Selenium Substitution During Radiotherapy of Solid Tumours – Laboratory Data from Two Observation Studies in Gynaecological and Head and Neck Cancer Patients

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Abstract. Objective: Selenium is an essential cofactor of the enzyme glutathione peroxidase (GSH-Px), which is important for the endogenous detoxification of free radicals. A reduced activity of GSH-Px is related to increased toxicities due to radiation therapy during primary cancer treatment. Therefore, selenium substitution may be a new supportive strategy to diminish radiation-associated side effects. Patients and Methods: The selenium blood concentrations of 121 radiotherapy patients were measured in two randomized observation studies (81 gynaecological tumours, 40 head and neck tumours). Measurements (atom absorption spectrometry) were performed on serum and whole blood (WB) samples before, in the middle of, at the end, and 6 weeks after radiotherapy. In cases of decreased selenium levels in WB, 63 patients (mean age 63.83±9.23 a) received selenium substitution (500 μg sodium selenite at RT days, 300 μg at the weekend) and 64 patients (mean age 63.03±10.47 years) were evaluated as control group without any selenium substitution. Both groups were well balanced according to tumour localization and stage. Reference values were 85-162 μg/l WB-selenium, and 65-135 μg/l serum-selenium. Results: We measured the following WB selenium (Se) levels (Se-group vs. control group, U-test): begin RT 64.17±13.98 μg/l vs. 64.50±14.47 μg/l (p=0.869); mid RT 92.48±26.68 μg/l vs. 65.80±18.04 μg/l (p<0.001); end RT 93.78±25.90 μg/l vs. 64.06±17.54 μg/l (p<0.001); 6 weeks after RT 74.01±20.06 μg/l vs. 69.66±17.83 μg/l (p=0.183). The serum levels were as follows: begin RT 59.18±13.49 μg/l vs. 61.99±15.72 μg/l (p=0.427); mid RT 104.75±31.41 μg/l vs. 62.37±16.23 μg/l (p<0.001); end RT 100.63±31.12 μg/l vs. 62.29±16.11 μg/l (p<0.001); 6 weeks after RT 72.73±26.53 μg/l vs. 64.17±17.22 μg/l (p=0.170). Conclusion: The used dosage of 500 μg sodium selenite per day is sufficient to treat selenium deficiency during radiotherapy. After substitution, the patient returns to their individual selenium status.

Selenium is known as an essential cofactor for the activity of glutathione peroxidase (1), which is an important enzyme system for scavenging of free radicals in the human body. Oncologists and radiotherapists are particularly interested in the nutritional supplementations with selenium and other trace elements (2). The use of scavengers during radiotherapy has been commonly criticized because of possible interactions between reduced concentrations of free radicals and possible negative effects on anticancer treatment (3).

The German study group “Trace Elements and Electrolytes in Oncology” has initiated two observation trials investigating the effects of selenium substitution during irradiation of patients with gynaecological (4) or head and neck cancer (5). Both studies are the first international projects in this field. The clinical results have already been published in detail. The determination of sufficient selenium dose in supportive therapy was the aim of the present study.

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Patients and Methods

Data of two clinical trials were summarized in this work. Both observation trials received approval of the Independent Ethical Committee of Freiburg. The inclusion time of both studies was between 2000 and 2006. The study included patients suffering from gynaecological or head and neck cancer who were irradiated because of their disease. All patients had demonstrated decreased serum and blood concentrations of selenium.

Patients were divided into two groups. Group 1 received 500 μg sodium selenite on the days of radiotherapy, and 300 μg sodium selenite at the weekend. Sodium selenite was given perorally. Group 2 received no selenium or other cytoprotective agents. Patients of group 2 were the control subjects.

The selected doses are the result of former studies of our group. We had seen no accumulation due to 500 μg doses during radiotherapy (6).

We collected blood samples from all patients before the radiotherapy course, midway though radiotherapy (normally week 4), at the last day of radiotherapy and 6 weeks after the end of irradiation. The samples were sent to the Laboratory of Biosyn Fellbach. Serum concentrations and whole blood concentrations of selenium were measured by atom absorption spectrometry (AAS). The laboratory data were analysed by various statistical procedures as described in the results. The analyses were performed at the Institute of Medical Statistics of Rostock University.

Results

We tested the balance between both groups regarding the age (selenium versus controls). The equality of variances was tested by Levene’s test. The equality of means was tested by the t-test for independent samples (two-tailed).

The mean age was 63.83±9.229 years (Se group) versus 63.03±10.471 years (Control group). The resulting standard error was 1.163 vs. 1.309.

The distribution of selenium blood levels was performed by tests according to Kolmogorov-Smirnov (Lilliefors Significance correction) and Shapiro-Wilk (see Table III. Both tests show no normal distributions.

Figures 1 and 2 show the development of whole blood as well as serum selenium concentrations of both groups during the radiotherapy course and a 6-week follow-up interval.

The balance of tumour type was tested by Chi-square tests. Cross tabulation of Table II shows the distribution.
A stratification according to tumour localization showed no differences.

Discussion

Both trials have shown no impact on the survival or control rates of the treated groups. This first result demonstrates that selenium substitution does not influence the effectiveness of anti-cancer irradiation.

The gynaecological study has further demonstrated a reduced number and grade of diarrhoea due to radiotherapy, an important benefit for the patients. For the first time, selenium substitution was established as a therapeutic option in supportive care.

The head and neck study has only shown limited clinical effects due to selenium substitutions. A significant improvement was only seen in loss of taste as an early symptom of changes in the mouth. At the end of radiotherapy...
the parameter dysphagia was also reduced by selenium substitution. No changes were seen in mucositis or xerostomia. Both symptoms are the main toxicities due to irradiation of the head and neck area. Similar results were reported with the radical scavenger amifostine (7). The controlled studies were often limited by a lack of measurable parameters and the specifics of head and neck cancer patients. ENT cancer patients are often less compliant and the toxicities are difficult to estimate.

All together, both trials were able to show clinical effects regarding the toxicity of anticancer treatment. The used dose of 500 μg improved the blood concentration after 3 weeks. To obtain earlier effects, the used doses need to be increased or the selenium therapy needs to be started already 10-15 days before the first irradiation. Hence it would be possible to have reduced toxicities during the first part of radiotherapy.

The dose of 500 μg seems to be sufficient to obtain a steady state in selenium concentration in the blood. We have used sodium selenite orally for this project. Selenium seems to act immediately, but it is not possible to reach the selenium reserves of the human body (8). If patients are using organic selenium (yeast) during irradiation, we have no information of accumulation in the selenium reserves as yet. Hence the substitution with selenium yeast will need further studies investigating the question of dose in order to prevent toxic reactions due to selenium.

References