Autologous Haematopoietic Stem Cell Transplantation and Systemic Sclerosis

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Systemic sclerosis (SSc) is a heterogeneous, systemic autoimmune disease characterized by small vessel vasculopathy, autoantibodies production, and fibroblast activation leading to fibrosis of the skin and internal organs. Autologous hematopoietic stem cells transplantation (AHSCT) has been employed as treatment for severe systemic sclerosis (SSc) with high risk of organ failure. In the last 25 years overall survival and treatment-related mortality have improved, in accordance with a better patient selection and mobilization and conditioning protocols.

Keywords: systemic sclerosis ; autologous hematopoietic stem cells transplantation (AHSCT)

1. Introduction

Systemic sclerosis (SSc) is a heterogeneous, systemic autoimmune disease characterized by small vessel vasculopathy, autoantibodies production, and fibroblast activation leading to fibrosis of the skin and internal organs [1]. The clinical manifestations and the prognosis of SSc are variable: the majority of patients have skin thickening and variable involvement of internal organs. Among the different forms of SSc, classified according to the extent of skin thickening [2], patients with the diffuse form (dcSSc) show earlier and more frequent organ involvement [3]. The most relevant complications for SSc are related to pulmonary involvement and these are the direct expression of the pathogenic features of the disease: pulmonary arterial hypertension (PAH), as the most aggressive manifestation of vascular damage, and interstitial lung disease (ILD), as the most life-threatening manifestation of the fibrotic process of SSc [4]. Among these, SSc-associated interstitial lung disease (SSc-ILD) represents the leading cause of mortality in patients with SSc with 3-year survival of only 52% [5]. The clinical course of SSc-ILD is variable: some patients show stable or improving forced vital capacity (FVC) while others show a progressive decline in lung function [6], that occurs more rapidly within the first few years after diagnosis and then in some cases slows down. The clinical heterogeneity of the disease in association with the poor survival rate makes clinical trial enrichment difficult and complicates stratification and therapeutic management [7].

Over the past 20 years, cyclophosphamide (CYC) has been considered the standard of care for SSc with early aggressive skin disease and concomitant progressive ILD [8][9], and more recently, mycophenolate mofetil (MMF) has been added to the therapeutic options for the management of SSc-ILD, after the results of the Scleroderma Lung Study II [10]. In addition, the most recent recommendations of the panel of experts support the use of hematopoietic stem cell transplantation (HSCT) in SSc patients with rapidly progressive disease and high risk of organ failure based on two randomized clinical trials (RCTs) that evaluated the efficacy and safety of high-dose immunosuppressive therapy with subsequent HSCT [11] [12]. Indeed, these trials showed that HSCT improves event-free survival compared to CYC, an endpoint that is not reached by any pharmacological treatment to date. Nonetheless, the clinical decision to address SSc patients to HSCT is further complicated by the identification of essential requirements: knowing with a degree of certainty that the disease is rapidly progressive, which depends also on the medications currently used by the patient; convincing the patient, which might be challenging since these are SSc patients at high risk of organ failure that do not realize the actual risk of their disease; assessing that the disease is progressing in a monotonic fashion without chances to slow down spontaneously to identify the appropriate timing.

As a form of intensive immunotherapy that targets the autoreactive adaptive immune system, HSCT deeply modifies the immune system, restoring the immunological balance that counteracts inflammation and fibrosis progression, enabling disease control and, eventually, tissue repair [13]. Briefly, HSCT consists of four steps: mobilization of hematopoietic stem cells using chemotherapy, such as CYC, and growth factors [granulocyte colony-stimulating factor (G-CSF)]; conditioning using myeloablative or non-myeloablative regimens to eradicate autoreactive immune cells; reinfusion of autologous stem cells and immune reconstitution [14]. In contrast to myeloablative stem cell transplant, non-myeloablative transplant differs

primarily in what happens prior to the transplant, since it employs much lower and less toxic doses of chemotherapy. Different combinations of mobilization and conditioning regimens have been used in randomized clinical trials in SSc-ILD.

2. Efficacy of HSCT in SSc-ILD

Two randomized controlled trials, ASSIST (American Scleroderma Stem cell versus Immune Suppression Trial) in 2011 and ASTIS (Autologous Stem cell Transplantation International Scleroderma trial) in 2014 [12], both using non-myeloablative regimen, demonstrated the superiority of AHSCT compared to CYC. In these two trials the conditioning phase consisted of a non-myeloablative regimen with CYC (200 mg/kg total dose) and rabbit antithymocyte globulin (rATG). The main differences were the CYC dose, and the selection of peripheral blood stem cells used for the mobilization phase.

