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EVALUATION OF FIBROSIS AND ENDOTHELIAL DYSFUNCTION IN SERA AND SKIN BIOPSIES OF PATIENTS WITH SYSTEMIC SCLEROSIS TREATED WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT)

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BACKGROUND

Autologous Hematopoietic Stem Cell Transplantation (AHSCT) has emerged as a treatment option for severe and rapidly progressive systemic sclerosis (SSc) patients. Here, we aimed to analyze if AHSCT changes the expression of endothelial and fibrosis markers in the skin and serum of transplanted SSc patients.

MATERIALS AND METHODS

Clinical data, sera (n=35) and skin biopsies (n=26) from the forearms of SSc patients were collected prior to, 6 and 12 months following the AHSCT. Biopsies were evaluated (immunohistochemistry) for expression of: MMP2, TIMP1, CD105, CD31, VEGF, picrosirius red and hematoxylin-eosin (HE). Immunostainings were analyzed by the software Image J. Sera were analyzed by multiplex (Magnetic Luminex Assay, R&D System Inc., Minnesota, EUA) for: IL-6, IL-8, vWFA2, CXCL8, CXCL4, EGF, VEGFA, pentraxin3, E-selectin, thrombomodulin, P-selectin, VCAM1, ICAM1 and endothelin1. These results were compared to a healthy control group.

RESULTS

Most participants were female (82,86%), with mean (standard deviation, SD) age of 35.9 (±9.76) years, white ethnicity (85,71%) and mean (SD) time from diagnosis of 45.5 (±37.7) months. The modified Rodnan's skin score (mRSS) decreased from before (mean±SD: 22.81±8.12) to 6 months (15.65±7.03, $p<0.0001$) and 12 months (14.26±7.54, $p<0.0001$) after AHSCT. Forced vital capacity and diffusing capacity for carbon monoxide did not change from before (73.47±19.47 and 75.68±20.7, respectively) to (75.44±15.69 and 69.86±16.39, respectively; $p>0.05$) after AHSCT. Paired analyses of biopsies showed reduction in skin thickness, measured by HE from before (726.6µm±19.37) to 6 months post-AHSCT (706.6µm±29.24; $p=0.0014$) and increase of TIMP1 expression from before (3.543±3.33) to 6 months after AHSCT (9.567±8.733; $p=0.376$). Paired analyses comparing pre and 12 months post AHSCT also showed reduction in skin thickness by HE (725.5µm±24.03 vs 693.1µm±25.62; $p=0.0002$), reduction of collagen measured by picrosirius staining (43.25±12.02 vs. 36.36±9.01; $p<0.0001$) and increase of CD105 (0.722±0.599 vs. 1.802±1.33; $p=0.0322$). Analyses of sera showed differences ($p<0.001$) between healthy controls and SSc patients for protein expression of IL-6, vWFA2, CXCL8, EGF, VEGFA, E-selectin, P-selectin, VCAM1 and endothelin1. On follow-up of transplanted SSc patients, thrombomodulin levels were different from before (4683.27±1516.84) to 6 months after AHSCT (5904,35±2475,99; $p=0.007$) and

vWFA2 levels were different from before (569,37±132,86) to 12 months after AHSCT (498.17±126.34; p=0.018).

CONCLUSION

AHSCT improves skin fibrosis in SSc patients, decreasing dermal thickness and collagen deposits. These measurements correlate with the clinical improvement measured by the mRSS. Serum analyses also confirm endothelial dysfunction, characteristic of SSc, which remains stable at one year after transplantation.