Autologous Hematological Stem Cell Transplantation for Systemic Sclerosis in Israel

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ABSTRACT: **Background:** Autologous hematological stem cell transplantation (HSCT) is a novel therapy for systemic sclerosis (SSc) that has been validated in three randomized controlled trials.

Objectives: To report the first Israeli experience with HSCT for progressive SSc and review the current literature.

Methods: Five SSc patients who were evaluated in our department and were treated by HSCT were included. Medical records were evaluated retrospectively. Demographic, clinical, and laboratory data were recorded. Continuous data are presented as the mean ± standard deviation. Categorical variables are presented as frequencies and percentages.

Results: Five SSc patients were treated with HSCT. Four patients were adults (mean age 53 ± 12 years) and one was a 12-year-old pediatric patient. All patients were female. HSCT was initiated 1.4 ± 0.8 years after diagnosis. Two patients were RNA POLIII positive, two were anti-topoisomerase 1 positive, and one only antinuclear antibodies positive. All patients had skin and lung involvement. The mean modified Rodnan Skin Score was 29 ± 4.7 before HSCT, which improved to 10.4 ± 9.6 after HSCT. The forced vital capacity improved from 68 ± 13% to 90 ± 28%. Diffusing capacity of the lungs for carbon monoxide increased by 6%. Among severe adverse events were cyclophosphamide-related congestive heart failure, antithymocyte globulin-related capillary leak syndrome, and scleroderma renal crisis. All symptoms completely resolved with treatment without sequela. No treatment related mortality was recorded.

Conclusions: HSCT is an important step in the treatment of progressive SSc in Israel. Careful patient selection reduces treatment related morbidity and mortality.

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Systemic sclerosis (SSc) is an autoimmune disease in which autoantibodies, vasculopathy, and tissue fibrosis are affected [1]. Vasculopathy includes Raynaud's phenomena in 95% of patients and may result in digital ulcers or critical ischemia (in about 30% of patients). Pulmonary arterial hypertension (PAH) is the second manifestation of vasculopathy that accounts for 26% of Ssc related deaths [2,3]. Scleroderma renal crisis (SRC) is the most severe manifestation of SSc vasculopathy, which occurs in about 2% of patients.

Fibrosis in target organs is the main characteristic of SSc. Skin involvement is the most prominent feature of SSc. Lung fibrosis, the second commonly involved target organ (about 60% in patients with diffuse disease), results in great morbidity and is the most common cause of mortality [2]. Another important target organ of fibrosis is the heart. Cardiac manifestations include pericardial disease, dilated cardiomyopathy, arrhythmias, and left or ventricular failure and diastolic dysfunction, which account for 26% of SSc related deaths according to EUSTAR [2,3]. Last, fibrosis may widely involve the gastrointestinal tract.

MORBIDITY AND MORTALITY IN SYSTEMIC SCLEROSIS

SSc result in impairment of quality of life as well as in mortality. Although overall 5 years survival is about 85%, patients with several risk factors such as age at diagnosis > 60 years, diffuse SSc subtype, SRC, severe dyspnea, forced vital capacity (FVC) < 70%, diffusion lung capacity for carbon monoxide (DLCO) < 70%, valvular disease, anemia, CRP > 8 mg/L, and cancer have higher mortality [4]. A study from EUSTAR database including 6927 patients revealed that a cluster of patients that include mostly diffuse SSc with high mRSS > 27 and high rate of internal organ involvement had a sixfold increase in mortality compared to patients with limited disease without lung involvement [5]. Finally, in the most comprehensive analysis of the EUSTAR database that included 11,193 patients using the SCOpE score with 15 domains that categorized patients into four prognostic quartiles, patients in the high-risk category were found to have

a 3-year survival rate of 53% compared to 98% in the low-risk category [6]. This fourth quartile that carries great mortality risk, similar to hematologic malignancies, should be treated accordingly with the most aggressive measures.

