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Accelerated Post-infarct Neovascularization and Tissue Repair by Chemotherapy-combined G-CSF May Be Related to Peripheral CD34+ Cells Increased via CXCR4-SDF-1 Axis

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Background. Recently, we reported that G-CSF combined with 5-fluorouracil (5FU) and cyclophosphamide (Cy) enhanced infarcted-tissue repair (neovascularization, myofibroblast proliferation, reducing old infarct area as fibrosis) and improved cardiac function and remodeling more than G-CSF alone in reperfused myocardial infarction (MI). In the present study, we investigated the mechanism of the beneficial effect. **Methods and Results.** MI-rabbits were treated with G-CSF after 5FU and Cy (5FUCyG), 5FU and Cy (5FUCy), G-CSF (G) or saline (S). 5FUCyG, compared with the other groups, significantly increased circulating $CD34^+$ cells expressing CXCR4, contributing to neovascularization. $RAM11^+$-macrophages in infarct area were significantly increased at acute and subacute stage of MI, which is favorable for sweeping of damaged tissues earlier. An increase of serum stromal cell-derived factor-1 (SDF-1: a chemoattractant of $CXCR4^+$ cells) and an upregulation of SDF-1 in the risk areas in 5FUCyG were shown. Western blotting revealed that matrix metalloproteinase (MMP)-1, a collagenase, were markedly enhanced from acute to subacute phase of MI. AMD3100, a CXCR4 antagonist, blocked the above effect of improving cardiac function, suggesting that CXCR4/SDF-1 axis may play an important role in whole the mechanism. **Conclusion.** The beneficial effect of G-CSF with chemotherapy may be related to mobilization of progenitor cells involved in CXCR4-SDF-1 axis, and expression of MMP-1.

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Differentiation of Monkey ES Cells into Cardiac Myocytes And Their Delivery into the Monkey Infracted Myocardium through PTCA Balloon Catheters

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Embryonic stem (ES) cell transplantation preserves left ventricular function following myocardial infarction in rodents. We previously reported that a histone deacetylase inhibitor, trichostatin A (TSA), acetylates a cardiac zinc finger protein GATA-4 as well as histones, and enhances myocardial cell differentiation in mouse ES cells. In order to perform pre-clinical studies in primates, we have established a system of monkey ES cell differentiation into cardiac myocytes and delivered these cells into the monkey infarcted myocardium. Embryonic bodies (EBs), produced by culturing ES cell aggregates, were transferred into gelatinized or non-gelatinized dishes, and then stimulated with TSA. The percentage of beating EBs was the highest in gelatinized dishes with TSA (8%) and the lowest (3%) in non-gelatinized dishes without TSA. Myocardial cell differentiation was also confirmed by immunocytochemistry for β-myosin heavy chain (MHC). After EB formation, we delivered monkey ES cells constitutively expressing yellow fluorescence protein (YFP) through the central lumen of PTCA balloon catheter following balloon occlusion for 60 minutes. At 10 days after the delivery without any immuno-suppressants, we observed YFP-positive cells around the infarcted area. Some of them were positive for both YFP and β-MHC. Thus, this system will be useful to test whether ES cell therapy for myocardial infarction will be applicable in human.

Congenital Heart Disease / Kawasaki's Disease 1 (M)

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Congenital Heart Disease Management in Developing Country: the Indonesian Experience

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Congenital Heart Disease (CHD) is the most common and most fatal congenital abnormality, without surgery fifty percent of the symptomatic patients die in the first month of life. The scope of services to babies and children with CHD in Indonesia is still low. Every year more than 40.000 babies born with CHD, sixty percent from that figure or at least 24.000 children need surgical intervention before they reached the age of one year. Figure of surgery for this kind of abnormalities in the whole country range at 600 - 700 cases per year, only a small percentage were infant. It means the appropriate treatment coverage for CHD is less than two percent. The high infant mortality rate in Indonesia could be due to this condition, many infants died with cardiorespiratory failure without appropriate diagnosis and treatment.

The reason for this extraordinary attrition are many. Perhaps the most important one is lack of awareness. The overwhelming majority of pediatricians receive little training in pediatric cardiology simply because there are only 20 pediatric cardiologist in Indonesia and half of them work in Jakarta. Only a small proportion of children with CHD are diagnosed in a timely fashion. After diagnosis, there is considerable delay in referral to a pediatric cardiac center because the critical need for early referral is not widely appreciated. There are major logistic hurdles as well. Vast area of Indonesia have no pediatric cardiac surgical facilities, there are only two pediatric cardiac surgeons serving for the whole country and both are working in the National Cardiovascular Center Harapan Kita (NCC-HK) where most of the cases were operated. Despite subsidies from hospital, voluntary organization, and the government, pediatric cardiac care is too expensive for the average Indonesian family.

The advances in pediatric interventional cardiac catheterization have changed the therapeutic strategy for many patients with CHD. Intervention such as Balloon Pulmonal Valvoplasty, Balloon Atrial Septostomy were routinely performed. Transcatheter closure for Patent Ductus Arteriosus and Atrial Septal Defect using Amplatzer devices were started since two years ago, but in Indonesia these procedures were substantially more expensive than surgical treatment.

With the advanced of myocardial preservation and post operative care, more babies and neonates underwent primary repair for their cardiac abnormalities in NCC-HK. All types of CHD were operated, except Hypoplastic Left Heart Syndrome. The overall mortality rate in this center range at 6 - 7%, the highest mortality rate is for arterial switch and modified Rastelly operation using self design monocusp, since homograft is not available.

In conclusion, based on this reality, Indonesia still has a long way to go before reaching an International standard of care for children with CHD.