EFFICIENCY OF STROMAL VASCULAR FRACTIONS OF ADIPOSE TISSUE

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ЭФФЕКТИВНОСТЬ СТРОМАЛЬНЫХ СОСУДИСТЫХ ФРАКЦИЙ ЖИРОВОЙ ТКАНИ

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Currently, radiation injuries of the skin and underlying tissues is the most frequently occurring consequence of human contact with the source of ionizing radiation. The difficulties of treatment of radiation injuries are caused by personal characteristics of patients a cascade of pathological changes in tissues, therefore surgical and medication therapy does not always allow to achieve the expected positive effects. The target of the search was to improve the effectiveness of using of SVF for the treatment of long-term non-healing radiation ulcers in the early and late periods after irradiation. Improvement of efficiency after the cell transplantation was assessed using planimetric methods of investigation. The results, which was obtained, that the use of SVF to restore the skin in severe radiation injuries has a pronounced therapeutic effect regardless of the time of initiation of treatment after irradiation.

Key words: radiation injuries, stromal vascular fraction, multipotent mesenchymal stromal cells

Introduction. Currently, local radiation injuries of skin and underlying tissues are the most frequently occurring consequences of a human contact with an ionizing radiation source [4]. Most cases of radiation injuries result from the X-ray therapy of tumors and non-tumor diseases [5]. However, this treatment method has significant side effects along with positive results of application. For example, after radiation therapy 41 % of patients have radiation injuries of skin and underlying tissues, in 3,5 % of clinical cases these injuries lead to long-term non-healing radiation ulcers (RU) [6].

The RU are hard to treat due to disorders in metabolic and proliferative processes in tissues, pathological changes of microcirculatory boodstream's condition in a damaged area [7,8]. The main method for treating late radiation injuries and severe and very severe injuries is a surgery, including necrectomy along with non-surgical measures. However, this method is not efficient enough, as it allows to achieve complete healing only among 21 % of patients [9].

Clinical studies of using autologous bone marrow MMSC in the therapy of patients with RU revealed positive results [10]. Still, despite positive results, this method has a number of flaws: painful and complicated procedure of bone marrow sampling and a mandatory long period of cell culture. Now that cell technologies get developed, adipose-derived minimum manipulated autologous cell products (stromal vascular fractions SVF in particular) gain popularity [11].

Article goal. The goal is to assess efficiency of using SVF in regeneration of skin after deep radiation injuries in early and late periods after irradiation.

Materials and methods. We used a test model of non-healing severe RUs [12] to conduct the experiment.

Sampling of a stromal vascular fraction. We sampled biomaterial from the animal that later on we injected with cell products. To reduce stress and pain, we used intravenous anesthesia to sample biomaterial from animals. We sampled subcutaneous adipose tissue by method of syringe liposuction in abdominal and inguinal areas. Sampling of a stromal vascular fraction was done in accordance with standard protocol for enzymatic treatment of adipose tissue.

Cell products. In order to assess efficiency of different cell products and clarify mechanism of their action, we conducted therapy of severe local radiation injuries on the 21st day after irradiation – in the beginning of ulcer formation and on the 160th day – chronic 4-month non-healing ulcers.

Statistical data processing. We applied planimetric methods to assess changes. We processed statistical data with IBM SPSS Statistics 19 statistical package.

Results. *Morphofunctional changes of skin tissues after local irradiation of 110 Gy dose.* Skin radiation injuries of rats after 110 Gy

irradiation are developed similarly to clinical picture of a human pathological process in severe cases. The latent period, when skin injury was not visually detected, lasted 7–9 days. After that, we observed hyperemia and a disrupted normal skin tone. In 12–13 after irradiation, rats were observed to have dry dermatitis. By 14–16 days dry dermatitis became moist dermatitis. Major processes during this period are epithelial desquamation, leukocytic infiltration of dead and dying tissues, destruction of collagenous framework of derm. In 17–25 days after irradiation, we observed formation of ulcers on skin of 60 % of rats. In 29–36 days ulcers were completely formed, after that we observed progression of necrotic process.

