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Autologous haematopoietic stem cell transplantation for immune mediated neurological diseases – what, how, who and why

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Figure 1 created with BioRender.com.

Abstract

In carefully selected patients, autologous haematopoietic stem cell transplantation is a safe, highly effective and cost-saving treatment modality for treatment-resistant, and potentially treatment-naive, immune-mediated neurological disorders. Although the evidence base has been growing in the last decade, limited understanding has led to confusion, mistrust and increasing use of health tourism. In this article, we discuss what autologous haematopoietic stem cell transplantation is, which immune-mediated conditions can be treated with it, how to select patients, what are the expected outcomes and potential adverse effects, and how cost-effective this treatment is.

Background

Haematopoietic stem cell transplantation (HSCT) is a broad description for a process involving the ablation and reconstitution of the myeloid and lymphoid systems aiming to eradicate malignant cells, or, when used for the treatment of autoimmune disease, to develop a new and 'tolerant' immune repertoire. Haematopoietic stem cells can be obtained from the peripheral blood following a short course of a growth factor, alone or in combination with a cytotoxic treatment, either from the affected patient (autologous) or a closely matched donor (allogeneic). Autologous HSCT (aHSCT) is currently used to 're-boot' the autoreactive immune systems in patients with specific immune-mediated neurological disorders, mainly multiple sclerosis (MS) but also chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), neuromyelitis optica (NMO), stiff person syndrome (SPS) and myasthenia gravis (MG) (1). Allogeneic HSCT is rarely used in the treatment of immune-mediated neurological disorders. Mesenchymal stem cells (MSCs) are another type of stem cells that have shown initial therapeutic promise, although in neurological disease this has not yet been borne out in clinical trials (2).

Although aHSCT is increasingly used as an evidence-based treatment modality for immune-mediated neurological disorders (1), many neurologists do not feel prepared to discuss it with their patients or counsel them about it (3). Patient organisations perceive the pace of the neurological community in adopting aHSCT to be slow, resulting in patients resorting to health tourism, sometimes from unregulated providers (3, 4).

Various misconceptions within both patient and clinician communities have further complicated this field. For some patients, their primary clinicians' unwillingness to discuss aHSCT has led to self-directed 'research' using a mixture of social media outputs, blogs, private providers' literature or informal discussions with other patients (5). The online literature offered by private providers has limited information regarding the treatment process and follow up care. Some claim that the treatment is risk-free and advertise it as a uniformly accepted cure (6). Nine of the top ten indications listed as being appropriate for transplantation by such providers are not recommended by any regulatory body and are not immune mediated conditions. These unsupported journeys often lead to poor quality information and decision making, particularly when patients are desperate for what they perceive to be a high efficacy treatment which is being withheld. This results in patients undergoing this intensive and relatively expensive procedure by unregulated providers with variable quality and safety and therefore exacerbating the unease and misunderstanding within the medical community.

How

Appropriately selected patients, outlined below, undergo detailed evaluation by a multi-disciplinary team with experience in stem cell transplantation, including an experienced neurologist, a transplant haematologist and a specialist transplant nurse, working in a centre with appropriate accreditation. This approach leads to an increased opportunity for better patient selection and engagement and

therefore better treatment outcomes. The nature of the treatment, its success rate and potential adverse events including, but not limited to, infections, chemotherapy toxicity, prolonged hospital stay, and treatment-related mortality (TRM), are discussed with patients. Fertility conservation procedures are discussed, and actioned, and patients are counselled that the intensity of the procedure, the period of isolation and the reduced peri-procedure mobility can make their condition transiently worse.

