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Health economics and patient outcomes of non-myeloablative hematopoietic stem cell transplantation versus disease-modifying therapies for relapsing remitting multiple sclerosis in the United States of America

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Abstract

Objective: To estimate differences in treatment costs and health outcomes between non-myeloablative hematopoietic stem cell transplantation (HSCT) and disease-modifying therapies (DMTs) for the treatment of relapsing-remitting multiple sclerosis (RRMS).

Methods: We collected data on costs and charges for patients who underwent HSCT for RRMS at Northwestern Memorial Hospital in Chicago (USA) between January 2017 and January 2019. The costs of HSCT were compared against those for DMTs in the United States, obtained from the literature. We also conducted a literature review to interpret the cost comparisons in terms of disease control and patients' wellbeing defined as no evidence of disease activity (NEDA), neurologic disability by the expanded disability status scale (EDSS), and quality of life by the short form SF-36, respectively.

Results: Outside of the data, herein, no other studies on cost of HSCT for RRMS were found in the literature. HSCT mean total costs, based on our own hospital, were $85,184 (range ($70,635 to $120,260). Mean revenue collected was $95,268 (range $16,544 to $173,204). In comparison, according to the literature, 2019 DMT costs in the USA ranged from $80,000 to $100,000 per year per patient. Compared to DMTs, studies of HSCT reported greater improvement in no evidence of disease activity, disability, and quality of life.

Limitations: Costs of HSCT would be expected to vary by conditioning regimen utilized, patient selection, center experience, and regional variation. No cost data on other HSCT regimens or on the three most recent DMTs, alemtuzumab, ocrelizumab and ocrelizumab, are available. Randomized trials for cost comparisons are missing and variations in HSCT designs, populations, and methodology preclude more precise cost estimates.

Conclusion: Costs of non-myeloablative HSCT after which DMTs are indefinitely discontinued, are approximately the same as those for one year of prescription DMTs. Since DMTs assessed in this analysis are given on an ongoing basis, whilst HSCT is not, HSCT is expected to produce long-term cost-savings. When considered alongside the available clinical evidence, which suggests that HSCT may generate more health gains than DMTs, HSCT is likely to represent a cost-effective use of resources. Model-based health economic analyses are required to substantiate this conclusion.

Introduction

Multiple sclerosis (MS) is a central nervous system demyelinating disease that has been reported to affect from 400,000 to 727,000 people in the United States (US) (1-3). It is a chronic disease with peak onset at the age of 30 years old but may present later in life or, less commonly, in teenage or childhood years (4,5). MS is second only to congestive heart failure in terms of the costs of care for a chronic illness (6).

Lifetime direct costs per patients are greater than $ 4 million US dollars (7), the majority of which are attributable to prescription drugs, i.e. disease-modifying therapies (DMTs). In the US, DMT prices have increased five to seven times faster than the rate of inflation (8-10). In the 1990s, interferons (first-generation DMTs) cost $8,000 to $11,000 per year (8). In 2004, the average yearly DMT costs per person were $26,050 (9). In 2013, average yearly DMT costs rose to $60,000 (8). In 2017, costs for most DMTs exceeded $70,000 per year (10), and by 2019, DMT costs were between $80,000 to $100,000 per year per patient (11). Despite having been available for a long time, and their comparatively lower efficacy, charges for older first-generation DMTs have continued to increase at a pace that is consistent with the newer second- and third-generation DMTs (10, 11). DMTs are expensive, and while a few such as alemtuzumab or cladribine are taken as pulses over 2 years, most DMTs have to be taken on a continuous, chronic, and life-long basis, resulting in the accumulation of substantial healthcare costs over the patient's lifetime as well as excessive out-of-pocket costs and onerous pharmacy benefit restrictions which can all negatively affect adherence to medications and medical advice.

Autologous hematopoietic stem cell transplantation (HSCT) is a therapeutic intervention in which chemotherapy and mono or polyclonal antibodies (the conditioning regimen) are given over several days, followed by the infusion of hematopoietic stem cells (HSCs) to hasten recovery of lympho-hematopoiesis. Autologous HSCT for RRMS is an immune-based therapy based on the concept that the conditioning regimen will cytoreduce disease-causing lymphocytes and stop inflammation (stop co-stimulation), while rapid immune regeneration without inflammation will reintroduce tolerance to self-epitopes via a rebound in regulatory and suppressor T cells. A normalization of pro-inflammatory gene expression profile and normalization of pro-inflammatory lymphocyte subsets ensues after HSCT (12-14). After an autologous non-myeloablative HSCT, hematopoietic and immune recovery will occur spontaneously, but autologous HSCs (collected before the conditioning regimen was given) are reinfused as an autologous supportive blood product to accelerate hematopoietic recovery.

HSCT is given as a once-only procedure, including a 14 to 15 day hospital stay. After discharge, outpatient blood work is checked weekly for 4 weeks and then every two weeks for 2 months, and while all DMTs and immune-based drugs are discontinued, oral antibiotics such as fluconazole and co-trimoxazole are taken orally for 3 months and acyclovir for one year. However, the vast majority of these costs are accrued within the 14 to 15 days required for hospitalization, with very few costs being incurred thereafter.

