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APPLICATION OF REGENERATIVE CELL TECHNOLOGIES IN THE TREATMENT OF SEVERE LOCAL RADIATION INJURIES IN VICTIMS OF EMERGENCY SITUATIONS: FROM THE EXPERIENCE OF THE SPECIALISTS OF THE FEDERAL MEDICAL BIOPHYSICAL CENTER NAMED AFTER A.I.BURNAZYAN OF THE FEDERAL MEDICAL AND BIOLOGICAL AGENCY OF RUSSIA

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Abstract. It has been noted that one of the most common types of radiation injuries when a person is exposed to ionizing radiation is radiation burns — severe local radiation injuries.
The aim of the study is to apply stromal and vascular fraction of adipose tissue to increase the efficiency of complex therapy for local radiation lesions.
Materials and methods of the study. In 2017-2019, 7 patients (all male; mean age — (54.83±9.41) years) with local radiation lesions of the skin — ulcerative-necrotic lesions of the skin and underlying tissues — were treated at the Federal Medical Biophysical Center named after A.I. Burnazyan of FMBA of Russia. For more than 6 months the patients received conventional conservative therapy of local radiation lesions and a single injection of cell suspension of autologous cells of stromal-vascular fraction of adipose tissue — the average number of cells was (60.33×106±64.04).
Results of the study and their analysis. All patients had no serious adverse events and reactions associated with the introduction of autologous regenerative cells of adipose tissue. During the whole period of observation after stromal-vascular fraction of adipose tissue was injected, late radiation ulcers remained without signs of inflammation and infiltration. The patients were discharged from the hospital in satisfactory condition.
According to the authors, the use of stromal-vascular fraction of adipose tissue in local radiation lesions provides favorable conditions: to increase the effectiveness of complex therapy; to reduce healing time of the wound surface; to regulate and activate immune and reparative processes in the dermis; to restore the damaged vascular network, lost skin without severe scarring changes; to heal and achieve a satisfactory result, decent quality of life of patients.

Key words: *ccell therapy, emergencies, radiation, regenerative cell technologies, severe local radiation injuries, stromal-vascular fraction of adipose tissue, victims*

Conflict of interest. The authors declare no conflict of interest

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ПРИМЕНЕНИЕ РЕГЕНЕРАТИВНЫХ КЛЕТОЧНЫХ ТЕХНОЛОГИЙ ПРИ ЛЕЧЕНИИ ТЯЖЁЛЫХ МЕСТНЫХ ЛУЧЕВЫХ ПОРАЖЕНИЙ У ПОСТРАДАВШИХ В ЧРЕЗВЫЧАЙНЫХ СИТУАЦИЯХ: ИЗ ОПЫТА РАБОТЫ СПЕЦИАЛИСТОВ ФЕДЕРАЛЬНОГО МЕДИЦИНСКОГО БИОФИЗИЧЕСКОГО ЦЕНТРА ИМ. А.И.БУРНАЗЯНА ФМБА РОССИИ

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Резюме. Отмечено, что одним из наиболее распространенных видов радиационных поражений при воздействии ионизирующего излучения на человека являются радиационные ожоги – тяжелые местные лучевые поражения (МЛП).
Цель исследования – применение стромально-васкулярной фракции (СВФ) жировой ткани (ЖТ) для повышения эффективности комплексной терапии при МЛП.
Материалы и методы исследования. В 2017–2019 гг. в Федеральном медицинском биофизическом центре им. А.И.Бурназяна ФМБА России были пролечены 7 пациентов (все – мужчины; средний возраст – (54,83±9,41) года) с МЛП кожных покровов – язвенно-некротическим поражением кожи и подлежащих тканей. В течение более 6 мес пациенты получали общепринятую консервативную терапию МЛП и однократное введение клеточной суспензии аутологичных клеток стромально-васкулярной фракции жировой ткани – среднее количество клеток составляло (60,33×106±64,04).
Результаты исследования и их анализ. У всех пациентов не было отмечено серьезных нежелательных явлений и реакций, связанных с введением аутологичных регенеративных клеток жировой ткани. За весь период наблюдения после введения СВФ ЖТ поздние лучевые язвы оставались без признаков воспаления и инфильтрации. Пациенты были выписаны из стационара в удовлетворительном состоянии.
По мнению авторов, применение СВФ ЖТ при МЛП обеспечивает благоприятные условия: для повышения эффективности комплексной терапии; сокращения сроков заживления раневой поверхности; регуляции и активации иммунных и репаративных процессов в дерме; восстановления поврежденной сосудистой сети, утраченных кожных покров без грубых рубцовых изменений; для заживления и достижения удовлетворительного результата, достойного качества жизни пациентов.

