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Meta-Analysis

Efficacy of hematopoietic stem cell formultiple sclerosis, an evidence based meta-analysis

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Abstract: Multiple sclerosis (MS) is thought to be a serious autoimmune disease. However, few therapy method was efficient for MS. The hematopoietic cell transplant (HCT) has been reported for a long time and can be used for MS. The clinical trials consisted of small samples and gave confusing results. This systematic review and meta-analysis aims to estimate the effects of HCT for adults with MS. We searched the database of CNKI, PUBMED, EMBASE, WEB of SCIENCE and the Cochrane Center Register of Controlled Trials to find initial studies and selected the appropriate researches included in the meta-analysis based on the inclusion and exclusion criteria. I^2 was used to evaluate the heterogeneity and meta-regression was used for finding the source. Random effort model was performed to pool the data and funnel plot was drawn to determine publication bias. Six or eight single-arm clinical trials studies were included. The I^2 value was 0.77 and 0.93, suggesting a heavy heterogeneity between studies. However, meta-regression analysis did not find the source of heterogeneity in which the publication country and follow up time were the influencing factors. Compared with baseline, the EDSS score of MS patients after HCT has a statistical decrease of 0.62 (95% CI 0.14, 1.10) at the 12^{th} month and 1.26 (95%CI: 0.38, 2.14) at the follow up time ending point respectively. Available evidence suggests some clinical benefits of HCT combined with immunotherapy on MS. Due to wide confidence intervals that are characteristics of small evidence bases, further investigations to provide enough baseline information according to the RCTs are needed for further analysis, such as subgroup analysis and meta-regression analysis.

Key words: Multiple sclerosis, hematopoietic cell transplant, MS, HCT, meta-analysis.

Introduction

Multiple sclerosis (MS) is thought to be an autoimmune disease because of the migration of immune cells into the central nervous system (CNS) causing myelin sheaths loss and axons degeneration in both the white matter and cortex (1). In most patients, MS usually begins as an inflammatory relapsing-remitting category disease with the production of proinflammatory cytokines (2). In spite of the standard therapies, 50 percent of patients will have a chronic progressive course and will develop to be unable to continue employment by 10 years after the onset of illness (3,4). About 75 percent of patients will require assistance to ambulate by 15 years from diagnosis (5), and the proportion will increase to 85 percent 25 years later (6).

The autologous hematopoietic cell transplant (HCT) following immunosuppressive therapy was first reported in 1990s in MS (7, 8). HCT was thought to be a more efficient therapy approach and designed to reset the immune system rather than depressing the deleterious immunologic effect with drugs (9-12).In some previous studies, several researches reported that HCT may have effects on the relapsing-remitting MS based on clinical trials in which participants themselves report their related clinical data (13). However, Burt (14) also found immune suppression combined with HCT was not suitable for MS patients with progressive disease and high pre-transplantation disability scores. In the same time, few participants were included in these studies mentioned above. Hence, the effect of HCT treatments is not affirmatory perfectly lacking powered evidence of the HCT therapy for the MS because of small samples and multicenter clinical trials. As a consequence, we performed a systematic review and meta-analysis of available clinical trials focused on using HCT for MS.

Materials and Methods

Literature search

All studies comparing outcomes of EDSS score with that before transplanting were suitable for this meta-analysis, regardless of the language and publication type limitations. The searches were performed for relative studies in the network database including CNKI, PUBMED, EMBASE, WEB of SCIENCE and the Cochrane Center Register of Controlled Trials databases. The last research time is December 1, 2015 and the research will be update per year according to the Handbook of Cochrane. We used the searching terms as follows, "hematopoietic stem cell" AND "multiple sclerosis" AND "scale OR EDSS"The references cited in the review articles were also searched in order to find the extra relative publications.

Inclusion and exclusion criteria

Studies that met the following criteria were included in this meta-analysis. 1) Patients diagnosed with MS

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were evaluated. 2) Comparative data were reported based on case-control or self control study. Control or self control group treated with nothing or placebo while participants from case group were treated with HCT. 3) Data for continuous variables reported within EDSS nmust be presented directly or could be calculated from the data shown in the publication. 4) Reviews, meeting abstracts, animal research were excluded. The literatures were searched and reviewed by two experts in the neurology field independently (C.L. and J.F.). The third researcher (S.C.) decided whether a study should be included only when controversial conclusion. Furthermore, we contacted authors whose research had raw data only for further information.

