. *Biometric data study patients.*

	Selenium group	Control group	Total
Tumour localization			
Oropharynx	11	7	18
Hypopharynx	3	2	5
Oral cavity	8	7	15
Unknown primary	0	1	1
Age (years)			
Median	62.8	63.5	63.2
Range	38.7-78.4	48.7-83.0	38.7-83.0
Gender			
Male	16	15	31
Female	6	2	8
Radiotherapy			
Definitive	2	0	2
Adjuvant	20	17	37

The individual patient file was transferred to the sponsor who was responsible for monitoring. Analyses of the toxicities were performed regarding the time of onset and the maximum levels of toxicity. Mean values and Student's *t*-tests were used to compare the toxicity at each week of radiotherapy (MS Excel 2003). Fisher's exact test was used to compare the maximum toxicities of both groups (http://www.langsrud.com/ stat/Fishertest.htm).

Results

Selenium concentration was substituted effectively in the selenium group. The detailed values are the object of a separate paper (10).

Four different toxicites were compared between both groups: dry mouth (xerostomia), inflammation of the oral mucosa (stomatitis), loss of taste (ageusia), and dysphagia (problems in nutrition).

Figures 1 to 4 summarise the development of toxicities during the course of radiotherapy. Comparing the mean values of xerostomia, no statistically significant difference can be seen between the groups. The mean grades of stomatitis were similar; a trend for higher grades in the selenium group was not statistically significant. Ageusia was milder in the selenium group, but the difference was not significant. The only significant difference was observed in dysphagia at week 7, when the selenium group had developed a mean value of 1.533 *vs.* 2.167 in the control group (p=0.05).

Twenty-three serious adverse events (SAEs) were seen in the selenium group, compared to 22 SAEs in the control group (p=0.476). Table II shows the summarised maximal toxicities of both groups. No statistically significant difference in toxicities were found using the two-tailed Fisher's exact test. A trend for a milder loss of taste was observed in the selenium group.

