Nitric Oxide Synthases Inhibitor T1023

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A nitric oxide synthase (NOS) inhibitor, compound T1023 induce transient hypoxia and prevent acute radiation syndrome (ARS) in mice. Significant efficacy and safety in radioprotective doses (1/5–1/4 LD10) can prove its ability to prevent complications of tumor radiation therapy (RT).

Keywords: nitric oxide synthase inhibitor ; radiotherapy ; radiation-induced tissue toxicity

1.introduction

The frequency of cancer incidence is steadily increasing in almost all countries of the world. Over 3 million patients are currently registered with cancer in the Russian Federa-tion [1]. About 50–70% of them receive different types of radiation therapy (RT) that re-mains one of the most effective tools in cancer therapy. The ongoing efforts towards de-signing new radiation treatment techniques are aimed to improve the quality of life of cancer patients and to minimize the toxicity of radiotherapy. Dose fractionation and con-formal radiation techniques along with molecular targeted therapy have improved the preservation of normal cells/tissues during radiation treatment[2]. But despite such efforts patients in 10–15% of cases (and in some locales tumors—up to 40%) are faced with the complications arising from radiation damage to normal tissues [3][4][5]. Such complications are able to limit the possibility of cancer therapy in full. Moreover, some pathologies, espe-cially late radiation injuries, which are based on the processes of fibrogenesis, are difficult to cure with conservative therapy[6][7]. In some cases, they can become threatening, capa-ble of lead to failure of internal organs and death[8][9]. It is obvious that minimizing such RT risks requires versatile efforts aimed at both further improving medical radiological techniques, methods of planning radiation exposure, and, on the other hand, developing new approaches to pharmacological prevention and treatment of radiation injuries[10][11][12].

The NOS inhibitor 1-isobutanoyl-2-isopropylisothiourea hydrobromide (compound T1023) is high-ly effective (dose modifying factor (DMF)—1.6–1.9) in the prevention of H-ARS and G-ARS in mice [18]. The data on the T1023 significant radioprotective activity and the relative safety of its effective dose (1/5–1/4 LD10) become the reason for studying its ability to pro-tect normal somatic tissues in models of acute radiation damage to the skin, as well as its radiation modifying effects in RT models.

2.Medical uses

The problem of developing pharmacological agents for the prevention and treatment of RT toxic effects have currently attracted considerable attention. The objects of research and development in this area are an extremely wide range of synthetic and biotechnolog-ical compounds with various types of biochemical and pathophysiological activity: the ability to limit the formation of primary radiation damage, modulate the processes of cell death, the activity of post-radiation repair, the course of immune-inflammatory processes and fibrogenesis [13][14][15].

The ability of ‘direct’ radioprotectors (that are effective during the physical and phys-icochemical stages of injury) to limit the development of radiation toxic effects seems to be quite natural, since primary molecular damage is the pathophysiological basis of such pathologies. This is confirmed by the presence of such abilities in aminothiol radioprotec-tors [16][17], adrenergic and serotonergic hypoxic radioprotectors[18][19][20], antioxidants[21] and inhibitors of radiolysis products [32,33]. NOS inhibitors may complement the list of such agents.

The prophylactic effect of T1023 against ARS (DMF—1.6–1.9) develops according to physiological mechanisms that are characteristic, among others, for the agonists of α1B-adrenoreceptors and serotonin 5-HT2-receptors[22][23]. Rapid and pronounced vas-oconstriction causes reflex changes in cardiac activity (decrease in strength and frequency of contractions) that limit systemic blood flow (for T1023: cardiac output is reduced by 40–50% within 90–120 min). The resulting transient hypoxia promotes to limit alteration un-der radiation exposure[24][25].

Considering such a mechanism of radioprotective activity, it is quite natural that T1023 is also capable of reducing the toxic effects of γ-radiation in normal tissues. The prophylactic use of T1023 in the optimal radioprotective dose (75 mg/kg; 1/4 LD10) leads to effective (DMF—1.4–1.7) and pronounced limitation of the development of radiation damage to the skin and underlying tissues in mice and rats. The histological data confirmed that these effects of T1023 developed due to a decrease in radiation alteration of normal tissues and the preservation of the functional activity of cell populations that are critical in the development of radiation burn.

Means of prevention of RT complications, acceptable for clinical use, must be protec-tive for normal tissues, it must not defense tumor cells and weaken the antitumor efficacy of radiation exposure. For example, the clinical radioprotector amifostine has such ability. The selectivity of its effects is associated with the accumulation of its active metabolite WR-1065, mainly in normal tissues, due to hypovascularization of solid tumors and low expression of alkaline phosphatase in tumor cells.

Researches on RT models of different solid tumors (ectodermal ESC in mice and mesodermal M1S in rats) showed that T1023 also fully implements the selective radioprotective effect. T1023 significantly limited the severity of RSR in normal animal tissues with all variants of RT (single or hypofractionated γ-ray LI). However, mani-festations of the radioprotective effect of T1023 in the malignant tissues of M1S and ESC have not been proved. T1023 and amifostine can offer equally effective selective protection for normal tissues. It is important to empha-size that T1023 was used in rather less toxic dose than amifostine.

3.Mechanism

There is no experimental data that directly reflect the mechanism of the selec-tivity of T1023 radioprotective effect. However, as with amifostine, the selectivity of T1023 appears to be due to the pathophysi-ology of solid tumors. It is known that atypical angioarchitecture and functional insuffi-ciency of the vascular network of such neoplasias determine the presence of chronic in-tratumoral hypoxia in their tissues[26][28][27]. According to clinical studies in solid human tumors, about 34% of cells are in deep chronic hypoxia ($pO2 < 5$ mm Hg), regardless of histogenesis and stage of the process, which halves their radiosensitivity. In contrast, in normal tissues such fraction does not exceed 0.5% [36,37]. Under these conditions, T1023-induced transient hypoxia significantly alters the level of oxygenation and radio-sensitivity of normal tissues. This provides prevention of ARS for γ-ray total body irradia-tion and toxic effects for γ-ray LI. However, in tissues of solid tumors, the scale of modifi-cation of oxygenation and radiosensitivity can be significantly limited by the initial intra-tumoral hypoxia and the initial radioresistance of neoplasia. In addition, the T1023 selec-tivity can also be facilitated by functional insufficiency of tumor vasculature, which, among other things, manifests in a weak, unstable and, often, paradoxical reaction of ves-sels and tumor blood flow to the action of vasopressors and vasodilators.

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