Data extraction

Data were extracted from the included studies with a standardized data extraction form. The first author collected the relational data from included studies while the second author resolved the errors. Data were abstracted as follows: first author, publication year, country, total participants enrolled in this study, baseline information (including mean age, gender distribution), type of MS, follow-up time, baseline EDSS score defined as the latest score testing result, treatment outcomes (EDSS scores). In terms of missing data, the available information such as the p-value and 95% confidence interval and range were converted to the effect value of mean and standard deviation. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of these included studies.

Statistical analysis

Meta-analyst software of version 3.13 (Biostat Inc., Englewood, NJ) was used to perform the one arm meta-analysis. The random-effect model would be applied when the heterogeneity was presented among the included studies. Otherwise, the fixed-effect model would be employed.

The MD and 95% CI were used to evaluate the MS effects based on the EDSS score. Heterogeneity was tested by I^2 and means of the Cochran Q. At last, Publication bias was assessed by funnel plot.

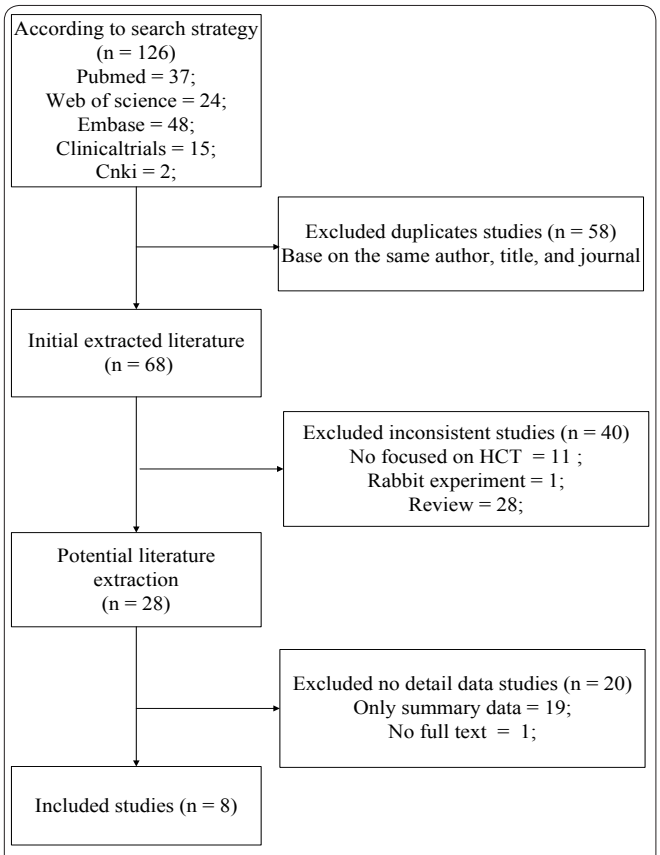

Figure1. Flow diagram of search results.

Results

Search results

At last, we found 126 studies in the initial research and 9 were included in the last single arm meta-analysis (15-23), according to the searching strategy and inclusion and exclusion criteria. The flow diagram for the recognition of included studies was shown in Fig.1.

Evidence of included studies

Of the 8 clinical trials, there were 68 and 115 participants included in this meta-analysis respectively. All studies were published from 2000 to 2012. The age ranges from 9 to 70 years. All participants included in this study were followed up from 10 to 84 months. The detail information of researches was presented in the Table1.

Table1. Evidence table of included studies.

Included studies		Methods				Baseline			Intervention	Follow up[l]
Reference	Country	Design	N-12[a]	N-L[b]	N-T[c]	Age	Gender	category		
Kozak 2000	Czech	Single-arm	2	5	11	23-44	F:9, M:2	MS	I[d]+HCT	1-5 Y[e]
Enric 2003	Spain	Single-arm	14	14	14	18-60	-	SPMS, RRMS	I +HCT	1 Y
Ni 2005	China	Single-arm	-	13	16	15-58	F:11, M:5	SPMS[h], PPMS[i], PRMS[g], MMS[j]	I +HCT	13-45 M[k]
Xu 2006	China	Single-arm		20	22	-	F:17, M:5	SPMS	I +HCT	10-59 M
Chitra 2008	American	Single-arm	9	9	9	18-70	-	MS	I +HCT	15-24 M
Richard 2009	American	Single-arm	20	20	21	18-55	-	RRMS	I HCT	1-6 Y
Fagius 2009	Sweden	Single-arm	-	9	9	9-34	F:6, M:3	MS	I HCT	23-47 M
James 2012	American	Single-arm	23	23	26	27-60	F:12, M:14	SPMS, PPMS, RRMS	I +HCT	12-84M

a, N-12, the participants by the 12th month. b, N-L, the participants by the longest follow up time. c, N-T, total participants.
d, I, immunodepression used as pretreatment of MS patients. e, Y, year. k, M, month. PRMS, progressive relapsing MS. h, SPMS, secondary progressive MS. I, PPMS, primary progressive MS. j, MMS, malignant MS. l, follow up, the longest follow up time from 10 months or longer.