Ключевые слова: *клеточная терапия, пострадавшие, радиация, регенеративные клеточные технологии, стромально-васкулярная фракция жировой ткани, тяжелые местные лучевые поражения, чрезвычайные ситуации*

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Introduction

One of the most common types of radiation injuries when a person is exposed to ionizing radiation is radiation burns — severe local radiation injuries. Local radiation injuries to the skin are common in radiation accidents and incidents involving sources of ionizing radiation.

Thus, on the territory of the former USSR in 1950-2000 there were 349 radiation accidents accompanied by the development of radiation injuries. Acute radiation sickness combined with local radiation injuries was diagnosed in 747 people. In the USA in 1944-2000 there were 246 radiation accidents accompanied by development of local radiation injuries of various localizations (92%) in 793 people; in China in 1949-1988 there were 14 major radiation accidents accompanied by development of local radiation injuries in 47 individuals. [1-8].

According to numerous studies, skin changes due to radiation damage occur early due to genetic damage to stem and proliferating epidermal cells due to reduced reparative processes. Damage of less radiosensitive cell and tissue elements is also important: vascular endothelium, fibroblasts, elastic and smooth muscle sheaths. A characteristic feature of clinical course of local radiation lesions is a high probability of late radiation complications. They develop 6 months and more after the period of visible recovery.

Local radiation lesions are very difficult to treat. Conservative methods of treatment of non-healing chronic radiation ulcers are ineffective. Surgical intervention is often required, which is not always possible because of the condition of the victim's body.

In this regard, the development of new ways to improve the complex conservative treatment of local radiation lesions of the skin is an important task of modern medicine.

One of promising methods of treatment of local radiation lesions is cell therapy. Its use in clinical practice in the complex treatment of local radiation lesions will reduce the healing time of ulcerous defects and improve the quality of life of patients. For cell therapy are used: mesenchymal stromal cells from various sources; autologous minimally manipulated products (regenerative cells) based on adipose tissue; paracrine factors derived from cultured stem cells, etc.

The successful use of mesenchymal stromal cells in the treatment of radiation burns is due to their secretory activity. This activity is related to their production of a wide range of cytokines and growth factors. Besides, mesenchymal stromal cells have immunosuppressive, anti-inflammatory and trophic effects [9-12]. Cases of successful application of mesenchymal stromal cells in the treatment of radiation ulcers caused by X-rays have been described [13, 14]. In clinical application the safety of cell therapy has been proved. It is also established that transplantation of mesenchymal stromal cells interrupts the pathological inflammatory phase of inflammation, leading to an acceleration of the healing rate. However, the proposed method of treatment requires long-term cultivation of mesenchymal stromal cells.

At the present time in plastic surgery and clinical practice for the treatment of bone defects and soft tissue volume, diseases of musculoskeletal system and other diseases adipose tissue — subcutaneous fatty tissue — is actively used. The effect of regenerative cells (stromal and vascular fraction of adipose tissue) is realized due to their differentiation and replacement of damaged tissue areas, production of paracrine factors providing immunomodulatory effect, prevention of cell death by apoptosis mechanism, neoangiogenesis, fibrous and connective tissue remodeling [15-17]. Studies on laboratory animals at the State Research Center — A.I. Burnazyan Federal Medical Biophysical Center of the Federal Medical and Biological Agency of Russia (hereinafter — A.I. Burnazyan Federal Biophysical Center) showed that the use of regenerative cells of adipose tissue improves the course of local radiation lesions of the skin. It also accelerates wound healing processes due to improved neoangiogenesis and increased proliferation of fibroblasts after local X-ray irradiation in the experiment [18, 19]. All this points to the possibility of successful application of adipose tissue cells in severe local radiation lesions.

Thus, the data of the studies demonstrate an important role of regenerative medicine and cell technologies in the treatment of local radiation lesions. Autologous regenerative cells of stromal and vascular fraction of adipose tissue appear to be the most promising for clinical application. They have the ability to differentiate due to their heterogeneity and secrete a huge range of cytokines and growth factors that play an important role in tissue regeneration. Studies on laboratory animals have demonstrated high efficacy and safety of application of autologous regenerative cells of stromal and vascular fraction of adipose tissue in treatment of severe local radiation lesions. However, there are no data on clinical application of autologous regenerative cells of stromal and vascular fraction of adipose tissue in the treatment of local radiation lesions in the victims. All this points to the possibility of successful application of regenerative cells of adipose tissue in the treatment of severe local radiation lesions in humans.

