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Can previous thyroid scan induce cytogenetic radioadaptive response in patients treated by radioiodine for hyperthyroidism?

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ABSTRACT

Background: Induction of radioadaptive responses in cells pretreated with a low dose radiation before exposure to a high dose is well documented by many investigators. The aim of this study is to determine the frequency of chromosomal aberration in peripheral blood lymphocytes of patients treated by radioiodine (^{131}I) for hyperthyroidism, with or without previous thyroid scan with ^{99m}Tc.

Materials and Methods: Venous blood samples were obtained from 35 patients one month after radioiodine therapy and cytogenetically evaluated using analysis of metaphase in two groups. The first group (n = 15, 13 females and 2 males, mean age= 44.7 ±11.5 years and mean weight 74.4±7.9 Kg) received 5 mCi ^{99m}Tc for thyroid scanning 38.6±19.9 days before radioiodine therapy with 10.4 ± 3.4 mCi ^{131}I. The second group (n = 20, 14 females and 6 males, mean age = 41.0 ± 10.8 years and mean weight = 68.1±9.2 Kg) didn't have history of thyroid scanning. We also studied a control group (n = 29, 11 Females and 8 males, mean age = 33.7±7.4 and mean weight = 70.0±8.8 Kg) who didn't have any history of diagnostic or therapeutic and also occupational exposure.

Results: The mean frequency of total chromosomal aberrations in the first and second groups and controls were 1.46 ±1.55, 1.65 ± 1.62 and 0.93 ± 0.92 respectively. Results also showed that the mean frequency of total chromosome aberration in two groups were higher than controls and significantly higher in patients who had not received ^{99m}Tc compared those who had undertaken thyroid scan before radioiodine therapy (p=0.03).

Conclusion: These findings may indicate the fact that the radiation dose received from ^{99m}Tc could induce resistance to subsequent higher radiation dose of ^{131}I in peripheral blood lymphocytes and it might be due to cytogenetic radioadaptive response. *Iran. J. Radiat. Res., 2004; 2 (2): 69-74*

Keywords: *Radioadaptive response, thyroid scan, radioiodine therapy, chromosome aberrations.*

INTRODUCTION

There is no doubt that low doses of ionizing radiation (conditioning dose) can induce resistance to subsequent higher (challenge) exposures. This phenomenon is termed radioadaptive response, first reported by Olivieri *et al*. in 1984. Later, many scientists supported this hypothesis (Shadley and Wolff 1987, Wang *et al.* 1991) and described the probable involved mechanisms (Wiencke *et al*. 1986, Woloschak *et al.* 1990, Sasaki 1995, Fornance *et al.* 1988). Induction of cytogenetic radioadaptive response was shown by *in vitro* pre-exposing of human cells to radiation (Shadley and Wolff 1987, Wang *et al.* 1991) as well as *in vivo* studies (Tedeschi *et al.* 1995, Mozdarani and Saberi

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1994). A cytogenetic adaptive response study in human lymphocytes of hospital workers occupationally exposed to X and gamma rays has shown that chronic (occupational) exposure to radiation make hospital workers' lymphocytes less sensitive to higher doses (Barquinero *et al.* 1995). A similar study showed that lymphocytes of radiation workers, who have received occupational chronic exposure for occupational experiences of 2 to 25 years, were less sensitive to challenge exposures than non-occupationally exposed individuals (Gourabi and Mozdarani 1998). Another study revealed that children who received low doses of radiation after Chernobyl accident, had significantly lower chromosomal damage compared to non-exposed controls (Tedeschi 1996). In this study we compared the frequency of chromosomal aberration in peripheral blood lymphocytes of patients treated by radioiodine ^{131}I, with or without previous thyroid scan with ^{99m}Tc. We also intend to present more confirmation regarding to *in vivo* radioadaptive response in human lymphocytes following low doses of gamma radiation in nuclear medicine.

