Diabetes & Metabolism xxx (2017) xxx–xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

Clinical benefits of autologous haematopoietic stem cell transplantation in type 1 diabetes patients

B. Gu [a,1], H. Miao [a,1], J. Zhang [a,1], J. Hu [b], W. Zhou [a], W. Gu [a,*], W. Wang [a,**], G. Ning [a,c]

[a] *Department of endocrine and metabolic diseases, Ruijin hospital, Shanghai Jiao-Tong university, school of medicine, Shanghai Key laboratory for endocrine tumours, Shanghai clinical centre for endocrine and metabolic diseases, Shanghai institute of endocrine and metabolic diseases and Shanghai E-institute for endocrinology, Shanghai, China*
[b] *Department of haematology, Ruijin hospital, Shanghai Jiao-Tong university, school of medicine, Shanghai, China*
[c] *Laboratory for endocrine & metabolic diseases, institute of health science, Shanghai JiaoTong university, school of medicine and Shanghai institutes for biological sciences, Chinese academy of sciences, Shanghai, China*

ARTICLE INFO

Article history:
Received 2 September 2017
Received in revised form 13 December 2017
Accepted 16 December 2017
Available online xxx

Keywords:
Cell therapy
Insulin therapy
Haematopoietic stem cell
Type 1 diabetes

ABSTRACT

Type 1 diabetes (T1D) is characterized by severe damage to pancreas islet function through immunological attack; therefore, it is also called 'insulin-dependent diabetes'. The present study aimed to evaluate the safety and clinical efficacy of autologous haematopoietic stem cell transplantation (AHSCT) in adolescent patients with newly diagnosed T1D. A phase-II prospective, parallel-assignment, non-randomized trial was conducted from March 2008 to December 2011 with 40 T1D patients, of whom 20 received AHSCT therapy and 20 were treated only with insulin injections. Of these patients, 14 (70%) in the AHSCT group became insulin-independent for 1.5 to 48 months compared with only one patient in the Insulin group. Of these 14 AHSCT patients, 11 relapsed within a median time of 19.5 (range 5.5–1) months and resumed insulin use. By the end of the 4-year follow-up, the difference in daily insulin dosages between the AHSCT and Insulin groups had become smaller (0.49 ± 0.32 IU/kg/day *vs.* 0.79 ± 0.18 IU/kg/day, respectively; $P < 0.01$). C-peptide levels increased significantly at 3 months in both groups and later decreased, with the insulin group showing more rapid deterioration. Most of the adverse events in the AHSCT group were transplantation complications. Our data suggest that AHSCT treatment was well tolerated and slowed deterioration of islet β-cell function while significantly decreasing daily insulin dosages. However, because of the high relapse rate, more information on longer-term outcomes is needed before AHSCT can be routinely considered for T1D patients. Significance: although this was a non-randomized clinical study, this phase-II trial demonstrated the beneficial effects of AHSCT in patients with newly diagnosed T1D by increasing C-peptide levels and inducing insulin independence, while showing its safety and good tolerability compared with conventional intensive insulin therapy. Thus, these results are helpful for increasing our understanding of the use of haematopoietic stem cell therapy in the treatment of T1D and for evaluating whether it can become more widespread in future.

Introduction

Several pioneering studies have assessed the short-term efficacy and safety of autologous haematopoietic stem cell transplantation (AHSCT) in newly diagnosed type 1 diabetes (T1D) patients [1,2]. The basic protocol for AHSCT includes high-dose immunosuppressive therapy with cyclophosphamide (CTX) and antithymocyte globulin (ATG), and transplantation of haematopoietic stem cells (HSCs) harvested from the peripheral blood of the patients themselves. The research has so far demonstrated that approximately half of AHSCT patients were insulin-independent for at least 6 months [3,4]. However, some questions have been raised concerning AHSCT therapy: Can AHSCT therapy confer sufficient long-lasting protection of islet β-cell function? Does it actually abrogate autoimmunity or just extend the 'honeymoon period'? What about the long-term safety of AHSCT? For these reasons, the present report is of the results of the long-term follow-up of patients in a prospective, parallel-assignment, non-randomized clinical study that has attempted to answer these very questions.