The procedure (see figure 1) has 3 stages; mobilisation and stem cell harvesting, conditioning and stem cell infusion and follow up. Whilst several treatment regimens exist, see table 1, we will refer to the most commonly used regimen in MS (1, 7). 'Mobilisation' of peripheral blood stem cells (PBSC) from the bone marrow to the peripheral blood is achieved by administering cyclophosphamide (Cy, commonly dosed at $2g/m^2$) usually as a day case or, sometimes, as a single night admission, followed by subcutaneous injections of granulocyte colony-stimulating factor (G-CSF). Cyclophosphamide counters potential G-CSF induced disease activity (8). Thereafter, PBSC are 'harvested' by apheresis. The 'conditioning' phase is delivered as an inpatient during which a short, but intensive course of cytotoxic chemotherapy, often combined with T-cell depleting 'serotherapy', commonly rabbit- or horse- derived anti-thymocyte globulin (ATG), are administered via a central venous access device. Unmanipulated autologous PBSC are then re-infused (usually via the same central venous access device) on 'day 0', and the patient receives supportive care measures, including prophylactic anti-infectives, transfusions of red cells and platelets, monitoring of fluid status, electrolytes, weight and bladder function. Engraftment occurs, typically, 2-3 weeks after re-infusion of PBSC. Whilst ex-vivo CD34+ selected autologous haemopoietic stem cells have been used (9), this extra step adds additional cost, may increase infection risk and delays time to engraftment and is not used routinely in clinical practice(1). The total inpatient stay usually lasts for 4 weeks during which the patient is cared for in protective isolation. The patient is then discharged home but is advised to shield for a period of three months whilst antifungal, anti-viral drugs and anti-pneumocystis prophylaxis are continued for variable periods according to centre protocols. Screening for CMV and EBV by PCR is dependent on centre protocol and may be performed for the first three months (and longer if necessary), with specific pre-emptive treatment delivered as required.

Patients are counselled that the intensity of the procedure and reduced mobility during the periods of isolation and shielding can contribute to profound fatigue, increased spasticity and reduced ability to ambulate in the immediate aftermath of the transplant. Specific guidelines have been produced to support pre and re-habilitation alongside routine transplant care (10).

Table 1: Currently used conditioning regimens.

Intensity	Examples of conditioning regimen (1, 7)	Mechanism of action	Comment
High	Busulfan, cyclophosphamide and ATG (BuCyATG).	Myeloablative	Now rarely used in immune-mediated neurological disorders outside of clinical trials. Data confirms long-term efficacy in RRMS, but higher risk of TRM and adverse effects.
Intermediate	Carmustine (BCNU) 300 mg/m^2, etoposide 800 mg/m^2, cytarabine-arabinoside 800 mg/m^2 and	Lympho-myeloablative	The most widely used regimens recommended by

	melphalan 140 mg/m2 and rabbit or horse ATG (BEAM-ATG).		the European Society for Blood and Marrow Transplantation for MS (1).
	Cyclophosphamide 200 mg/kg and rabbit ATG (Cy-ATG) with steroid cover.	Lymphoablative	
Low	Chemotherapy alone (e.g cyclophosphamide at mobilisation and conditioning)	Lymphoablative	Limited data suggests lower efficacy.

Whilst serious adverse events can occur, none have been reported in the largest randomised controlled trial for MS (11). The most common adverse events were febrile neutropenia, electrolyte disturbances and transient elevated transaminases. Infections (typically urinary tract and respiratory infections) occurred at a rate of 0.19 per patient per year, similar to that encountered with the use of standard disease-modifying treatments (DMTs). aHSCT is a one-off elective procedure with most of the risk being concentrated to the peri-transplant period. TRM, defined as mortality within 100 days, has improved since the early studies in MS with a reduction from 1.3% between 2001 and 2007 to 0.2% between 2012 to 2017 and thereafter (8, 12). This reduction has been attributed to better patient selection and the use of intermediate-intensity treatment regimens, and, arguably, compares favourably with the associated early mortality risks of common elective surgical procedures such as cholecystectomy, hip and knee replacement (1%, 1.20% and 0.9% respectively) (13, 14) or with the reported longer-term mortality risks related to use of some high efficacy disease modifying treatments such as natalizumab and alemtuzumab (0.13% and 0.18% respectively) (15, 16). Where previous DMTs have been used, including B and T cell depleting therapies, safety does not differ between previous agents (17).

Beyond 3 months, the majority of follow up can be delivered in specialist neurological clinics, with, ideally, input from neurologists and transplant haematologists. As with any HSCT procedure, long term follow-up in a specialist setting is also required for advice on vaccination and to monitor for secondary autoimmune diseases, most commonly thyroid disease (10%) or immune thrombocytopenic purpura (ITP) (2-3%), infertility, malignancy, and other 'late effects'(18). Whilst secondary malignancy has been occasionally associated with the use of aHSCT for other indications, in the largest cohort of 507 patients, no cases occurred (19). Healthy babies have been born to both male and female patients post aHSCT, although large cohorts of long-term data are lacking (20).

Although aHSCT use was restricted during the peaks of the high transmission rates of the COVID-19 pandemic, it is now being offered to suitable patients with careful monitoring (21). A recent review of European Society for Blood and Marrow Transplantation (EBMT) registry data showed that non-relapse mortality rate (which is defined as death from any cause) between 2015 and 2020 has remained stable (12).