In this paper, we provide a preliminary comparison of the costs and outcomes in terms of no evidence of disease activity (NEDA) (15), improvement in neurologic disability i.e. decrease in Expanded Disability Status Scale (EDSS) (16), and changes in physical component summary, mental component summary, and total score of the quality of life short form 36 (SF-36) associated with non-myeloablative HSCT, compared with those for DMTs. First generation DMTs i.e. copaxone or interferons have a 2-year NEDA of approximately 30% (44) while second or third line DMTs have a 2-year NEDA up to 50% (44). An improvement in neurologic disability (defined as a decrease in the EDSS by 0.5 to 1.0) (17) or a minimal clinical meaningful improvement in the SF-36 by 5 points (18) has not, to our knowledge, been achieved by DMTs in any study cohort. The aim, herein, is to inform judgments and stimulate more inquiry into the value of the money spent for HSCT versus DMTs in the US setting.

Methods

Setting and design

Enrolment in the MIST randomized trial of HSCT versus DMTs for RRMS was completed in 2016 and the results were published in January 2019 (30). As the costs of HSCT were not captured in that study, we elected to assess the costs of HSCT using the same treatment regimen utilized in MIST for patient with RRMS that were treated at the same center using the same eligibility, conditioning regimen, and same standard of care guidelines between January 2017 and January 2019.

Patient selection

Patients were offered autologous non-myeloablative HSCT if they fulfilled the MIST inclusion and exclusion criteria (30). In brief, patients were 18 to 55 years old, had an established diagnosis of RRMS based on the McDonald's 2010 diagnostic criteria (46) with two acute relapses, or one relapse with MRI evidence of disease activity at a separate time point, within the last year despite the use of DMT and an EDSS of between 2.0 and 6.5. Patients were excluded for primary or secondary progressive multiple sclerosis; hereditary neurologic diseases; pregnancy; pulmonary, cardiac, renal, or liver dysfunction; abnormal platelet or white blood cell counts; active infection; prior treatment with alemtuzumab or mitoxantrone; or use of natalizumab within the prior 6 months, fingolimod within 3 months, or teriflunomide within 24 months (unless they underwent successful accelerated elimination procedure).

Hematopoietic stem cell collection and transplantation procedure

All patients were treated per the MIST protocol. Peripheral blood stem cells (PBSC) were collected as an outpatient 10 days after a 23-hour admission for intravenous cyclophosphamide (2 g/m^2). Outpatient subcutaneous filgrastim was given starting 5 days after cyclophosphamide at 5 to 10 μg/kg per day until day 10. Two weeks later patients were admitted to the hospital for the conditioning regimen consisting of

intravenous cyclophosphamide 50 mg/kg per day on days –5 to day -2 before stem cell transplantation and rabbit anti-thymocyte globulin, 0.5 mg/kg on day -5, 1.0 mg/kg on day -4, and 1.5 mg/kg on days -3, -2 and -1. Methylprednisolone (1000 mg) was infused 30 min prior to rabbit anti-thymocyte globulin infusion. Beginning on day 0, daily oral prednisone was dosed at 60 mg for 3 days, 40 mg for 2 days, 20 mg for 2 days, and 10 mg for 2 days. Filgrastim (5–10 μg/kg per day) was started on day +4 and continued until engraftment.

Hydration (125–150 mL normal saline per hour), diuretics, and intravenous mesna were continued until 24 h after the last dose of cyclophosphamide. A Foley catheter was placed in patients with greater than 60 mL of postvoid urinary residual. Intravenous cephalosporin was started on day 0. Intravenous vancomycin was added for a febrile episode. Methylprednisolone (250 mg) was infused for rabbit anti-thymocyte globulin–related fever. Patients remained hospitalized until recovery of peripheral blood counts which occurred a mean of nine days after hematopoietic stem cell infusion for a total hospital stay of 14 days.

Oral acyclovir was started on admission and continued for 1 year. Oral fluconazole was started on day +2, and oral trimethoprim-sulfamethoxazole or monthly nebulized pentamidine was started after platelet engraftment and continued for 3 months. Cytomegalovirus viral load was monitored for 90 days and was treated preemptively by switching from acyclovir to oral valganciclovir (900 mg twice daily) until testing negative by quantitative polymerase chain reaction.

Hematopoietic stem cell costs

Costs for HSCT incorporated outpatient pre-transplant work-up and mobilization and harvesting of PBSCs. These costs included blood draws, magnetic resonance imaging (MRI), echocardiograms, electrocardiograms, chest radiograph, and PBSC leukapheresis and cryopreservation. Charges for inpatient transplantation included the conditioning regimen drugs (cyclophosphamide and ATG), PBSC reinfusion, all pharmaceutical medications including antibiotics and anti-emetics, intravenous fluids, nursing care, blood draws, laboratory tests, blood transfusions including packed red blood cell and platelets, and room charges until the time of hematopoietic recovery and discharge. The only direct costs not captured because they were under a different revenue stream were those related to physician initial outpatient assessments and daily inpatient follow ups.

Analysis of HSCT costs was separated into direct costs related to patient care (e.g. medications, laboratory tests, imaging studies, transfusions, nursing care), and overhead costs which are necessary to operate a hospital but not directly related to inpatient care (e.g. management, supervision, medical records, accounting, information systems, marketing, legal, malpractice insurance, building maintenance and depreciation, house-keeping). The costs were the sum of direct and overhead costs. And the total net income is net revenue collected.