The aim of the study is to apply stromal and vascular fraction of adipose tissue to increase the efficiency of complex therapy for local radiation lesions.

Materials and methods. In 2017-2019 7 patients with local radiation lesions of the skin — ulcerative-necrotic lesions of the skin and underlying tissues were treated at the A.I. Burnazyan Federal Medical and Biological Center of the Federal Medical and Biological Agency of Russia. All patients were men, mean age — (54,83±9,41) years, mean body weight — (72,67±16,12) kg, mean height — (175,65±8,07) cm, mean body surface area — (1,95±0,17) m2, mean body mass index (BMI) — (26,37±3,23). For more than 6 months the patients received conventional conservative therapy of local radiation lesions.

All patients underwent laboratory tests (clinical blood test, serological reactions, biochemical blood test, coagulogram, clinical urinalysis) and instrumental methods of investigation.

All patients had the results of laboratory indices and instrumental methods of investigation within the normal range and there were no contraindications for adipose tissue sampling and for application of stromal-vascular fraction of adipose tissue.

Indications for the use of stromal-vascular fraction of adipose tissue in patients with local radiation lesions:

1. History of exposure to ionizing radiation.
2. Ulcerative-necrotic lesions/ lesions of the skin and underlying tissues lasting more than 6 months.
3. A negative urine pregnancy test result, consent to abstain from sexual intercourse completely or to use reliable contraception for women of reproductive age for the duration of the study.
4. Patients read the information sheet and signed the informed consent form.

Contraindications for the use of stromal and vascular adipose tissue fraction in patients with local radiation lesions:

1. Refusal of a patient with local radiation lesion or of his close relatives to use stromal-vascular fraction of adipose tissue.
2. Chronic diseases of internal organs in subcompensated or decompensated forms.
3. Delayed physical development.
4. Cancer registered in the last 5 years.
5. Depression or other clinically significant mental illness.
6. Significant weight loss (>10% of body weight in the previous year) of unspecified etiology.
7. Active infectious and inflammatory diseases.
8. Pregnancy or breastfeeding period.

Рис. 1. Схема получения регенеративных клеток жировой ткани для клинического применения
Fig. 1. Fig. 1. Algorithm of decision making about the necessity of using regenerative cells of stromal-vascular fraction of adipose tissue in local radiation damage in medical facilities

9. Drug abuse, current or history of drug and/or alcohol abuse.
10. Therapy with immunosuppressive drugs, including chemotherapy, in the last 5 years.
11. Autoimmune diseases requiring regular immunosuppressive therapy.
12. Clinically significant abnormalities in the results of laboratory tests.