Table 2. Pooled data as follow-up times (12th months or more) and heterogeneity information.

	Estimate	95% Confidence Interval		I^2	Q	P-Value
Pooled N-12	0.620	0.140	1.101	0.77	17.288	0.002
Pooled N-L	1.260	0.376	2.144	0.93	94.242	0.000

The heterogeneity test

The I^2value were0.77 and 0.93, suggesting there were heavy heterogeneity in these studies and the random-effect model was used correctly (shown in Table2). Thus, meta-regression analysis was needed to find the source of the heterogeneity.

The meta-regression analysis

We set European country as "1", American as "2", and China as "3". For 12 months and longest follow up time, the meta-regression plot showed that studies were not near the regression line suggesting that country was not the source of heterogeneity (Fig.2).

We also set the mean follow up time as factor. The meta-regression plot showed the follow up time had no statistical impact on the between-study heterogeneity (Fig2C). Meanwhile, the plot indicated the mean difference of scores between baseline and the follow up ending point was not influenced by the follow up time (Fig.2).

The pooled data results

The pooled mean difference, based on random-effect model, of the EDSS score between the baseline and the 12th month was 0.62 (95% CI 0.14, 1.10) while between the baseline and the follow up time ending point was 1.26 (95%CI: 0.38, 2.14) respectively (Fig.3).

Publication bias

The funnel plot suggested that most studies included in this meta-analysis were in the better funnel which has the narrow top and wide bottom. At the same time, the better funnel indicated a low likelihood of publication bias with regard to the effect of MSC for ALS in both 12th month and the longest follow up time ending point (Fig.4).

Discussion

In recent years, three types of stem cells, including neural, mesenchymal, and hematopoietic stem cells, have been reported to be used in the therapy of MS. In 2015, one multi-center clinical research found that high-dose immunosuppressive therapy combined with hematopoietic stem cells therapy was effective for MS (24). Some researchers tried to use high-dose immunotherapy to treat MS patients without hematopoietic stem cells translation. However, some toxic effects occurred (25). Moreover, hematopoietic stem cells can be expanded by human umbilical cord mesenchymal stem cells (26). Although, high-dose immunotherapy and hematopoietic stem cells therapy are effective, some unknown side

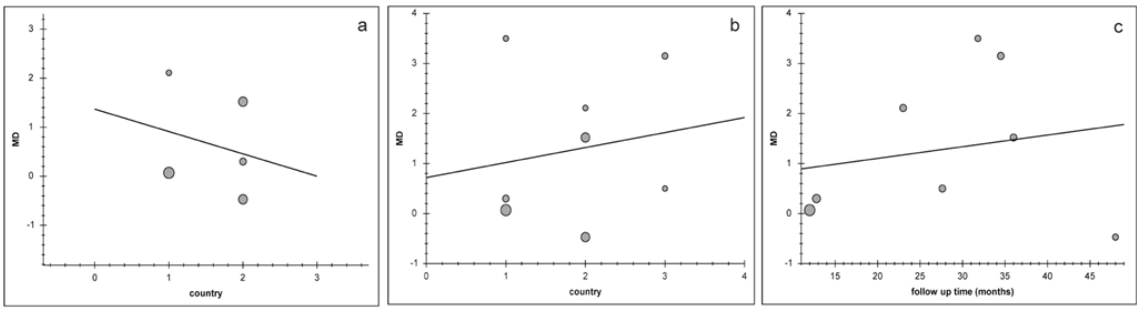

Figure 2. A, the meta regression plot where the country is influence factor (the follow up time is 12 months); B. the meta regression plot where the country is influence factor (the follow up time is the longest); C, the meta regression plot where the follow up time is influence factor. Circles means the studies; MD means the mean difference.

