INTRODUCTION

Cell therapy is a newly emerging field, which leads to many scientific disciplines such as stem cell biology, molecular biology, immunology, tissue engineering, regenerative medicine and clinical research. The use of stem cells keeps developing between years to meet the needs of alternative medicine for kidney diseases. In Indonesia, chronic kidney disease is one of the highest prevalence for un communicable diseases, with around 0.2%. Chronic kidney disease (CKD) is characterized by an irreversible and progressive deterioration of renal function until it reaches end-stage renal disease (ESRD). The etiology of this condition could be classified based on the location, such as at the glomerular (diabetes mellitus, glomerulonephritis), tubulointerstitial (systemic infection, autoimmune, stone obstruction), vascular disease (hypertension, vasculitis, atherosclerosis), and cyst or congenital diseases (renal dysplasia).

When the patient reaches end-stage renal disease, the patient should get renal replacement therapy as in hemodialysis, continuous ambulatory peritoneal dialysis (CAPD) or renal transplantation. These therapies will greatly burden the patient's financial and social aspects of life. Therefore, we need other alternatives in managing kidney disease to prevent the progression leading to end-stage renal disease.

Stem Cells

The stem cell is a pluripotent fibroblast-like cell that could renew itself and go through multilineage differentiation. Aside from bone marrow, the mesenchymal stem cell can be derived from umbilical cord blood, umbilical cord wall, amniotic fluid, peripheral blood, skeletal muscle, adipose tissue, kidney, and dental pulp (Figure 1). Only stem cells derived from bone marrow, umbilical cord, amniotic fluid, and adipose tissue have been widely used to treat many diseases. In Cipto Mangunkusumo National Hospital, the umbilical cord-derived mesenchymal stem cells have been used widely in orthopedic, neurologic, and endocrine treatments.

Human Umbilical-Cord Mesenchymal Stem Cells (HUCMSCs)

The umbilical cord is one of many sources of mesenchymal stem cells. It produces embryonic stem cells that can differentiate into almost all types of cells in the body or call pluripotent. Stem cells can be isolated from Wharton’s Jelly, cord lining, and perivascular region. The HUCMSCs with theirs pluripotent capabilities can differentiate to mesoderm (adipocytes, osteocytes, cartilage), ectoderm (neuron, astrocytes, glial cells), and endoderm (liver, islet cells) (Figure 2).

HUCMSCs and Kidney Diseases

Multiple stem cell types have been for their advantages in treating kidney disease. A choice between autologous or non-autologous stem cells is also important before the transplantation. Non-autologous stem cells have to face host immunologic reactions. Bone marrow was the first reported source of stem cells and used to treat many diseases. However, it has its disadvantages: the highly invasive procedure in the donation process, deterioration of cells number, and decrease in its differentiation potential with increasing age. Nonetheless, many studies were trying to find another better source. There are significant differences regarding morphology and immune phenotype of the MSCs between stem cells derived from bone marrow, umbilical cord blood, and adipose tissue. Umbilical cord blood stem cells show a lower success rate on isolating MSCs. However, it shows the highest proliferation capacity, shortest culture period, no adipogenic differentiation capacity, and it could be expendable to higher numbers. Collins et al. reported that human MSCs from...
healthy bone marrow and umbilical cord significantly improved renal disease in mice, while lupus bone marrow only delayed disease progress. Aside from the effect of stem cells in treating kidney diseases, this study described that the source of stem cells should be selectively chosen. Many studies have been conducted using HUCMSCs for kidney diseases, particularly using animal models. Most of the studies showed that implantation of HUCMSC shows positive results for kidney diseases. A meta-analysis from Wang et al. analyzed the route of delivery, number of MSC, type of injury and MSC type. It described various types of delivery routes, such as intravenous, intrarenal, intraperitoneal, and via renal artery or carotid artery. Route of delivery was one of many factors influencing the cells’ capacity for homing and engraftment. Direct implantation to renal artery shows approximately 4-15% retention rates compared to engraftment rate of intravenously implanted MSC in non-human primates ranging from 0,1 to 2,7%. The Intraparenchymal/intrarenal route is also proven to give renoprotective effects, but it was not easy to implement in humans. Number of MSC used in many studies ranged from $7.5 \times 10^4$ to $9 \times 10^6$ cells with sources from rat bone marrow-derived MSC, human MSC from fetal membranes, and human bone marrow-derived MSC.