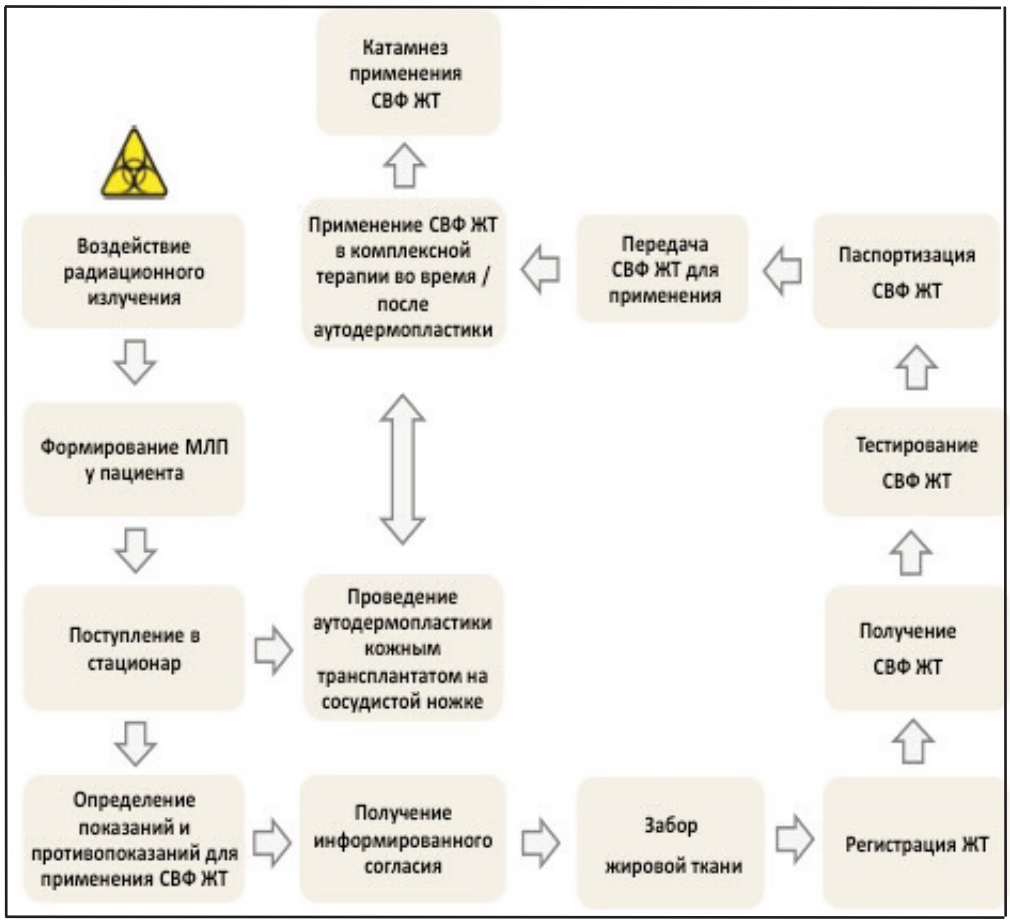

Рис. 2. Алгоритм принятия решения о необходимости применения регенеративных клеток СВФ жировой ткани при лечении пациента с МЛП в лечебной медицинской организации
Fig. 2. Scheme of obtaining regenerative cells of adipose tissue for clinical use

13. Patients receiving anticoagulants due to any disease, as well as patients who received anticoagulants for at least 1 h before lipoaspiration.

14. Patients who are or were receiving glycoprotein IIB/IIIA inhibitors before the study.

15. Patients with contraindications for local anesthesia or with a history of allergic reactions to local anesthetics.

16. Confirmed carriers of HIV or hepatitis B or C.

17. Presence of any other comorbidities that put the patient's safety at risk for participation in the study or will affect the safety assessment, including: diabetes mellitus; obesity — BMI > 35 kg/m2; bronchial asthma; epilepsy, migraine, seizures or other central nervous system disorders, including a history of them; cardiovascular and cerebro-vascular diseases, including a history of them; presence of thrombosis — venous and/or arterial, thromboembolism or thrombophlebitis — current or history of it.

Basic requirements for safety and efficiency of adipose tissue sampling, its processing, obtaining stromal-vascular fraction of adipose tissue and its application:

1. Manipulations for taking biological material of adipose tissue and isolation of stromal and vascular fraction of adipose tissue must be performed by qualified personnel in sterile conditions.

2. Manipulations with biological material must be performed in sterile rooms with appropriate certified equipment and consumables.

3. The list of necessary equipment should include: laminar flow cabinet, CO2 incubator, cell counter, centrifuge, cytofluorimeter, disposable consumables, and other reagents.

4. It is necessary to create strictly controlled and standardized methods and procedures for processing and obtaining stromal-vascular fraction of adipose tissue — reagents, enzymes, etc.

5. Testing of stromal-vascular fraction of adipose tissue, including number and viability of cells, immunophenotyping of surface antigens, sterility control, and passportization.

6. Application (local injection) of stromal-vascular fraction of adipose tissue complex for treatment of local radiation lesions should be performed by qualified personnel in sterile conditions.

After signing an informed consent to obtain biological material of adipose tissue for cell therapy, aspiration liposuction in the lower third of the anterior abdominal wall was performed in the operating room under general anesthesia. The average volume of lipoaspirate adipose tissue was (42.32±13.98) g. For clinical use, adipose tissue was washed, enzymatically treated with collagenase, centrifuged, and stromal and vascular fractions of adipose tissue were obtained. The number of cells in the stromal-vascular fraction of adipose tissue was counted using an automatic Counterss Invitrogen cell counter (Invitrogen). The average number of cells in the stromal-vascular

Таблица / Table

Распределение пациентов по этиологии и дозе радиационного поражения
Distribution of patients by etiology and doses of radiation exposure