DMT costs

In order to provide a basis for comparing the costs of HSCT and DMT, we conducted a simple PubMed search for all published papers using the term "multiple sclerosis healthcare costs" and the subject headings of HSCT and DMT for the same time interval of January 2017 to January 2019.

Outcomes for HSCT versus DMTs in RRMS

In order to provide a basis for understanding the implications of the differences in outcomes between alternative treatment approaches, we undertook an additional search in PubMed to identify studies reporting on clinically relevant outcomes for HSCT and/or DMTs in RRMS populations. The search was limited to studies published in the English language between 2010 and January 2020 and included the terms "multiple sclerosis disease modifying therapy" or "multiple sclerosis hematopoietic stem cell transplantation" and the subject headings of "no evidence of disease (NEDA) (12), quality of life SF-36, or EDSS scale (13)". The purpose of this search was not to systematically identify and review all available evidence, but rather to provide an overview of the comparative effectiveness of HSCT and DMTs in terms of clinical outcomes and quality of life (QoL).

To identify DMT studies, we used pivotal phase 3 clinical trials for each approved DMT: ADVANCE (pegylated interferon beta-1a) , AFFIRM (natalizumab), CARE-MS I (alemtuzumab), CARE-MS II (alemtuzumab), CLARITY (cladribine), CLIMB (standard of care), CombiRx (combined interferon beta-1 alpha and glatiramer acetate), CONFIRM (dimethyl fumarate), DEFINE (dimethyl fumarate), FREEDOMS (fingolimod), FREEDOMS II (fingolimod), OPERA I and II (ocrelizumab), SENTINEL (natalizumab), TEMSO (teriflunomide), TOWER (teriflunomide), and TRANSFORMS (fingolimod). FDA approved drugs that have been removed from market, e.g. daclizumab, or are no longer commonly prescribed, e.g. mitoxantrone, were excluded.

Health outcomes were operationalized in our synthesis using three commonly measured outcomes of disease activity and disability: no evidence of disease activity (NEDA) (15), expanded disability status scale (EDSS) (16), and quality of life short form 36 (SF-36). NEDA is defined as no relapses, no progression, and no new or enhancing lesions on magnetic resonance imaging (15). The mean change in EDSS score was used to evaluate neurologic disability (16). Analysis of EDSS was limited to studies that reported EDSS change for the entire study group. The numerical EDSS disability score ranges from 0 (no neurologic disability) to 10 (death due to MS) in 0.5-point increments (17). Neurologic improvement is usually defined as a decrease of EDSS by 1.5, 1.0, or 0.5 points for an enrollment EDSS of < 2.0, 2.0 to 5.5, or ≥ 6.0, respectively (17). Similarly, quality of life was limited to studies reporting the SF-36 QOL questionnaire that is composed of a physical component summary (PCS), a mental component summary (MCS) and total scores (TS). To achieve a minimal clinically meaningful difference in QOL scores requires a change of 5 points (18). When multiple studies were available, we limited results to the initial study or the first post-hoc analysis. We excluded studies of secondary progressive or primary progressive MS.

Statistical analysis

DMT costs obtained from the literature were informative analysis of mean or median costs per drug which was not based on direct comparison of DMT treatment arms in randomized trials. Similarly, we calculated the mean, median, range, standard deviation (SD) of HSCT cost in our cohort. Outcome measures of NEDA, EDSS, and SF-36 published in the literature on DMT and HSCT were summarized in order to stimulate future definitive cost outcome comparison in randomized trials.

Results

Costs of non-myeloablative HSCT versus DMTs for RRMS

Cost analysis was available on 37 patients. The cohort had a mean age of 38 years, (range 26 - 51), with a female to male ratio of 2.7, and a mean EDSS score of 3.7 (median of 3.5, and range of 2 to 6.5). All had previously received DMTs including interferon-beta-1a=25/37 (66%), interferon beta 1b = 7/37 (19%), glatiramer acetate = 24/37 (65%), natalizumab = 16/37 (43%), dimethyl fumarate = 20/37 (54%), fingolimod = 9/37 (24%), teriflunomide = 6 / 37 (16%), ocrelizumab = 3/37 (8%), cladribine = 1/37 (2.7%). They also received other immune suppressants including corticosteroids = 37/37 (100%), rituximab=1 /37 (2.7%), intravenous immunoglobulin (IVIG)=2/37 (5%), mycophenolate mofetil = 1/37 (2.7%), mesenchymal stem cells = 1/37 (2.7%), hydroxychloroquine = 2/37 (5%), and leflunomide = 1/37 (2.7%).

Our search identified three publications that documented annual DMT costs (10, 11. 19), of which only one study reported costs of DMTs for patients with RRMS during the same time period as HSCT data were collected, i.e. from 2017 to 2019 (11). This study reports that the mean drug acquisition costs for DMTs in the US are more than $86,000 per patient per year. This estimate excludes all other costs associated with the management of the disease, for example, physician visits, other medications, imaging, and management of relapses; hence, the true costs of treating RRMS patients on DMTs will be higher. Given previous trends in increasing prices of DMTs, it is reasonable to expect that these costs will continue to rise in the future

Comparison of health outcomes for non-myeloablative HSCT versus DMTs in patients with RRMS

Figure 2 presents a comparison of change in EDSS scores reported within the HSCT and DMT studies identified by the search. With the exception of natalizumab (20,21) and alemtuzumab (22,23), no DMT trial have reported improvement in EDSS on the entire study cohort in their per protocol analysis. The alemtuzumab CARE-MS I study reported a decrease (improvement) in EDSS of 0.13 and 0.14 at 1 and 2 years (22), while the alemtuzumab CARE-MS II study reported a decrease in EDSS of 0.14 and 0.17 at 1 and 2 years (23). The Tysabri (natalizumab) Observational Program (TOP) reported an EDSS score decrease of 0.2 at 1, 2, 3, and 4 years (24). HSCT trials for RRMS reporting EDSS for the study cohorts have demonstrated decreases (improvements) of > 0.5 point or more (Figure 2) (25-30).

