

Polyamines as biochemical indicators of radiation injury

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Abstract

The search for parameters of different nature to quantify radiation damage is carrying on from many years in humans and lab animals. The polyamines (spermidine and spermine) are ubiquitous polycations with many metabolic functions and can be easily assayed by HPLC method. Their involvement in cell proliferation has been evidenced in healthy and tumour tissues. Statistically significant reductions have been demonstrated in tissues and in red blood cells (RBC), in animals and in patients treated by total body irradiation (TBI) before bone marrow transplantation (BMT). In rats submitted to TBI with 3 Gy of gamma radiations, tissue polyamines significantly decrease during the early phase of the injury in tissues with high proliferative activity (small intestine, spleen) whereas do not show any modification in kidney. When recovery takes place, the polyamines significantly increase and return to control levels when a normal morphology is restored.

In patients submitted to radiation therapy, polyamines have been determined in urine and in RBC of patients with carcinoma of uterine cervix, head and neck and prostate, treated by external radiotherapy, and with thyroid cancer treated with iodine-131 therapy.

The most interesting results has been obtained with RBC: in patients treated on the pelvis for prostate cancer a significant reduction during radiotherapy occurs, followed by the maintenance of low levels in patients with favourable outcome. It should be noted that polyamine levels before treatment appeared significantly higher than in healthy controls. After TBI the RBC polyamines show a dramatic fall to extremely low levels during the phase of marrow aplasia. The values show an increase corresponding to the engraftment of transplanted cells and to the following marrow repopulation. These evidences make the RBC polyamines very interesting parameters to monitor the radiation effects on humans.

KEYWORDS: Polyamines, TBI, BMT, prostate cancer.

1. Introduction

Polyamines (spermidine and spermine) are ubiquitous polycations involved in the stabilization of DNA strands and essential for cell proliferation and differentiation [1, 2].

Previous studies on healthy and neoplastic tissues demonstrate the capability of polyamines, mostly spermidine and spermidine/spermine ratio, to represent the level of proliferative activity [3-7].

1.1. Irradiation of animal tissues

To evaluate the relationship between these molecules and the radiation damage, female Wistar rats were whole body irradiated with 3 Gy of γ rays from ^{60}Co , and the modifications of tissue polyamines were compared with the uptake of ^3H thymidine, injected 1 hour before killing. From tissues or erythrocytes, the cytosolic polyamines were assayed as dansyl-derivatives by HPLC method (C-18 column and gradient elution with water:methanol).

In high proliferating tissues (small intestine and spleen) a statistically significant decrease of these molecules within few hours after irradiation well demonstrates cell loss and block of proliferation. The repopulation phase corresponds to a significant increase of polyamines, mostly spermidine. Moreover, the results demonstrate that the levels and the time when modifications appear to depend on the proliferation level and turnover time of the tissues [8, 9].

In the kidney of the same animals, where this dose did not show early injury, polyamine levels remain similar to controls during the postirradiation time.

1.2. Prostate cancer

In patients submitted to radiotherapy for cancer, polyamines were assayed in red blood cells (RBC), where the molecules are concentrated. Studies on patients with prostate cancer (B₂ stage) treated with X rays (25 MV photons, 2 Gy \times 5 days/week up to 70 Gy) confirmed the statistical significant decrease during the acute injury, corresponding to the first week of treatment, and the gradual increase when repopulation takes place.

The baseline value of polyamines in these patients was significantly higher than normal and in cases without presentation of relapse and metastasis, low levels of polyamines are maintained during follow up [10, 11].

1.3. Bone marrow transplantation (BMT)

A group of 124 patients with leukemia or lymphoma is submitted to the pre-BMT conditioning with radio-chemo regimen (45) or chemotherapy alone (79). TBI was administered by 11 fractions of 1.2 Gy in 4 days. The BMT was performed with autologous or allogeneic cells, or by staminoapheresis.

RBC polyamines decrease to very low levels during both conditioning regimens, cause of the extensive injury produced by supralethal doses given to the whole body. It is worth noting that the treatment with ionising radiation and chemotherapy produces an early and more severe reduction of polyamines than the chemotherapy alone.

The inversion of the negative trend represent a very rapid signal of engraftment, earlier than by means of white blood cells counts. The following rapid increase indicate the intensive proliferation during bone marrow repopulation [12-14]

The polyamine trends can point out the differences existing between allogeneic and autologous BMT, as well as after transplantation by apheresis.

2. Conclusions

The results obtained by the different experimental models demonstrate the ability of polyamines to monitor both cell death during the acute radiation damage, and the following repopulation of highly proliferative tissues.

The usefulness of the determination of polyamines in the monitoring the effects of cytotoxic agents in humans is well documented, being able to describe all phases of tissue response by means of blood sample and a quite simple determination.

At present some studies are in progress to analyze the sensitivity of RBC polyamines to recognize the effects of lower doses of ionising radiation.

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