Пациент Patient	Возраст, лет Age, years	Год, получения радиационного поражения Year of radiation exposure	Вид радиационного поражения Type of radiation damage	Этиология радиационного поражения Etiology of radiation damage	Доза радиационного поражения Dose of radiation exposure		
					предполагаемая доза, Гр Estimated dose, Gy	цитогенетика, Зв Cytogenetics, Sv	ЭПР эмали зуба, Гр Electron paramagnetic resonance of tooth e enamel, Gy
К. / K.	57	1990	Пучок электронов Beam of electrons	Нарушение техники безопасности на производстве Violation of industrial safety	НД - нет данных N/A - no data available	0,30	0,11
Ф. / F.	48	2000	Иридий-192 Iridium-192	Нарушение техники безопасности на производстве Violation of industrial safety	30–70 Частота дицентриков - 1,75Гр Dicentric frequency - 1.75 Gy Кариология - 2,0 Гр Karyology -2.0 Gy Нейтрофилы - 1,2 Гр Neutrophils -1.2 Gy	1,09	2,6±0,2
Н. / N.	70	2006	Рентген X-ray	Медицинское лечение Medical treatment	2,7	1,4	НД / N/A
Л. / L.	57	2007	Иридий-192 (60 Кюри 11,2 ТБк (активность 302 Ки) Iridium-192 (60 Curie 11.2 TBq (activity 302 Ci)	Нарушение техники безопасности на производстве Violation of industrial safety	25–30	0,29	НД / N/A
Л. / L.	48	2008	Иридий-192 Iridium-192	Нарушение техники безопасности на производстве Violation of industrial safety	30-50	0,48	НД / N/A
Д. / D.	45	2012	Иридий-192 Iridium-192	Нарушение техники безопасности на производстве Violation of industrial safety	НД / N/A	0,28	НД / N/A
Л. / L.	78	2013	Гамма Gamma	Медицинское лечение Medical treatment	60	НД / N/A	НД / N/A

fraction of adipose tissue was 60.33x(106±64.04) per sample. Immunological evaluation (immunophenotype) and viability were performed by flow cytofluorimetry — BD FACS Canto II, USA. Monoclonal antibodies to the following antigenic markers were used to examine the phenotype of the stromal and vascular fraction cells: CD45, CD34, CD31, CD105, CD73, CD90, CD146, and a 7-ADD viability dye (Fig. 1). The staining was performed according to the manufacturer's recommendations.

Results of the study and their analysis. To decide on the necessity of using regenerative cells of adipose tissue in patients with local radiation lesions we used the developed algorithm (Fig. 2). Patients with radiation lesions of the skin and underlying tissues with ulcerative-necrotic lesions of the skin and underlying tissues due to distant consequences of local radiation lesions of varying severity and with duration of its course over 6 months — were hospitalized in the hospital (Table). Such patients underwent standard local conservative therapy of local radiation lesions in combination with radical necrectomies. In case of impaired gliding function of tendons, a comprehensive standard therapy for its restoration was performed.

Before the stromal-vascular fatty tissue fraction therapy, an in vivo pathological-anatomical examination of biopsy (surgical) material in each patient showed an erosive-ulcerous epidermal defect with scarring changes in the dermis and the presence of focal lymphocytic infiltrates in it. Degenerative changes of derma, its sclerosis, coarsening of derma collagen were observed along the periphery of the erosive-ulcerous area. Hypertrophied nerve trunks resembling neuromas of tactile endings were found in deep parts of the dermis. The bone was represented by cancellous bone with enlarged medullary cavities filled with fatty tissue. No reliable morphological signs of osteomyelitis were detected. The conclusion was that these histological changes could be a manifestation of late post-radiation dermatitis with erosive-ulcerative skin changes and scarring-sclerotic changes of the deep tendon.

After signing the informed consent, adipose tissue was taken by syringe liposuction in the lower third of the anterior abdominal wall under operating room conditions. See Fig. 1 for the technique of isolation of regenerative cells of adipose tissue for clinical use.

Autologous regenerative cells of the stromal and vascular adipose tissue fraction were isolated. The obtained cells of stromal and vascular fraction of adipose tissue were sterile when tested for sterility (infectious safety). The stromal-vascular fraction of adipose tissue consisted of stromal cells (15-30%, of which 3% were stem cells and progenitor cells — positive expression of CD105, CD90, CD73); endothelial cells (10-20% — positive expression of CD31); blood cells (5-15% — positive expression of CD45); pericytes (3-5% — positive expression of CD146); hematopoietic stem cells (<0.1% — positive expression of CD34) — (Fig. 3). The viability of the stromal and vascular fraction of adipose tissue was (98.32±2.98)%.