It is recommended that procedures are performed in centres accredited by JACIE (Joint Accreditation Committee of International Society for Cellular Therapy, ISCT, and EBMT), or equivalent organisations providing minimum quality standards for haematopoietic cellular therapy. As per other transplant indications, patient data should be routinely reported in accordance with regulatory standards to the EBMT and/or equivalent international registries, where specific minimal essential data (MED) forms have been developed for MS and other autoimmune diseases to enable audit of activity and retrospective analyses to be undertaken.

Who

As of 2021, the EBMT registry has collected data for 3502 patients treated specifically with HSCT since 1994 for various severe autoimmune disorders (ADs), including neurological, rheumatological, gastroenterological and other AD indications (12). The majority had MS (1875) and other immune-mediated neurological disorders included CIDP (65), NMO (27), MG (10) and SPS (8) (1, 12).

Initial reports of treatment success were limited to case reports. Despite the lack of commercial interest, a few phase II trials and one phase III trial (in RRMS) have now been completed across a range of disorders (table 2). In these trials patients typically had either highly active or treatment-resistant diseases, making the outcomes even more notable. Trial outcomes, including measures of disability, reversal of positive antibody status and freedom from relapse or progression, have been improving steadily as patient selection and treatment regimens are refined (22).

Table 2: Selected data from patients undergoing autologous haematopoietic stem cell transplantation for various immune-mediated neurological disorders.

	MS (11, 12, 23-26)	CIDP (27, 28)	NMO (22, 29)	SPS (30)
Reported number of procedures[+]	1875 in EBMT centres (mainly Europe)	64	27	36
Freedom from disease activity*	78.5% (RRMS)	73-83%	48-90%	47%
TRM	0.2%	No reported mortality	No reported mortality	No reported mortality
Follow up	Mean of 34 months^	Median of 54 months^	Median 47 months (29) and 60 months (22), respectively.	Mean of 42 months^
Trial status	Few phase II trials and one phase III trial completed, further phase III trials ongoing (Star-MS)	Phase II trial complete	Phase II trial complete	Phase II trial complete

*TRM = transplant related mortality. [+] clinical trials and EBMT registry data or case reports. *Specific to individual diseases; MS = no evidence of disease activity (freedom from MRI activity, disability worsening and relapses), CIDP = freedom from ongoing immunotherapy or relapses, NMO = progression free survival, SPS = freedom from ongoing immunotherapy or relapses. ^in the largest reported studies, detailed in 'Patient outcomes'.*

Why

Patient outcomes

Initial trials in MS concentrated on patients in the progressive phase of the disease with high levels of disability. A shift to treating patients whose primary pathology is thought to be active inflammation has subsequently occurred with results showing high levels of freedom from disease activity and lower TRM (table 2). The previous experience should not be overlooked; pooled analysis of trials with a majority of progressive patients (either primary or secondary, both active and inactive) demonstrated a 24.8% chance of disability progression at 2-year (31). Whilst it is not possible to compare this mixed meta-analysis with studies of populations containing just secondary progressive MS, they are of interest when comparing to a 20% risk of disability progression, at a shorter time point of 6 months, with Siponimod therapy and a 45% risk of progression at 2 years with interferon- beta-1a (32, 33). Suppression of relapses, but not disability progression or brain atrophy, have been demonstrated (34, 35), which may indicate a future role for aHSCT in patients

with progressive MS with active inflammation (see case report on SPMS), although further well-designed randomised trials are required.

For highly active RRMS the high degree of efficacy demonstrated in the only prospective clinical trial to date is impressive (11, 23). High rates of progression free survival (90.29%) and relapse free survival (84.6%) at 5 years were observed in the MIST trial (aHSCT vs clinician selected DMT, including natalizumab but not other high efficacy DMTs with a mean follow up of 2.8 years). The open label cross over design led to 31/51 patients switching from DMT to aHSCT. Due to the historic nature of the study, the only high efficacy DMT included was natalizumab and the relapse rate of 64.8% at 1 year in the standard treatment arm was higher than expected. Despite this, reductions in MRI activity, improvements in clinical assessment and across various domains of quality of life were also seen. TRM was 0%. This study provided the first direct comparison between aHSCT and traditional DMTs. No evidence of disease activity (NEDA), defined as absence of clinical progression, relapses and MRI activity, was proven in 78.5% of patients post aHSCT and 2.97% in the DMT treatment arm at 5 years. aHSCT is now recommended with Grade I evidence as standard of care for patients with highly active RRMS who fail DMTs (1, 36). Further phase 3 randomised controlled trials are currently recruiting, including in the UK (Star-MS, ISRCTN88667898), where aHSCT is being compared to high efficacy DMTs in treatment resistant RRMS or treatment naïve patients with rapidly evolving severe MS (37).