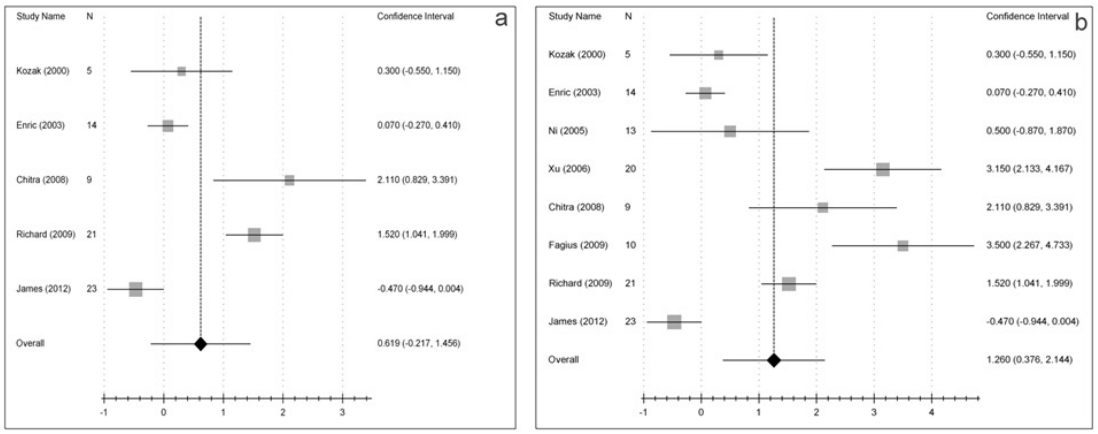

Figure 3. A, the forest plot for the 12 month follow up time; B, the forest plot for the longest follow up time; Squares are study-specific relative risk; Diamonds are summary odds ratio. Horizontal lines represent 95% confidence intervals.

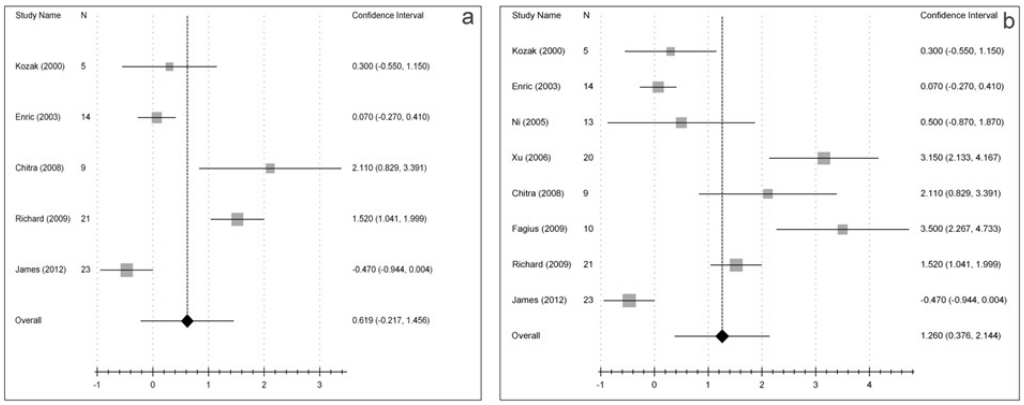

Figure 4. A is the funnel plot for studies whose follow up time is 12 months while B is for the longest follow up time; The circles are studies.

effects also still exist and may limit the further application. Because of the failure influence of this therapy, some unifying standards should also be established after treatment failure (27).

During this systematic review and meta-analysis, 126 studies were reviewed after the initial searching of the database. Eight studies with 68 and 115 subjects were included in the present meta-analysis. Pooled effect analysis of EDSS score of the baseline level versus those after HCT was performed according to the random-effect model.

Meta regression was conducted to find the source because of the high heterogeneity between studies. A random-effect model was performed to calculate the MS of the baseline versus the score after HCT as there was no factor contributing to the heterogeneity. Meanwhile, we did not conduct the subgroup analysis since we did not find the corresponding source of the heterogeneity via meta-regression analysis.

Our research showed that compared with the baseline information, HCT for MS patients can reduce the EDSS score at 12th month or the longest follow up time ending point which is more than 10 months. That is to say HCT could improve the status of MS patients. Meanwhile, the meta-regression also suggested the effect of HCT on MS cannot be influenced by the time. However, additional several clinical trials but with no detail data suggested that HCT has long term effect on the MS (13, 28-30).

Furthermore, our study still has some limitations. First of all, the quality of the included studies was not evaluated as there was no good scale especially used for the single-arm research. Second, we found only limited baseline information about individual age, gender, MS type, etc, and thus, these characteristics could not help us to find the source of heterogeneity through meta-regression analysis though the random-effect model was used. Third, only single-arm clinical trials researches were included in this meta-analysis resulting in the low level of the evidence. It has come to light that random clinical trial (RCT) was best and has the most power evidence over case control studies. Fourth, further systematic review and meta-analysis focused on the side effects of high-dose immunotherapy combined with hematopoietic stem cells therapy on MS is needed.

In sum, our results showed that HCT was beneficial for MS and that was not affected as time passed. However, clinical benefit of HCT of MS needs further investigation and reevaluation according to the RCTs. As a consequence, enough baseline information is still needed for further analysis such as subgroup analysis and meta-regression analysis.

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