Technoleg Iechyd Cymru
Health Technology Wales

HEALTH TECHNOLOGY WALES (HTW) GUIDANCE 019 (July 2020)

Autologous haematopoietic stem cell transplantation to treat people with previously treated relapsing remitting multiple sclerosis

HTW Guidance:

The evidence supports the routine adoption of autologous haematopoietic stem cell transplantation (AHSCT) for people with relapsing-remitting multiple sclerosis (RRMS), in patients who have recurrence of symptoms despite previous treatment with disease modifying therapies (DMTs).

The use of AHSCT increases progression-free survival, slows the onset of disability and improves quality of life compared with DMTs. Patient selection for AHSCT should be undertaken by specialist MS-AHSCT Multi-Disciplinary Teams (MDTs) with neurological and haematological representation. The AHSCT treatment should be delivered in professionally accredited centres with neuro-rehabilitation and support services available to maximise the patient benefits of the treatment. Patient consent should include the provision of sufficient information to support shared decision-making and ensure that patients understand the safety, efficacy and uncertainties associated with AHSCT as well as alternative therapies.

A cost-utility analysis found that treatment with AHSCT is more effective and less costly than DMTs in people with highly active RRMS.

Further research into the effectiveness of AHSCT using RCTs and appropriate high efficacy DMTs over longer timeframes is recommended

Why did Health Technology Wales (HTW) appraise this topic?

Relapsing-remitting multiple sclerosis (RRMS) is a condition that is characterised by a recurring pattern of disabling neurological symptoms. Over time, approximately two thirds of patients develop progressive disability and the diagnosis evolves into secondary progressive multiple sclerosis. Standard treatment for RRMS are immune system targeted disease modifying therapies (DMTs) that are most likely to be effective for the relapsing remitting phase of MS but are less effective as the disease progresses. Due to the lack of effective therapies for progressive MS, it is important to treat RRMS early and aggressively so that disease progression can be delayed or halted. Autologous haematopoietic stem cell transplantation (AHSCT) is an intensive,

inpatient, one-off treatment that aims to reset a patient's immune system. Based on the estimated number of people in Wales with RRMS, clinical experts estimate that there is a small cohort of people with inadequately controlled disease despite high efficacy DMTs who may be eligible for treatment with AHSCT. No AHSCT for patients with MS currently exists in Wales, although some patients from Wales have received AHSCT treatment in England through their involvement in research studies.

This topic was notified to HTW by Welsh Health Specialised Services Committee (WHSSC).

The status of HTW guidance is that NHS Wales should adopt this guidance or justify why it has not been followed. HTW will evaluate the impact of its guidance.

Evidence Summary

Refer to Evidence Appraisal Report 019 (EAR019) for a full report of the evidence supporting this Guidance.

This EAR is adapted from the advice statement produced by the Scottish Health Technologies Group (SHTG), " Autologous haematopoietic stem cell transplant for patients with highly active relapsing remitting multiple sclerosis not responding to high-efficacy disease modifying therapies" , published in 2019. One randomised control trial (RCT), the Multiple Sclerosis International Stem Cell Transplant Trial (MIST), was included in the SHTG advice statement and no further RCTs comparing AHSCT with current practice for people with MS (specifically RRMS or related terms) were identified for this report. Four systematic reviews were identified, of which one had been included in the SHTG advice statement. Ten additional primary studies were identified that had not been included in the systematic reviews. The evidence in the primary studies is limited by the variability in treatment protocols (conditioning regimens), patient inclusion criteria, outcome definitions, lack of comparator treatment and short follow up periods.

The evidence extracted from the RCT, the relevant studies in the systematic reviews and the ten additional primary studies related to numerous relevant clinical outcomes (over twenty). Two measures reported most widely (including by the RCT) are 'no evidence of disease activity' (NEDA) and expanded disability status scale (EDSS). NEDA-3 was attained by 76% and 70% of patients at 24 months and five years post-AHSCT respectively (two studies, RRMS population) with NEDA-4 reached by 50% at five years post-AHSCT. A third study described NEDA-3 attainment by 90%, 70% and 60% of RRMS patients at one-, two- and three-years post-AHSCT respectively. A non-randomised study reported NEDA-3 to be higher for AHSCT compared with alemtuzumab for RRMS patients while the MIST RCT also found NEDA-3 to be significantly higher for AHSCT compared with DMTs. EDSS decreased from baseline with AHSCT in all studies, with the exception of one, that reported this endpoint (seventeen studies). EDSS also decreased where reported for RRMS specifically (six studies). The MIST RCT found the difference in EDSS between AHSCT and DMTs at one-year post-AHSCT to be statistically significantly in favour of AHSCT.