CURRENT STATE-OF-THE-ART THERAPY FOR DIFFUSE SYSTEMIC SCLEROSIS WITH LUNG DISEASE

Until recently the gold standard therapy for diffuse SSc with lung involvement was cyclophosphamide, which was evaluated in the scleroderma lung study 1 (SLS1) [7]. Unfortunately, this treatment resulted only in a modest initial beneficial effect on lung function, dyspnea, thickening of the skin, and the health-related quality of life that was not evident after 24 months. After 11 years there was no difference in mortality between cyclophosphamide therapy and placebo (more than 70% mortality) [8]. Mycophenolate mofetil (MMF) soon replaced cyclophosphamide as a safer and more tolerable drug. In the SLS2 study, the hypothesis that cyclophosphamide would have greater efficacy at 24 months than cyclophosphamide was not confirmed [9]. There was no significant difference in the time to death between treatment arms in SLS I or II. Thus, current gold standard therapies have a marginal effect on skin and lung disease and do not improve mortality. Some other immune modulatory agents that have been evaluated including methotrexate, azathioprine, intravenous immunoglobulins (IVIG), and biologic therapies such as tocilizimab (anti IL-6) and rituximab (anti- IL-20) as a single therapy and in combination with MMF. All of these agents have some beneficial effect on skin and lung but have not been demonstrated to change the course of the disease or mortality. Finally, some new antifibrotic drugs, such as nitedanib (a thyrosine kinase inhibitor with beneficial effect on lung fibrosis), pirfenidone (anti TGF agents), and lenabasum (cannabinoid receptor type 2 agonist) are being evaluated as possible future therapy.

AUTOLOGOUS HEMATOLOGICAL STEM CELL TRANSPLANTATION IN SYSTEMIC SCLEROSIS

In 1997 Tyndall presented his first experience of treatment of two severe SSc patients with autologous HSCT in *Lancet* [10]. SSc is a complex autoimmune disease, which involves numerous immunological pathways within the innate and adaptive immune system that result in the wide spectrum of clinical phenotypes of disease including arthritis, myositis, calcinosis vasculopathy, and fibrosis. Experience has taught us that trying to block one pathway does not result in a change in the natural history of disease. HSCT is an intense therapy directed at many targets that are not affected by other therapies including long-lived plasma cells, dendritic cells, and regulatory T and B cells [11]. HSCT aims to eradicate the autoreactive hematopoietic cells and reconstitute a healthier immune system with a new immune repertoire, immune resetting, thus changing the balance from autoimmunity to tolerance [12]. HSCT can re-establish immunological tolerance as evident by an increase in number of regulatory T cells [13] with a reestablished T-cell receptor diversity and reactivation of thymic function that potentially leads to a tolerant, "juvenile" immune system as evident by recurrence of thymic emigrating cells, characterized by T-cell receptor excision circles (TREC) and CD31 expression [14].

EFFICACY

Currently three randomized controlled trials (RCT) have been reported and all three have shown the superiority of HSCT over cyclophosphamide. In 2011 Burt and colleagues [15] reported the results of the ASSIST trial, a single center randomized phase II study. In this trial patients were younger than 60 years with diffuse SSc, a mRSS of more than 14, and internal organ involvement or restricted skin involvement (mRSS < 14) but co-existent pulmonary involvement. The primary outcome at 12 months follow-up showed a decrease in mRSS (> 25%) or an increase in FVC of more than 10%. All ten patients randomly allocated to receive HSCT improved, compared with none of nine allocated to cyclophosphamide. In 2014 Van-Laar [16] reported the results of the ASTIS trial, a phase 3, multicenter, randomized clinical trial conducted in 10 countries at 29 centers with 156 patients, of whom 79 allocated for HSCT and 77 to cyclophosphamide treatment. The primary endpoint was event-free survival, defined as the time to the occurrence of death or the development of major organ failure (e.g., heart, lung, kidney). After the first year, there were more events in the HSCT group (13 events [16.5%], including 8 treatment-related mortality [TRM]) than in the control group (8 events [10.4%], with no TRM), yet after 2 years a clear advantage to the HSCT group was noticed and After 10 years of follow-up, 22 events recorded in the HSCT group (19 deaths and 3 irreversible organ failures) and 31 in the control group (23 deaths and 8 irreversible organ failures, of whom 7 patients died later) [16].

