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Expert Opinion

Human neural stem cells in chronic spinal cord injury

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Translational research is inherently challenged to bridge the gap between preclinical research discoveries and clinical applications and discovering how to embed new knowledge into meaningful treatment concepts and eventually apply this in patients. The same is unquestionably true in spinal cord injury where specific challenges in the translation from bench to bed need to be considered.

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1. The translational dilemma

Translational research in human spinal cord injury (SCI) involving the application of stem cells is not only challenged by principal ethical and epistemological considerations about the transplantation of 'allogenic prospering cells' but also how to bridge the gap between preclinical models and traumatic human SCI [1]. A clear rational alignment between preclinical models and human SCI is inherently limited as so far proven estimations across different species are missing (uncertainties in many domains like: time, i.e., how acute is acute and what is a meaningful duration of treatment; route of application; number of cells needed; outcome measures etc.) to ultimately give a resilient recommendation for a specific first application in humans [2,3]. The following editorial alludes to some considerations regarding stem cells as have been considered in the ongoing Human CNS Stem Cell trial in sub-acute thoracic human SCI [4].

2. Why consider cell replacement therapies in SCI

In the treatment of patients suffering from complete or severe spinal cord injury (about 50% of SCI patients remain sensory–motor complete while additional 20 – 30% present long-lasting severe functional impairments although being classified as incomplete) conventional rehabilitation programs show serious limitations, which can't be effectively overcome even by intensifying or prolonging rehabilitation efforts [5]. In principle two major basic conditions are probably underlying these limitations: i) the restricted capacity for regeneration and repair of damaged spinal fibre tracts (no effective spontaneous re-myelination or axonal regrowth within injured fibre tracts or as collateral sprouting) as well as the limitation in neural plasticity (conveying neuronal information across ancillary pathways is less effective comparably to disorders of the brain, i.e., stroke and traumatic brain injury (TBI)), and ii) the permanent post- traumatic neural loss (in humans post traumatic cystic cavities can range from a few mm up to 3 – 5 cm) leaving a structural definite neuronal gap which prohibits that effects of neural regeneration or plasticity that can overcome this morphological challenge (funnel effect) [6].

3. What clinical condition to target

The translation of preclinical findings into clinical application has to follow very much regulated corridors where sequentially safety (an absolute requirement) and effectiveness needs to be rigorously addressed to eventually proceed with any clinical applications (in time the latter can even deviate from the initially intended purposes, when safety has been proven satisfactory and unexpected beneficial effects appear).

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Regulatory agencies (across many countries) preferably consider primary testing of safety (typical Phase I study) to be performed in SCI patients with the most severe and mutually permanent impairment (complete SCI = American Spinal Injury Association (ASIA) impairment scale A). In addition the level of SCI lesion considered to be acceptable for a safety study is within less eloquent areas of the spinal cord (typically thoracic SCI) where a severe adverse event (like non-intentional damage due to the route of application or local toxic effect) is less likely to induce a life-threatening and clinically shattering impairment (in patients with cervical SCI the additional lesion of even only one segment induces a clinically obvious and for patients relevant deterioration) [7-9]. However, it must be emphasized that it is precisely some of these cautious considerations that seriously affect the ability to identify safety aspects where subtle changes (that could be of disastrous effect in incomplete or high-level SCI patients) are probably masked in thoracic complete SCI. In this context trial protocols even in the early Phase I studies should consider if and how patients with incomplete SCI might be targeted to increase the sensitivity for detecting both adverse and beneficial effects [10].

4. How long after injury

In almost all treatments an optimal time window for the therapeutic intervention needs to be defined that allows best possible outcomes (window of opportunity) and tries to be in line with the assumed underlying pathophysiology. Again in Phase I studies the later aspect might not be satisfyingly met while considerations of safety are at the forefront. In novel treatments transplanting cells directly into the injured spinal cord choosing a chronic SCI condition warrants some advantages that need to be held against potential disadvantages (i.e., missing the best window of opportunity). For the interest of safety patients within the chronic stage of SCI (this time window is defined by conventions of expert groups rather than clear biological landmarks and based on definitions ranges from 6 to 12 to 24 months after injury) have some clear advantages: i) the patients are probably in a more stable condition where acute medical complications associated with the trauma will be less likely to confound the safe application of cells, ii) the prediction of the clinical course will be much more consolidated (in thoracic patients 3 months after injury the functional outcome can be reliably predicted) and each single patient might to some extent be taken as their own control where at least any unexpected or unusual deterioration might indicate a true adverse event [11,12], and iii) the consent of a patient will be improved by less pressure due to time constraints (the patients will have more time to consider participation and to appropriately address questions and shun the trap of a therapeutic misconception) and the already partially lived experience of the disabilities (to learn what it means to be paralyzed and how to cope with it) is almost a prerequisite for providing an informed consent.

