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Richard K Burt, Roumen Balabanov, Julio Voltarelli, Amilton Barreira and Joachim Burman

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Autologous hematopoietic stem cell transplantation for multiple sclerosis – if confused or hesitant, remember: 'Treat with standard immune suppressive drugs and if no inflammation, no response'

In 1995 autologous hematopoietic stem cell transplantation (HSCT) was first suggested in the medical literature as a treatment for multiple sclerosis (MS).[1] At that time, HSCT was viewed as a high-risk procedure to be utilized as a salvage therapy in late progressive disease, a perception that still lingers to this day.

The first partial misconception that HSCT is a high-risk procedure needs to be placed in perspective with the drug regimen utilized, as well as with the risks of current FDA-approved disease-modifying therapies. There are three variables that determine the safety of HSCT: 1) the regimen (drugs) used; 2) patient selection; and 3) a center effect (experience with transplant for MS).[2-5] It is important to recognize that the terminology 'autologous hematopoietic stem cell transplantation' is in reality a misnomer. There is no transplant, only the infusion of an autologous supportive blood product, analogous to a surgeon collecting before and then reinfusing autologous packed red blood cells after an operation. Before receiving the stem cell infusion (transplant), patients with autoimmune diseases receive a 'conditioning regimen' of drugs (chemotherapy, biologics, and/or radiation). The early and late toxicity from HSCT depends upon the specific drugs in the conditioning regimen and not the infused autologous blood product, i.e. hematopoietic stem cells.

The toxicity and risk of agents used in various conditioning regimens such as anti-thymocyte globulin, alemtuzumab, rituximab, busulfan, cyclophosphamide, carmustine, melphalan, cytosine-arabinoside, or total body irradiation are unique and different from each other. However, if autologous stem cells are given as a supportive blood product after any of these agents and then termed 'transplant', there is a tendency to subsequently misconstrue all transplant risk and morbidity as identical. The perception of a high-risk treatment was also perpetuated by study investigators, because several initial trials utilized cancer-specific high-risk and extreme regimens that included agents such as total body irradiation or high-dose busulfan,[6–9] some of which were complicated by treatment-related mortality.[7–9]

Extreme conditioning regimens that include total body irradiation or high-dose busulfan cause irreversible bone marrow failure that mandates hematopoietic stem cell reinfusion for recovery, and are termed myeloablative. Such extreme regimens are complicated by increased risks of infections, late leukemia, myelodysplasia, solid tumors and, in the case of high-dose busulfan, fatal veno-occlusive disease of the liver.[7-9] In contrast, non-myeloablative regimens are far less extreme and consist of relatively lymphocyte-specific chemotherapy (cyclophosphamide or fludarabine) and anti-lymphocyte antibodies (e.g. anti-thymocyte globulin (ATG) or rituximab) that halt inflammation without altering the bone marrow's ability to recover, and are safer with less short and long-term toxicity.[2,3,10] Autologous hematopoietic stem cells do not need to be infused after a non-myeloablative regimen, but shorten the duration of neutropenia which facilitates an earlier recovery and discharge.

In this issue of *Multiple Sclerosis Journal*, the position paper by Saccardi et al.[11] advocates an intermediate intensity regimen, BEAM, that is safer than the extreme irradiation or high-dose busulfan-containing regimens but still utilizes the anti-cancer chemotherapeutic agents **B**CNU (carmustine), **e**toposide, **A**ra-c (cytosine-arabinoside), and **m**elphalan. Another option that we advocate and utilize for numerous autoimmune diseases including systemic lupus erythematosus,[12] systemic sclerosis,[13] type 1 diabetes[14,15] and MS[16] are non-myeloablative conditioning regimens that contain only immune suppressive drugs normally used to treat autoimmune disorders, such as cyclophosphamide (cytoxan) and ATG. In this issue of *Multiple Sclerosis Journal*, the position paper by Saccardi et al. recommends BEAM/ATG because of concern for higher relapse rates with less-intense regimens. However, risk–benefit for treatment versus the disease being treated needs to be carefully balanced. In a bicentric comparison study between BEAM/ATG and cyclophosphamide/rATG, there were no deaths in the latter group versus 7.5% mortality in the first group of patients.[17] Even if it can be argued by Saccardi et al. in this issue of *Multiple Sclerosis Journal* that the rATG dose used in the BEAM/ATG group was too high, what is more important is the absence of death in the non-myeloablative cyclophosphamide/rATG regimen. The rationale behind the conditioning regimen for treating autoimmune diseases is

to induce an immediate immune ceasefire, allowing the infused autologous hematopoietic stem cells to regenerate a new immune system that defaults to self-tolerance in the non-inflammatory post-conditioning environment (in immunologic vernacular, no costimulation). This may be achieved with extreme myeloablative regimens, intermediate anti-cancer chemotherapeutic regimens, or non-myeloablative conditioning regimens containing only drugs and biologics normally used for immune suppression.

Non-myeloablative regimens that contain only standard immune suppressive drugs, e.g. cyclophosphamide and rATG, should, in experienced centers, be viewed as having a favorable risk–benefit profile compared with current FDA-approved second-line drugs such as mitoxantrone (Novantrone), fingolimod (Gilenya), or natalizumab (Tysabri). Mitoxantrone may cause late congestive heart failure or myelodysplastic syndrome and leukemia.[18] Use of fingolimod is complicated by cardiac arrhythmias, and there have been recent reports of sudden death which are under investigation,[19,20] while natalizumab is associated with progressive multi-focal leukoencephalopathy.[21] In addition, these medications are usually continued indefinitely or until complications arise. Whether funded through government or private health care providers, the treatment cost of these drugs is not inconsequential, in US dollars approximately $42,000 and $50,000 per year for natalizumab and fingolimod, respectively.[22] In addition to the medication cost, there is also cost for monitoring (magnetic resonance imaging (MRI)) and treatment of adverse reactions. In comparison, HSCT is a one-time treatment after which all immune-based therapies are discontinued.