Figure 3 presents a summary of NEDA outcomes reported within the identified HSCT and DMT studies. For peginterferon beta-1a (ADVANCE study), NEDA was 34% at one year (31). In the AFFIRM trial of natalizumab, NEDA was 47% and 37% at one and two years, respectively (32). For alemtuzumab (CARE-MS I study), NEDA was 39% at two-years (22). The CLARITY oral cladribine study had a two-year NEDA of between 44 and 46% with a placebo of 16% (33). The CombiRx study demonstrated that the combination of interferon and glatiramer acetate provided a three-year NEDA of 33% versus 21% for interferon alone and 19% for glatiramer acetate alone (34). When NEDA was evaluated in clinical practice independent of a specific DMT, the Harvard Comprehensive Longitudinal Investigation of Multiple Sclerosis (CLIMB) study had a NEDA of only 15% at 5 years and 7.9% at 7 years (35). When data from the DEFINE and CONFIRM studies were combined, the two-year NEDA for dimethyl fumarate versus placebo was 26% and 12%, respectively (36). For Fingolimod (FREEDOMS study) the reported NEDA at two-year is 33% versus 13% for placebo (37). The TRANSFORMS study of fingolimod reported a one-year NEDA of 38% (38). For combined OPREA I and II trials, ocrelizumab achieved a two-year NEDA of 47% (39). In summary, for first generation DMT (interferon and glatiramer acetate) NEDA is approximately 30% to 35% at two years, while second and third generation DMTs have reported a NEDA of approximately 40% to 50% at 2 years. In contrast, after HSCT for RRMS, NEDA is roughly 70% to 90% at 2 years and 60% to 80% at 5 years (25-30).

Figure 4 summarizes SF-36 outcomes reported within the HSCT and DMT studies. Most DMT trials report only the SF-36 physical component summary (PSC) while omitting mental component summary (MCS) or total scores (TS). PCS improved by 0.33 points with use of ocrelizumab (40), by 1.03 points with natalizumab (41), and by 2.4 points with alemtuzumab at 2 years (42). In comparison, the SF-36 QOL after HSCT with the same non-myeloablative regimen of cyclophosphamide and ATG led to a clinically meaningful increase of 16 to 22 points at 2 years (25-30).

Discussion

Although the data related to the costs of DMTs and clinical and MRI outcomes for both DMTs and HSCT for RRMS have been obtained from the published literature, we present herein the first report to our knowledge on the costs and reimbursements of HSCT for RRMS and comparison of durability of important outcomes of NEDA, improvement in neurologic disability (i.e. EDSS), and quality of life after treatment with either DMTs or HSCT. Based on our own data from Northwestern using the MIST conditioning regimen, the mean direct costs of HSCT were $42,295 (range $33,887 to $57,704) and mean overhead costs were $42,888 (range $33,653 to $62,555). The mean charges for HSCT are $98,000. This one-time cost of HSCT compares favorably with the historical one-year costs of outpatient pharmaceutical drugs (DMT) that are reported to be between $80,000 and $100,000 per year (11) We separated costs into direct patient care costs and overhead institutional costs, because the costs for doing a non-myeloablative HSCT for RRMS in public health systems such as the UK's National Health System (NHS) is approximately 30,000 – 35,000 pounds (full analysis pending) which at first glance appears to be half of the cost of HSCT in the USA.

However, in public health systems the overhead costs are not counted inpatient costs, whereas in the American private health care system both overhead and direct costs are counted because both must be recovered from the patient's private health insurance.

The true costs of DMTs are impossible to ascertain because of the commercial sensitivities and variability in insurance reimbursement, but the annual average DMT cost for an uninsured patient in the USA is $86,000 per year. Assuming approximately 85% of HSCT-treated patients will remain relapse-free and drug-free for 5-years, a conservative estimate for the net savings in drug charges will be approximately $292,400 per HSCT-treated patient over this period ($86,000 x 0.85 x 4 years). This cost saving is likely to represent an underestimate, as it assumes that DMT prices will remain stable over time; given previous trends in inflating prices for DMTs, in reality, it is more likely that these will continue to increase well above the rate of inflation. In contrast, HSCT regimens employ generic patent-expired drugs whose costs are unlikely to increase faster than inflation.