* Corresponding author at: No. 197, Ruijin Er Road, Shanghai Ruijin Hospital, Shanghai 200025. P.R. China.
** Co-corresponding author.
E-mail address: weiqionggu@hotmail.com (W. Gu).
[1] These three authors contributed equally to this study.

https://doi.org/10.1016/j.diabet.2017.12.006
1262-3636/© 2017 Published by Elsevier Masson SAS.

Design, setting and participants

Between March 2008 and December 2011, patients with newly diagnosed T1D were prospectively screened and enrolled. T1D was diagnosed according to the 2006 American Diabetes Association (ADA) criteria, and the newly diagnosed diabetes was defined as a disease duration < 6 months. Inclusion and exclusion criteria have been reported elsewhere (clinical trial registration number NCT00807651) [4]. Eligible patients who opted to undergo AHSCT therapy were placed in the AHSCT group, while those taking multiple insulin injections or continuous subcutaneous insulin pump therapy were categorized into the Insulin group. The study was approved by the Ethics Committee of Shanghai Ruijin Hospital, and all patients and/or their parents in the AHSCT group provided their written informed consent.

Study design

The study consisted of primary and secondary outcomes: the former was the exogenous insulin dosage; and the latter were C-peptide levels during oral glucose tolerance tests (OGTTs), specifically, fasting C-peptide levels, peak value (C_{max}) and area under the curve for C-peptide (AUCC), HbA_{1c} levels and anti-glutamic acid decarboxylase (anti-GAD) titres.

In brief, the AHSCT protocol was as follows: HSCs were mobilized with CTX (2.0 g/m^2) and granulocyte colony-stimulating factor (10 μg/kg/day), then collected from peripheral blood by leukapheresis and cryopreserved. Cells were injected intravenously after conditioning with CTX (200 mg/kg) and rabbit ATG (4.5 mg/kg).

Statistical analysis

These analyses [descriptive data analysis, calculation of standard deviations (SDs) and analysis of variance (ANOVA)] were performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA). ANOVA with the model adjusted for age, gender and baseline values of the dependent variables was calculated between the two groups and with different follow-up times (baseline and 3, 6, 12, 18, 24, 36, 48 months). Differences between classified variables were tested using Chi-square (χ^2) or Fisher's exact tests if the expected number of subjects in any cell was < 5. Time-to-event distributions were calculated by Kaplan–Meier estimates and compared by log-rank tests over the observation period. A P-value < 0.05 was considered statistically significant.

Results

Participants' baseline demographics and laboratory characteristics

Of the 65 screened participants newly diagnosed with T1D, 40 patients, who had a mean age of 17.9 ± 4.2 (range 11–30) years and were 35% male (14/40), were enrolled; 20 patients opted for AHSCT therapy (AHSCT group), and 20 were using insulin therapy (Insulin group). Of these 40 recruited participants, five were lost to follow-up (one in the AHSCT group and four in the Insulin group), and four of the AHSCT group dropped out. Thus, a final total of 31 participants were included in the analyses of the primary and secondary endpoints at the end of follow-up (AHSCT group, n = 15; Insulin group, n = 16). A flow chart of patients' recruitment into the study is shown in Fig. 1. The two groups did not differ significantly in terms of age, gender and body mass index (BMI) at enrollment. Baseline disease duration, islet β-cell function evaluated by fasting C-peptide, C_{max}, AUCC and human leucocyte antigen (HLA) genotype were well matched in the two groups (Table 1 and Table S1; see supplementary material associated with this article online).