The initial trials, despite using what were previously cancer-specific intense myeloablative or intermediate intensity regimens, did provide valuable insight into disease pathogenesis, and the data refute the second misconception that HSCT should be used as salvage therapy for progressive disease. Initial trials tended to select patients for secondary progressive disease with an increase in permanent disability of 0.5–1.0 Expanded Disability Status Scale (EDSS) steps within the prior 12 months. Despite using intense regimens, the patients' disability did not improve and even continued to progress at a rate not convincingly different than the natural history of progressive MS.[6,7] Immune analysis of samples collected before and after HSCT demonstrated an immune reset with a surge in recent thymic emigrants (naïve T cells) and change in T-cell receptor (CDR3) repertoire skewing.[23] Therefore, in progressive MS, despite aggressive immune ablative therapy resulting in a post-transplant immune reset, patients did not improve and disability progressed within the post-transplant follow-up reported.

The initial HSCT clinical outcomes reaffirmed that progressive MS is an axonal degenerative disease and not primarily immune mediated.[24] Transplant results also suggest that the relatively common and often unchallenged clinical practice of treating progressive MS with FDA-approved therapies, all of which are immune-based interventions, should be viewed as an ineffective and costly expenditure of limited financial resources. It also implies that a more aggressive immune-based intervention needs to be initiated earlier in selected patients with relapsing–remitting disease, before a patient enters the progressive phase.

In patients with relapsing–remitting MS and frequent relapses despite interferon, we reported that a non-myeloablative, non-cancer derived, immune-specific transplant regimen reverses neurologic disability.[15] To date, it is the only study of any therapy to demonstrate significant improvement in disability, i.e. an improvement (decline) in subjects' mean EDSS by at least 1.0 point. Based on that pilot trial, the current ongoing Multiple Sclerosis International Stem cell Transplant (MIST) trial (www.clinicaltrials.gov NCT00273364) randomizes patients with two or more steroid-treated relapses within 12 months despite first-line therapy with interferon or copaxone to either HSCT (cyclophosphamide/ATG) or best available approved second-line therapy (Novantrone, Tysabri, or Gilenya). In this issue of *Multiple Sclerosis Journal* the position paper by Saccardi et al.[11] recommends an intermediate intensity regimen of BEAM/ATG after most patients have failed second-line therapy with either Tysabri or Gilenya. Waiting until failure of second-line treatment runs the risk of losing the window of opportunity for optimal effective outcome of any immune-based therapy, including HSCT. Further, both Tysabri and Gilenya increase the risk of lethal viral infections,[19,21] and transplant may be complicated by lethal viral infections if there is not a sufficient time interval separating HSCT from prior treatment with Tysabri or Gilenya.

The final factor that determines transplant safety is a center effect, i.e. experience performing HSCT in patients with MS. Ideally, in order to avoid skewing toxicity results, centers should have experience in non-randomized phase I or II transplant trials for MS before joining pivotal randomized trials. The toxicity of transplant depends on understanding unique aspects of each disease, as recently pointed out in HSCT for systemic sclerosis, in which high mortality can be prevented by an extensive pre-HSCT cardiac evaluation.[13,25-27] In patients with MS, one such unique toxicity is irreversible neurologic decline from ATG-related fever that may be prevented by decreasing the first dose of ATG, intravenous methyl-prednisolone before each rATG infusion, and a rapid prophylactic steroid taper beginning on the day of stem cell infusion (day 0).

Transplant center expertise also determines outcome. Immune-based treatment, including HSCT, is not effective in progressive MS. Patients with a long disease duration, older age, or high EDSS scores without active inflammation on MRI, until proven otherwise, should have their diagnosis of relapsing–remitting MS

questioned. In this issue of *Multiple Sclerosis Journal*, Mancardi et al.'s multi-center Italian study reported some patients recorded as having relapsing–remitting disease who had a disease duration of up to 18 years, were up to 52 years old, and or had an EDSS as high as 7.5.[28] This emphasizes the importance of auditing patients enrolled at each site to ensure appropriate selection and universal understanding of the difference between inflammatory versus progressive MS. Patient selection is essential for good outcome following HSCT for MS since 'no inflammation, no response'.

As there are no completed randomized studies on HSCT for MS, the final results of both randomized trials – MIST, that compares cyclophosphamide/rATG as a second-line therapy for interferon/copaxone failures and the BEAM/ATG regimen as a predominantly third-line therapy as proposed in this issue of *Multiple Sclerosis Journal* – will be important to evaluate medium- and long-term outcome of both regimens, including their toxicity.

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Richard K Burt[1], Roumen Balabanov[2], Julio Voltarelli[3], Amilton Barreira[4] and Joachim Burman[5]
[1]Division of Immunotherapy, Department of Medicine, Northwestern University Feinberg School of Medicine Chicago, USA
[2]Department of Neurology, Rush University Medical Center, Chicago, USA
[3]Hemocentro Regional-RP, Department of Neurosciences, University of Sao Paulo, Brazil
[4]Division of Neurology, Department of Neurosciences, University of Sao Paulo, Brazil
[5]Department of Neuroscience/Neurology, Uppsala University, Sweden

Corresponding author:
Richard K Burt, Division of Immunotherapy, Department of Medicine, Northwestern University Feinberg School of Medicine 750, North Lake Shore Drive, Suite 649, Rubloff Building, Chicago, USA.
Email: rburt@northwestern.edu