We did not include indirect costs of loss of work productivity that would likely favor HSCT. In the USA, loss of employment results in loss of insurance. Since, for most people, DMT prices are unaffordable as an out-of-pocket expense, the result will be untreated disease with acceleration of disease activity and progression. In comparison, after HSCT, all DMT drugs are normally discontinued and loss of insurance due to unemployment will not increase out-of-pocket disease-related financial burden or risk of disease progression for patients that remain in long-term drug-free remission. Since compared to 1st and 2nd generation DMT, the 3rd generation higher efficacy DMT drug natalizumab has been reported to improve work efficiency and attendance (43), HSCT which provides a meaningful improvement in QOL (44), may translate into a more pronounced impact on work productivity. Over the longer-term, it is reasonable to expect that compared with DMTs, HSCT may both improve patient health whilst also accumulating substantial cost-savings which may be far greater than the estimate presented here.

Comparisons of published data on change in NEDA, EDSS, and SF-36 indicate that HSCT is a highly effective therapy in well-selected patients with RRMS. Each of these three instruments capture a different aspect of treatment outcome. NEDA captures no evidence of new disease, i.e. stable disability; EDSS captures improvement in neurologic disability, i.e. reversal of disability; while SF-36 captures the physical and mental components associated with improvement in quality of life. Currently, the most effective DMTs report NEDA of approximately 50% at 2-year while HSCT reports a NEDA of 80–90% during the same time interval. DMTs do not improve (decrease) EDSS scores in patients with RRMS with the exception of alemtuzumab and natalizumab (Fig. 2) which decrease EDSS scores by 0.2 point, less than what is needed to be clinically significant (i.e. 0.5 point). In comparison, HSCT for RRMS results in a clinically significant improvement (decrease) in EDSS by 0.7 to 2.5 points (Fig. 2). In the MIST trial, HSCT improved mean EDSS scores by 1.0 point while the mean EDSS scores worsened (increased) by 1.0 point in the DMT arm (30). Although

the improvement in EDSS scores after HSCT may be due to "regression to the mean", such an improvement was not observed in the DMT arm of the randomized MIST trial. In fact, EDSS scores in MIST DMT arm worsened (increased) during the trial period, and no previous DMT study has achieved a sustained regression to the mean that was clinically meaningful (a decrease of 0.5 points or more) as demonstrated in the various HSCT studies.

The study presented herein is subject to several limitations. Firstly, the cost estimates for HSCT were obtained from a single center; costs for HSCT would be expected to vary by conditioning regimen utilized, patient selection, center experience, and regional variation. Costs could vary significantly between different conditioning regimens for example the term HDIT (high dose immune therapy) is an acronym used for myeloablative regimens that some centers are utilizing for multiple sclerosis (28). Herein and in our prior publications, we utilize an immune specific non-myeloablative regimen. A second limitation is that retrospective comparison between different studies which have their own settings and patient populations is difficult. Undertaking robust cost-effectiveness analyses of treatment modalities whether between different DMTs or between DMTs versus HSCT requires a head to head comparison in a randomized trial. As this is the first manuscript on health economics of HSCT for RRMS, we hope that this publication will stimulate the interest of physicians and providers, whether private insurance or governmental, to look further into this subject. We also caution that costs will depend on the HSCT regimen used which in this analysis was based on a less expensive non-myeloablative regimen. While patients stop and remain off DMTs after HSCT and no immune based therapy is given after hospital discharge, other post-transplant 100 day costs of monitoring blood draws were not captured. We also are not able to factor in offsetting costs of proprietary outpatient pharmaceutical rebates which can reduce net DMT costs (45). National variations in HSCT treatment regimens and patient populations preclude more precise cost estimates.

Summary

It is not just cost of a treatment but also its clinical efficacy that is important in terms of optimal health care. Data collated from the published literature and summarized herein suggests that HSCT may be a 'win-win' in terms of both cost and clinical efficacy. On the basis of the information presented here, it is reasonable to expect that HSCT may generate cost-savings and additional health gains for well-selected RRMS patients, compared with standard DMTs, although properly designed randomized trials will be needed. Formal model-based health economic analyses are required to substantiate this conclusion.

