

Influence of the management of cervical carcinoma on the activity of catalase and glutathione peroxidase in erythrocytes

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Summary

Purpose of investigation: The aim of the study was to determine the effect of different types of management on the activity of catalase (CAT) and glutathione peroxidase (GPx) in women with cervical carcinoma. *Methods:* The patients were divided into three groups according to the mode of treatment. Patients from the first group were treated brachytherapy prior to surgery. The second group received teletherapy before brachytherapy and additionally chemotherapy. The third group was treated with teletherapy after brachytherapy sessions. *Results:* CAT activity was higher while GPx activity was lower before and during therapy in all groups as compared to controls. Six months after the end of therapy, the activity of studied enzymes reached the values characteristic of healthy women. No significant differences in enzyme activity among the three groups were revealed. *Conclusion:* Normalization of CAT and GPx activity may prove the efficacy of applied therapy in cervical cancer patients, however enzyme activity recovery was not dependent on treatment mode.

Key words: Catalase; Glutathione peroxidase; Cervical cancer; Radiotherapy.

Introduction

A great number of studies point to the existence of disturbances in the functioning of the antioxidant system in the course of cancer disease. The main research problem is to determine whether impairment in antioxidant defense mechanisms is involved in carcinogenesis or whether those disorders are only the results of the disease. Thus, interpretation of deleterious effects of reactive oxygen species (ROS) in cancer has to be analyzed not only as a function of the amount of ROS but also relative to the efficacy of the antioxidant system [1]. This system is mainly based on antioxidant enzyme activity, which include superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx).

Tumor control and patient morbidity might be improved with the understanding of the response of organisms to therapy [2]. Biochemical diagnostics of carcinomas are mainly based on detecting changes in the activity or concentration of different compounds of body fluids, which may occur in the course of disease or as a response to treatment. The results of such studies are widely used in clinical follow-up for anti-cancer therapy, but also in determination of patient response to the treatment or in evaluation of side-effects [3].

The curative treatment for cervical carcinoma usually consists of surgery or radiotherapy with chemotherapy

used in a neoadjuvant, concomitant or adjuvant fashion [4]. The effects of radiotherapy as well as chemotherapy are mediated by the action of ROS. Since the ROS concentration in cells is controlled by antioxidant enzymes, the antioxidant status is likely to be linked to therapy response. Hence, the determination of CAT and GPx activity in patients may be a useful parameter both in the follow up and in the treatment efficacy in relation to antioxidant status. The aim of this study was to determine whether the type of management influences the activity of CAT and GPx in patients with cervical carcinoma.

Patients and Methods

The study was conducted on women with carcinoma of the uterine cervix irradiated intracavitary by the Selectron LDR brachytherapy unit. Brachytherapy was performed twice with an interval of seven to ten days and the given dose was from 1500 cGy to 3000 cGy for reference point A. Additionally, all women were treated with different modalities according to clinical stage. Group 1 consisted of 45 patients with clinical Stage IB and IIA (an average age of 49). This group received neoadjuvant brachytherapy a month before the surgery. Group 2 involved 25 patients with clinical Stage IIIB and IV (an average age of 53). The patients from Group 2 received neoadjuvant brachytherapy the month before external teletherapy. The given doses were 4600 cGy (cobalt 60) for a period of four weeks in 23 sittings with each fraction being the order of 200 cGy or 5040 cGy (cobalt 60) for a period of five weeks in 28 fractions with each fraction being the order of 180 cGy. Patients from Group 2 also received chemotherapy (cisplatin and 5-fluorouracil) in five or six doses for a period of 21-24 days. Group

3 consisted of 16 patients with clinical Stage IIB and IIIB (an average age of 54) treated with brachytherapy and adjuvant external telecobalt therapy for periods of four to five weeks. The given doses were the same as in the second group.

Blood samples were obtained before brachytherapy, after two therapy sessions and about six months after the end of treatment. Controls were collected once from 37 healthy females (volunteers) without any known disease (average age 45).

The Beers and Sizer [5] method was used to determine CAT activity. This method is based on the measurement (at a wavelength of 240 nm) of absorbance decrease of hydrogen peroxide decomposed by catalase. GPx activity was assayed according to Paglia and Valentine [6]. This method is based on the measurement of absorbance changes at a wavelength of 340 nm, caused by oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is one of products of the reaction catalyzed by GPx. CAT activity was expressed as 10^4 IU/gHb and GPx as U/gHb.

All the data were statistically analyzed by means of a one-way ANOVA test. The level of $p < 0.05$ was considered as significant.

Results

CAT activity in patients with cervical cancer before the therapy and after two therapy sessions was statistically significantly higher than in control subjects (Table 1). After six months of follow-up CAT activity in Group 2 was still higher than in healthy women ($p < 0.01$), while in Groups 1 and 3 it decreased to the level observed in healthy subjects. In Group 1 after the end of therapy CAT activity was statistically significantly lower than after two therapy sessions and the other alterations were statistically insignificant. No statistically significant differences in CAT activity among patients from Groups 1, 2 or 3 treated with different modalities were found.

