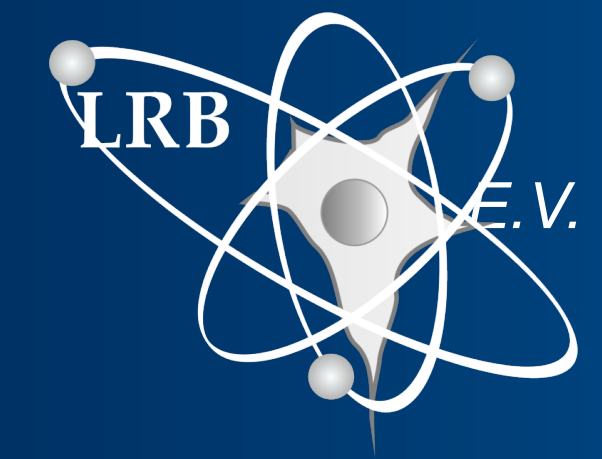
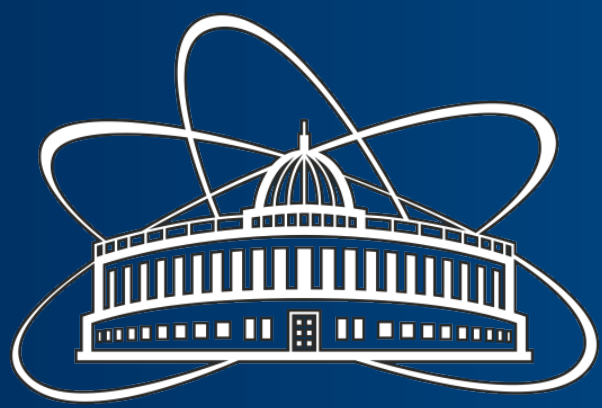




LONG-TERM EFFECTS IN IMMUNOCOMPETENT ORGANS DURING SIMULATION OF RADIOCHEMOTHERAPY IN MATURE RATS



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Relevancy

This work is part of a larger JINR LRB study on the simulation of radiochemotherapy in mature rats. The use of cytosine arabinoside as a promising medication in combination with proton irradiation requires the study of many of its radiobiological effects.

Goal

The aim of the work was to study the effect of the combined use of protons at a dose of 3 Gy and AraC on the physiological parameters of immunocompetent organs on the 90th day.

Materials and methods



Fig. 1. AraC administration



Fig. 2. Commercial form of AraC medication, lyophilisate for injection

- Animals.** Sprague Dawley rats, 8 weeks old, randomized by body weight into 4 groups:
 - 1) control
 - 2) irradiated animals group
 - 3) animals only with the administration of AraC medication
 - 4) irradiated animals with the administration of AraC medication
- Irradiation.** At The Phazotron facility at JINR, the animals were irradiated totally with protons in the cranio-caudal direction at a dose of 3 Gy with an energy of 170 MeV, the dose rate was 0.8 Gy/min.
- Measurement of body weight and immunocompetent organs.**
- White blood cell count (WBC) and leukogram** was carried out by standard cytological methods.
- Statistical analysis.** Statistical processing of the obtained results was carried out in the PAST and OriginPro 2018 programs.



Figure. 3 Irradiation of a rat at the Phasotron JINR

The results of measuring the mass of immunocompetent organs

Group	Average body weight	Average thymus weight	Average spleen weight	Average WBC count
Control	447±10	0,46±0,03	0,90±0,03	11,4±0,1
AraC	440±13	0,43±0,03	0,81±0,04	17,1±1,0 **
Protons 3 Gy	433±15	0,33±0,04	0,78±0,06	10,8±0,6
Protons 3 Gy + AraC	422±7	0,28±0,02 *	0,85±0,02	9,9±0,3

* - statistically significant differences (Mann-Whitney test, $p \leq 0.05$ in relation to the control group and the AraC group)

** - statistically significant differences (Mann-Whitney test, $p \leq 0.05$ for all groups)



Fig. 4. Radiochromic film for exposure control

Blood test results

Group	% of neutrophils	% of monocytes	% of lymphocytes	% of eosinophils
Control	8,8±1,6	1,3±0,8	89,8±1,9	0
AraC	8,4±1,7	1,2±0,4	90,4±1,8	0
Protons 3 Gy	12,6±1,5	1,0±0,6	85,2±1,6	1,0±0,4
Protons 3 Gy + AraC	14,3±4,4	0,3±0,2	83,8±4,4	0,7±0,5

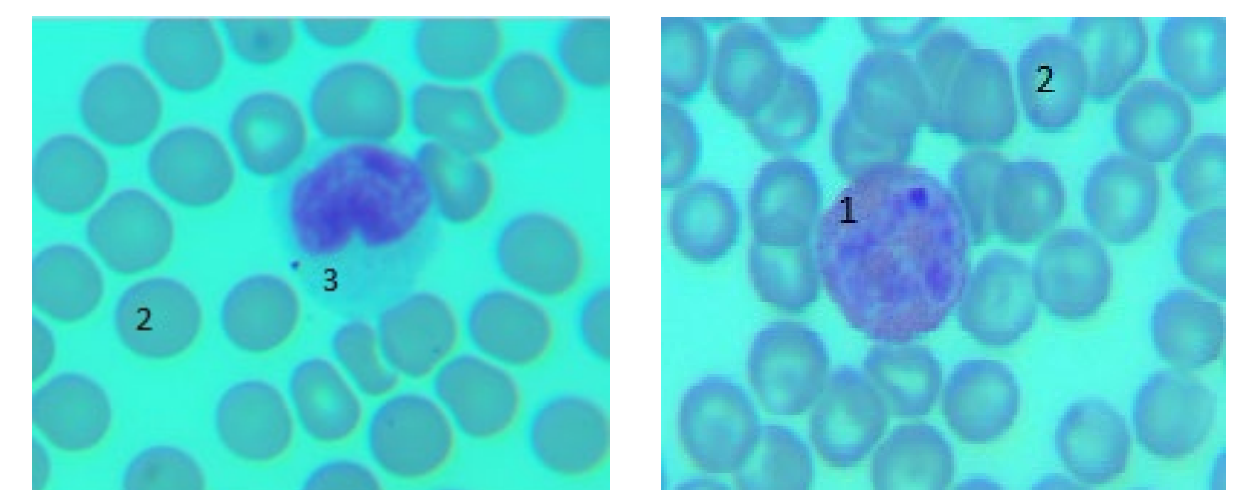


Fig. 5. Blood smear. Members of leukocyte (1,3) and erythrocyte (2) hematopoietic germ. 1- eosinophil 2 – erythrocyte 3 - monocyte

Conclusion

1. A comparative analysis of the number of leukocytes revealed a significant difference in the AraC group (tables 1, 2), however, the average values in all groups are included in the reference interval for rats of this line of this age, and a cytological examination of all blood smears did not reveal any abnormalities from the clinical norms, nor changes in the leukogram.
2. A comparative analysis of the thymus mass showed a significant decrease in this indicator in the “Protons + AraC” group, which is the expected effect with total irradiation.
3. The data obtained did not reveal functionally significant differences in the side effects of proton therapy when it was modified with cytosine arabinoside, since all significant changes correspond either to the physiological norm of rats (p. 1) or the expected effects of total irradiation (p. 2).

The results of the study on normal tissues indicate that the use of cytosine arabinoside in combination with proton irradiation does not lead to significant side effects in the long term, therefore, it can become a promising method of therapy. Further studies in tumor models are needed to determine efficacy and the presence of unrecognized side effects.