News & Future Directions

New Findings
News Briefs
Podcasts
News Synthesis
Essays & Opinions
Blogs

Contents of this article

The results
ÒExtraordinary evidence still neededÓ
Burden of proof
Key open questions
Disclosures and sources of funding
References

COMMENT | RETURN TO TOP

NEW FINDINGS | 29 JAN 2015

More Encouraging Results From Stem-Cell Transplants

A new study shows good outcomes using a less intense conditioning regimen, suggesting it may be possible to perform successful stem-cell transplants in multiple sclerosis patients with less risk of infection

CYNTHIA MCKELVEY

Cartoon by Cynthia McKelvey.

According to some, 2015 is the year of the future. And that tongue-in-cheek superlative (derived from the 1989 movie, *Back to the Future Part II*) may be deserved, at least in the field of medicine. Earlier this month, MSDF covered a story about optimistic results from the phase 2 ÒHALT-MSÓ trial testing hematopoietic cell transplantation (HCT) in relapsing-remitting multiple sclerosis (RRMS) patients (Nash *et al.*, 2014). More recently, another research team published results from a separate phase 2 trial testing a different HCT method that had similar results to HALT-MS (Burt *et al.*, 2015). It seems in 2015, the question isnÕt ÒCan we do this?Ó but ÒHow should we do this?Ó

The goal of autologous HCT is to ÒresetÓ the patientÕs immune system. ItÕs a multistep process. First, stem cells must be harvested from the patientÕs bone marrow, or in the case of allogeneic transplants, from a healthy volunteer. Then the patient is subjected to a conditioning regimen to knock back the immune system. Finally, the stem cells are reintroduced, and if everything goes according to plan, the procedure reboots the patientÕs immune system.

Conditioning regimens come in two flavors: myeloablative and nonmyeloablative. Myeloablative regimens, like those used in HALT-MS, aim to eradicate the patientÕs bone marrowÑand thereby the immune systemÑin order to give the patient a clean slate. But myeloablative regimens put the patient at high risk for infection. In contrast, nonmyeloablative regimens, such as the one used in the more recently published study, are less risky because they leave some of the bone marrow intact.

The results

In that study, led by Richard Burt, M.D., of Northwestern University Feinberg School of Medicine in Chicago, 123 patients with RRMS and 28 patients with secondary progressive MS have so far received nonmyeloablative HCT. Of those 151 study participants, 145 had outcome data available with a median follow-up of 2 years.

Before the transplant, patients scored a median of 4.0 on the Expanded Disability Status Scale (EDSS). By 6 months post-transplant the median score had dropped to 3.0, and by 3 years it dropped even further to 2.5. ItÕs important to note, however, that sample size decreased as the length of follow-up increased, because not all the patients included in the study began at the same time. As reported in the paper, only 25 patients had reached 5 years of follow-ups.

Eighty percent of patients were relapse-free (no acute relapses) after 4 years. In HALT-MS, 78.4% of

Related Content

REFERENCES | 21 JAN 2015
Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis.

Click Here to Support MSDF

Click Here to Support MSDF

Most Popular News & Future Directions

VIEWED | COMMENTED ON | E-MAILED

È Partnership and Consent in MS Decision-Making
È More Than Meets the Eye
È Does Diet Matter in Multiple Sclerosis?
È MS Patients Positive for Oligoclonal Bands Have Greater Brain Atrophy
È Portable Neuromodulation Device May Improve Walking in MS Patients

SEE FULL LIST È

Search News & Future Directions

Category
All
CLINICAL RESEARCH MEETINGS
DRUG DEVELOPMENT METHODS
LABORATORY RESEARCH PEOPLE

Posting date
FROM
Year Month
TO
Year Month
Search Clear

the patients showed no signs of disease activity (NEDA) after three years, but NEDA was defined as Òsurvival without death or disease activity from any one of the following outcomes: (1) confirmed loss of neurologic function, (2) clinical relapse, or (3) new lesions observed on magnetic resonance imaging.Ó Burt *et al*. (2015) also saw significant decreases in gadolinium-enhanced lesions on MRI scans, as well as improvements in the Timed 25-Foot Walk and the Nine-Hole Peg Test.

ÒExtraordinary evidence still neededÓ

Though neither HALT-MS nor BurtÕs study were controlled or randomized, their strong results bolster hope for a new, effective, and less expensive treatment for people with aggressive RRMS. But which conditioning regimen is best remains an unanswered question. Physicians originally developed HCT as a treatment for patients with leukemia, in which total obliteration of the immune system is necessary. Additionally, since leukemia is a terminal disease, the risk/benefit analysis was more in favor of high-risk, high-reward treatments.

Burt told MSDF that he learned 30 years ago that HCT patients had to be reimmunized with vaccines most people receive in childhood. ÒIt occurred to me thatÕs exactly what you want to have happen in autoimmune disease. You want to lose your memory cells for autoantigens,Ó Burt told MSDF.

