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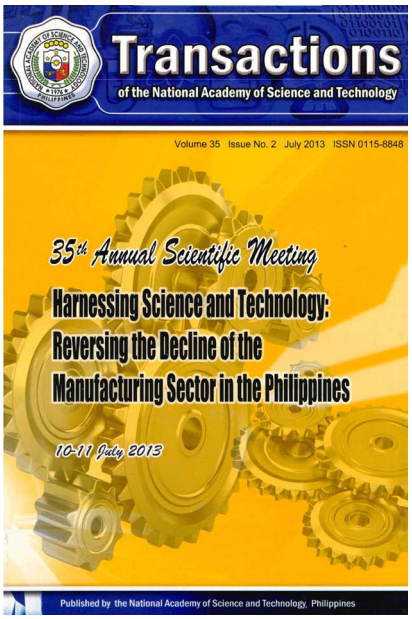

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ETHICAL CONSIDERATION IN STEM CELL THERAPY AND RESEARCH IN RESOURCE POOR COUNTRIES

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Abstract

Success in bone marrow transplantation and the discovery of pluripotent embryonic cells have fueled much scientific interest in the potential therapeutic uses of stem cells. The recent development of techniques to grow human embryonic stem cells in culture and an increased understanding of the pathways of cell differentiation have expanded the clinical prospects for the use of stem cells.

The term "stem cell—based products" is used to refer to products intended to be administered to a patient and that contain or are derived from stem cells. "Stem-cell–based products" may not always contain stem cells. In some cases, multipotent cells might be transplanted, which would give rise to terminally differentiated cells in vivo (direct administration). In other cases, it might be desirable to allow the cells to differentiate fully in culture before transplanting them or to transplant a mixture of multipotent cells and differentiated cells (tissue engineering).

Claims of clinical effectiveness must show that the cells home to the diseased or injured tissue. They must engraft, not just fuse with cells that are already there. They have to function. They must persist.

The use of embryonic stem cells is controversial because of the lack of agreement regarding the personhood of embryos. The discovery of the multipotential charateristics of adult stem cells has relegated this issue to the fringes. The main ethical issue is the difficulty of balancing risks and benefits because of cell cuture techniques being potential sources of undesirable agents causing harm and because of the uncertainty of risks and long-term effects of stem cell administration. Moreover, there is lack of good animal models for target diseases so that the first in human trials is very difficult to justify and put up. Ethical review of stem cell research protocols has thus become very complicated.

Ethical issues arise from the vulnerability of people in resource-poor countries – cognitively, deferentially, medically, allocationally and infrastructurally. Further – there is no quality assurance system in place. Conflict of interest situations exist when the stem cell producer is also the health care provider. Finally, social justice needs to be addressed to ensure that the divide in health care service between the rich and the poor is not widened when stem cell therapy is integrated into the health system.

It is recommended that wider consultations and conversations with the community be conducted so that a better understanding of the stakes in stem cell use is generated. A quality assurance system must be put in place to ensure quality stem cell products. Scientific and ethical review systems must be strengthened in all institutions so that conflict of interest situations may be effectively addressed. Publication of positive and negative experiences in the use of stem cells should be mandated. Finally, a national policy on the use of stem cells must take into consideration social justice.

Keywords: Stem cell products, stem cell therapy, ethical issues in use of stem cells

Introduction

Success in bone marrow transplantation and the discovery of pluripotent embryonic cells have fueled much scientific interest in the potential therapeutic uses of stem cells. The recent development of techniques to grow human embryonic stem cells in culture and an increased understanding of the pathways of cell differentiation have expanded the clinical prospects for the use of stem cells. This presentation shall be a discussion not only of general ethical issues but also about unique ethical concerns in the conduct of experimental therapies using stem cells and related research activities in a resource-poor country like the Philippines.

Topic Sequence

I shall first clarify what stem cell based products are, and the meaning of clinical effectiveness. Then, I shall proceed to the identification of general

ethical issues in stem cell therapy and research; and the unique ethical issues in resource poor countries like the Philippines. Finally, I would like to make some suggestions on how we can address these ethical issues.

Definitions

Stem cell products refer to materials intended to be administered to a patient that contain or are derived from stem cells. This means that some so called stem cell products do not really contain stem cells. This is because there are three (3) ways of presenting stem cell products.

One way is when stem cells are directly transplanted into the body with the expectation that terminal differentiation will take place *in vivo*. This is what happens in therapeutic stem `cell transplantation in the bone marrow or when one aims to foster tissue repairs in the central nervous system.

The other way is by transplantation of differentiated stem cell progeny. Meaning, stem cell are harvested, then differentiation is induced *ex-vivo* (outside of the body) and what is introduced into the body are the differentiated cells. In this manner, the product no longer contains the stem cells, instead it contains differentiated cells.

