Multiple sclerosis is an autoimmune disease of the central nervous system in which autoreactive lymphocytes damage oligodendrocytes (myelin sheaths) and axons. Chemotherapy with autologous stem cell support (Hematopoietic Stem Cell Transplant, HSCT) is an established cancer treatment and is performed routinely in university hospitals. What is less well known is that this treatment also works against multiple sclerosis and other autoimmune diseases (1, 2).

Over the course of almost 20 years, protocols for chemotherapy with autologous stem cell support in multiple sclerosis have been improving. Treatment results are good (3, 4) and mortality and side effects are at an acceptable level. In centres experienced in the method, treatment mortality is well below 1 % (and well below 0.5 % for non-myeloablative chemotherapy protocols) (5, 6). Five years after treatment, 70 % of patients have no signs of disease activity (5). The demand for treatment stems from the very low quality of life of many patients with multiple sclerosis, as well as the method’s therapeutic window: The effect is greatest early in the disease and smaller or absent later on.

The most effective treatment for multiple sclerosis is hardly used
In many patients with multiple sclerosis, quality of life is so low that HSCT treatment appears to be the best option – a one-off treatment with medium/low dose (myeloablative/non-myeloablative) chemotherapy, which eradicates autoreactive lymphocytes. This gives the patient a good chance of escaping chronic health problems due to disease activity, functional decline, medication side effects and the transition to secondary progressive multiple sclerosis (chronic neurodegeneration) (3).

Disease-modifying drugs have the same therapeutic window as HSCT, but have only an immunomodulatory/immunosuppressive effect on autoreactive lymphocytes and can neither halt the disease nor prevent the transition to secondary progressive multiple sclerosis (3). Side effects significantly reduce quality of life in many patients, and the most effective disease-modifying drugs have serious side effects that limit their duration of use. Health problems often persist because of continued disease activity.

Internationally, however, most neurologists still consider chemotherapy with autologous stem cell support to be an experimental treatment, even though it has yielded good results for more than ten years (7). Many countries require that such treatment be performed within prospective randomised controlled trials, in which the control group receives disease-modifying drugs and the intervention group HSCT treatment. Neurologists expect it takes several years before there are sufficient data to judge whether the treatment can be offered outside such studies.

The inclusion criteria for these studies are very stringent – they are based upon the type of multiple sclerosis, age, annual relapse rate, contrast-enhancing lesions on MRI and unsatisfactory effect of at least two disease-modifying drugs. Phase 2 studies from university hospitals in Sweden, Italy, Israel and Russia, among others, suggest that HCST treatment is also effective in progressive multiple sclerosis, in elderly patients, in those who do not have annual relapses and in those without contrast-enhancing lesions (8). Today, these patients have few if any places to which they can turn for HSCT treatment.

For me, it is incomprehensible that one of the inclusion criteria is that patients must have used two disease-modifying drugs. For many, this means that they no longer fulfill the criteria regarding age and secondary progressive multiple sclerosis, that they suffer increasing irreversible nerve damage, and that the treatment comes too late.

Obstacles
The first HSCT studies included mainly patients with advanced primary and secondary progressive multiple sclerosis. In these patients, the treatment effect was smaller and there were more complications. Many neurologists still believe that treatment mortality lies at several percent and that HSCT treatment is indicated only in younger patients with very frequent relapses or when all other treatments have failed (3). Requests for this treatment are rejected on the grounds that it is too dangerous or that the patient’s disease is too stable. I find the latter also hard to understand, since the disease course in patients with multiple sclerosis is usually impossible to predict (9). Of patients with relapsing-remitting disease, 80 – 85 % eventually go on to develop secondary progressive multiple sclerosis (3). Twenty years after disease onset, more than half will have left the workforce completely (10).

Researchers lack funding. They receive little from the public purse and nothing from pharmaceutical companies, which focus on their own disease-modifying drugs. The result is a real lack of momentum for clinical trials on HSCT treatment for multiple sclerosis. For example, European and American researchers met in 2008 to discuss the design of a prospective randomised controlled multicentre study. After a further meeting in 2009, they published in 2012 the progress made in planning such a study (11). The study is still not underway.

Neurologists decide whether HSCT treatment is indicated, but it is haematologists who perform it. This requires cooperation. In Norway, both professions are questioning whether there are sufficient resources available to expand treatment provision.

HSCT treatment in Norway
Only three patients with multiple sclerosis have received HSCT treatment in Norway (Haukeland University Hospital). The Nor-
Ethics
For more than ten years, haematologists and neurologists who have conducted research on HSCT treatment for multiple sclerosis have been calling for funding for prospective randomised controlled trials. In the meantime, more and more results have become available from phase 2 studies. When phase 1–2 studies of serious diseases show that a new treatment is moderately or considerably better than the established one, prospective randomised controlled trials are unethical. Instead one has for example used historical controls, to ensure that as many patients as possible receive the best treatment as soon as possible.

An ethical prerequisite for randomised controlled clinical trials is that there should be no clear indication beforehand as to who will come out best – the treatment or the control group (13–16). I believe that this prerequisite is no longer fulfilled when it comes to HSCT treatment for multiple sclerosis. Historical controls from studies of disease-modifying drugs (data from many thousands of patients with multiple sclerosis) constitute a sufficient basis for comparison (17, 18).

Sigbjørn Rogne

Sigbjørn Rogne (born 1965) is a specialist in gastroenterology and in geriatrics and works as an advisor in the Department of Clinical Medicine, University Hospital of North Norway. The author has completed the ICMJE form and declares the following conflict of interest: He himself has multiple sclerosis.

References


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