In 2018 the SCOT trial was published. SCOT is a randomized controlled trial comparing 36 patients who received myeloablative autologous HSCT to 39 patients who received cyclophosphamide. The primary endpoint was a global rank composite score based on disease features: death, event-free survival (survival without respiratory, renal, or cardiac failure), FVC, disability index, and mRSS. At 72 months, event-free survival (74% vs. 47%) and overall survival (86% vs. 51%) favored transplantation [17]. Overall in the ASTIS and SCOT studies 26 of 115 patients died in the HSCT groups compared to 44 of 116 patients in the cyclophosphamide group, $P = 0.0147$. It is now well accepted that HSCT is a game changer in severe progressive SSc with lung and skin involvement and this is evidenced by an EBMT and EULAR recommendations [18,19].

TREATMENT RELATED MORTALITY, THE HEART OF THE PROBLEM

The great caveat of HSCT is treatment related mortality (TRM) within the first year. During the last 20 years, experience and

understanding of risk factors have enabled us to achieve reduced TRM of less than 10% [15-17,20]. Burt's group [15] was one of the first to note that most of the TRM was attributable to heart failure and constrictive pericarditis during the conditioning. They suggested decreasing hydration in the conditioning and including more meticulous cardiac screening before HSCT that includes echocardiogram with TAPSE, right heart catheterization with and without 500 ml normal saline fluid challenge, that may unmask subclinical pulmonary arterial hypertension (PAH) and cardiac MRI with gadolinium. Patients with underlying cardiac disease should not be referred for HSCT [20]. These cardiac screening guidelines were subsequently endorsed by the EBMT [Table 2] [21].

HSCT: WHO WILL BENEFIT THE MOST?

The ideal candidates

HSCT has a very good effect on skin and overall mortality, while only a moderate effect mostly of stabilization or mild improvement on the lung. Ideal candidates are patients who are at high risk for mortality, who have a severe and rapidly progressive skin involvement (mRSS > 15), and who experience mild to moderate lung involvement [18].

Contraindications

High-risk patients who already show signs of severe organ damage as DLCO below 40% predicted, chronic kidney disease or heart failure with ejection fraction of less than 45% or cardiac involvement as delineated above should clearly avoid HSCT. Moreover, patients with cardiac involvement seem to have less improvement in DLCO and lung function after HSCT.

Smoking

Analysis of both the ASTIS and the SCOT trial revealed that current and even history of smoking was related to worse outcome, thus current smokers are not good candidates for HSCT [15,17].

Timing

It is our understanding that SSc is not a linear disease and that most of the damage is inflicted during the first 5 years of disease. Accordingly, the three RCT reported and the EBMT guidelines suggest HSCT only during the first 4 to 5 years of disease [19].

Location

HSCT requires great expertise, experience and the collaboration of a multi-disciplinary team. It has been found that progression free survival after HSCT is related experience (≥ 23 transplants for autoimmune diseases) and learning (time from first HSCT for autoimmune disease ≥ 6 years). It is suggested that HSCT for SSc should be conducted in dedicated centers in each country [22].

Table 1. Patients clinical and demographic characteristics and outcome of the first five patients who underwent hematological autologous stem cell transplantation treatment for systemic sclerosis in Israel