Tissue engineering is a therapeutic approach for rebuilding whole tissues like bone or vascular walls. Here, stem cells and differentiated cells are put together in consideration of the variety of cell types that constitute the tissue. Thus, in this case, one has a mix of stem cells and differentiated cells.

How about clinical effectiveness? I think this is very important to understand in the evaluation of the efficacy or effectiveness of stem cell therapy. When one claims that a particular stem cell therapy is effective, it must first be demonstrated that the stem cells have reached the diseased or injured tissue like if one is using liver stem cells these are supposed to home on to the liver. Then, there must be evidence of engraftment not just fusion with the other liver cells. This means that the stem cells must function and must persist. If the cells disappear right away or they do not function - there is no successful engraftment. In this case, there is no basis to claim clinical effectiveness.

Use of Stem Cells

There are several contexts when one talks about stem cell therapy.

One may be referring to standard stem cell treatment which at the moment has been established only for hematopoietic disorders. In his lecture, Dr. Chung mentioned the 2010 permission to use the dendritic cell application for prostate cancer. Well, technically speaking – dendritic cells are not stem cells. Aside from these, there are no other standard treatment using stem cells.

The other possible stem cell applications are in clinical trials. Dr. Chung mentioned thousands of approved clinical trials in different phases, i.e., phase 1, phase 2, or phase 3 clinical tials. I believe that most are in phase 1, (meaning first in human trials), while a few are in phase 2. Very few will be in phase 3. Please note that in phase 1, the first in human trial, the study is not on effectiveness, but on safety,

The third possible use of stem cells is in experimental therapy. Now, this is the gray area. **Helsinki 2008 (Statement 35)** says that in *the treatment of a patient where proven interventions do not exist or have been ineffective, the physician after seeking expert advice with informed consent from the patient or a legally authorized representative may use unproven interventions. If in the physician's judgment, it offers hope of saving life, re-establishing health or alleviating suffering, the goals of medicine. Whenever possible, the intervention should be made, the object of research (*so it becomes now clinical trial, designed to evaluate its safety and efficacy). *In all cases, new information should be recorded and when they are publicly made available.* So, that's the guideline from Helsinki. This guideline emphasized several items in the use of experimental therapy, viz, (1) proven interventions do not exist or have been ineffective, (2) expert advice must be sought, (3) voluntary informed consent of the patient or legally authorized representative, (4) The intervention should be made the object of a research and (5) New information should be recorded and made publicly available.

What these mean is that aside from the basic requirements for good motives (untainted with financial interests) and voluntary informed consent , innovative therapy cannot go on and on without a publicly disseminated scientific report!

General Ethical Issues in the Use of Stem Cells:

Now let me now go to the general ethical issues in stem cell research. Here we apply the ethical principles of (1) respect for person, (2) the principle of maleficence, (3) the principle of nonmaleficence and (4) the principle of justice.

First ethical concern is the source of the stem cells. Several years ago, in the initial discussions on the use of stem cells, embryonic cells were the main source. It was a big controversy because of the questions on the status of personhood of embryos and how to respect a potential person. The use of adult stem cells and the induction of pluripotent stem cells have helped deflect the discussion to other issues even if adult stem cells are not entirely satisfactory because they may be partly differentiated are present in scarce amounts and may contain genetic defects.

One other issue is that of safety, specifically, the safety of cell culture techniques. To start with - there is yet no safe, robust, reproducible stem cell production for large scale use. This is what many laboratories are trying to develop. But the safety issue lies on the use if animal serum and feeder cells when the stem cells are expanded in the laboratory. These are potential sources of undesirable agents that affect stem cell performance and, most important, safety.

There are still many uncertainties in the use of stem cells as therapy, at this point. (1) There can be an immune rejection of transplanted mesenchymal stem cells or human embryonic stem cell derived tissues in allogeneic settings (when the stem cell source is another adult, not the patient himself/herself). This is highly probable in the use of commercial stem cells. (2) Tumorigenesis is also a possibility in the systemic administration of mesenchymal stem cells. These cells have the potential to multiply and if they decide to settle down in another organ and grow, a tumor develops. (3) Teratoma formation from undifferentiated human embryonic stem cells is also another outcome that one has to look out for. And, as we pointed out earlier, (4) there is potential transmission of harmful components when one uses animal seeder cells and serum in the expansion of the stem cells in the laboratory.

Another difficulty of scientists involved in stem cell studies is the lack of good animal models of target diseases which are important in pre-clinical trials for stem cell therapy. It is very difficult to demonstrate cognition and affect in animals when the target disease involves cognition and affect. Our requirements on having good animal experiments prior to clinical studies cannot be complied with because of the absence of good animal models.