The GPx activity in cervical cancer patients from all three groups both before therapy and after two therapy sessions was statistically significantly lower than that in the control group (Table 1). In patients that had completed the treatment GPx activity increased significantly and there were no statistically significant differences in comparison to the control group. GPx activity was also found to be statistically insignificantly altered at different points of treatment. When comparing different treatment modalities there were no statistical differences in GPx activity among the patients from the three groups.

Discussion

In the present study higher activity of glutathione peroxidase with simultaneously lower catalase activity was revealed in the erythrocytes of women with uterine cervical carcinoma as compared to healthy subjects. Our results suggest that in cervical cancer patients there may be a greater burden for CAT than GPx in H_2O_2 removal. Both enzymes are involved in defense against oxidative damage caused by H_2O_2 , but GPx seems to be more effective at low H_2O_2 concentrations while CAT at high H_2O_2 concentrations [7]. As there is an enormous production of reactive oxygen species in the neoplastic tissue [8],

Table 1. — Catalase (CAT) and glutathione peroxidase (GPx) activity in erythrocytes of patients with cervical cancer treated with different types of therapy and the control group (values are given as means \pm SD).

Control group (healthy women)		Patients		
		Before treatment	After two therapy sessions	Six months after the end of therapy
		<i>CAT (10^4 IU/gHb)</i>		
51.3 ± 9.3	Group 1	169.4 ± 15.4^{aaa}	72.7 ± 19.9^{aaa}	57.4 ± 21.1^b
	Group 2	63.8 ± 21.3^{aa}	63.6 ± 14.5^{aaa}	62.5 ± 17.8^{aa}
	Group 3	70.8 ± 14.5^{aaa}	78.3 ± 20.2^{aaa}	56.0 ± 18.1
		<i>GPx (U/gHb)</i>		
14.7 ± 4.0	Group 1	10.7 ± 4.1^{aaa}	8.6 ± 2.6^{aaa}	14.8 ± 4.4
	Group 2	8.8 ± 3.3^{aaa}	11.9 ± 5.0^a	12.7 ± 3.5
	Group 3	10.4 ± 4.6^{aa}	10.8 ± 5.2^{aa}	13.0 ± 5.7

Group 1: brachytherapy prior to surgery; Group 2: teletherapy before brachytherapy + chemotherapy; Group 3: external beam radiation adjuvant to brachytherapy.

— statistically significant differences in comparison with the control group: $^a p < 0.05$, $^{aa} p < 0.01$, $^{aaa} p < 0.001$;

— statistically significant differences in comparison with patients after two therapy sessions: $^b p < 0.05$.

CAT is supposed to become more active in cancer patients. On the other hand, reactive oxygen species have been shown to inactivate GPx [9].

The literature shows highly variable data of radiotherapy effects on the antioxidant system in cancer patients. Significant decreases in the activity of antioxidant enzymes such as: SOD, CAT, GPx, or glutathione-S-transferase (GST) in blood of oral cancer patients in comparison to healthy subjects with further reduction after radiation treatment was demonstrated by Sabitha and Shyamaladevi [10]. The alterations in enzymatic activity after radiation treatment appear to be dependent on tissue, location, time of the control and dosage [11].

Some data show evidence for a relationship between elevated antioxidant enzymes levels and increased resistance to therapy [12]. Recent studies have pointed out that increased levels of glutathione (GSH) and GSH-related enzymes may be responsible for the resistance to radiation therapy and chemotherapy as well [13]. Depletion of cellular GSH sensitizes tumors to chemotherapy and radiation, but the usefulness of this depletion depends on whether the levels of GSH can be reduced in the tumor relative to normal tissue [14].

In the presented study no statistically significant changes in CAT and GPx activity were observed after two therapy sessions. However, GPx activity increased and CAT activity decreased in cervical cancer patients six months after the treatment was completed and reached values comparable to the healthy women, which is in conformation with earlier reports about effect of brachytherapy on antioxidants status and lipid peroxidation in patients with uterine cervix cancer [15]. Bhuvaramurthy *et al.* [16] observed differences in the activity of CAT, SOD and GPx as well as the level of lipid peroxidation products in serum and erythrocytes of women with uterine cervical carcinoma after different treatment modalities as compared to patients before therapy. The activities of antioxidant enzymes and the level of lipid peroxidation were brought back to normal in patients who received therapy.

Recovery of this enzyme activity may prove the treatment efficacy. The alleviation of symptoms and a curb on disease progression express the correct functioning of the majority elements of the antioxidant system.

Conclusion

In the present study no statistical differences in CAT and GPx activity were demonstrated between patients who received different types of therapy, which may testify to the fact that the mode of applied treatment has no effect on recovery of antioxidant enzyme activity in patients with carcinoma of the uterine cervix.

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