MATERIALS AND METHODS

Venous blood samples were drawn from 35 patients one month after radioiodine therapy into heparinized vacutainers and cytogenetically evaluated using analysis of metaphase in two groups. The first group (n = 15, 13 females and 2 males, mean age = 44.7 ± 11.5 years and mean weight 74.4 ± 7.9 Kg) received 5 mCi ^{99m}Tc for thyroid scanning 38.6±19.9 days before radioiodine therapy with 10.4 ± 3.4 mCi ^{131}I. The second group (n = 20, 14 female and 6 male, mean age= 41.0 ± 10.8 years and mean weight= 68.1 ± 9.2 Kg) didn't have history of thyroid scanning but treated with 11.1 ± 2.8 mCi ^{131}I. We also studied a control group (n = 29, 11 Female and 8 male, mean age= 33.7 ± 7.4 and mean weight= 70.0 ± 8.8 Kg) who didn't have any history of radiation diagnostic procedure for at least one month before sampling as well as therapeutic and occupational exposure. Every attempt was made to match samples from donors with controls in as many aspects as possible. The mean weight of the first and the second showed no statistically significant difference. The dose distribution of radionuclides is a function of body weight and standard radioisotope dosimetry tables used in this study were valid for typical adults (ICRP-80 1999). No medicines were taken by the donors for at least a month before sampling. Whole blood culture were prepared by adding 0.5 ml blood to 4.5 ml culture medium consisting of RPMI-1640 (Gibco BRL) supplemented with 0.2 mM L-glutamine, 15% fetal calf serum (Gibco BRL), 100 IU/ml penicillin and 100 µg/ml streptomycin. PHA (Gibco BRL) at a concentration of 5 µg/ml was used to stimulate division of lymphocytes in culture. Blood cultures were incubated at 37 °C for 48 hours and 2 hours prior to harvesting, colcemid (Gibco BRL) was added to cultures at a final concentration of 0.1µg/ml to arrest the dividing lymphocytes in mitosis. The cells were collected by centrifugation and treated with a hypotonic solution containing 0.075 M KCl, for 10 min to obtain good preservation of the cytoplasm. After centrifugation, lymphocytes were fixed in a 3:1 mixture of methanol:glacial acetic acid and then dropped onto cooled, clean slides and air dried. Slides were stained with 5% Giemsa (Merck). The culture technique is followed according to protocol recommended by International Atomic Energy Agency (IAEA 1986). One hundred mitoses were analysed for each sample and chromosomal aberrations were scored. Statistical analysis was done by student's *t-test.*

RESULTS

The percentage of the total chromosomal aberrations (CA%) in control non-exposed individuals (patients) who received 5 mCi ^{99m}Tc for thyroid scanning, and those who didn't have any history of thyroid scanning before radioiodine therapy are shown in table 1.

Although we didn't calculate the effective dose for each patient, literature indicates that it is about 1.95 mSv for patients who receive 99mTc for thyroid scan (NCRP 1988). Because

Table 1. The percentage of total chromosomal aberration of lymphocytes in non-exposed controls, patients who received ^{99m}Tc for thyroid scanning and those who didn't have any history of thyroid scanning before radioiodine therapy.

Treatment	Number of cases	No. Metaphases analysed	Frequency of chromosomal aberrations				Total aberrations%
			Iso-Gap	Deletion	Dicentrics	Rings	
Tc-99m + I	15	1500	9	6	6	1	1.46 ± 1.55
I-131	20	2000	17	11	3	2	1.65 ± 1.62
Control	29	2900	21	4	2	0	0.93 ± 0.92

the effective dose is not a relevant quantity for therapeutic doses of radionuclides, there is no effective dose data regarding ^{131}I in treatment of hyperthyroidism (ICRP-80 1999). Cytogenetic assessment is a very good and reliable method for measuring whole body dose in research and even in clinical applications such as radiation therapy (Durante *et al.* 1999). Figure 1 shows the frequency of various types of chromosomal aberrations.

DISCUSSION

Results showed that the mean frequency of total chromosome aberration in two groups were higher than the controls. This finding might be due to the fact that the mean age of control group is less than the two other irradiated groups (Norman 1984). However, some reports indicate no clear correlation between the frequency of chromosome aberrations and age in the occupationally exposed individuals (Jha and Sharma 1991, Monfared *et al.* 2003). Results also showed that the frequency of total chromosome aberration was significantly higher in patients who had not received ^{99m}Tc compared with the ones who had undertaken thyroid scan before radioiodine therapy (p=0.03). Considering that ^{99m}Tc at diagnostic doses could not produce chromosome aberration (Jacquet *et al.* 1999), this finding may indicate that the radiation dose delivered from ^{99m}Tc could induce resistance to subsequent higher radiation dose of ^{131}I in peripheral blood lymphocytes; this might be due to cytogenetic radio-adaptive response. The effective dose received by patients due to thyroid scan with ^{99m}Tc is low but it is still in the range of conditioning doses which are believed to be sufficient for induction of radioadaptive response (1-100 mGy Gamma rays) (Bonner 2003). This amount of radiation dose is nearly in the same range for routine X-ray studies but in