A retrospective review of a cohort of patients with 'aggressive RRMS' (defined as clinical and radiological features in keeping with an aggressive clinical course and poor prognostic markers) who were treated first line with aHSCT showed a NEDA rate of 100% over a median follow up of 30 months (26). Progression of brain atrophy, in patients with 'aggressive RRMS' who receive aHSCT, reverts to that of healthy controls (9).

Whilst the trial data for CIDP is at an earlier stage, similar promising results have been seen in patients resistant to at least two first-line therapies with 83% freedom from ongoing immunosuppressive therapies and stable or improving clinical examination, improvement in independent ambulation from 33% to 83% and improvement of various domains of neurophysiological examination (27). Mean follow up was 54 months and there were no transplant-related deaths. aHSCT is recommended as a clinical option for patients with IVIg resistant or dependent CIDP (1).

A retrospective review of 16 patients with treatment resistant NMO, who were treated with aHSCT utilising a mixture of low and intermediate intensity conditioning regimens, demonstrated a progression free survival of 48% over a median follow up of 47 months (29). 100% of patients remained seropositive and TRM was 0%. However, a subsequent small (n=12) open-label trial in treatment-resistant NMO patients, utilising an intermediate conditioning regimen with adjuvant rituximab and plasmapheresis, led to a 90% progression free survival at 5 years, 81% reversal of antibody status, and improvements across various quality of life domains over a mean follow up of 57 months (22). There were no transplant-related deaths.

Stiff person syndrome responds variably to aHSCT (30, 38). Trial experience shows that whilst 74% of patients entered an immunosuppressive free period, 47% of these relapsed within 3.5 years. Symptom load reduced and ambulation appeared to improve in the responders.

Whilst a trial has not yet been successfully reported for patients with MG, collated case series provides preliminary data that aHSCT may provide sustained remission from symptoms, freedom from immunotherapy and, in some cases, reversal of antibody status (39).

Case vignette – RRMS failing DMTs

A 27-year-old female presented with sensory symptoms in 2009 followed by speech disturbance in 2011. An MRI showed evidence of demyelination and cerebrospinal fluid (CSF) analysis demonstrated unmatched oligoclonal bands supporting a diagnosis of RRMS. Treatment with Glatiramer Acetate did not prevent further relapses 2013 and 2014. Following escalation to fingolimod further relapses with MRI evidence of disease activity in January and April 2015 contributed to an EDSS of 4. aHSCT (Cy 2m/m^2 + G-CSF for stem cell mobilisation followed by Cy 200mg/kg + rabbit ATG 6mg/kg with methylprednisolone cover) was provided in October 2015. Just over 12 months post procedure her EDSS had dropped to 1.5 and, although the post-transplant period was significant for hypothyroidism, her condition has remained clinically and radiologically quiescent ever since. The patient has had no further symptoms she attributes to MS, runs frequently, including a half-marathon, and has successfully delivered a healthy child following IVF 2.5 years post-transplant.

Case vignette - treatment naive RRMS

A 33-year-old female experienced numbness of both legs resulting in falls in March 2013, followed by weakness and incoordination of the left leg one year later with incomplete recovery. Left optic neuritis was followed by sensorimotor symptoms of her left leg in July and October 2014, respectively. An MRI showed evidence of demyelination and CSF demonstrated unmatched oligoclonal bands supporting a diagnosis of RRMS. DMT was planned but before initiation, two further relapses occurred: in February 2015 (right leg weakness) and April 2015 (right-sided ataxia) contributing to an EDSS of 6.5. Repeated imaging demonstrated several enhancing lesions. With criteria for rapidly evolving severe RRMS being met, aHSCT (Cy 2m/m^2 + G-CSF for stem cell mobilisation followed by Cy 200mg/kg + rabbit ATG 6mg/kg with methylprednisolone cover) was performed in May 2015 with no adverse effects. EDSS improved to 3.0 in June 2016 and was 2.5 in October 2021 with exercise tolerance being unlimited. Two children were conceived and born uneventfully by normal vaginal delivery in 2016 and 2019.