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean ± SD
Age	64	58	12	54	35	44
Sex	Female	Female	Female	Female	Female	100% Female
Years since diagnosis	1	1	2	8 months	2.5	1.4 ± 0.8
Serology	SCL-70	RNA POLIII	ANA	RNA POLIII	SCL-70	
Treatment before HSCT	Cyclophosphamide	MMF	MTX, AZA, MMF	MMF	HCQ, MMF	
FVC (% predicted) before HSCT	87%	65%	55%	66%	63%	68 ± 13
FVC (% predicted) after HSCT	95%	99%	51%	116%	NA	90 ± 28
DLCO (% predicted) before HSCT	67%	59%	73%	63%	56%	64 ± 6.7
DLCO (% predicted) after HSCT	70%	83%	55%	77%	NA	71 ± 12
mRSS before HSCT	33	21	31	31	28	29 ± 4.7
mRSS post-HSCT	20	0	21	8	3	10.4 ± 9.6
mRSS post-transplant improvement	13	21	10	23	25	18.4 ± 6.5
FVC improvement (%)	8%	34%	-4%	50%	NA	22 ± 24%
DLCO improvement (%)	3%	24%	-18%	14%	NA	5.85 ± 18%
ANA seroconversion	No	yes	unknown	yes	yes	60%
Serious complications	Aspergillus pneumonia resolved, Late cytoxan cardiac toxicity resolved	None	None	SRC pericarditis	Capillary leak syndrome	
Relapse	1 year	No	No	No	No	20%

ANA = antinuclear antibodyl, AZA = azathioprine, DLCO = diffusion lung capacity for carbon monoxide, FVC = forced vital capacity, HCQ = hydroxy-chloroquine, HSCT = hematopoietic stem cell transplantation, MMF = mycophenolate mofetil, MTX = methotrexate, SD = standard deviation, SRC = scleroderma renal crisis

HSCT IN ISRAEL

In March 2015 Prof. Dominique Farge was a guest lecturer in the France–Israel meeting that took place in Haifa, Israel. Farge shared her knowledge and insights about HSCT in SSc and a strong and fruitful academic collaboration with the rheumatology unit at Bnai Zion Medical Center began and led to the establishing of HSCT as possible treatment for SSc patients in Israel. We report herein our first experience with five patients that have undergone autologous HSCT, after evaluation in the rheumatology unit of Bnai Zion medical center with consultations of prof Farge.

PATIENTS AND METHODS

CRITERIA FOR HSCT IN ISRAEL

SSc patients under 65 years old, with a recent onset disease (< 5 years), rapidly progressive disease, a mRSS of more than 15 and lung fibrosis with deteriorating lung function tests (FVC or DLCO less than 70% predicted) despite standard therapy were evaluated.

PATIENTS EVALUATION

All patients underwent clinical evaluation, laboratory tests, chest and abdomen CT scan, pulmonary function tests, endoscopy if anemia was evident and complete cardiac workup that included ECG, echocardiography, MRI, right heart catheterization with fluid 500ml challenge, 24-hour ECG, NT pro-BNP, and troponin.

HSCT PROTOCOL

Most patients had been transplanted in the Rambam stem cell transplantation unit under the supervision of Zuckerman. HSCT protocol included mobilization with G-CSF without CD34+ selection and conditioning with 200 mg/kg of cyclophosphamide and 7.5 mg/kg of anti-thymocyte globulin (ATG) [Figure 1].

RESULTS

Twenty-three patients were screened, of whom nine were eligible for HSCT. Four patients were excluded after careful evaluation due to risk factors, two because of DLCO below 40% and two because of cardiac involvement. Five SSc patients were treated with HSCT. Four patients were adults (mean age 53 ± 12 years) and one was a 12-year-old pediatric patient. All patients were female. HSCT was started 1.4 ± 0.8 years after diagnosis. Two patients were RNA polymerase III (Pol III) positive, two were SCL-70 positive, and one only was antinuclear antibodies (ANA) positive. All patients had skin and lung involvement. The mRSS was 29 ± 4.7 before HSCT and improved to 10.4 ± 9.6 after HSCT. The forced vital capacity improved from 68 ± 13% predicted to 83 ± 22% predicted. DLCO was stable with only mean 6% improvement.Among severe adverse events were cyclophosphamide-related congestive heart failure, ATG-related capillary leak syndrome, and SRC, all completely resolved with treatment without sequela. No treatment-related mortality was recorded. One relapse was noted after 12 months (patient 1) [Table 2].