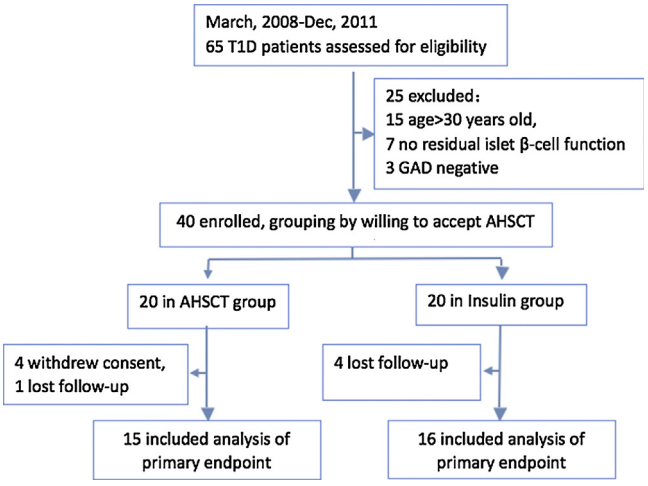

Fig. 1. Flow chart of patient recruitment into our trial of autologous haematopoietic stem cell transplantation (AHSCT). GAD: glutamic acid decarboxylase.

Safety evaluation of AHSCT vs. *insulin therapy*

Most patients treated with AHSCT experienced febrile neutropenia (n = 9), nausea and vomiting (n = 11), alopecia (n = 19) and blood component transfusions due to bone marrow suppression (severe anaemia and/or thrombocytopenia, n = 5). No severe acute drug toxicity, infection or organ damage was seen. Most side-effects disappeared 2 to 4 weeks after AHSCT, with recovery from neutropenia taking the longest. One patient, who had autoimmune hyperthyroidism before transplantation, developed hypothyroidism after the procedure and continued to be treated with levothyroxine. Two patients were diagnosed with Graves' disease after transplantation and were treated with tapazole. Three

Table 1
Patients' demographic and clinical characteristics at baseline.

	AHSCT group (n = 20)	Insulin group (n = 20)
Age (years)		
Mean ± SD	18 ± 3.9	18 ± 4.5
Median (range)	18 (14–27)	17 (11–30)
Male gender [n (%)]	7 (35)	7 (35)
Days from diagnosis to group classification		
Mean ± SD	68 ± 45.5	51 ± 37.8
Median (range)	67 (17–177)	34 (16–153)
Weight (kg)	50.9 (7.7)	51.1 (7.7)
Body mass index (kg/m^2)	18.5 (1.45)	18.8 (2.29)
AUCC (μmol/L)	4.65 (1.94)	4.10 (1.27)
HbA_{1c} (%)	10.59 (2.51)	11.88 (3.60)
Total daily insulin dose (IU/kg/day)	0.66 (0.25)	0.65 (0.24)
DKA at onset [yes; n (%)]	6 (30)	6 (30)
Diabetes-associated HLA alleles present [n (%)]		
High predisposing[a]	12 (60)	4 (20)
Predisposing[b]	6 (30)	10 (50)
Neutral[c]	2 (10)	6 (30)

Data are means ± standard deviation (SD), medians (range) or n (%). ANOVA for continuous variables (age, days, weight, body mass index, AUCC, HbA_{1c}, insulin dosage) was between the two groups; the difference between classified variables (percentage of DKA and HLA alleles) was tested using χ^2 or Fisher's exact test if the expected number of subjects in any cell was < 5; P < 0.05 was considered statistically significant; AHSCT: autologous haematopoietic stem cell transplantation; AUCC: area under the curve for C-peptide; DKA: diabetic ketoacidosis; HLA: human leucocyte antigen.

[a] DR3/DR4, DR3/DR9, DR4/DR9.
[b] DR3/DRX, DR4/DRX, DR9/DRX.
[c] DRX/DRX.

Please cite this article in press as: Gu B, et al. Clinical benefits of autologous haematopoietic stem cell transplantation in type 1 diabetes patients. Diabetes Metab (2018), https://doi.org/10.1016/j.diabet.2017.12.006