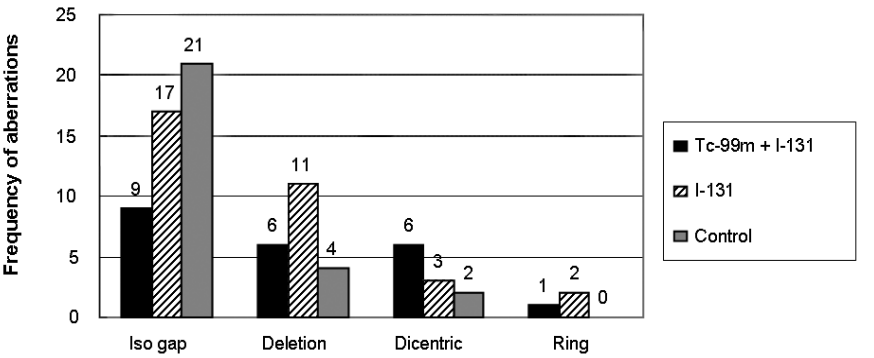

Figure 1. The frequency of various types of chromosomal aberration in non-exposed controls, patients who received ^{99m}Tc for thyroid scanning and those who didn't have any history of thyroid scanning before radioiodine therapy.

different dose delivery conditions, such as total/ partial body exposure and dose rate. The condition of receiving adapting dose is an important factor that affects induction of chromosome aberrations (Lorenz *et al.* 1993), as well as radioadaptive response (Monfared *et al.* 2003). The induction of adaptive response by whole body low dose radiation is well documented by *in vitro* as well as *in vivo* studies (Ikushima 1999, Yu *et al.* 1995, Makedonov 1997, Sasaki 1996). In the present study, adapting and challenge dose were applied *in vivo*. The time interval between them (38.6±19.9 days) had a wide range and also, depended on the prescription time of referral endocrinologist and nuclear medicine physician for thyroid scan and radioiodine therapy. Depending on the different condition of applying adaptive and challenge dose, various reports indicate the minimum requirement from 6 hours interval for full expression of a radioadaptive response (Shadley and Wolff 1987), to 7-days when adapting dose applied by radioiodine (Monsieurs 2000) and even about a 10 year period, for children, who showed ^{137}Cs contamination due to persistent continuous exposure to low doses of ionizing radiation (Tedeschi 1996). Regarding to long interval in the present study, another statistical analysis was carried out by splitting the data of patients who received Technetium and Iodine on the basis of time interval (more or less than 15 days). Although the outcome was nearly the same considering the fact that pre-irradiated cells with low dose could keep this memory for a limited time, to investigate the reproducibility of this unusual finding, further experiments are needed to be carried out. The average effective half life of ^{131}I is about 177 hours. (Maxon and Saenger 2000). It roughly depends on the level of hyperthyroidism. The higher the level of thyroid hormones the lower the effective half life (Links 2000). As the patients were not included on the basis of thyroid hormones' level in this study to make sure that the level of ^{131}I releasing into the blood by thyroid hormones is too low to play an important role as a confounding factor. Samples were collected 30 days (4 effective half life-remaining activity about 10%) after radioiodine therapy. Obviously, waiting such a long period of time, could lead to decrease unstable chromosome aberrations like dicentrics, as it is shown in figure 1. Hence, we compared the total chromosome aberrations between groups. The dicentrics are well known as the most reliable biomarkers. However, adaptive response is reported by showing the decreased sensitivity to the cytogenetic effects of bleomycin in individuals exposed to ionizing radiation using the frequencies of chromatid breaks as well as gaps (Barquinero *et al.* 1996). It is also shown that stable chromosome aberration frequency are solely useful for population-based risk assessment (Cologne *et al.* 1988). The possible mechanism of radioadaptive response might be the induction of initial DNA damage in these cells leading to sufficient induction of an active DNA repair mechanism (Joiner 1994) but other different mechanisms may be involved (Park *et al.* 2000, Zhou and Rigaud 2001, Shimizu *et al.* 1999). Similar to some other studies the mean frequency of total chromosomal aberrations in all the three groups had nearly wide standard deviations (Balasem *et al.* 1992, Wang *et al.* 1991). Thus, we suppose that it could be due to the existence of significant inter-individual variations (Huber *et al.* 1992) that can be related to systematic inter-individual differences in radiosensitivity (Almassy *et al.* 1987). Considering these uncertainties, further investigations are necessary.

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