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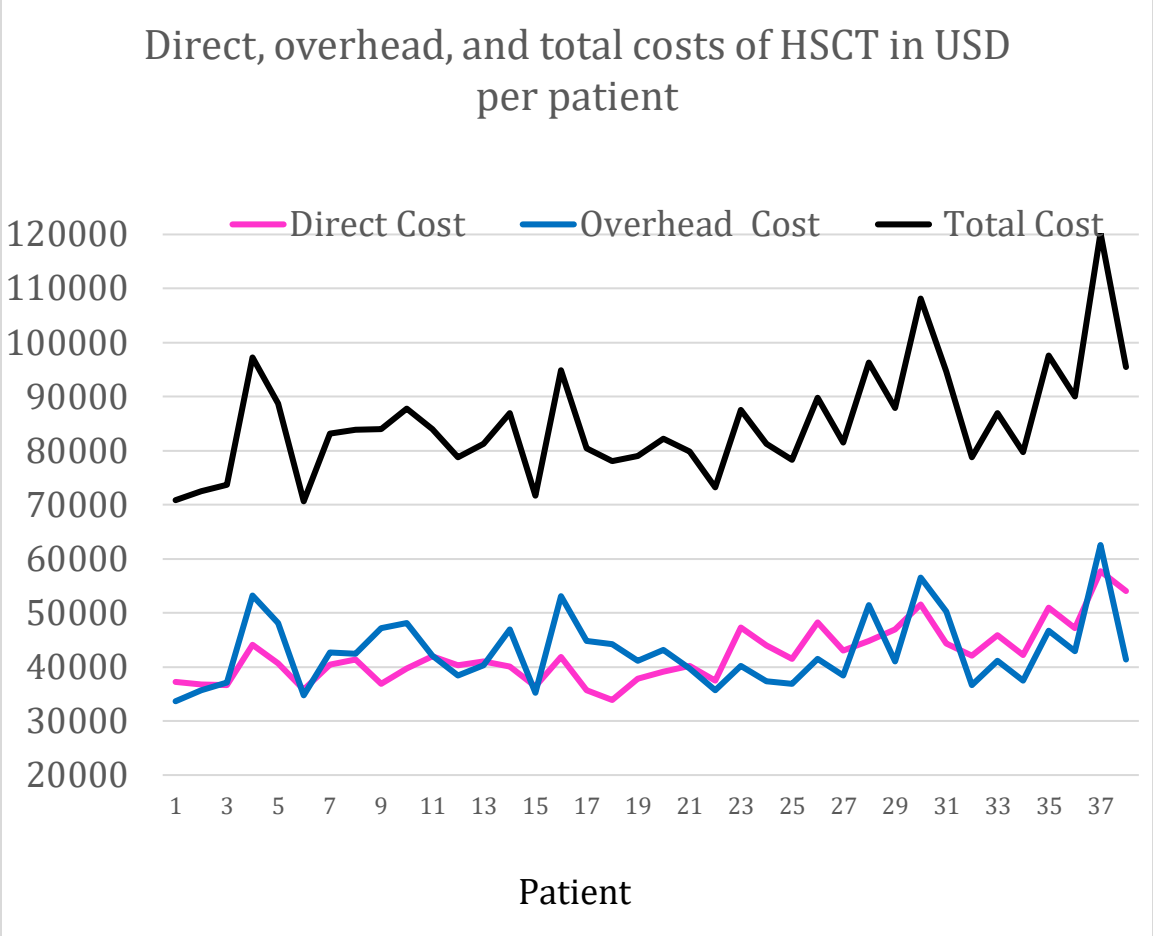
Table 1: Comparison of financial outlay of non-myeloablative HSCT versus DMTs

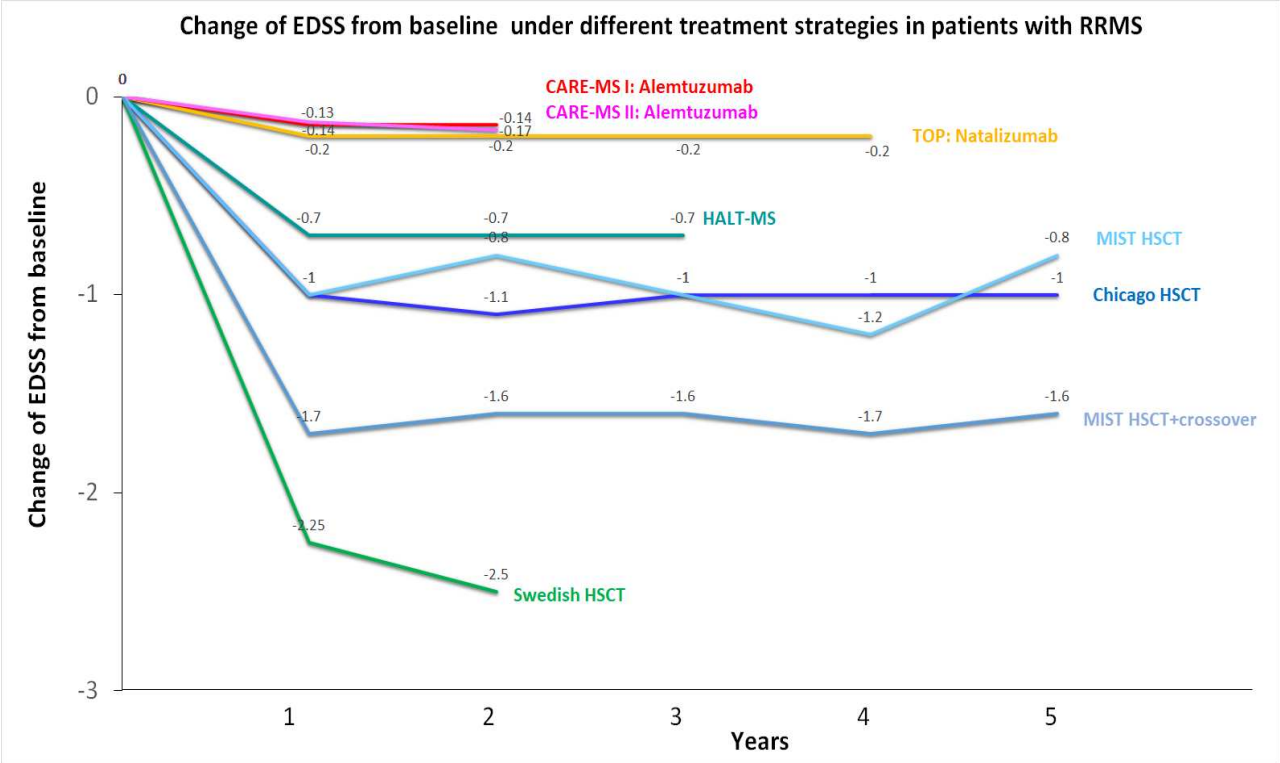
Parameter	Mean / median (range) (Standard deviation, SD) in US dollars
Non-myeloablative HSCT	
HSCT direct costs	$ 42,295 / $41,432 ($33,887-$57,704) (SD= $5,361)
HSCT overhead costs	$ 42,888 / $41,456 ($33,653 - $62,555) (SD = $6,533)
HSCT total costs	$ 85,184 / $83,480 ($70,635 - $120,260) (SD=$10,336)
HSCT reimbursement (net revenue)	$ 95,268 / $101,141 ($16,544 - $173,204) (SD = $39,239)
DMT	
Annual DMT charge	$ 86,000 (NA) (NA)

Figure 1: Cost in US dollars for non-myeloablative HSCT in 37 patients with relapsing-remitting multiple sclerosis.



