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RESEARCH ARTICLE

CELL THERAPY OF BRONCHOPULMONARY DYSPLASIA IN INFANTS

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ABSTRACT

The review contains information on preclinical and clinical studies of cell therapy for bronchopulmonary dysplasia (BPD) in premature infants. It includes an analysis of 53 scientific publications devoted to this issue. It is important to remember that cell therapy for BPD is at the stage of experimental and clinical trials. Currently, there are no standards of its use in infants with this disease. When deciding on the use of stem cells for therapeutic purposes, in addition to drug therapy, the physician should take into account the medical legislation of the country regarding cell therapy and comply with all legal formalities.

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INTRODUCTION

The progress in neonatology have led to significant improvements in survival rates of premature infants. However, bronchopulmonary dysplasia (BPD) is a common complication for very preterm (28-32 weeks) and extremely preterm (<28 weeks) infants (20, 21, 22). BPD occurs in 45% of infants with very low birth weight (43). According to Lee JH. et al. (2019), BPD frequency increases from 5 to 88% in preterm infants with decreasing of gestational age from 32 to 22 weeks (23). Mortality remains high among children with BPD up to 5 years (48). Surviving infants with moderate or severe BPD are at high risk of developing chronic diseases of the respiratory system and the nervous system that can lead to disability (20-22,28). BPD is a multifactorial disease (20-22,43). An important role in its development play the following facts: premature birth (low gestational age and low body weight at birth), the immaturity of organs and tissues, including respiratory and immune systems, a deficiency of surfactant, the need for long-term aggressive mechanical hardware ventilation of the lungs with the supply of high concentrations of O_2 under high pressure, inflammation, "ventilator-associated" pneumonia (14, 20, 22, 30).

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Intrauterine infection increases the risk of BPD (22, 35). BPD affects the formation of nosocomial bacterial and virial respiratory infection (22, 36). It was found that the BPD in infants in conjunction with the respiratory syncytial virus is the basis of the development of chronic obstructive pulmonary disease in adults (33). BPD pathogenesis is rather complicated. It involves breach of vascular development, the defective (impaired) or a closed alveolarization, inflammation of the lung, fibrosis (2,14,20,23,32,43). Intensive studies on the possibility of using stem cells for the treatment of BPD are carried out over recent years. It notes genetic disposition to the formation of this disease (6,13,15,16,20,21,27,37,39,50). Cell therapy. The great interest of researchers to the possibility of using stem cell therapy in infants with BPD is associated with the fact that it is a serious chronic disease that leads to disability and death, difficult to treat with drug therapy (6,32,40,41). Many authors even called BPD as incurable disease (1,24,52,53). According to studies, over the past 50 years, no safe drug therapy had no significant effect on the frequency and severity of BPD (15). The use of stem cell therapy has caused great excitement in the world in recent years. Reviews of physicians on the use of stem cells in the treatment of patients with highly controversial and are the subject of debate (1,3,4,11,13,26,30,42,51). The positive aspect of the use of stem cells in medicine are the following: to achieve the desired clinical effect, a partial restoration of the lost functions of organs, improving quality of life, reducing the rate of disease progression and development of complications (42,48).

The downside of cell therapy are the following factors: First of all, the use of donor stem cell carries a risk of infection by viruses, mycoplasma and other intracellular microorganisms. Secondly, it is unknown how donor cells will adapt. The third problem is a legal question that should always be agreed upon. The fourth problem is that we do not know exactly what is happening with stem cells extracted from their familiar environment, and how they change during the culture in the laboratory. However, it is known that stem cells after multiple divisions can generate malignant telomerase which stimulates the growth of tumors. The fifth and the last question - what is the potency (and therefore, the clinical efficacy) of stem cells as donor and autogenic (4,5,30,32,42,48) ? Currently, a study on the possibility of using stem cell therapy for the treatment of BPD is carried out in two directions: experimental animal studies and limited clinical trials in infants (40,46,53).