He began to test his theories on animal models, including experimental autoimmune encephalomyelitis. After successes in the lab, he took his protocol to the bedside.

ÒI think [BurtÕs] results are very encouraging that you can get by with a somewhat less intense conditioning approach,Ó Jeffrey Cohen, M.D., of the Mellen Center at the Cleveland Clinic told MSDF. But Cohen also noted a caveat emphasized in a commentary published along with BurtÕs study in *JAMA* (Hauser, 2015): ÒItÕs hard to know how these patients would have done on other available therapies. And itÕs still somewhat unclear to what extent the benefit was from the conditioning immunosuppressive regimen.Ó

In the commentary, Stephen Hauser, M.D., of the University of California, San Francisco, challenged the credibility of the changes in EDSS. He suggested that healthier patients may have been more likely to come to the clinic for follow-up exams, that some patients may have recovered naturally from their disabilities, and that drugs like alemtuzumabÑwhich was used in the conditioning regimenÑhave been shown to lead to improvements in EDSS.

Hauser, also wrote, Òthere is little evidence in the literature and none in the current study to support any claim that potentially pathogenic clones have been eliminated or that the immune system has been reset by the nonmyeloablative regimen used in this study.Ó

Burt told MSDF that only 22 patients received alemtuzumab before the researchers started using another drug, thymoglobulin, because patients on alemtuzumab developed secondary autoimmune disorders.

ÒOf course itÕs the conditioning regimen that stops the inflammation,Ó Burt told MSDF. And stopping the inflammation is the key to the immunological reset, Burt explained. By stopping inflammation through the use of the conditioning drugsÑcyclophosphamide and thymoglobulinÑthe lymphocyte count gets a chance to rebalance toward a more normal, healthy distribution of different types of immune cells.

The patients would recover without the stem cells, Burt said, but the stem cells help them recover faster.

ÒThere were some negative things that [Hauser] said and some of them are what weÕre trying to address: Is it really stem cell transplantation or is it really immunosuppression?Ó Michael Racke, M.D., of Ohio State University told MSDF. Racke is also one of the co-authors on the HALT-MS study. Though Racke is skeptical of the durability of BurtÕs regimen, he said that he was impressed with the outcomes. He also noted that it is difficult to prove immunological reset.

ÒIf we did lumbar punctures at the 3-year follow-up point, [the patients] still have oligoclonal bands,Ó Racke said. Oligoclonal bands are biomarkers for MS patients that are generally indicative of immune activity. ÒBut when the pathologist looks at the cells and the cell number, theyÕll say thereÕs no

evidence of an inflammatory response, which is what you would want to see.Ó

Burden of proof

The optimal conditioning regimen may show itself in due time, or perhaps there is no optimal regimen. In an interview with MSDF for the article about HALT-MS, Mark Freedman, HBSc, MSc, MD, CSPQ, FAAN, FRCPC, of the Ottawa Hospital Research Institute suggested that more of the patients involved in these studies may eventually start to show disease activity again or may experience adverse effects from the conditioning regimens. Freedman believes that the HALT-MS conditioning regimen may not have been intense enough. Racke also questioned the durability of BurtÕs protocol. Only time will tell if either of them is correct.

But in the meantime, both HALT-MS and BurtÕs study are gearing up for phase 3 trials.

ÒThe burden of proof is on us for phase 3. WeÕve done this over 30 years how youÕre supposed to do it,Ó Burt said. ÒAll the data has been very consistent, very encouraging.Ó

Key open questions

- If HCT turns out to be a viable option for patients with aggressive RRMS, will patients with less-aggressive RRMS seek out the treatment?
- What are the consequences of additional Òmedical tourismÓ resulting from these encouraging stem-cell results?
- How should physicians and patients manage the complex risk-benefit balance of choosing the right protocol for HCT?

Disclosures and sources of funding

The research was supported by the Danhakl family, the Cumming Foundation, the Zakat Foundation, the McNamara Purcell Foundation, and Morgan Stanley and Company.
Cohen has received personal compensation for consulting for Genentech.
Racke was a consultant for Biogen Idec, Novartis, Questcor, and Revalesio.

References

Editors' Pick

Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis.
Burt RK, Balabanov R, Han X, Sharrack B, Morgan A, Quigley K, Yaung K, Helenowski IB, Jovanovic B, Spahovic D, et al.
JAMA. 2015 Jan 20; 313(3):275-84. PMID: 25602998. Abstract

Hematopoietic stem cell transplantation for MS: extraordinary evidence still needed.
Hauser SL
JAMA. 2015 Jan 20; 313(3):251-2. PMID: 25602994. Abstract

SEE FULL LISTÈ

DOI: doi/10.7493/msdf.10.16608.1