Treatment of radiation injuries in certain periods after irradiation. 40 animals were irradiated during preparation for the experiment. By 160th day after irradiation (the first day of injection of cell products), only 36 rats survived, 4 of them had their ulcers completely healed by the 50th day. The treatment was carried once on the 160th day after irradiation.

Planimetry results revealed that by 14th day after SVF injection, the damaged area diminished by 50 %, compared to initial size, and made 1,36 ± 0,63 cm^2. By the end of observation, dynamics in healing of radiation injuries remained stable in test groups and ulcer areas diminished up to 33 % (0,87 ± 0,47 cm^2) by the 34th day of observation. We presented results for key points, having chosen the moment of cell products' injection as a zero point.

Treatment of radiation injuries in early periods after irradiation. The treatment of RU was carried once on the 21st day after irradiation. In the test group we noticed active recovery in defected area. By the end of observation, animals revealed no inclination for worsening course, they had no wound suppuration and no inflammatory response, atrophic scars began to form in areas of radiation injuries. In control group, we noted remaining considerably sized injuries, as well as signs of inflammatory response and suppurating wounds during the whole observation period.

Planimetry results revealed that by the 5th day after SVF injection, there was an insignificant positive effect, and on the 13th day (32th day after irradiation) there were more distinctive differences: the damaged area was reduced up to 1,6 ± 0,6 cm^2. By the 62nd day of the therapy, results reached statistical significance, the defect area was reduced up to 0,83 ± 0,3 cm^2. By the final period of observation, epithelial integrity was not fully recovered, still, there was no ulcer defect of tissues and this local area was filled with granulation tissue.

Conclusions. The obtained results indicate that application of SVF for skin regeneration after severe RU has a positive therapeutic effect regardless of the period of treatment beginning after irradiation.

СПИСОК ЛИТЕРАТУРЫ:

1. Yakovlev M.Y., Fesyun A.D., Datiy A.V. Analysis of the main manifestations of meteopathic reactions of patients // Bulletin of restorative medicine. 2019. № 1. P. 93–94.
2. Parfenov A.A., Datiy A.V., Makarova E.V., Marchenkova L.A., Zaborova V.A. Main types of medical clays of Tambov region // Bulletin of restorative medicine. 2019. № 3.
3. Dubovskoy a.v., Gilmutdinova I.R., Gumenyuk S.A., Fesyun O.A. Use of natural therapeutic factors // Bulletin of restorative medicine. 2019. № 3.
4. Soloviev V.Y., Bushmanov A.Y., Barabanova A.V. at al. Analysis of professional affiliation of victims in radiation incidents in the territory of the former USSR. Medical-biological and socio-psychological problems of security in emergency situations. 2011. №1. P.5–9.
5. Kotenko K.V., Eremin, I.I., Moroz, B.B., at al. Cellular technologies in the treatment of radiation burns: the experience of the FMBC A.I. Burnazyana // Cell Transplantation and Tissue Engineering. 2012. T.VII. №2. P. 97–102.
6. Stuart F.A. The ICRP report on tissue reactions, early and late effects in normal tissues and organs – threshold doses for tissue reactions in the context of radiation protection. Chelyabinsk: Publishing House Book. 2012. Study Guide.
7. Albrecht H. Durbin-Johnson B., Yunis R. et al. Transcriptional response of ex vivo human skin to ionizing radiation: comparison between low- and high-dose effects // Radiat. Res. 2012. T.177. №1. P.69–83.
8. Fan M. Ahmed K.M., Coleman M.C., Spitz D.R., Li J.J. Nuclear factor-kappa B and manganese superoxide dismutase mediate adaptive radioresistance in low-dose irradiated mouse skin epithelial cells // Cancer Res. 2007. T.67. №7. P.3220–3228.
9. Galstyan I.A., Nadezhina N.M., Barabanov A.V., at al. Diagnostics, treatment of local radiation injuries and their long-term consequences // Federal Clinical Recommendations. 2015. Approved Deputy Hands FMBA of Russia E.Yu. Khavkina, FKR FMBA Russia 2.6.7. P.39
10. Eremin I.I., Zhgutov Y.A., Kotenko K.V. at al. The method of complex treatment of burn wounds of various etiologies using autologous mesenchymal stem cells. Bulletin of aesthetic medicine. 2011; 10 (4): 36–41.
11. Forcheron F., Agay D., Scherthan H. et al. Autologous adipocyte derived stem cells favour healing in a minipig model of cutaneous radiation syndrome. PLoS One. 2012; 7(2): e31694
12. Kotenko K.V., Moroz B.B., Nasonova T.A., Dobrynina O.A., Lipengolts A.A., Gimadova T.I., Desheva Yu.B., Lebedev V.G., Lyrschikova AV, Eremin II. Experimental model of severe local radiation lesions of the skin after the action of x-rays. Pathological physiology and experimental therapy. 2013; 4: 121–123.

