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Review

Transplantation of Umbilical Cord Blood–Derived Cells for Novel Indications in Regenerative Therapy or Immune Modulation: A Scoping Review of Clinical Studies

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A B S T R A C T

Although used mainly for transplantation of hematopoietic stem cells in the treatment of blood disorders, umbilical cord blood (UCB)-based therapies are now being used increasingly for novel applications in non-hematopoietic diseases and as a form of cellular regenerative therapy or immune modulation. We performed a systematic scoping review by searching Medline, EMBASE, and the Cochrane Library for published articles, and we searched www.clinicaltrials.com and the World Health Organization International Clinical Trials Registry Platform to describe the breadth of published studies and ongoing clinical activity in umbilical cord-based cellular therapy for regenerative therapy and immune modulation. The most commonly published area of expertise in the use of UCB-derived cellular transplantation for novel indications is for neurological disorders and this remains the most active area of study in ongoing registered trials. An increasingly broad range of disorders, however, are reflected in ongoing registered trials, which suggests greater activity, interest, and investment in UCB-derived cellular therapy. Interestingly, adult patients compose the majority of patients reported in published reports and registered ongoing clinical studies continue to enroll predominantly adult subjects. Geographically, Asian countries appear most active in UCB-derived cellular therapy and our analysis of ongoing studies suggests this trend will likely continue. Regular assessment of published and ongoing activity in UCB transplantation for emerging novel indications will be critical for informing UCB banking establishments and funding agencies to guide changes in banking practices related to emerging trends in cell therapy.

INTRODUCTION

Transplantation of cells derived from human umbilical cord blood (UCB) has demonstrated increasing promise in the treatment of both malignant and nonmalignant diseases [1-3]. Following the first successful transplantation of UCB in 1988 for the treatment of Fanconi's anemia [4], the past decades have led to increased use of cord blood as a source of cells for hematopoietic stem cell transplantation to treat a range of hematological and nonhematolgioical diseases [5]. UCB also contains nonhematopoietic stem and progenitor cells capable of differentiating into epithelial [6] or endothelial cell progenitors [7,8], mesenchymal stromal cells (MSCs), unrestricted somatic stem cells [9], and neural progenitor cells [10]. The therapeutic potential of stem and progenitor cells in UCB to treat a broad range of disorders has led to increasing use of UCB transplantation to treat patients with nonhematopoietic diseases, including applications in regenerative therapy and modulation of refractory autoimmune diseases.

UCB cells can be cryopreserved and stored for years without significant loss of viability, making them readily available for immediate transplantation in most instances [11,12]. Public banking of UCB has become more widespread in many parts of the world [13], providing easy access to UCB units from worldwide registries [12]. Private banking of cord blood is also available in many jurisdictions. The increased demand for UCB banking has led to the development of regulatory bodies for quality control, including the American Association of Blood Banks and the Foundation for Accreditation of Cellular Therapy [14,15].

Although used mainly for transplantation of hematopoietic stem cells in the treatment of blood disorders, UCB-based therapies are now being used increasingly for novel applications in nonhematopoietic diseases and as a form of cellular regenerative therapy or immune modulation. In this systematic scoping review, we describe the breadth of published studies and ongoing clinical activity in umbilical cord-based cellular therapy for regenerative therapy and immune modulation. Our primary goal was to identify current trends in cell-based therapy using UCB that would inform cord blood banking establishments and transplantation centers regarding current and emerging trends related to methods of cell manipulation and indications for using cord blood in regenerative medicine and immune modulation.

MATERIALS AND METHODS

Searching for Relevant Published Trials

We sought to identify studies that described the use of human UCB to treat patients for nonconventional indications that addressed regenerative therapy or modulation of immune disorders. A systematic scoping review of all published trials was performed in accordance with guidelines suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [16]. We performed a search on the following databases using the OVID interface: (1) MEDLINE (1950 to week 26 of 2012), (2) EMBASE (1980 to

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Search Strategy:

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1 Fetal Blood/cy, tr (5693)
2 fetal blood/ and Hematopoietic Stem Cell Transplantation/ (1115)
3 Cord Blood Stem Cell Transplantation/ (1875)
4 uc blood.tw. (50)
5 (umbilical adj2 blood).tw. (8402)
6 (cord adj2 blood).tw. (19258)
7 (placenta$ blood adj2 transplant$).tw. (17)
8 or/1-7 (22852)
9 Regenerative Medicine/ (2141)
10 exp Regeneration/ (157579)
11 regener$.tw. (104758)
12 Basilar Artery/su or (basilar adj2 arter$ dissection$).tw. (505)
13 Ischemia/ or (Limb$ adj2 ischemia$).tw. (44373)
14 Cardiomyopathy, Dilated/ or (congestive adj2 cardiomyopath$).tw. or (familial idiopath$ adj2 cardiomyopath$).tw. or (cardiomyopath$ adj2 dilat$).tw. (17665)
15 Hypoplastic Left Heart Syndrome/ or (hypoplasti$ adj3 left heart syndrome$).tw. (2051)
16 Diabetic Foot/ or (diabet$ adj3 foot$).tw. or (diabet$ adj3 feet$).tw. (7001)
17 Spinal Cord Injuries/ or (spinal cord adj3 contusion$).tw. or (spinal cord adj3 injur$).tw. or (spinal cord adj3 trauma$).tw. or (spinal cord adj3 laceration$).tw. or (myelopath$ adj3 post-traumatic).tw. or (myelopath$ adj3 posttraumatic).tw. or (traumatic adj3 myelopath$).tw. or (spinal cord adj3 transection$).tw. (33613)
18 Cerebral Palsy/ or cerebral pals$.tw. or (diplegia$ adj2 spastic).tw. or little$ disease.tw. (18522)
19 Cerebellar Ataxia/ or (Incoordination$ adj3 cerebellar).tw. or Adiadochokin$.tw. or Hypermetria$.tw. or (Ataxia$ adj3 cerebellar).tw. or (cerebellar adj2 hemiataxia$).tw. or dysmetria$.tw. (6336)
20 Brain Injuries/ or (encephalopath$ adj3 post concussive).tw. or (traumatic adj3 encephalopath$).tw. or (brain adj3 laceration$).tw. or (trauma$ adj3 brain).tw. or (injur$ adj3 brain).tw. or (contusion$ adj3 brain).tw. or (cortical adj3 contusion$).tw. (57956)
21 Hypoxia-Ischemia, Brain/ or (Anoxi$ adj3 ischemia$).tw. or (hypoxi$ adj3 ischemi$).tw. (9085)
22 Brain Ischemia/ or Stroke/ or (Encephalopath$ adj3 ischemi$).tw. or (Ischemia$ adj3 cerebral).tw. or (Brain adj3 ischemi$).tw. or (chronic ischemi$ adj3 stroke).tw. (89138)
23 Amyotrophic Lateral Sclerosis/ or (disease adj2 guam).tw. or (Gehrig$ adj2 disease$).tw. or (amyotrophic adj4 lateral sclerosis).tw. or als.tw. or motor neuron disease.tw. (21881)
24 Diabetes Mellitus, Type 1/ or (Autoimmun$ adj3 diabet$).tw. or (Diabete$ mellitus adj4 sudden onset).tw. or (Diabete$ mellitus adj4 brittle).tw. or iddm.tw. or (diabetes mellitus adj5 insulin dependent).tw. or (ketosis prone adj4 diabetes mellitus).tw. or (juvenile onset adj5 diabete$ mellitus).tw. or (type 1 adj4 diabete$).tw. (72905)
25 Liver Cirrhosis/ or (Fibros$ adj3 liver).tw. or (Cirrhos$ adj2 hepatic).tw. or (Cirrhos$ adj2 liver).tw. (66791)
26 Thromboangiitis Obliterans/ or (Buerger$ adj2 disease$).tw. or thromboangitis obliterans.tw. (2841)
27 exp Eye Diseases/ or ocular surface disease$.tw. or ocular surface disorder$.tw. or asthenopia.tw. or cogan syndrome$.tw. or conjunctival disease$.tw. or corneal disease$.tw. (425213)
28 exp Hearing loss/ or Acquired hearing loss.tw. (51193)
29 Infant, Premature/ or premature$ infan$.tw. or preterm infan$.tw. or extremely low birth weight$.tw. (50626)
30 or/9-29 (1140445)
31 8 and 30 (2366)
32 clinical trial.pt. (476541)
33 exp clinical trial/ (705850)
34 randomized controlled trial.pt. (342317)
35 controlled clinical trial.pt. (85680)
36 randomi?ed.ab. (309312)
37 placebo.ab. (141651)
38 trial.ti. (111077)
39 exp Clinical Trials as Topic/ (264111)
40 multicenter study.pt. (152981)
41 exp epidemiologic studies/ (1487306)
42 (cohort adj2 (study or analysis)).tw. (72043)
43 (case adj2 (control$ or series or report$)).tw. (400611)
44 case reports.pt. (1609515)
45 or/32-44 (3879201)
46 31 and 45 (471)
47 animals/ not humans/ (3717560)
48 46 not 47 (451)
49 limit 48 to yr="1860 - 2012" (451)
50 ("20120726" or "20120727" or "20120728" or "20120729" or "20120730" or "20120731" or 201208$ or 201209$ or 201210$ or 201211$).ed. (460226)
51 49 not 50 (434)

Figure 1. Search Strategy used in Ovid MEDLINE(R) In-Process and Other Nonindexed Citations and Ovid MEDLINE(R), 1946 to present; limited to July 25, 2012.