No studies evaluating the cost-effectiveness of AHSCT for previously treated relapsing remitting multiple sclerosis were identified.

HTW developed a cost-utility analysis to determine the cost effectiveness of AHSCT compared with DMTs for people with highly active RRMS. A Markov model was used to estimate costs and quality-adjusted life years (QALYs) over a five year time horizon, from the UK NHS and personal social services perspective. Costs and QALYs were discounted at 3.5% per year as recommended in the NICE reference case. AHSCT was found to be dominant (more effective and less costly than DMTs) in most modelled scenarios with some notable exceptions. In these scenarios, AHSCT was still found to be more effective but it was also found to be more costly. When compared against all DMTs, the ICER was found to be £38,359 per QALY gained indicating that AHSCT was not cost-effective as the ICER was above the threshold of £20,000 per QALY gained. When compared against natalizumab only, the ICER was found to be £2,741 per QALY gained indicating that AHSCT was cost-effective as the ICER was below the threshold of £20,000 per QALY gained. Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The model is run 10,000 times. At a threshold of £20,000 per QALY, AHSCT was found to have a 100% probability of being cost-effective while standard care with DMTs had a 0% probability of being cost-effective.

The appropriate mechanism for patient engagement was determined and the patient perspective was considered where possible.

Appraisal Panel considerations

- The clinical experts described to the Appraisal Panel that RRMS is an aggressive and disabling disease and that when symptoms recur despite the use of DMTs, treatment options are limited. The experts explained patients with RRMS are often young and are difficult to manage with the prospect of advancing disability if DMTs become less effective.
- The clinical experts described to the Appraisal Panel the current care pathway for patients with RRMS and explained that different DMTs have different levels of treatment efficacy. Those with moderate efficacy have a moderate risk of adverse events while higher efficacy therapies, are associated with a higher risk of adverse events. The experts explained that most people are stabilised through the use of high efficacy DMTs.
- The clinical experts explained to the Panel that AHSCT is currently considered as third or fourth line therapy when symptoms recur despite the use of DMTs. The experts also explained, however, that as evidence emerges, it is possible that the threshold for AHSCT may lower with the intention of establishing better control of the RRMS symptoms at an earlier stage of the disease, although this is currently speculative.
- The Appraisal Panel received a verbal account from a patient representative who described her individual experience leading up to the diagnosis of MS, her investigation and consideration of treatment options. The patient described her experience of receiving AHSCT (outside the UK) and her symptomatic improvement since undergoing treatment. The patient representative recounted the physical and emotional aspects of the underlying disease as well as the treatments received as well as the impact that this has had on her family life and experiences outside of the home. The patient explained to the Appraisal Panel that she considered that AHSCT has halted but not cured her disease but she reported considerable improvements in physical and mental well-being and overall quality of life. The patient representative was grateful for the benefits that she has received from AHSCT and expressed no regrets about the treatment that she has received.
- In its decision-making process, the Appraisal Panel considered the published evidence as well as the input of clinical and patient experts. The Panel concluded that clinical evidence supports the efficacy of AHSCT in patients who have symptom recurrence despite treatment with DMTs. The clinical studies indicate that AHSCT leads to a significant increase in progression free survival, delay in disability and improvement in quality of life when compared with DMTs. The Panel concluded that the written and verbal evidence from the clinical experts also corroborates the efficacy of AHSCT. The Panel noted that there are ongoing clinical trials comparing AHSCT with different high efficacy DMTs and the results of these studies will add to and strengthen the clinical evidence base in due course.
- The Panel were informed by the clinical experts that life-threatening adverse events are possible with AHSCT but that with improvements in treatment delivery (specifically conditioning regimens) a decrease in transplant related mortality has been observed in their practice. The Panel concluded that the safety of AHSCT in the context of the aggressive nature of the underlying disease being treated is acceptable.
- The Panel considered the health economic evidence, most notably the novel cost-utility analysis that was undertaken by HTW on the basis of the MIST trial data. The Panel accepted the findings of the cost-utility analysis and concluded that AHSCT for patients with highly-active RRMS is more effective and less costly than DMTs.
- The Appraisal Panel concluded that the evidence supports the routine adoption of AHSCT but considered that the delivery of AHSCT in Wales for this indication requires a number of important additional considerations. The Panel were informed by the experts about the importance of careful patient selections through the work of an All Wales Multi-Disciplinary Team with representation from neurological and haematological experts. The importance of establishing an agreed clinical pathway to support this was emphasised by the experts. Treatment should be delivered in professionally accredited centres in an integrated manner