Pre-clinical experimental studies: To study the effectiveness of stem cells in animal experiments BPD special biological models have been developed, which is formed by artificial means (8,9). Many animal models mimic the phenotype of BPD person (alveolar development arrest, violation of vascularization, extracellular matrix remodeling with development of fibrosis, broncho-obstructive syndrome). Small models (mice and rats) are well suited for basic research of specific mechanisms of disease development. It is necessary to generate new hypotheses (8,9). Large vented model (premature baboons and lambs) are well used to transfer the developed methods into clinical practice. A rabbit model is also promising for this purpose. It includes prematurity factor and it is a medium-sized model.

By now research has accumulated experimental data on the effectiveness of BPD cell therapy with multipotent mesenchymal stem / stromal cells (MSCs). These cells have the ability to self-renew and differentiate into tissue-specific cells. Their therapeutic efficacy confirmed in animal models of pulmonary disorders, as well as the early stages of clinical trials, acute respiratory distress syndrome (RDS) (31). In recent years, a variety of pre-clinical studies have shown that stem cell therapy significantly reduces the damage to the respiratory system in newborn animals with BPD models (5). The experiment proved the high efficacy of the transplantation of human umbilical cord blood-derived mesenchymal stem cells (UC-MSCs), against hyperoxic lung damage in newborn animals with simulated (models) of BPD (8). Intratracheal administration of stem cells is significantly diminished lung tissue damage in these animals. Alveolar and vascular growth disorders in the lungs were significantly reduced, and the inflammatory process in the airways was also weakened (1). However, according to Chang YS. et al. (2013), intratracheal transplantation of US-MSCs provided the greatest protective effect only at the early stage but not in the late stage of inflammation. There was no synergism with the combined early and late transplantation MSCs (9). Absent also oncogenic effect cell, short or long term toxicity (9,34). There were no gross or microscopic abnormalities in the heart, the liver or the spleen associated with MSCs transplantation (1,34). The mesenchymal stem cells derived from human umbilical cord (hUC-MSCs) showed a good therapeutic effect on oxygen model BPD in the study of Hou C. et al. (2017). The hUC-MSCs were injected intratracheally in neonatal rats exposed to hyperoxia. These cells improved expression of elastin stimulated by 90% O_2 in human lung fibroblasts (HLF-a), and inhibited the transdifferentiation of HLF-a into myofibroblasts, suppressed the increased activation of TGFβ1. The hUC-MSCs inhibited elastase activity lungs and reduced aberrant elastin expression and its deposition in the lungs of rats with BPD (18). Allogeneic cell transplant can be an effective method of the prevention and treatment BPD. However, the main obstacle to the use of this method is the “graft-versus-host” (GVHR), the possibility of rejection of allogeneic cells. The studies are being conducted that allow successful induction of immune tolerance of allogeneic cell transplantation in premature infants to solve this problem (26).
A recent meta-analysis of preclinical animal studies is clearly demonstrated the benefits of mesenchymal stem cells for the treatment of BPD (44). Such therapeutic efficacy can be attributed to the biologically active substances which are removed from the MSCs (“secret" or “secretoma”). These include conditioned media (CM) and extracellular vesicles (EV). They play a major role in the regenerative function of MSCs. EV, secreted by MSCs, can carry many bioactive factors. They are involved in biological processes. They have properties of angiogenesis, antiapoptosis, antifibrosis, antioxidation, chemoattractation, immunomodulation, proliferation. These factors include a variety of chemicals: angiopoietin 1, chemokine ligand, chemokine (C-X-C motif) ligand, fibroblast grofth factor, granulocyte monocyte stimulating factor, hepatocyte grofth factor, hemeoxygenase 1, indoleamine 2,3-dioxygenase, isulin like grofth factor 1, interleukin, IL-1 receptor antagonist, kerratinocyte grofth factor, leukemia inhibitory factor, human cathelicidin, metalloproteinase, monocyte chemoattractant protein 1, plateled derived grofth factor, prostaglandin E2, stem cell-derived factor 1, stanniocalcin 1, tissue inhibitor of metalloproteinase 1, transforming grofth factor beta, tumor necrosis factor- stimulated gene-6, vascular endothelial grofth factor (31).