The first in human trials, therefore, becomes very complex especially because of safety. The type of stem cell, the site of transplantation, (for example, when you are doing central nervous system stem cell therapy, you have to start first on the site which is least harmful, e.g., the lumbar section first before going straight to the brain), the method of delivery are all very important considerations. These make the first in human trial a very complicated endeavor.

Ethical Review of Stem Cell Research

The institutional ethics review committee has the big responsibility of providing the ethical clearance for a stem cell research. Aside from the evaluation of the protocol based on the usual elements of social value, scientific and ethical soundness including the appropriateness of the expertise of the researcher and adequacy of facilities, the committee faces certain difficult issues.

The review will specially focus on the informed consent to ascertain if the research subject can really understand what the research is about and what s/he is going into. The research subject must fully understand the permanency of the therapy. It's not like drug therapy where drug effects will eventually stop when drug intake stops. In this case, once you inject the stem cell, it's stays in the system because of its potential to multiply. There is no way of withdrawing the stem cells. Will the patients involved in the first in human trial understand that? Do the patients understand that in research, the therapy may not work? That there is a possibility that they may not be helped? Is it understood that the research is novel and experimental?

The second difficulty of the ethics review committee will be in the risk analysis because it is very difficult to gauge the risk of something permanent and cannot be undone and that can lead to lasting adverse effects.

Finally, how do you adequately compensate the patient who will undergo these uncertain risks?

Specific Ethical Issues in Resource-Poor Countries:

Aside from the general ethical issues – there are unique ethical issues in stem cell research in a resource-poor country like the Philippines.

The first concern is the vulnerability of the population. Kopnis (Kenneth Kopnis, Univ of Hawaii, 2010) enumerated different kinds of vulnerability, viz, cognitive, deferential, medical, allocational and infrastructural vulnerabilities. Filipinos possess all these. Do the people understand what stem cell therapy about? The risks involved? The possible side effects? Stem cell scientists are admired and highly regarded in this country. This may give them a magic-like aura that people tend to invest them with unreasonable powers. Patients may think that there is no other therapy for them but what is being offered. What is being offered them as stem cell therapy may be regarded as manna, a chance to receive and access care where there was none and was difficult before.

But the second very unique ethical issue in a resource-poor country is the lack of Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) standards specific for stem cell-based products. Dr. Chung described their new advanced set-up in Makati Medical Center. What we now need is a third party, an objective facility that can check whether the alleged product is actually present in the preparation and that its quality is according to standards. We don't yet have this facility in the Philippines. Meaning, we don't have an objective laboratory that will check whether the stem cell product is what is claimed to be. That's a very basic issue. Without that, how are we sure, how can we know that what is being advertised is what the patients are getting? Quality, in this situation, is not assured.

A conflict of interest situation exist when the stem cell producer is also the health care provider. Economic interest may impact decision making in health care where the primary interest should be patient welfare. This should be managed with transparency and accountability as major considerations.

Finally, ethics calls for social justice which means that unless we, in a resource-poor country, can ensure the provision of the same quality of

service to both the poor and the rich, we should not invest on something that will make the divide in the care of the poor and the rich, wider.

Recommendations

Now, here are my insights and recommendations.

First of all, I wish to congratulate NAST for including this in the session because in fact, we should involve the wider scientific community in discussions like this. It will be good, too, if we had another session involving patients, patient advocates, the non-science community.

My second recommendation – is we should now establish a quality assurance system. Without that, the whole community becomes vulnerable to hype.

The third is that the conduct of clinical trials must be subject to prior scientific and ethical review. For example, voluntary informed consent must be ensured. Therapeutic misconception must be managed. This is the usual problem in clinical trials: patients thinking that they are receiving standard therapy instead of experimental therapy.

Fourth is to set up guidelines and systems for appropriate management of conflict of interest situation. We should ensure that the stem cell provider/producer is not also the attending physician.

Next, we need to establish the indicators of clinical effectiveness. I mentioned some of the indicators earlier but maybe we should agree on more specific ones for particular diseases.

Because we need scientific evidence, there should be publication of findings of the clinical trials and of experimental therapies. These should include negative results and adverse effects.

And finally, in crafting the national policy on the use of stem cells for therapy and research, costs and benefits should be seriously considered.

Conclusion

Stem cell based therapies are fraught with uncertainties and serious risks. They should be introduced to clinical practice only after clinical trials demonstrate their efficacy and safety.

The ethical conduct of clinical trials using stem cells must abide by the guidelines for all clinical research and subjected to rigorous scientific and ethics review. There must be assurance of voluntary informed consent and publication of findings of the clinical trial including negative results and adverse effects.

Stem cell based therapies are expensive and technologically demanding, the low-resource healthcare systems need to consider a specific national policy and to weigh costs and benefits when considering making such treatments available.

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