Under aseptic conditions an insulin syringe with a 0.45mm×12mm 26 Gx½ needle was used to inject a single cellular suspension of autologous stromal and vascular fractions of adipose tissue in 10-15 points around the ulcerous surface at a depth of 3-5 mm (Fig. 4). The volume of injected cell suspension containing autologous regener-

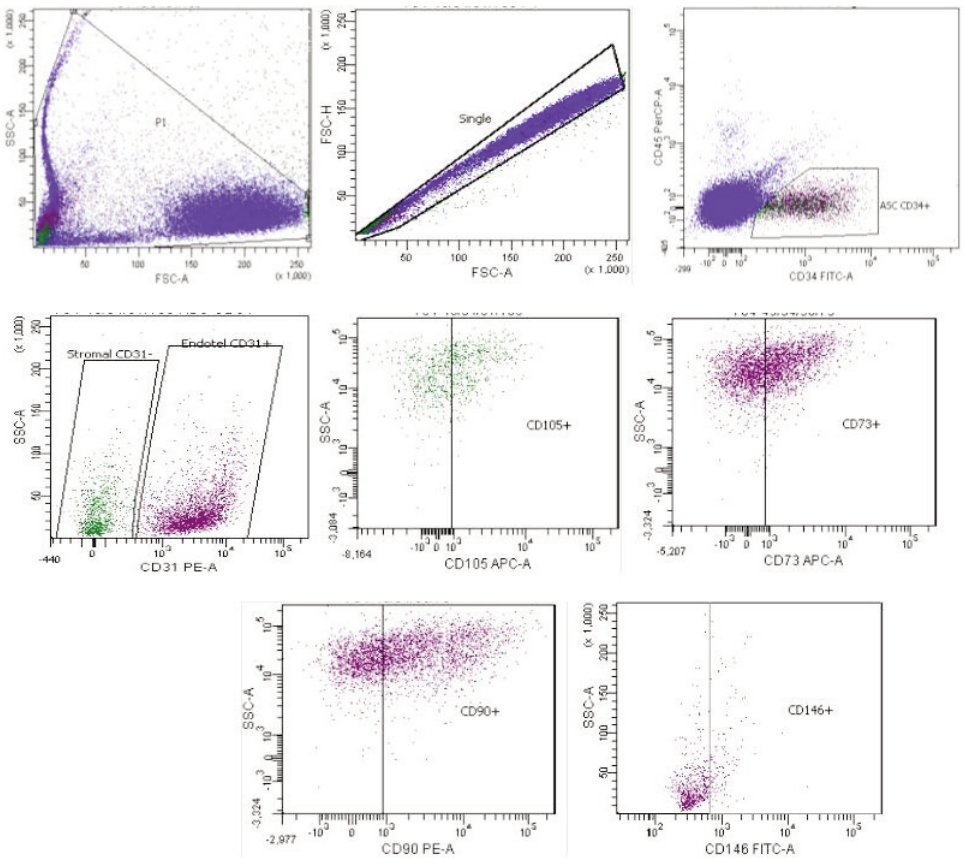

Рис. 3. Иммунологическая оценка регенеративных клеток жировой ткани: CD45+CD34+/CD31+/CD105+/CD73+/CD90+/CD146+

Fig. 3. Immunological evaluation of regenerative adipose tissue cells: CD45+CD34+/CD31+/CD105+/

Рис. 4. Введение клеточной суспензии СВФ ЖТ
Fig. 4. Injection of cell suspension of adipose tissue stromal-vascular fraction

ative cells of adipose tissue is 5 ml. The recommended dose of autologous regenerative cells of adipose tissue is 0.5-1.0 ml/cm^2.

All patients had local soreness and slight swelling in the area of injection without changes in vital functions and laboratory abnormalities after injection of a suspension of autologous regenerative cells of adipose tissue for one day. This phenomenon was regarded as a local tissue reaction to the injection. No adverse events, deviations of vital functions and laboratory parameters were registered during the entire period of observation. This can testify to the safety of introduction of autologous regenerative cells of adipose tissue in humans. There were no serious adverse events and reactions associated with the introduction of autologous regenerative cells of adipose tissue.