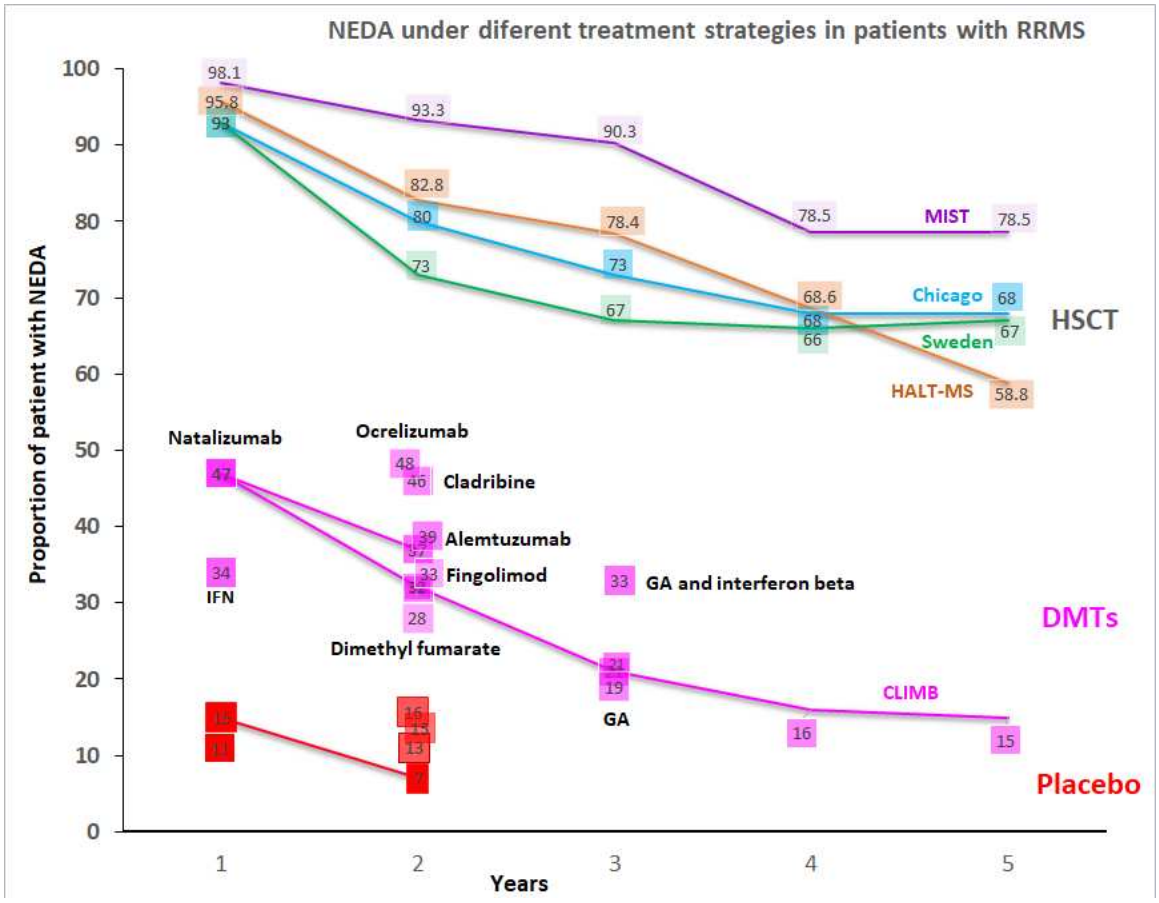
HSCT = hematopoietic stem cell transplantation, USD = United States dollars

Figure 2: Improvement in neurologic disability after HSCT versus DMT



CARE MS = Comparison of Alemtuzumab and Rebif Efficacy Multiple sclerosis, CARE MS 1 (ref 22), CARE MS 2 (ref 23), TOP= TYSABRI Observational Program (ref 24), DMT = disease modifying therapy i.e. prescription drug therapy e.g. Alemtuzumab or Natalizumab (Tysabri), EDSS=expanded disability status scale (lower number is improvement in neurologic disability), HSCT = hematopoietic stem cell transplantation. HSCT = hematopoietic stem cell transplantation studies i.e. Multiple sclerosis international transplant (MIST) (ref 30), Chicago study (ref 25), Sweden study (ref 26,29), High-Dose Immunosuppression and Autologous Transplantation Multiple sclerosis (HALT-MS) study (ref 28)