Case vignette – SPMS

A 30-year-old male had an episode of transverse myelitis in early 2000 with incomplete recovery, followed by a subacute sensory lower limb disturbance in late 2000. A subacute episode of lower limb weakness which improved with steroids then occurred in late 2007. Following this, investigation with brain and spinal MRI and CSF examination resulted in a diagnosis of RRMS, with an EDSS of 6.0. Interferon beta-1a was commenced but a further relapse occurred in 2008. Decline in mobility, balance and sphincter control thereafter prompted a diagnosis of secondary progressive MS with an EDSS 6.5 in 2012. Two further relapses with multiple enhancing lesions on brain and spinal MRI scans occurred in 2012, following which he underwent aHSCT (Cy 2m/m^2 + G-CSF for stem cell mobilisation followed by Cy 200mg/kg + rabbit ATG 6mg/kg with methylprednisolone cover). The post-transplant period was complicated by neutropenic septicaemia requiring intensive care support, a tracheostomy and prolonged inpatient neurorehabilitation. Whilst further evidence of clinical and MRI activity has been absent, disability level has gradually progressed with the latest EDSS, in May 2022, being 8.0.

Case vignette – Treatment resistant CIDP

A 49-year-old female was diagnosed with CIDP in 2005. The initial phase of illness ran an aggressive course with progression to tetraplegia within the same year. Although some clinical improvement occurred, over time her illness became refractory to treatment with glucocorticoids, immunoglobulin and plasma exchange. In 2013 further deterioration, despite ongoing immunomodulation, resulted in limited hand function and significant lower limb weakness requiring

the use of a walking stick and bilateral ankle-foot orthoses. In 2014, some 9 years post-diagnosis, treatment with aHSCT (Cy 2m/m^2 + G-CSF for stem cell mobilisation followed by Cy 200mg/kg + rabbit ATG 6mg/kg with methylprednisolone cover) was provided with no significant adverse effects. Since then, there is freedom from immunosuppression, an ability to walk independently for 2 miles, and remarkable sustained improvements in neurophysiological parameters and objective clinical examination.

Health economics

Immune-mediated neurological disorders cause a wide range of financial implications including medical and non-medical health care-related costs and loss of productivity. Detailed analysis of the direct comparison of the costs of aHSCT versus ongoing immunomodulation treatment for neurological conditions within the NHS is required.

Single centre estimate of the one-off cost of aHSCT in the NHS is approximately £35,000 (40). Whilst not a direct comparison, as list prices do not include administration, follow up or any negotiated discounts, the BNF prices of highly efficacious DMTs include natalizumab at £13,560 per annum, ocrelizumab at £19,160 per annum and alemtuzumab and cladribine at £56,360 and £28,662 for two-year courses, respectively (41). Whilst the cost of the former two depend on the duration of the treatment, the latter two are considered as complete courses in most patients. In CIDP, the cost of continued IVIg use for UK patients has been reported to be £49,430 per annum (42).

The potential elimination of the need for ongoing use of DMTs and/or immunosuppression and reduction in relapses and disability accumulation, the improved productivity of the affected patient and the reduction in the cost of medical and non-medical interventions, makes this treatment modality a very attractive option. Health technology reports for NHS Wales and NHS Scotland found aHSCT in treatment resistant or highly active RRMS to be both more effective and less costly than DMTs (43, 44).

Conclusion

aHSCT is a relatively safe, cost-effective procedure for carefully selected patients with refractory or highly active immune-mediated neurological disorders. Whilst its peri-procedure burden and potential risks have to be considered carefully, in contrast to most DMTs it is a one-off treatment with no cumulative toxicity or treatment burden. Based on current evidence it is recommended as a standard of care for patients with highly active relapsing-remitting MS failing DMTs and a clinical option for treatment naïve patients with aggressive MS, patients with progressive MS and active inflammation, and some patients with treatment-resistant CIDP, NMO, MG and SPS. Further studies are required to evaluate its utility as a first-line therapy. To ensure quality of care, patients should be treated in a transplant centre with JACIE (or equivalent) accreditation. Where possible, patients should be enrolled in clinical trials which will not only further our understanding of this treatment, but also support the development of greater numbers of specialised centres with combined experience, ultimately targeting this intensive but effective treatment option appropriately and easing the limited availability and unmet clinical needs within our health services.

