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Cell-based therapy for pediatric traumatic brain injury: not (yet) an update to the TBI guidelines

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A few short years ago it would have been hard to imagine that anyone might suggest a bone marrow transplant for pediatric traumatic brain injury. The concept of bone marrow-derived cell-based therapies is, however, not a new concept. Nearly 150 years ago, Cohnheim observed that intravenous dye delivery in animals resulted in dye-labeled scar tissue at distal injury sites [1]. This startling discovery suggested that progenitor cells within the bone marrow could become something other than circulating red blood cells, leukocytes, and platelets. Although more than a century has passed since this pluripotent “potential” of bone marrow-derived cells was first described, in many ways our understanding of the mechanisms and relevance of this exciting phenomenon remain surprisingly rudimentary.

In the present study by Liao, et al, ten children who acutely suffered from a moderately severe traumatic brain injury (initial GCS 5–8) had their bone marrow harvested and the mononuclear fraction of cells isolated, characterized, purified, and concentrated, and then delivered back to them intravenously within 48 hours of injury[2]. Enrollment of these patients occurred in 2006–2008 and was previously reported in 2011 as a safety study demonstrating there were no severe adverse events associated with the therapy and that 7 of the 10 patients enrolled had good outcomes as measured by Glasgow Outcome Scores [3]. The current report examines how these same 10 patients fared in comparison to retrospectively obtained controls. The authors concluded that the cell-treated patients required a reduced treatment intensity to manage their intracranial hypertension as measured by the Pediatric Intensity Level of Therapy (PILOT) scale [4]. In addition, they found a shorter duration of intracranial pressure (ICP) monitoring in the treated group.

Although the treatment and control groups were small, the authors identify some compelling associations that suggest possible benefit in the treated patients. Because the outcome measures are limited to early therapy and ICP management, the comparison groups needed to be as similar as possible. In order to do this, the authors used two comparison groups, one historical (from 2000–2006, 14 patients) and one concurrent to their own study (from 2006–

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2008, 5 patients). One confounder to these comparison groups was the difference in serum sodium, a change not accounted for in the PILOT scale, but with possible clinical relevance. Everyone in the experimental group received hypertonic saline and achieved a mean serum sodium of 163 meq/L compared to the concurrent control group, who also received hypertonic saline but to a statistically significantly higher level of 170meq/L. In addition, half the study patients underwent craniectomy compared to 24% of the controls, a confounder that was not statistically significant but likely clinically relevant given the small number of patients studied overall. Despite these limitations, it appeared that in this small cohort treated with bone marrow-derived cells that there were not any significant adverse reactions and that managing intracranial hypertension in this group was potentially easier than that seen in the retrospectively obtained controls.

The use of bone marrow-derived mononuclear cells as a basis for therapy for a variety of diseases has been around for many years. There are many active or recently completed human clinical trials using a similar strategy of isolating autologous bone marrow-derived mononuclear cells and delivering them either intravenously or intra-arterially to patients suffering from a variety of acute and chronic diseases [5]. The most well-characterized and studied population comprises adults receiving similar therapy for acute myocardial infarction. A recent Cochrane analysis reviewed 33 randomized controlled trials that included nearly 1800 patients. It found no overall differences in mortality or morbidity between treated and control groups, although some studies did show evidence of long-term improvements in left ventricular function in the treated population [6]. Studies in humans and animals using similar approaches have been used for most diseases involving acute severe organ failure necessitating ICU management including acute renal failure, acute respiratory distress syndrome, acute liver failure, and a variety of acutely presenting neurological disorders [7–10]

As with all studies involving traumatic brain injury where heterogeneity is high, mortality is low, and morbidity is significant, surrogates for outcome are – unlike those for cardiac disease – much less well defined and controversial. Here, the authors use intensity of therapy as measured by the PILOT scale as the surrogate for outcome and observe a correlation between therapy intensity and treatment. Since the development of the PILOT scale, however, management of pediatric TBI has evolved, particularly in regards to osmolar therapy; therefore, the PILOT scale may not be as relevant as it was when first developed[11]. This study clearly underscores the need for reliable surrogates predictive of outcome in pediatric traumatic brain injury.

Finally, assuming there may be a therapeutic effect of bone marrow-derived cell-based therapies such as the one described here, it still remains unclear what the underlying mechanism might be. Originally these therapies were developed as cell replacement strategies, with the idea that pluripotent stem/progenitor cells would hone in on the diseased tissue by reacting to local cytokine release or some other marker of injury, and then differentiate into the tissue specific to what was lost due to injury[1]. There is some biological plausibility to this idea, although in sophisticated experimental studies mostly in chimeric mice, we know that this is not usually the case. Instead, it is more likely that the transplanted cells work as trophic support to nourish or guide locally acting facilitators of

injury repair[12]. In the present work, the authors hypothesize that the transplanted cells provide an anti-inflammatory environment for the injured brain, which attenuates the resultant cerebral edema. While there is justification suggesting that this might be the case, it remains just one of many possibilities. The actual cells being delivered are quite heterogeneous within the mononuclear fraction as described from their flow cytometry data. Ultimately, if there proves to be a meaningful therapeutic response using such therapies, it will be most compelling and practical if the mechanisms are revealed in a way that allows one to maximize therapeutic effect while minimizing potential adverse actions. Although not ready for routine use, cell-based therapies such as the one described here remain a promising potential alternative, particularly in such a common and debilitating disease for which we have so little to offer beyond basic supportive care.

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