CD133$^+$ cells: How could they have an IMPACT?

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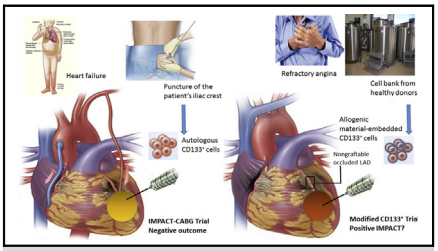

IMPACT: Today and tomorrow?

Central Message

Injections of CD133 cells combined with CABG did not improve outcomes but a greater therapeutic effect might be achieved by controlling bioactivity and selectively targeting patients with ischemia.

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The Implantation of Autologous CD133$^+$ Stem Cells in Patients Undergoing CABG (IMPACT-CABG) trial reported in this issue of the *Journal* by Noiseux and colleagues[1] randomly assigned 34 patients undergoing coronary artery bypass grafting to receive concomitant intramyocardial injections of CD133$^+$ progenitor cells (n = 19) or a placebo solution (n = 14). The results documented the safety of the procedure but failed to show a significant improvement of the functional outcome in the treated group. This study should not be considered "negative," however, because some clinically relevant lessons can be drawn from its results. At least 3 are worth discussion.

The first lesson pertains to the choice of the cells in relation to the target patient population. There is now compelling evidence that cells expressing the CD133 antigen, a marker for immature endothelial progenitor cells, do not transdifferentiate into cardiomyocytes. They are rather credited to act predominantly through the release of factors that paracrinally activate several endogenous pathways, particularly those involved in angiogenesis.[2] Because the IMPACT-CABG trial did not include measures of myocardial perfusion,[1] it remains unknown whether the injected CD133$^+$ cells exerted any angiogenic effect similar to those reported in the Cardio133 trial,[3] in which similar intramyocardial injections of CD133$^+$ cells combined with coronary revascularization increased myocardial perfusion relative to the control placebo-injected group but without a concomitant improvement in left ventricular function. Altogether, these data question whether left ventricular dysfunction represents the best indication for this type of angiogenesis-targeted cell. On the basis of the postulated mechanism of action of these cells, refractory angina could be a more appropriate target, an assumption supported by the trend toward reduction in angina frequency and the improvements in total exercise time in patients receiving endomyocardial injections of CD34$^+$ cells,[4] cells endowed with angiogenic properties similar to those expressing the CD133 marker. In line with this reasoning, another currently ongoing CD133$^+$ cell trial (NCT 02870933) has selected myocardial perfusion as the primary outcome measure.

A second lesson is related to dosing and function of the cells. In this trial, 6.5 ± 3.1 million cells were injected with a very wide range (0.8-9.8 × 10^6). Given the high rate of cell death shortly after injections, the residual number of those that initially survived may have been too low for inducing measurable cardioprotective effects. Indeed, almost all CD133$^+$ cell trials have faced this dosing issue, because these progenitors only represent a tiny fraction of bone marrow cells. Because the yield recovered after immunomagnetic sorting is not easily scalable in vitro, the common means of increasing the number of CD133$^+$ cells is to boost their mobilization from the bone marrow by means of cytokines, such as the granulocyte-colony stimulating factor, but this procedure was not implemented in the IMPACT-CABG trial. Admittedly, Noiseux and colleagues[1] reported that they did not see a correlation between the number of injected cells and the functional outcome; however, this finding is at variance with the data from the Cardiovascular Cell Therapy Research Network–sponsored Use of Adult Autologous Stem Cells in Treating People 2 to 3 Weeks After Having a Heart Attack trial (Late-TIME study),[5] in which changes in left ventricular ejection fraction in patients with a recent myocardial infarction were positively correlated with the number of CD133$^+$ cells. Aside from dosing, however, the functionality of the cells may be a more strongly predictive factor of a therapeutic success. Unfortunately, no conclusion can be drawn from the data of Noiseux and colleagues,[1] because the