Studies of HUCMSCs have also been conducted in larger animals, such as swine and cats. In these studies, bone marrow-derived MSC could inhibit or delay the chronic kidney disease progression induced by renal fibrosis in swine. Not only for swine but studies on porcine showed that MSC or its derivation could attenuate renal inflammation and improve glomerular and tubular function, leading to renal recovery. The efficacy and safety of MSC are also supported by research in cats. Feline allogenic mesenchymal stem cells have renoprotective effect and improve renal function in cats with CKD. However, contradictive results...
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<td>Li, 2017</td>
<td>rats</td>
<td>Chronic renal failure</td>
<td>8 x 10^6 cells + icariin</td>
<td>Decreasing in inflammatory responses, upregulation of expression of growth factors, protection of injured renal tissues</td>
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were still found where other studies show only a little effect of MSC implantation, thus needing longer time to follow up and assess factors influencing the effect.16,17

Aside from trials in animal models, human studies concerning the effect of HUCMSCs have been conducted (Table 1). Salim et al. used injection HUCMSCs intrathecally and intravenously for the patient who was previously diagnosed with spinal cord entrapment with chronic kidney disease as comorbidity. This paper reported an improvement in patients’ movement and kidney function.18 Deng et al. did a study to evaluate the efficacy of HUCMSCs for lupus nephritis. They concluded that even HUCMSCs did not show any obvious additional effects on lupus nephritis, but it have been demonstrated clear results on other conditions such as graft versus host disease.39 Despite that MSC has been used for kidney disease, the implantation of MSC is more widely used in other aspects, such as cardiovascular, neurological, oncological/hematological, and gastrointestinal diseases.30 MSC-based clinical trials for kidney disease only accounted for 1.8% of 493 MSC-based clinical trials. Despite studies with animal models showing promising results, MSC-based clinical trials for kidney disease remain in early phases, determining the safety and efficacy of the implantation of allogeneic MSC.22 Current clinical trials conducted worldwide using MSC to treat kidney diseases mostly use autologous or allogeneic bone marrow MSC and adipocyte-derived MSC. The use of allogeneic umbilical cord MSC is not as frequent as the other types of MSC. Currently, HUCMSCs are used to treat lupus nephritis and systemic lupus erythematosus. However, MSC from many sources shows us wide applicability for kidney diseases, from acute kidney injury, chronic kidney injury, focal segmental glomerular sclerosis, diabetic kidney disease, autoimmune disease, and kidney transplantation.22 For example, kidney transplants require MSC injection several days before the transplantation to induce tolerance before the engraftment and prevent graft-versus-host disease.23,24

The efficacy and the safety of HUCMSCs implantation remain controversial. There are some reports regarding the safety of HUCMSCs implantation, such as nephrotic syndrome in patient with acute lymphoblastic leukemia and thromboembolism. However, these conditions can be treated well.42,43 Lalu et al. conducted a meta-analysis which concluded that MSC therapy via intravascular appears safe, but further studies are needed to ensure the results, particularly larger randomized controlled trials. Generally, primary adverse events were fever, organ dysfunction, graft versus host disease, and death. However, in this study, we have not found any studies concerning the adverse effect of MSCs in chronic kidney disease therapy.

**CONCLUSION**

Transplantation of HUCMSCs for renal diseases shows promising results. However, further studies were needed to ensure the safety of the treatment.

**DISCLOSURE**

**Author Contribution**

All authors contributed equally in writing and editing this article.

**Ethical Consideration**

None.

**Conflict of Interest**

All authors stated no conflict of interest regarding writing and publishing this article.

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