with sufficient training and expertise to achieve the best possible clinical outcomes at the lowest possible risk to patients. The treatment centres should be supported by neuro-rehabilitation and support services to maximise the patient benefits of the treatment. Patient consent should include the provision of sufficient information to support shared decision-making and ensure that patients understand the safety, efficacy and uncertainties associated with AHSCT as well as alternative therapies.

- The Appraisal Panel were advised by the clinical experts that there are likely to be as few as two to eight patients each year in Wales who currently meet the inclusion criteria that are included in this assessment, but this number may change as the evidence emerges from on-going studies. It was agreed by the experts that the current lack of provision of an AHSCT service in Wales is potentially inequitable and that the offer of AHSCT in Wales is likely to lead to better access to treatment for this difficult to manage group of patients. The Appraisal Panel noted that patients from Wales who fit the criteria for inclusion in the ongoing UK based clinical trials (STAR-MS), can be offered treatment in London or Sheffield as part of the study but that this is secured only after commissioner approval of an Individual Patient Funding Request. The panel recognised the importance of supporting ongoing research studies with UK sites, such as STAR-MS and BEAT-MS, encouraging the participation of eligible Welsh patients where possible. The Panel concluded that the establishment of an AHSCT service for the treatment of patients with RRMS in Wales with commissioner support would not only improve access to care but also allow for patients to be more easily recruited into national and international studies.

Responsibilities for consideration of this Guidance

Health Technology Wales (HTW) was established by Ministerial recommendation[1,2] to support a strategic, national approach to the identification, appraisal and adoption of non-medicine health technologies into health and care settings. The HTW Appraisal Panel comprises senior representation from all Welsh boards with delegated authority to produce guidance 'from NHS Wales, for NHS Wales'. The status of HTW guidance is 'adopt or justify'. There is an expectation from Welsh Government that HTW guidance is implemented with adoption regularly audited by HTW.[3]

The guidance in this document is intended to assist Welsh care system decision makers to make evidence-informed decisions when determining the place of health technologies and thereby improve the quality of care services.

The content of this HTW guidance was based upon the evidence and factors available at the time of publication. An international evidence base was reviewed and external topic experts and HTW committee members consulted to contextualise available evidence to Wales. Readers are asked to consider the generalisability of the evidence reviewed to NHS Wales and that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. It is acknowledged that evidence constitutes only one of the sources needed for decision making and planning.

This guidance does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

No part of this guidance may be used without the whole of the guidance being quoted in full. This guidance represents the view of HTW at the date noted. HTW guidance is not routinely updated. It may, however, be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the guidance given.

Standard operating procedures outlining HTWs evidence review methods and framework for producing its guidance are available from the HTW website.

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Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by HTWs Assessment Group. However, reviewers had no role in authorship or editorial control and the views expressed are those of Health Technology Wales.

Chair, Health Technology Wales Appraisal Panel

1. National Assembly for Wales, Health and Social Care Committee. Access to medical technologies in Wales. December 2014.
2. Response to Recommendations from the Health & Social Care Committee: Inquiry into Access to Medical Technologies in Wales. February 2015.
3. Gething, V. Letter to all Health Board Chairs re Funding for Sacral Nerve Stimulation in Wales. VG_01655_17. September 2017.