These factors are able to modulate the function of recipient cells using various mechanisms (ligand-receptor interaction, direct membrane fusion, endocytosis, phagocytosis) (29,31).
MSCs can respond to hypoxia (e.g., with RDS) and stress signals from the damaged tissue, particularly pneumonia and bronchopulmonary dysplasia. They secrete many soluble factors. So, MSCs increase the production of angiogenic and antiapoptotic factors are: interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), monocyte chemotactic protein (MSR) and other (7,19). Thus, CM and EV, derived MSCs are potential therapeutic agents for lung disease. These secrets extracted from MSCs, appears to possess biological and logistical advantages compared with therapy living cells. However, further studies are needed to determine the safety and efficacy of these ingredients in the fight against lung disease (31,40). Studies have found that exosomes of mesenchymal stem cells (MSC EXO) are the therapeutic vector these cells in the murine BPD model (12,29). During this experiment the conditioned medium and MSC EXO fraction were isolated from the culture of early gestational age human umbilical cord – derived MSC (hUC-MSCs). Newborn mice were injected intraperitoneally with BPD model MSC EXO fraction or its exosomal factor TSG-6. The immunomodulatory glycoprotein TSG-6 was detected in MSC EXO. It was called the exosomal factor alpha-stimulated gene-6 of the tumor necrosis factor (TSG-6). The prescription of TSG-6 to mice weakened the course of BPD and the associated pathology of the lungs, heart, and brain. The result indicates early systemic intervention using TSG-6 as a reliable option for cell-free treatment of BPD. (12).

Human amnion epithelial cells (hAEC) have been proposed for cell therapy, which are easy to obtain in large quantities from the placenta. These cells do not require culture propagation. They express low HLA levels and have immunomodulatory effects in preclinical models of neonatal lung diseases (52). The hAECs have also been shown to prevent alveolar simplification and pneumonia in newborn animals and are well tolerated after exogenous administration in preclinical BPD models (49).Thus, preclinical studies in animal with BPD models showed a protective effect on the lungs of stem cells. This led to early clinical trials (24,47,53).

Clinical trials: There are first reports in the scientific literature about the effectiveness of stem cell therapy in infants with BPD. So, Liem NT. et all (2017) reported the successful cell therapy in the 30-week-old infant with BPD. This baby needed continuous administration of oxygen for 4 months. Then he was transplanted with autologous bone marrow mononuclear cells (BM MNCs). Bone marrow was obtained from the iliac crests of the patient as a result of a puncture, and the mononuclear cells were isolated by density gradient centrifugation. BM MNCs were injected intravenously and endotracheally. After transplantation BM MNCs were observed positive clinical dynamics. The baby had an improvement in oxygen saturation and CT of the lung. The patient was gradually reduced oxygen subsidy. The authors believe that BM MNCs transplantation is a promising treatment for BPD (24). During another clinical study, allogeneic mesenchymal stem cells were administered to two premature infants with severe and steam-progressing BPD. MSCs were obtained from bone marrow. This study confirmed the following: the safety of the proposed treatment method, its anti-inflammatory effect and the reduction of pro-inflammatory cytokines, serum factors and tracheal contents factors. However, infants had a fatal outcome as the cell therapy was performed at very late stages of BPD with very severe pulmonary fibrosis. Nevertheless, the authors consider cell therapy with the use of MSCs promising, but it should be used in the early stages of the disease (3).