REFERENCES:

1. Yakovlev M.Y., Fesyun A.D., Datiy A.V. Analysis of the main manifestations of meteopathic reactions of patients // Bulletin of restorative medicine. 2019. № 1. P. 93–94.
2. Parfenov A.A., Datiy A.V., Makarova E.V., Marchenkova L.A., Zaborova V.A. Main types of medical clays of Tambov region // Bulletin of restorative medicine. 2019. № 3.
3. Dubovskoy a.v., Gilmutdinova I.R., Gumenyuk S.A., Fesyun O.A. Use of natural therapeutic factors // Bulletin of restorative medicine. 2019. № 3.
4. Soloviev V.Y., Bushmanov A.Y., Barabanova A.V. at al. Analysis of professional affiliation of victims in radiation incidents in the territory of the former USSR. Medical-biological and socio-psychological problems of security in emergency situations. 2011. №1. P.5–9.
5. Kotenko K.V., Eremin, I.I., Moroz, B.B., at al. Cellular technologies in the treatment of radiation burns: the experience of the FMBC A.I. Burnazyana // Cell Transplantation and Tissue Engineering. 2012. T.VII. №2. P. 97–102.
6. Stuart F.A. The ICRP report on tissue reactions, early and late effects in normal tissues and organs – threshold doses for tissue reactions in the context of radiation protection. Chelyabinsk: Publishing House Book. 2012. Study Guide.
7. Albrecht H. Durbin-Johnson B., Yunis R. et al. Transcriptional response of ex vivo human skin to ionizing radiation: comparison between low- and high-dose effects // Radiat. Res. 2012. T.177. №1. P.69–83.
8. Fan M. Ahmed K.M., Coleman M.C., Spitz D.R., Li J.J. Nuclear factor-kappa B and manganese superoxide dismutase mediate adaptive radioresistance in low-dose irradiated mouse skin epithelial cells // Cancer Res. 2007. T.67. №7. P.3220–3228.

9. Galstyan I.A., Nadezhina N.M., Barabanov A.V., at al. Diagnostics, treatment of local radiation injuries and their long-term consequences // Federal Clinical Recommendations. 2015. Approved Deputy Hands FMBA of Russia E.Yu. Khavkina, FKR FMBA Russia 2.6.7. P.39
10. Eremin I.I., Zhgutov Y.A., Kotenko K.V. at al. The method of complex treatment of burn wounds of various etiologies using autologous mesenchymal stem cells. Bulletin of aesthetic medicine. 2011; 10 (4): 36–41.
11. Forcheron F., Agay D., Scherthan H. et al. Autologous adipocyte derived stem cells favour healing in a minipig model of cutaneous radiation syndrome. PLoS One. 2012; 7(2): e31694
12. Kotenko K.V., Moroz B.B., Nasonova T.A., Dobrynina O.A., Lipengolts A.A., Gimadova T.I., Desheva Yu.B., Lebedev V.G., Lyrschikova AV, Eremin II. Experimental model of severe local radiation lesions of the skin after the action of x-rays. Pathological physiology and experimental therapy. 2013; 4: 121–123.

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