Commentary

The Royal Society of Medicine

Journal of the Royal Society of Medicine; 0(0) 1–3
DOI: 10.1177/0141076819851657

Transplanted stem cells survive a long time: do they make you sick?

Greg Maguire
BioRegenerative Sciences Inc., San Diego, La Jolla, CA 92037, USA
Corresponding author: Greg Maguire. Email: gregmaguire5@gmail.com

Adult stem cell transplants have been used for over 40 years[1] to save the lives of those with severe blood diseases. Success with this procedure has given widespread optimism for developing additional stem cell-based therapies for a wide range of diseases. Scientists have even made progress in repairing organs or generating new organs from stem cells, including, for example, kidney tissue.[2] While we have learned much about stem cell biology, and indeed stem cell therapeutics in the last decade, disappointments in translating this knowledge into approved medical therapies are many.[3] The many mechanisms of action arising from stem cell transplants, including those leading to adverse events, are still poorly understood. For example, even in well-controlled clinical trials when transarterial administration of autologous bone marrow stem cells were administered, an inflammatory response, including macrophage expansion, was observed when compared to control patients.[4] Haematopoietic stem and progenitor cells are responsible for generating and maintaining the extremely diverse pool of blood cells, everything from red blood cells to T-cells, for our lifetime. For treating blood diseases such as acute myeloid leukaemia, HSPC transplantation, also known as bone marrow transplantation, remains the only approved stem cell therapy, even though unapproved stem cell transplants for a variety of other indications continue to burgeon, especially in the USA,[5] often with disastrous results including loss of vision.[6] The approved, clinical transplantation of human haematopoietic stem and progenitor cells from an allogeneic healthy donor can effectively replenish defective blood cell production caused by congenital or acquired disorders, but, as with most medical products or procedures, there are risks involved. Many case studies have reported the approved stem cell transplants to be associated with the later development of cancer,[7] and unapproved stem cell transplant procedures are notorious for adverse side effects, including the development of cancer.[8] Recent studies show that the transplanted stem cells may survive for years in the transplanted patient,[9] presenting a long-term source of potential adverse side effects. Unfortunately, with most drugs and many medical procedures, the long-term consequences to health are unknown. Often, when considering drugs, not until phase IV, post-market approval are the long-term consequences of a drug discovered. There are many drugs pulled from the market or with newly discovered safety issues three to four years after their original approval.[10,11] Even more unfortunate, the problem is worse with medical procedures.[12] Such is the case with approved stem cell transplants. The effects of approved stem cell transplants in causing, or being involved, in cancer relapse are not well understood but are thought to involve epigenetic factors in the stem cells used for the transplant.[13] In addition, any type of stem cell transplant may cause ageing of the tissue as measured in T-cells using a p16 biomarker,[14] indicating the increased level of cellular senescence in the surrounding tissue.

So what are some of the possible mechanisms for stem cells to cause these untoward and unpropitious side effects? First, a new study shows that transplanted stem cells (haematopoietic stem and progenitor cells) can survive a long time in human patients, such that they can be maintained independently of their continuous production from endogenous haematopoietic stem and progenitor cells.[9] Second, we know that processed stem cells can carry an increasing number of genetic mutations as they are expanded, particularly the p53 mutation associated with many cancer phenotypes.[15] Furthermore, stem cells have memory and change their phenotype, for at least many months, when they have experienced a wounding, inflammatory event.[16] The new phenotype that Naik et al.[16] measured was one of an increased probability to proliferate, a cancer-like cellular behaviour. An underlying mechanism for the increased probability of proliferation appeared to be epigenetic, where the DNA was less tightly bound around its histone protein. If we synthesise these data, stem cell

transplants using cells that have genotypic, epigenotypic and phenotypic changes conducive to proliferation, and given the cells ability to engraft, survive and remain viable for long periods means that the cells may be a cause of cancer. Furthermore, consider that the differentiated state of a cell, normal or malignant, is unstable and that the state is dependent on the cell's extracellular matrix and microenvironment,[17] such that, for example, p53 is regulated by laminin and the basement membrane in the cell's microenvironment.[18] These mechanisms underlie, in part, the ability of the extracellular matrix acting though mechanical forces to revert the cancerous phenotype to a normal somatic phenotype.[19] Therefore, if the stem cells transplanted into the patient implant and survive in a dysregulated extracellular matrix/microenvironment, the cancerous phenotype may be expressed. The aforementioned factors, coupled with the possible induction of ageing in the surrounding tissue,[14] another risk factor for cancer, suggest that stem cell transplants may pose a significant risk for cancer as well as other potential problems because of the way they are processed.[20] Problems, such as genetic instability of the stem cells to be transplanted, can likely be overcome with further study. For example, adipose-derived mesenchymal stem cells possess better genetic stability than do bone marrow stem cells as they age and replicate. Adipose-derived mesenchymal stem cells cultures retained the normal diploid (2n) karyotype better than did bone marrow stem cells up to passage 20 for human bone marrow stem cells and passage 30 for human adipose-derived mesenchymal stem cells.[21] Furthermore, as mesenchymal stem cells double in culture, adipose-derived mesenchymal stem cells are less inclined to express the senescent phenotype than are bone marrow stem cells.[22] Thus, a better understanding of stem cell types and their various phenotypes, providing a knowledge base for use in cell selection, may very well overcome many of the current challenges in stem cell transplantation. The problems with stem cell transplants also leads to the argument for the development of a 'systems therapeutic' using stem cell released molecules,[23] instead of the cells,[24] for many indications, such as amytrophic lateral sclerosis and other neurodegenerative diseases.[25] While the promise of stem cell therapeutics is currently being realised with approved stem cell transplants for blood diseases, and a wide array of treatments are on the horizon, as wide ranging as oesophageal replacement[26] and central nervous system repair,[27] the current problems with stem cell transplants means that they should be carefully used in life-threatening conditions or where their benefits clearly outweigh the risks.

With further research, the development of stem cell-based therapeutics will likely benefit many medical issues, including, for example, solid organ transplantation that provides life-saving therapy for patients with end-stage organ disease but lifelong requirements for immunosuppressive drugs that increase the risk of infections, cancer and toxicity. Already, normothermic machine perfusion, a technique for repairing marginal organs before transplantation,[28] has been successfully used to reduce delayed graft function and to improve renal function at one-year post-transplantation.[29] Given that adipose-derived mesenchymal stem cells, and their released molecules acting as a 'systems therapeutic', may induce host tolerance to alloantigens associated with the graft versus host disease,[30] machine perfusion of the donor organ with stem cells or their molecules as well as the recipient patient may provide a new means to increase the success rate of organ transplants, even when marginal organs are used. Furthermore, the need for immunosuppressive drugs may be eliminated or reduced using these combined methodologies. In time with more research and development, the risk versus reward of stem cell therapy will be better understood, and the ratio more skewed toward reward.

Declarations

Competing Interests: GM has equity in BioRegenerative Sciences Inc.

Funding: None declared.

Ethics approval: Not applicable.

Guarantor: GM.

Contributorship: Sole authorship.

Acknowledgements: None.

Provenance: Not commissioned; peer-reviewed by Maria Irene Bellini.

ORCID iD

Greg Maguire https://orcid.org/0000-0001-5484-6157

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