Key points

1. aHSCT should be offered as standard of care to patients with active RRMS failing disease-modifying treatment and considered as a treatment option in treatment naïve patients with rapidly evolving severe MS.
2. The use of aHSCT should be considered in patients with other treatment-resistant immune-mediated neurological disease.

3. Patients should be appropriately selected, and treatment should take place in accredited centres with appropriate cross-disciplinary teams and as part of clinical trials, where relevant.
4. aHSCT may represent a long-term economic saving.

Further reading

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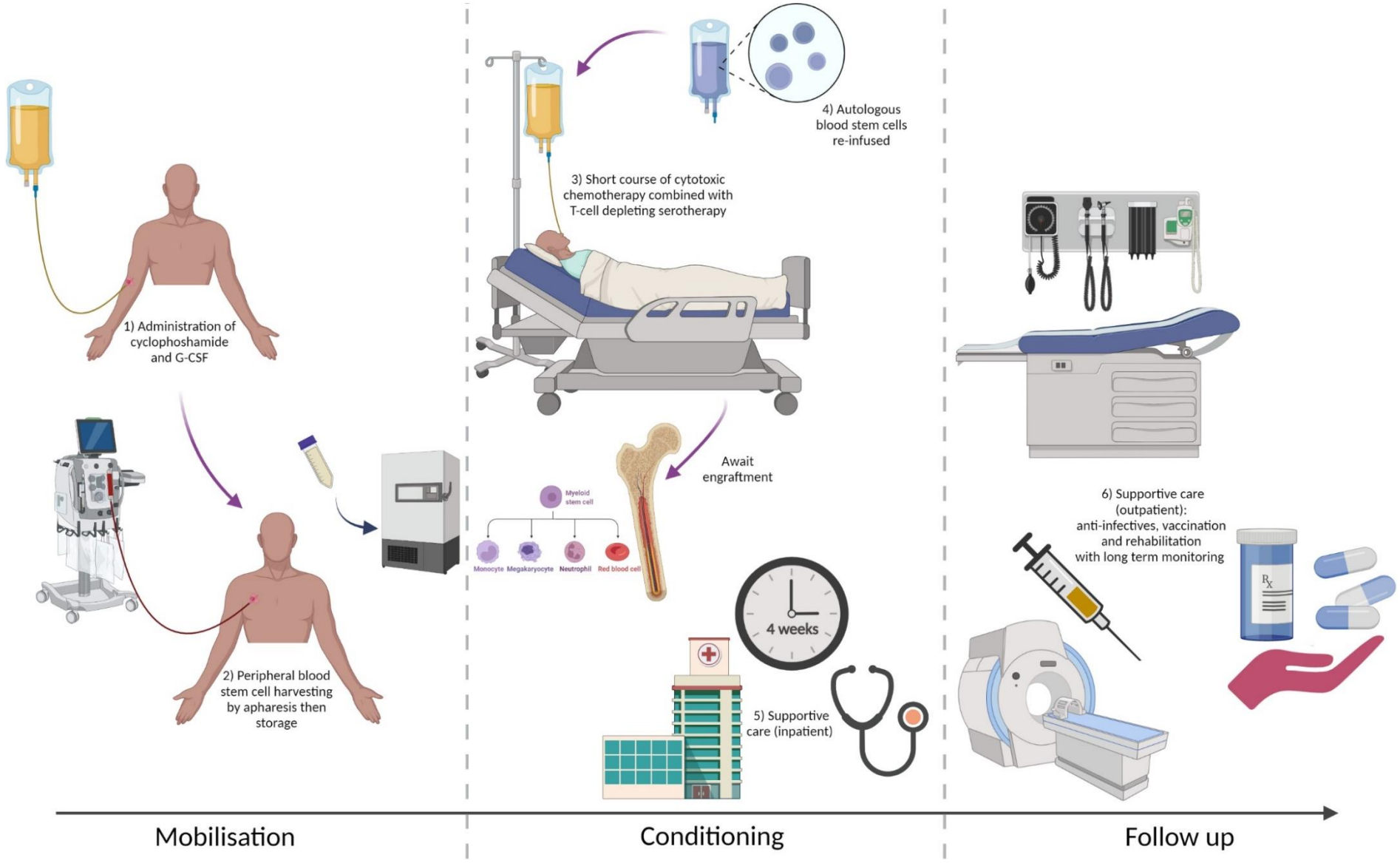

Figure 1: Representation of the usual treatment pathway for autologous stem cell transplantation. G-CSF = granulocyte colony-stimulating factor.

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