MedicalXpress

New stem cell transplantation method may halt multiple sclerosis symptoms long-term, but therapy comes with high risk

June 9 2016

A new use of chemotherapy followed by autologous haematopoietic stem cell transplantation (aHSCT) has fully halted clinical relapses and development of new brain lesions in 23 of 24 patients with multiple sclerosis (MS) for a prolonged period without the need for ongoing medication, according to a new phase 2 clinical trial, published in *The Lancet*. Eight of the 23 patients had a sustained improvement in their disability 7.5 years after treatment. This is the first treatment to produce this level of disease control or neurological recovery from MS, but treatment related risks limit its widespread use.

MS is among the most common chronic inflammatory diseases of the central nervous system, with around 2 million people affected worldwide. It is caused when the immune system attacks the body, known as autoimmunity. Some specialist centres offer aHSCT for MS, which involves harvesting bone marrow stem cells from the patient, using chemotherapy to suppress the patient's immune system, and reintroducing the stem cells into the blood stream to "reset" the immune system to stop it attacking the body. However, many patients relapse after these treatments, so more reliable and effective methods are needed.

Dr Harold L Atkins and Dr Mark S Freedman from The Ottawa Hospital and the University of Ottawa, Ottawa, Canada, and colleagues tested whether complete destruction, rather than suppression, of the immune

system during aHSCT would reduce the relapse rate in patients and increase long-term disease remission. They enrolled 24 patients aged 18-50 from three Canadian hospitals who had all previously undergone standard immunosuppressive therapy which did not control the MS. All patients had poor prognosis and their disability ranged from moderate to requiring a walking aid to walk 100m, according to their Expanded Disability Status Scale (EDSS) scores.

The researchers used a similar method of aHSCT as is currently used, but instead of only suppressing the immune system before transplantation, they destroyed it completely using a chemotherapy regimen of busulfan, cyclophosphamide and rabbit anti-thymocyte globulin. Dr Atkins explains that this treatment is "similar to that used in other trials, except our protocol uses stronger chemotherapy and removes immune cells from the stem cell graft product. The chemotherapy we use is very effective at crossing the blood-brain barrier and this could help eliminate the damaging immune cells from the central nervous system."

The primary outcome of the study was multiple sclerosis activity-free survival at 3 years (as measured by relapses of MS symptoms, new brain lesions, and sustained progression of EDSS scores) which occurred in 69.6% of patients after transplantation.

Out of the 24 patients, one (4%) died from hepatic necrosis and sepsis caused by the chemotherapy. Prior to the treatment, patients experienced 1.2 relapses per year on average. After treatment, no relapses occurred during the follow up period (between 4 and 13 years) in the surviving 23 patients (figure 2). These clinical outcomes were mirrored by freedom from detectable new disease activity on MRI images taken after the treatment. The initial 24 MRI scans revealed 93 brain lesions, and after the treatment only one of the 327 scans showed a new lesion (figure 2).

Furthermore, progressive brain deterioration typical of MS slowed to a rate associated with normal aging in 9 patients with the longest follow-up, and 8 (35%) of 23 patients had a sustained improvement in their EDSS score at 7.5 years after treatment. At 3 years, 6 patients (37%) were able to reduce or stop receiving disability insurance and return to work or school. Eight (33%) of the 24 patients had a moderate toxic effect and 14 (58%) patients had only a mild toxic effect related to transplantation.

Dr Freedman highlights the need to interpret the results with caution: "The sample size of 24 patients is very small, and no control group was used for comparison with the treatment group. Larger clinical trials will be important to confirm these results. Since this is an aggressive treatment, the potential benefits should be weighed against the risks of serious complications associated with aHSCT, and this treatment should only be offered in specialist centres experienced both in multiple sclerosis treatment and stem cell therapy, or as part of a clinical trial. Future research will be directed at reducing the risks of this treatment as well as understanding which patients would best benefit from the treatment."

Writing in a linked Comment, Dr Jan Dörr, from the NeuroCure Clinical Research Center, Charité-Universitätsmedizin, Berlin, Germany, says: "These results are impressive and seem to outbalance any other available treatment for multiple sclerosis. This trial is the first to show complete suppression of any inflammatory disease activity in every patient for a long period...However, aHSCT has a poor safety profile, especially with regards to treatment-related mortality."

He adds: "So, will this study change our approach to treatment of multiple sclerosis? Probably not in the short term, mainly because the mortality rate will still be considered unacceptably high. Over the longer term (and) in view of the increasing popularity of using early aggressive

treatment, there may be support for considering aHSCT less as a rescue therapy and more as a general treatment option, provided the different protocols are harmonised and optimised, the tolerability and safety profile can be further improved, and prognostic markers become available to identify patients at risk of poor prognosis in whom a potentially more hazardous treatment might be justified."

More information: *The Lancet*, www.thelancet.com/journals/lan … rticle/PIIS0140-6736

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