In the ASSIST trial, 2 g/m^2 CYC was administered, and unmanipulated peripheral blood stem cells were infused, while in the ASTIS trial stem cells were mobilized with 4 g/m^2 CYC and CD34+ selected peripheral blood stem cells were infused. Both trials used similar inclusion criteria (patients age between 18 and 65 years, with dcSSc and a maximum disease duration of 4 years, minimum modified Rodnan skin score (mRSS) of 15 and involvement of heart, lungs, or kidney). The ASSIST trial showed that non-myeloablative AHSCT improves skin and pulmonary function for up to 2 years. In the ASTIS trial the superiority of AHSCT vs. CYC was confirmed. Despite the occurrence of early treatment-related mortality during the first year after AHSCT (16.5%), and an increase in serious adverse events, especially characterized by respiratory and cardiac failure, the use of AHSCT was associated with increased long-term event-free survival [12].

In 2018 an additional randomized clinical trial, the Scleroderma: Cyclophosphamide or Transplantation trial (SCOT) was published. In this trial similar inclusion criteria were used, with GCS-F for mobilization and with CD34+ selected cells. The myeloablative regimen employed conditioning using a lower dose of CYC (120 mg/kg total dose) plus total body irradiation (TBI) (800 cGy/4 fractions over 2 days/200 cGy to lungs and kidneys with shielding) and equine ATG [15]. The trial enrolled 75 patients with severe SSc. Thirty-four were assigned to HSCT and 39 to CYC, ending at month 54, with a maximum follow-up to 72 months. One of the main differences, in comparison to previous RCTs, is the selection of the primary endpoint. This was identified in the global rank composite score (GRCS), an analytic tool which includes multiple disease features, including death and event-free survival, FVC, the Disability Index of the Health Assessment Questionnaire (HAQ-DI) score, and the mRSS. After 54 months, a large percentage (67%) of patients, treated with HSCT, reached the primary endpoint, the improvement of GRCS when compared with CYC arm (33%). Of note, the exclusion criteria were rigorous. These included active gastric antral vascular ectasia, a diffusing capacity of the lung for carbon monoxide (DLco) of less than 40% of the predicted value, an FVC of less than 45% of the predicted value, a left ventricular ejection fraction of less than 50%, a creatinine clearance of less than 40 mL per minute, pulmonary arterial hypertension, or more than 6 months of previous treatment with CYC. Treatment-related mortality, in the transplantation group, was 3% at 54 months and 6% at 72 months, when compared with 0% in the CYC group. However, transplant-related mortality was lower than previous reports, but the reason is still unknown, and it might be partly explained by the differences in inclusion criteria (in the SCOT trial none of the patients had cardiac involvement) and in conditioning regimens (in the ASTIS trial high-dose regimen of CYC may has been toxic, especially in the presence of heart disease).

Notably, in this trial, treatment of severe scleroderma with myeloablative therapy and CD34+ selected autologous hematopoietic stem-cell transplantation led to superior long-term outcomes as compared with standard therapy and fewer scleroderma relapses, defined as the need for disease-modifying antirheumatic drugs (DMARD) therapy after non-myeloablative regimen, probably due to T cell depletion after total body irradiation. However, the adverse events occurring in the first 2 years after transplantation, such as viral infections and secondary cancers due to total body irradiation exposure, were relevant (96% in the transplant group vs. 71% in the CYC group). Cancers occurred in four participants: three in the transplantation group (one had papillary thyroid cancer and two had the myelodysplastic syndrome) and one in the CYC group (breast cancer). A total of 21 deaths occurred over a period of 72 months in this trial, 14 in the CYC group and 7 in the transplant group.

3. Future Directions

HSCT has been used for more than 20 years as a specific treatment in a wide range of autoimmune disease [16][17]. The rationale for HSCT is based on its capacity to reset the immune system after eradication of the autoreactive cells with high immunosuppressive or myeloablative conditioning regimen, allowing the reconstitution of immune tolerance. The UPSIDE trial is ongoing and investigates AHSCT in early disease compared to other immunosuppressive therapy with the specific aim to treat the immunosuppressive arm with AHSCT as a rescue therapy if the response is poor [18]. In SSc, the debate on the potential benefits and risks of transplantation and the correct identification of high-risk subjects remains difficult and

the recent approval of new immunosuppressive and anti-fibrotic drugs offers the possibility to provide long-term beneficial effects for the management of ILD both before and after AHSCT [19]. Notwithstanding the new drug approvals and the ambiguities of protocol in its use, AHSCT remains the only intervention to offer proven survival benefit in SSc thus far.

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