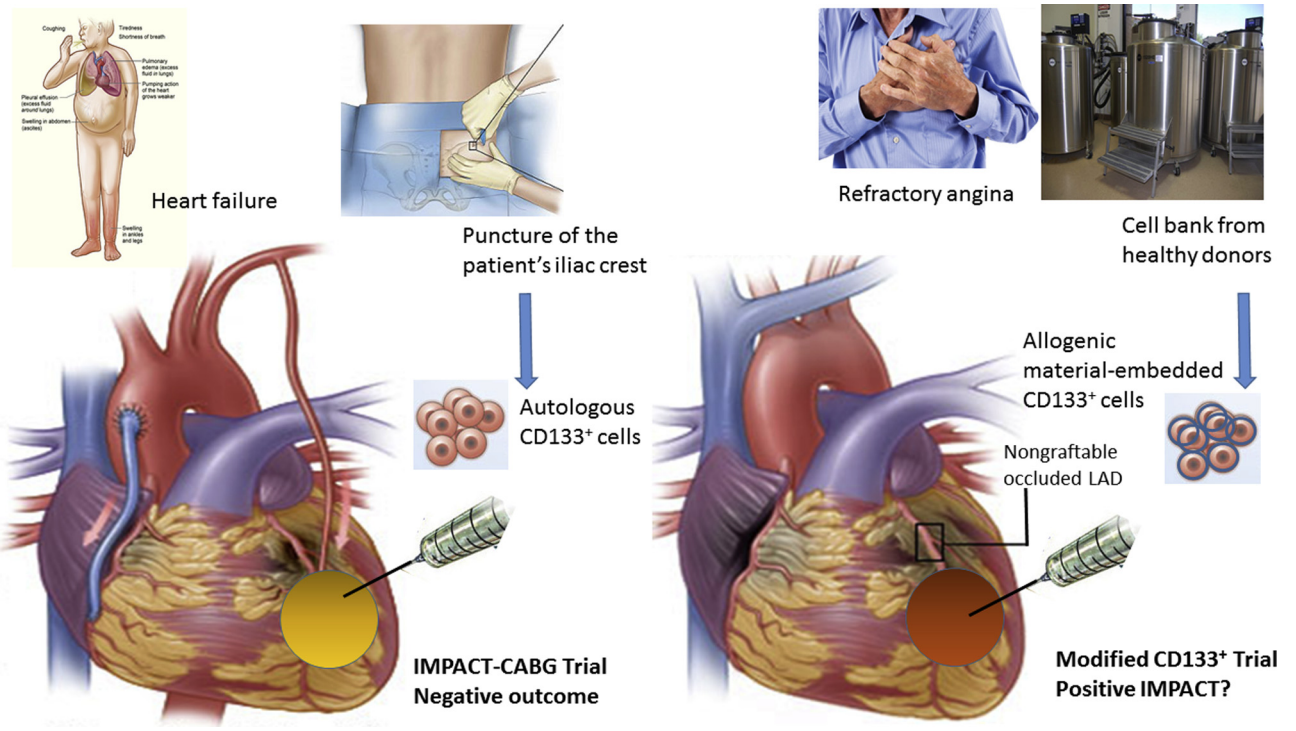

FIGURE 1. The IMPACT-CABG trial has had negative results. Might a modified protocol with allogeneic rather than autologous CD133$^+$ cells delivered in nonrevascularizable areas in patients with refractory angina show success? *LAD*, Left anterior descending coronary artery; *IMPACT-CABG*, Implantation of Autologous CD133$^+$ Stem Cells in Patients Undergoing CABG.

bioactivities of the individual cell preparations were not assessed for subsequent correlation with patient outcomes. One might expect, however, that it varied in concert with multiple risk factors, such as age and the extent of coronary artery disease.[6] This likely heterogeneity in cell function may have contributed to different responses among patients that, once pooled together, resulted in an overall neutral outcome. Collectively, these data raise the possibility of transplanting allogeneic CD133$^+$ cells[7] derived from a functionally well-qualified cell bank, provided their incorporation within a biomaterial delays their expected rejection and consequently gives them enough time to release the factors underpinning their protective effects.[8]

The third lesson relates to the modalities of cell delivery. In the IMPACT-CABG trial, all patients but 1 received CD133$^+$ cells in myocardial areas that were simultaneously revascularized. The possibility thus cannot be excluded that the positive effect of coronary bypass outweighed that of the cells, thereby precluding the researchers from unraveling their possible cardioprotective effect. Targeting the same areas for revascularization and cell injections is also conceptually questionable if one admits that CD133$^+$ cells primarily act by improving angiogenesis, a pathway that is also targeted by the bypass conduits. Transplantation of CD133$^+$ cells exclusively in areas that have both documented ischemia and still-viable myocardium but are unsuitable for surgical revascularization should allow to more selectively assess the potential benefits of these cells. Such a design has been adopted in the Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial, which entails the transplantation of mesenchymal stem cells.[9]

In summary, even though the primary end point of the IMPACT-CABG trial was not met, the analysis of the possible causes of this neutral result suggests that CD133$^+$ cells might acquire a clinically relevant therapeutic impact if their bioactivity were to be leveraged to a functionally well-qualified allogenic product delivered as a standalone treatment in patients whose clinical presentation is dominated by ischemic symptoms (Figure 1).

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