5. Mode of action

Conceptually the application of stem cells could offer the ability to serve a very single specific aim like neuroprotection, regeneration or cell replacement of a specific cell type (like oligodendrocytes or neurones), however, there is as yet, even in preclinical models, no proof which of the various effects are most probably involved in some of the observed beneficial outcomes and how to reliably distinguish them. The perspective that cell treatments could be a means to provide rather long lasting treatments (i.e., surviving and eventually integrated cells could be a source for delivering neurotrophic factors for a long period of time) could be a tremendous asset in the treatment of human SCI. Clinical experience teaches that the human spinal cord has a huge capacity for plasticity as for example witnessed by MRI studies in patients with enormous deformations of the cord (like compression, benign tumour formation or syringomyelia, albeit with no or only subtle neurological deficits). In these instances the cord can show extensive changes in morphology, which however require a very slow progression of the underlying disorder [13]. The later aspect might be of importance specifically in patients with severe and rather large areas of spinal cord damage where prolonged treatment might be essential to fully exploit the effects of regeneration and plasticity.

6. Study design

Obviously the study design should be best fitted to the assumed most important aspects of a novel intervention. While specifically Phase I studies are challenged to focus on safety than efficacy the study design often suffers from compromises (many of which are obligated by regulatory agencies) that bear risks in many aspects. In addition early translational trials frequently fall short as they incorporate clinically meaningful primary and secondary outcomes (besides many safety readouts) rather than provide valuable surrogates [14] (the later have been found by the FDA to considerably accelerate the approval process). Surrogates (markers related to clinical endpoints) that are able to reveal the activity of the intervention by blood or cerebrospinal fluid (CSF) markers or changes in neurophysiological–morphological assessments in the absence (almost the default finding of human Phase I trials in neuroscience) of clinically promising improvements can be of high value to objectify either subtle changes (not yet clinically effective but would need some amplification) or to reveal novel insights in humans that in return might be relayed back from bed to bench [14-16].

7. Conclusions

In conclusion it becomes obvious that clinical Phase I studies are challenged on many ends while safety aspects unquestionably are key that inevitably affects the stratification of most suitable patients. In addition, there

is no standard protocol that could be applied in clinical SCI Phase I/II trials covering the very varied approaches and comparisons between such studies are rather limited.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Kimmelman J, London AJ. Predicting harms and benefits in translational trials: ethics, evidence, and uncertainty. PLoS Med 2011;8(3):e1001010
2. Courtine G, Bunge MB, Fawcett JW, et al. Can experiments in nonhuman primates expedite the translation of treatments for spinal cord injury in humans? Nat Med 2007;13:561-6

•• **The paper discusses the most important considerations in translational research.**

3. Dietz V, Curt A. Neurological aspects of spinal-cord repair: promises and challenges. Lancet Neurol 2006;5:688-94
4. StemCells, Inc. Study of Human Central Nervous System Stem Cells (HuCNS-SC) in Patients With Thoracic Spinal Cord Injury. ClinicalTrials.gov NCT01321333. Available from: http://clinicaltrials.gov/ct2/show/NCT01321333?term=NCT01321333&rank=1
5. Fawcett JW, Curt A, Steeves JD, et al. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord 2007;45:190-205

• **These guidelines allude to the pattern and extent of recovery in human SCI that need to be accounted for in clinical trials.**

6. Kakulas BA. Neuropathology: the foundation for new treatments in spinal cord injury. Spinal Cord 2004;42:549-63
7. Steeves JD, Lammertse D, Curt A, et al. Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. Spinal Cord 2007;45:206-21
8. van Hedel HJ, Curt A. Fighting for each segment: estimating the clinical value of cervical and thoracic segments in SCI. J Neurotrauma 2006;23:1621-31
9. Zariffa J, Kramer JL, Fawcett JW, et al. Characterization of neurological recovery following traumatic sensorimotor complete thoracic spinal cord injury. Spinal Cord 2011;49:463-71
10. Zorner B, Blanckenhorn W, Dietz V, Curt A. Clinical algorthithm for improved prediction of ambulation and patient stratification after incomplete spinal cord injury. J Neurotrauma 2010;27:241-52
11. van Middendorp JJ, Hosman AJ, Donders AR, et al. A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study. Lancet 2011;377:1004-10

•• **This prospective study reveals prediction rules in traumatic human SCI applicable in clinical trials for stratification and evaluation of outcomes.**

12. Burns AS, Lee BS, Ditunno JF Jr, Tessler A. Patient selection for clinical trials: the reliability of the early spinal cord injury examination. J Neurotrauma 2003;20:477-82
13. Curt A. The translational dialogue in spinal cord injury research. Spinal Cord 2011;published online 8 November 2011; doi:10.1038/sc.2011.113
14. Fleming TR. Surrogate endpoints and FDA's accelerated approval process. Health Aff (Millwood) 2005;24:67-78
15. Curt A, Van Hedel HJ, Klaus D, Dietz V. Recovery from a spinal cord injury: significance of compensation, neural plasticity, and repair. J Neurotrauma 2008;25:677-85
16. Curt A, Schwab ME, Dietz V. Providing the clinical basis for new interventional therapies: refined diagnosis and assessment of recovery after spinal cord injury. Spinal Cord 2004;42:1-6

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