A clinical study was conducted in 9 premature infants aged 7-10 days with a high risk of developing BPD (1,5,8,9,34), based on preclinical data demonstrating the protective effect of transplantation of MSCs against hyperoxic lung damage in newborn animals (10). The authors evaluated the safety of a single intratracheal transplantation of allogeneic human umbilical cord blood-derived mesenchymal stem cells. Gestational age was 24-26 weeks, birth weight was 630-1030 g. It was found that the severity of BPD was significantly lower in transplant recipients compared with the control group. It was concluded that this method of transplantation is safe for preterm infants. A positive effect of cell therapy is reported in the article devoted to the rehabilitation of infants with BPD. Six infants with BPD between the ages of 1 and 2 years old along with acupuncture corticosteroids received an intravenous infusion mesenchymal stem cells of human umbilical cord blood (hUCB-MSC). Positive clinical dynamics were noted in these infants. One infant successfully discontinued oxygen therapy. No adverse events associated with hUCB-MSC infusion were observed in any infant (26). A study was conducted to determine the safety of the introduction of allogeneic human amnion epithelial cells - hAEC in six premature babies with BPD (5 boys and 1 girl). The gestational age of infants at birth was from 24 to 28 weeks, body weight at birth was from 450-990 g.

Three infants were dependent on invasive mechanical ventilation, the next 3 infants were dependent on CPAP for the time of introduction of the cells. Safety assessment of cell therapy included determination of a possible adverse reaction at the infusion locus, anaphylaxis, infection, and rejection characteristics (including fever, weight loss, changes in the kidney, liver, heart, lung function). Serial blood tests, chest X-ray, echocardiograms, ultrasound of the skull and abdomen and magnetic resonance imaging of the brain (MRI) were also performed in the dynamics of observation. The hAEC cells were injected at a dose of 1 million / kg body weight. The first infant received cells by slow manual intravenous infusion with a suspension of cells of 2 million / ml normal saline solution. This infant had temporary impaired cardiorespiratory function during the administration of cells, including sudden acute hypoxia and bradycardia without changing blood pressure. Cellular administration was discontinued in the middle of the infusion followed by recovery. In connection with this event, the tactics of cell infusion for other infants were changed, including dose reduction to 0.25 million live hAEC / ml saline and the use of an integrated filter. There was no significant change in the requirements for respiratory support after hAEC therapy. All the infants were discharged home with extra oxygen (with additional oxygen conten). The main results of the study showed that allogeneic hAEC are safe and well tolerated by premature infants (25).

However, according to some scientists, the use of cell therapy is safe fantastic breakthrough in medicine (11,25,26,40), but this method is not independent at present time. Keep in mind that cell therapy is not a panacea. It cannot cure an infant with BPD completely or cancel the traditional drug therapy (glucocorticosteroids, anti-inflammatory drugs, caffeine, myelorelaxants, vitamin A, budesonide-surfactant) and non-aggressive mechanical ventilation measures. At the present stage of development of science, the stem cells can only improve the clinical status of patients with BPD and improve the efficiency of traditional treatment, which cannot be canceled (11,30,38,40). The development of stem cells therapy methods for newborns should include the solution of a number of serious problems. This is definition of indications for stem cell therapy, and determining a patient who needs such treatment. This is the selection of optimal cells for a particular patient, the determination of the method of introducing cells, route of administration, time and dose of cell administration. It is necessary to work out criteria for long-term safety and effectiveness of cell transplantation. In addition, it is necessary to solve the problem of expanding the production processes of cell production and development of standardization methods (11). Pediatricians especially pay attention to the selection of young patients for cell therapy. These should be newborns with a very high risk of developing BPD. The risk should be established by analyzing prenatal, perinatal, and postnatal risk factors. It is also important to determine the dose of cells and the research of cell therapy's safety (17). When deciding on the use of cell therapy in infants with BPD, it is important to maintain a balance between the temptation of its active use and the desire to help severely ill patients and a cautious approach to the use of a new treatment method, and these practice the doctors only accumulate (47).

Conclusion

It is important to remember that cell therapy for BPD is at the stage of experimental and clinical trials. Currently, there are no

standards of its use in infants with this disease. When deciding on the use of stem cells for therapeutic purposes, in addition to drug therapy, the physician should take into account the medical legislation of the country regarding cell therapy and comply with all legal formalities.

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