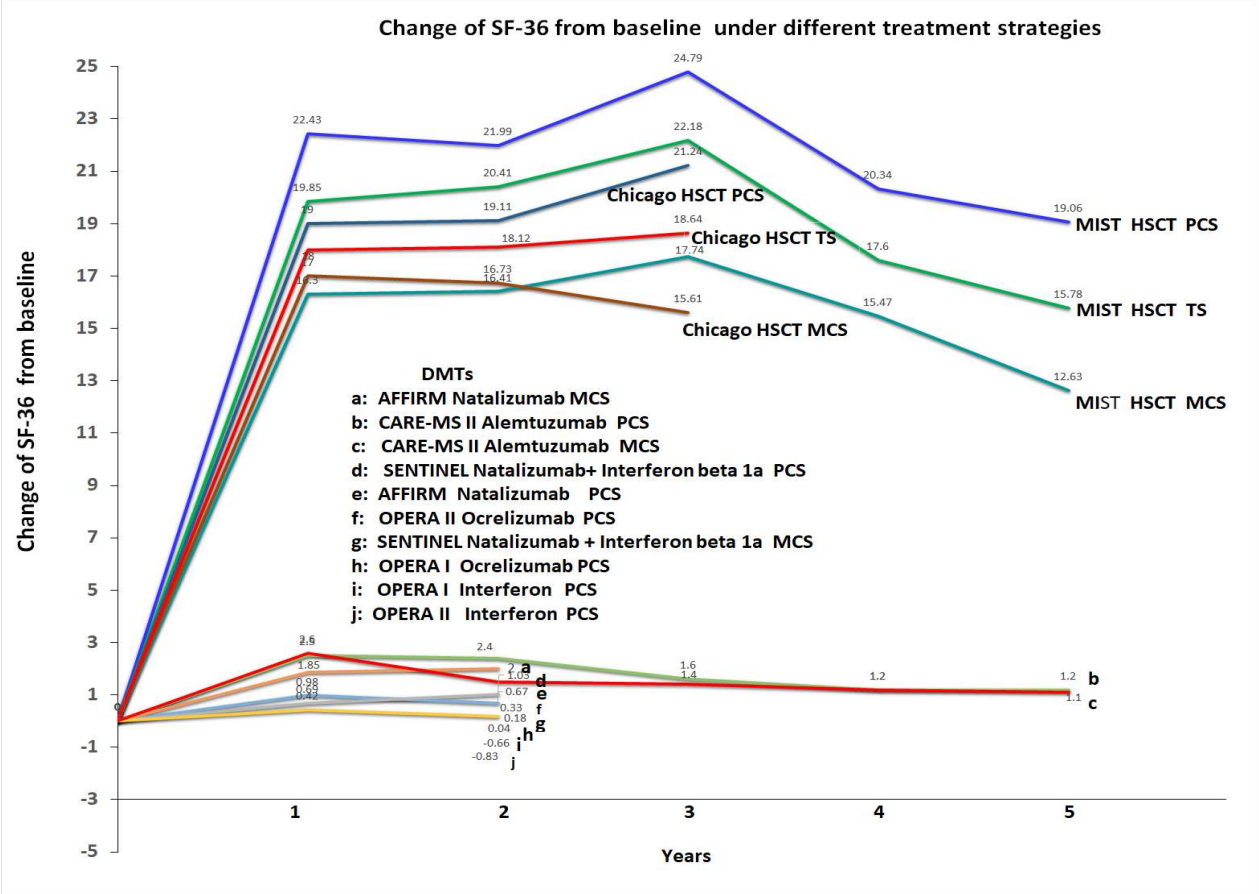
Figure 3: No evidence of disease activity (NEDA) after HSCT versus with DMT



Chicago=single center HSCT trial (ref 25), DMT = Disease modify therapy, i.e. prescription drugs HSCT = hematopoietic stem cell transplantation studies. HALT-MS=High-Dose Immunosuppression and Autologous Transplantation Multiple sclerosis (ref 28), MIST = Multiple sclerosis international transplant (ref 30), NEDA = no evidence of disease activity, i.e. no relapses, no progression, no new or enlarging or enhancing lesions on magnetic resonance imaging, Sweden= single country HSCT trial (ref 29).

NEDA for the following DMT trials: ADVANCE trial (peginterferon beta-1a) 34% at 1 year (ref 31); AFFIRM (natalizumab) 47% and 37% at 1 and 2 years, respectively (ref 32); CARE MS I (alemtuzumab) 39% at 2 years (ref 22); CLARITY (cladribine) 44% at 2 years (ref 33); CombiRx (interferon plus glatiramer acetate) 33% at 3 years (ref 34); CLIMB (standard of care) 15% at 5 years (ref 35), CONFIRM and DEFINE (dimethyl fumarate) 26% at 2 years (ref 36); FREEDOMS (fingolimod) 33% at 2 years (ref 37); OPERA (ocrelizumab) 47% at 2 years (ref 39).

Figure 4: SF-36 quality of life after for RRMS HSCT versus DMT



AFFIRM and SENTINEL (natalizumab) trials (ref 41), CARE MS I and II (alemtuzumab) trials (ref 42). Chicago HSCT trial (ref 25), HSCT=hematopoietic stem cell transplantation. MCS = mental component summary of SF-36, MIST = Multiple sclerosis International Stem cell Transplant trial (ref 30), OPERA I and II (ocrelizumab) trials (ref 40), PCS=physical component summary, TS = total score.