Abstract

Although cardiosphere-derived cells (CDCs) improve cardiac function and outcomes in patients with single ventricle physiology, little is known about their safety and therapeutic benefit in children with dilated cardiomyopathy (DCM). We aimed to determine the safety and efficacy of CDCs in a porcine model of DCM and translate the preclinical results into this patient population. A swine model of DCM using intracoronary injection of microspheres created cardiac dysfunction. Forty pigs were randomized as preclinical validation of the delivery method and CDC doses, and CDC-secreted exosomes (CDCex)-mediated cardiac repair was analyzed. A phase 1 safety cohort enrolled 5 pediatric patients with DCM and reduced ejection fraction to receive CDC infusion. The primary endpoint was to assess safety, and the secondary outcome measure was change in cardiac function. Improved cardiac function and reduced myocardial fibrosis were noted in animals treated with CDCs compared with placebo. These functional benefits were mediated via CDCex that were highly enriched with proangiogenic and cardioprotective microRNAs (miRNAs), whereas isolated CDCex did not recapitulate these reparative effects. One-year follow-up of safety lead-in stage was completed with favorable profile and preliminary efficacy outcomes. Increased CDCex-derived miR-146a-5p expression was associated with the reduction in myocardial fibrosis via suppression of proinflammatory cytokines and transcripts. Collectively, intracoronary CDC administration is safe and improves cardiac function through CDCex in a porcine model of DCM. The safety lead-in results in patients provide a translational framework for further studies of randomized trials and CDCex-derived miRNAs as potential paracrine mediators underlying this therapeutic strategy.