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ISCT WHITE PAPER

Cell therapy medical tourism: Time for action

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What is medical tourism?

Medical tourism may be defined as 'travel (usually international, occasionally local) to acquire healthcare, often on a temporary basis'. Cell therapy medical tourism is, by extension, travel for the purposes of acquiring cell therapy-related healthcare. In the USA, an estimated 750 000 individuals traveled for medical tourism in 2007 and this volume is projected to increase to 1.6 million patients by 2010 (1). Similar trends in medical tourism are appearing in other countries. Globally, many countries offer cell therapies to international patients, especially in south-east Asia (2–5).

A number of factors play a role in why so many people travel to seek cellular therapy treatments. First, there is an increasing elderly patient population with an attendant increase in degenerative and chronic diseases, many of which do not respond to standard therapies. Second, cellular therapy treatments are expensive, and the lower costs advertised by some clinics may drive international travel. Third, the internet and media interest have enabled and facilitated the proliferation of clinics advertising cellular therapies, with many making unfounded and dubious safety and efficacy claims supported only by testimonials and anecdotes (6). Fourth, many patients, especially those in wealthier nations, have discretionary income for traveling for medical care, and the enormous media attention given to cellular and stem cell therapy research in recent years has convinced many that it is worthwhile to do so. Finally, by travelling to a country where regulations may be more permissive or unenforced than in the country of origin, medical tourists may be able to obtain treatments not available in their homelands.

As pointed out by Caplan & Levine (7), there is a long and inglorious tradition of providing bogus medical treatments to desperate patients who are willing and able to travel and deplete their life and retirement savings. These unregulated medical services pose risks to patients because the cell therapy products may be harmful and also delay standard, more effective, therapies, or render patients ineligible for bone fide experimental treatments. One example is a boy with ataxia telangiectasia treated with repeated intracerebellar and intrathecal injections of human

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fetal neural stem cells at a clinic in Moscow. Four years later, he was diagnosed with a glioneuronal tumor, not of host origin and containing cells from two or more donors (8). Other equally serious side-effects have been reported (9). An additional, often overlooked, hazard is the potential lack of recourse to legal avenues, including compensation for unexpected complications or unsatisfactory outcomes. These avenues may not be accessible in destination countries where medical indemnity is not adequately enforced or observed.

There is also a risk to the medical and scientific integrity of the field of cell therapy (10). The work of established, reputable clinical trialists and scientists may be called into question in the court of public opinion because of the practices of fraudulent or unproven cell therapy practitioners. The general public and lay press may not differentiate between cell therapy medical quackery and legitimate scientific research. This blurring of the distinction between real research and unethical outlier practices could jeopardize support and funding for the entire field. In spite of the risks, mainstream medicine has done little to acknowledge this situation and to protect patients' welfare and rights. A more proactive and pragmatic approach is needed.

Increasing the level of knowledge and understanding

Within the scope of scientifically validated and medically ethical treatment, it is important to recognize the difference between clinical trials of experimental treatments and medical innovation. Cellular therapy clinical trials generally involve controlled investigations using methods to minimize bias, with a focus on outcome measures geared toward assessing safety and understanding efficacy. Clinical trials are usually run by academic medical centers or commercial entities with the ultimate goal of obtaining regulatory approvals. Without such controlled clinical trials, the field of cell therapy is unlikely to progress (11).

Medical innovation in cellular therapy may be viewed as ethical and legitimate use of non-approved cell therapy by qualified healthcare professionals in their practice of medicine (12). Patients not eligible for controlled clinical trials should be able to choose unproven but scientifically validated cell therapy medical innovations, if the researchers are competent and those seeking treatment are truthfully and ethically informed. There is a place for both paradigms in the cell therapy global community.

Patients therefore need to be equipped to understand the difference between (a) formal clinical trials and the innovative practice of medicine (where their rights are protected and risks are communicated) and (b) fraudulent cell therapy practice (where there are no protections, no demonstration of competency and misinformation is the rule). In practice, a continuum exists between these two extremes, with varying levels of scientific diligence. The following guidelines are useful in assessing scientific rigor and for differentiating between legitimate cell therapy medical services (including clinical trials and medical innovation) and fraudulent cell therapies.

- Peer review and transparency: consumers of cell therapy medical innovation should evaluate evidence from peer-reviewed publications, professional society presentations and scientific recognition. They should be encouraged to seek multiple professional opinions and have all questions answered to their satisfaction.
- Safety and regulatory history: patients should consider the reputation of the investigator and clinic, as well as the record of disciplinary activities against these entities.
- Informed consent: patients should expect to be informed fully and accurately of the risks, benefits, costs, safety, compensation for injury, investigator conflicts of interest and alternative therapies, as a minimum (13,14).