To ensure the patient's well-being and to prevent possible complications, the necessary registered medications were used in accordance with the treatment standards for the underlying disease.

In all 7 patients during the whole period of observation after injection of a suspension of autologous regenerative cells of the stromal and vascular fraction of adipose tissue, late radial ulcers remained without signs of inflammation and infiltration (Fig. 5). The patients were discharged from the hospital in a satisfactory condition.

Рис. 5. Последствия местного лучевого поражения до и через 6 мес после введения СВФ ЖТ: А – пациент Д.; Б – пациент К.; В – пациент Л.; Г –пациент Л.
Fig. 5. Consequences of local radiation lesions before and after the injection of adipose tissue stromal-vascular fraction after 6 months: A – Patient D., B – Patient K., C – Patient L., D – Patient L.

Discussion of the results of the study. The relevance of the study is determined by the complexity and duration of local radiation lesions treatment, large financial expenses for treatment, long loss of working capacity, need for rehabilitation and disability of patients. One of the cornerstones in the treatment of local radiation lesions is skin repair. Patients with local radiation lesions of the skin need surgical plastic interventions, since the independent process of epithelialization is impossible. The formation of ulcers, pathological scars and contractures, rejection of grafts significantly increase the duration of treatment process, worsen the results of treatment and quality of life. Therefore, the improvement of the system of medical care for patients with local radiation lesions is one of the pressing problems of modern surgery, which requires a search for new methods of treatment.

At present, necrectomy with one-stage or delayed autodermoplasty with a skin graft is used to heal the damaged skin. Autografting is considered to be the most acceptable variant of plasty. However, this kind of plasty does not always provide satisfactory functional and cosmetic results. One of the promising methods of treatment of skin lesions and its appendages is cell therapy, the use of which in clinical practice will reduce the period of graft engraftment and improve the quality of life of patients.

A known method of treating local radiation lesions of the skin using autotransplantation of adipose tissue obtained as a result of liposuction. However, the use of freshly isolated lipoaspirate without specific laboratory steps for its purification from blood cell elements and isolation of stromal-vascular fraction did not provide restoration of the regenerative potential of dermal cells and necessary vascularization of the skin [20].

Currently, adipose tissue is actively used in plastic surgery and clinical practice for the treatment of bone defects and soft tissue volume, diseases of the musculoskeletal system, etc. The effect of regenerative cells of adipose tissue is realized due to their differentiation and replacement of damaged tissue areas; production of paracrine factors providing immunomodulatory effect, prevention of cell death by apoptosis mechanism, neoangiogenesis, fibrous and connective tissue remodeling. The results of numerous studies on laboratory animals showed that the use of regenerative cells of adipose tissue improves the course of the inflammatory process, accelerates the healing of lesions by improving neoangiogenesis and enhancing the proliferation of fibroblasts. All this testifies to the possibility of successful application of adipose tissue cells in local radiation lesions of the skin.

The results of the present study showed that application of autologous regenerative cells of stromal and vascular fraction of adipose tissue contributed to activation of reparative processes in the dermis, reduction of the local inflammatory reaction, healing, acceleration of skin elasticity restoration with reduction of fibrosis severity.

Thus, in order to increase the efficiency of ulcer surface healing in local radiation lesions of the skin, the specialists of A.I. Burnazyan Federal Medical and Biological Center of the Federal Medical and Biological Agency of Russia suggest using own regenerative cells of the stromal and vascular fraction of adipose

tissue during routine surgical treatments of the ulcer surface according to the developed algorithm. These cells and the growth factors and cytokines produced by them take part in reparative processes, in the restoration of the damaged vascular network, as well as in the regulation of immune processes. In our opinion, due to the high availability of obtaining adipose tissue in a sufficient volume from almost any patient, the possibility of using the obtained regenerative cells of the stromal and vascular fraction of adipose tissue immediately after their isolation without long-term cultivation will be of great importance when performing reconstructive-plastic operations.

Conclusion

The presented algorithm of decision-making on the use and application of stromal-vascular fatty tissue fraction in patients with local radiation lesions provide favorable conditions: for increasing the efficiency of complex therapy; for reducing the healing time of the wound surface; for regulating and activating immune and reparative processes in the dermis; for restoring the damaged vascular network and lost skin without severe scarring changes; for healing and improving the quality of life of patients.

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