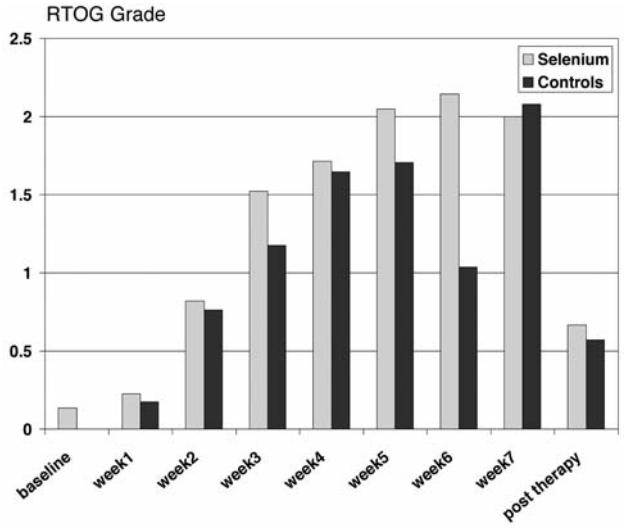

Figure 1. *Development of mucositis during radiotherapy course.*

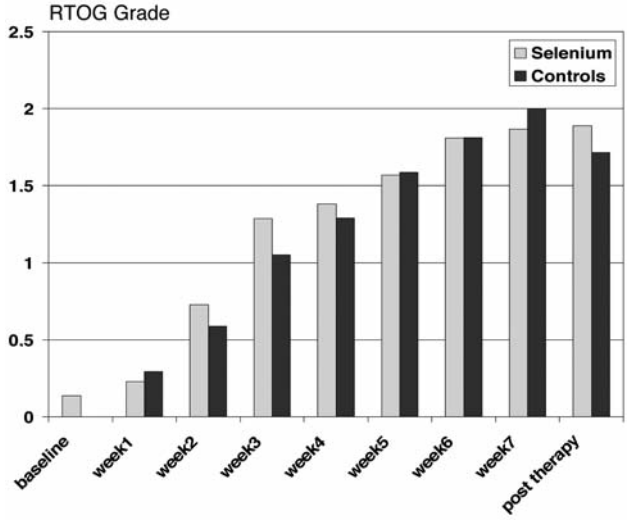

Figure 2. *Development of xerostomia during radiotherapy course.*

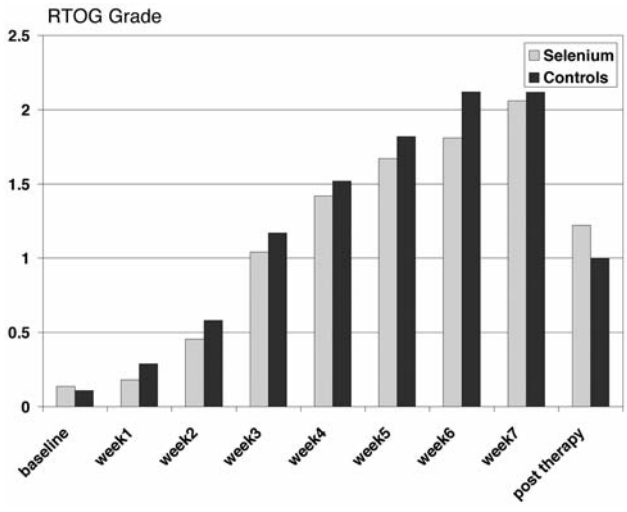

Figure 3. *Development of loss of taste during radiotherapy course.*

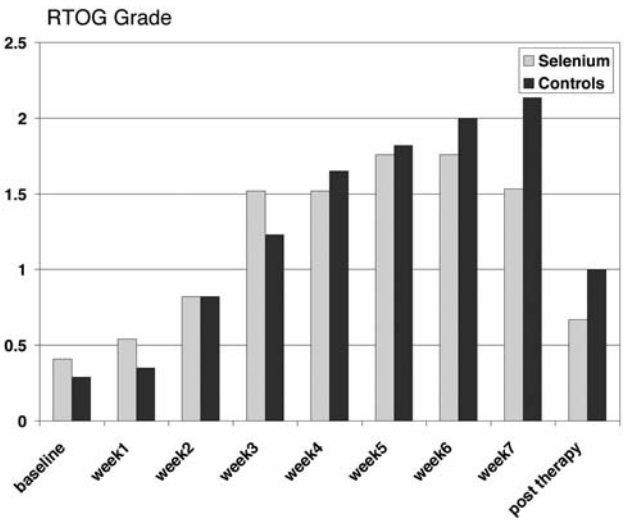

Figure 4. *Development of dysphagia during radiotherapy course.*

Discussion

This study is the first randomised investigation focused on the effects of selenium in the supportive treatment of irradiated head and neck cancer patients. A randomised phase III trial to investigate this question was planned in 2000, with an original hypothesis of the reduction of xerostomia 2/3 RTOG from 50% to 30%. A total of 60 patients per arm were required for a statistical power of 80%.

After 7 years of recruitment, blood samples of 113 patients were measured and only 39 out of 93 patients with selenium deficiency decided to take part in the study. Therefore it was necessary to finish the investigation at this time, giving data of only limited value. Nevertheless, the data offered results in the sense of a controlled phase II study, presenting a hypothesis for future work in field.

The decreased serum selenium levels in this group of cancer patients have already been reported (10). The rate of 93 out of 113 patients with decreased selenium supported those former results. Interestingly, there was no difference between decreased levels in serum and whole blood. The evaluation of serum selenium is often criticised in the literature (11) and instead whole blood measurements should show more chronic alterations.

Table II. *Maximal toxicities of both groups.*

Maximal toxicity	Selenium group (n=22)					Control group (n=17)					
RTOG grade	0	1	2	3	4	0	1	2	3	4	*p*-Value
Dysphagia	2 (9.1%)	5 (22.7%)	10 (45.5%)	5 (22.7%)	0	0	5 (29.4%)	6 (35.3%)	6 (35.3%)	0	0.476
Loss of taste	2 (9.1%)	6 (27.3%)	9 (40.9%)	5 (22.7%)	0	2 (11.8%)	1 (5.9%)	6 (35.3%)	8 (47.1%)	0	0.172
Dry mouth	2 (9.1%)	5 (22.7%)	10 (45.5%)	4 (18.2%)	1 (4.5%)	1 (5.9%)	6 (35.3%)	6 (35.3%)	4 (23.5%)	0	1
Stomatitis	0	4 (18.2%)	10 (45.5%)	8 (36.4%)	0	0	5 (29.4%)	7 (41.2%)	4 (23.5%)	0	0.494

The present study has shown only limited effects of selenium substitution in the reduction of radiation-associated side-effects in head and neck cancer patients. Already current amifostine trials have observed borderline effects in this field (8). To find the reasons for this, first one should consider that supported detoxification is only one of many exit routes from the human body. The mild reduction of free radicals (MDA) is reflecting this point. It is interesting to note that early symptoms such as loss of taste were influenced by scavenging free radicals. Symptoms of damaged tissues (mucositis and xerostomia) were not influenced by selenium or amifostine.

Secondly, the study design should also be scrutinised carefully. The RTOG criteria are the only classifications of acute toxicities, but they are only semi-quantitative. Differences between the grades are subjective and minor, with a certain level of inconsistency between individual evaluations.

Thirdly, the study has shown the importance of dysphagia as a symptom. Dysphagia appears to be the result of a combination of mucositis, xerostomia, and ageusia. It is important that the grade of dysphagia was reduced by selenium substitution at the end of radiotherapy, presenting a better final outcome for patients.

Through this study it can therefore be hypothesised that selenium substitution may be able to reduce typical radiation-associated toxicities in head and neck cancer, albeit with limited effects. Combinations with other scavengers such as amifostine should be investigated in future studies (9).

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