Figure 1. Summary of hematological stem cell transplantation. **Mobilization** Using G-CSF infusion after cyclophosphamide (2 gr/m2), stem cells (cd34+) are mobilized to peripheral blood and are being extracted (with or without CD34+ cells selection) frozen and stored. **Conditioning** High dose chemotherapy, cyclophosphamide 200 mg/kg and subsequently ATG 7.5 mg/kg is used to ablate the bone marrow (or lower dose of 120 mg/kg cyclophosphamide with total body irradiation). **Infusion of stem cells** stem cells are thawed and re-infused to the patient, homing the bone marrow. While awaiting immune reconstitution, supportive measures are used including blood transfusions (adapted from Jessop et al [25])

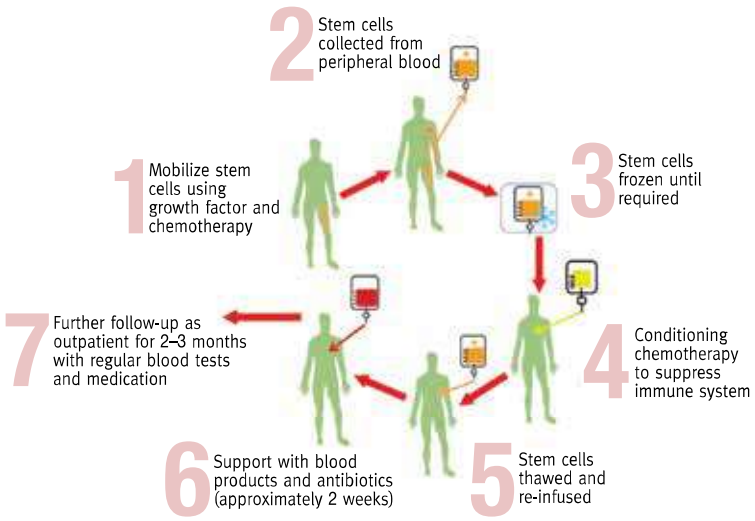


Table 2. Cardiac exclusion risk factors for hematological autologous stem cell transplantation for patients with systemic sclerosis adapted from Frage et al. [22]

- Baseline (resting PASP › 40 mmHg or mPAP › 25 mmHg
- PASP › 45 mmHg or mPAP › 30 mmHg after fluid challenge
- Decrease or lack of augmentation of CO after fluid challenge
- Pulmonary vascular resistance › Wood units
- D-sign of septal bounce on cardiac MRI
- LVEF ‹ 45%
- Unrevascularized severe coronary artery disease
- Untreated severe arrhythemia
- Cardiac tamponade
- Constrictive pericarditis