Patients seeking medical treatment for cellular therapies have the following rights that must be respected by healthcare providers and all associated with their care.

- The right to seek treatment: patients and their families/partners have the right to seek treatments for their diseases. No entity should withhold this fundamental right unless there is a high probability of harm to the patients.
- The right to information: patients have the right to an accurate representation regarding the safety and efficacy record of the cell treatment. This includes probable side-effects and a truthful record of efficacy.
- The right to informed consent: patients have a right to a true informed consent process that includes all the elements described above.

We acknowledge the primary role and jurisdiction of the local regulatory authority in ensuring the safety of patients seeking cellular therapy. However, the scale and quality of regulation and safeguards vary markedly globally and are often not enforced (15,16). In the face of weak local regulation, independent ethics committees will play a key role in protecting patients' rights. There is clearly a need for more regulatory harmonization in the field of cellular therapy. Achieving a common understanding of trial registration, data

reporting and safety standards would be a significant step in the quest to ensure patients' rights are protected. Finally, professional and industry-based organizations should become more active in this area, providing information and evaluations of those programs offering cell therapies.

Cellular therapy investigators and physicians are responsible for ensuring their activities are in compliance with all relevant regulatory authorities and ethics committee requirements. This includes compliance with good clinical practice (GCP) standards and other regulations designed to ensure patient safety. Investigators should register their trials and publish their results, including negative results, to ensure the field of cellular therapy benefits, and to enable certain patients and healthcare professionals to have access to the most timely and relevant information. Investigators must be responsible for any advertising for clinical trials and/or experimental therapies to ensure that safety and efficacy claims are not misstated or inflated, and to make certain their own enthusiasm does not mislead patients (17). Investigators must also report adverse events and side-effects promptly to regulatory authorities as well as include such reports in publications. If investigators have a financial interest in the provision of the cellular therapy, this should be disclosed. Finally, investigators should arrange for appropriate patient supportive care, follow-up and communication with the patients' healthcare professionals in their home countries.

What can the International Society for Cellular Therapy do?

Simple warnings do not suffice! The International Society for Cellular Therapy (ISCT) should work to mitigate and reduce patient risks by:

- promoting scientific development of the field
- enabling ethical and compassionate early access to promising cellular therapies (18)
- engaging in outreach to other industry and relevant scientific/professional organizations to leverage/share existing processes and resources with potential patients
- providing tools to the consumer that can be used as guidance in evaluating a potential treatment
- being available to the media to discuss claims of efficacy using cellular therapy.

We are proposing a 'Cell Therapy Guide for Patients and Caregivers'. This essential guide would build on existing work (19,20) and be a 'living document', accessible publicly on-line and include regular updates. Ideally, this ISCT guide would be integrated or cross-referenced with a web-based information resource, as proposed recently by the International Society for Stem Cell Research (21). The guide could explain the hierarchy of evidence and data supporting cell therapies. In addition, the guide would clearly define and differentiate among:

- approved/standard therapies (e.g. hematopoietic stem cell transplant and other cellular therapies approved for marketing)
- controlled clinical trials
- valid compassionate use of unapproved therapies
- treatments not subject to independent scientific and ethical review.

ISCT should leverage its global expertise in regulatory affairs to promote global regulatory harmonization. This could be achieved through co-operation with organizations such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (22) and by partnership with other regulatory authorities.

ISCT should partner with and provide resources to patient advocacy groups, including the Genetics Policy Institute, to ensure a personalized and empathetic connection with patients searching for information on novel cell-based therapies. This would provide patients with access to experts, assessment of emerging technology/treatments and professional recommendations. The patient advocacy groups would provide a trusted source of information to patients and ISCT could be the hub for networking with experts in the field.

In conclusion, cellular therapy medical tourism is here to stay. Although there are many legitimate cell therapies regulated appropriately by local authorities (23), there are also many unethical and potentially dangerous cell therapies currently on offer. ISCT members are positioned uniquely to use their scientific, translational, ethical and regulatory expertise to help patients and the field by ensuring the highest standards and ethical principles are employed. We have proposed several actionable steps to bring safe and effective cellular therapies to patients and to enable early access to promising experimental therapies and medical innovations. We look forward to working with the ISCT membership and the broader cell therapy community to achieve these goals.

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May 2010. See www.celltherapy2010.com/Public_Session.html for more information (accessed on 1 July 2010). ISCT is organizing a presidential task force to investigate cell therapy medical tourism, prioritize issues and develop actionable steps to ensure the protection of rights, safety and access to care for patients around the globe. Please watch for announcements regarding this task force on the ISCT website, www.celltherapysociety.org (accessed on 1 July 2010).

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