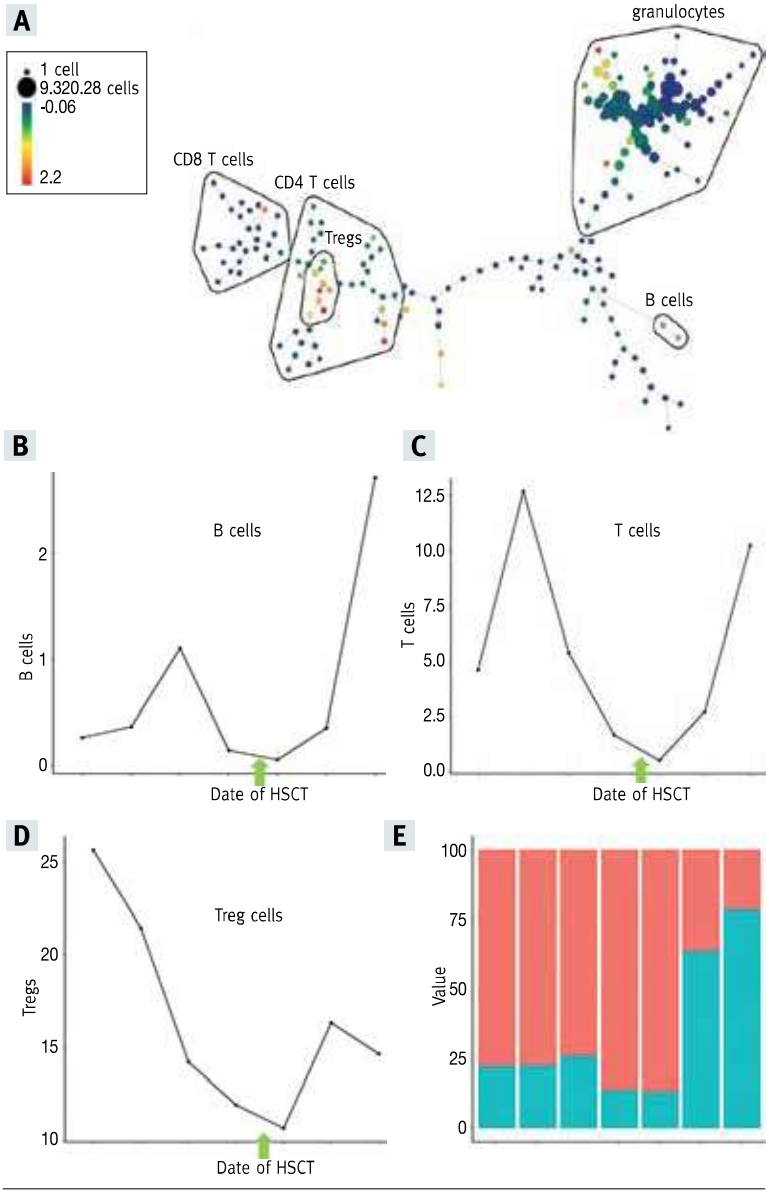
LVEF = left ventricular ejection fraction, mPAP = mean pulmonary arterial pressure, PASP = pulmonary artery systolic pressure

PATIENT 1

A 64-year-old female had been diagnosed with diffuse SSc 4 months prior her evaluation. She reported a weight loss of 7 kg. Clinical exam revealed a mRSS of 33, digital ulcers, and contrac-

tures of fingers. There was evidence of non-specific interstitial pneumonia (NSIP) on her computed tomography (CT) scan. Pulmonary function tests revealed FVC of 89% predicted and DLCO of 67%. Cardiac workup was normal. She was SCL-70 positive, her albumin was slightly decreased 3 g/dl and mildly elevated CPK 183 IU/L. She was treated with cyclophosphamide 500 mg twice a month, yet after 4 month her mRSS increased to 36 and DLCO further decreased. She was treated with HSCT. In the post-transplant period, she presented with *Aspergillus pneumonia* that was treated with voriconazole and late cytoxan cardiotoxicity that resolved completely with conventional treatment. Her mRSS soon decreased to 20, her FVC rose to 95% predicted, and DLCO to 70% predicted. Her ANA remained positive. Using mass cytometry, we followed her immune system and noticed a rise in her B cells, T cells, and specifically CD8+ T cells after a year of remission and she relapsed [Figure 2]. The mRSS increased to 35 again and she lost weight again. Three and a half years after HSCT she was treated with rituximab. Her condition stabilized but did not improve.

Figure 2. The immune system after hematological stem cell transplantation (HSCT) **[A]** SPADE diagram of PBMCs analyzed by CyTOF mass cytometry; **[B-E]** B cells, T cells, T regulatory cells, and CD3 to CD4 ratio. Green arrows denote the date of HSCT



PATIENT 2

A 58-year-old female presented with polyarthritis and developed severe skin fibrosis within 2 months with a mRSS of 21. Her CT scan revealed NSIP with 30% of the lung involved and an FVC of 81% and DLCO of 72% predicted. Serology tests revealed ANA positive, RNAPOLIII positive, and mild anemia. She was treated with iloprost bosentan and MMF 2000 mg QD but after 3 months skin was not improved and she became dyspneic with pulmonary function tests deterioration, FVC of 65%, and DLCO of 59% predicted. Full cardiac workup was normal. She underwent HSCT 12 months after presentation with an unremarkable course. She had no severe complications and her skin shortened after softened, an mRSS score of 7 three months after HSCT and none after a year. Her pulmonary function tests improved as well, FVC 99% and DLCO 83% and she returned to work as a nurse 8 months after HSCT.

PATIENT 3

A 12-year-old female presented with proximal muscle weakness, face swelling, Gorton's papules, Raynaud's phenomena, mildly elevated CPK, and mild edema of proximal thigh muscles on T2 sequence MRI consistent with myositis. Chest CT revealed NSIP and pulmonary function tests revealed a restrictive disease with an FVC of 55% and DLCO 73%. Serology tests were positive only for ANA. Echocardiography was normal. She was treated with prednisone and methotrexate that was substituted for azathioprine because of elevated liver enzymes. Subsequently, she developed skin thickening telangiectasia and rapidly progressive skin fibrosis, mRSS 31. MMF was prescribed without improvement. Two years after her presentation she underwent HSCT without any major complications. Six months after HSCT her skin fibrosis regressed to a mRSS of 21 and CPK normalized, yet her lung function tests did not improve.

PATIENT 4

A 54-year-old female began to show signs of Raynaud's phenomena, arthritis, and rapidly progressive skin thickening with a mRSS of 26 after 4 months of disease. She showed mild finger contractures with friction rub, mild pulmonary fibrosis on her CT scan with abnormal lung function tests, FVC 66%, and DLCO 63% predicted. A cardiac workup was normal, except for trace pericardial effusion. She had mild anemia, hemoglobin

10.4 g/dl, and antibodies to RNA POLIII. Gastroscopy revealed gastric antral vascular ectasia (GAVE) without evidence of hemorrhage. She was treated for 3 months with MMF but worsened clinically and mRSS increased to 30. Eight months after her symptom started, she underwent HSCT that was complicated with SRC after one month. She was treated aggressively with pericardiocentesis, high dose captopril, bosentan, and IVIG. After one month she had a normal creatinine level and normal heart function without pericardial effusion. One year after HSCT she reported good quality of life, had a mRSS of 8, normal pulmonary function tests, FVC 116%, and DLCO 77%.

PATIENT 5

A 36-year-old female was diagnosed with diffuse SSc, SCL-70 positive, 2.5 years before evaluation in our department. On admission she had a mRSS of 28, mild contractures of the fingers, a 20% lung involvement on her CT scan, FVC of 63% predicted, and DLCO 56% predicted. A cholestatic liver impairment, hepatosplenomegaly, and positive antimitochondrial antibody were diagnosed as primary biliary cirrhosis and ursodeoxycholic acid was initiated. Her cardiac workup was normal. She was treated by MMF. After 3 months without improvement, HSCT was suggested. During HSCT she presented with capillary leak syndrome due to ATG that needed mechanical ventilation and resolved with steroid therapy. One month after HSCT, her skin improving greatly to 3, her hepatosplenomegaly regressed, and she has been discharged from hospital.

DISCUSSION

We have presented the first Israeli experience with autologous HSCT for SSc. Overall success rate was encouraging, and no treatment-related mortality was evident.

It took 20 years, three trials, and 534 SSc patients who had been treated in numerous medical centers, to substantiate and solidify the place of autologous HSCT as a treatment for SSc. The growing experience and understanding have enabled better selection of cases and greater success rate but raised many unanswered questions.

The short time frame for HSCT (5 years from diagnosis) should be reevaluated, considering recent reports that found better results in patients with a fibroproliferative blood genetic pattern than in patients with acute inflammatory pattern [23]. Mobilization protocol currently includes cyclophosphamide (as in the ASSIST and ASTIS trial) that may decrease the number of autoreactive T cells and thus decrease relapse, However, as in the SCOT trial, some centers (including ours in Israel) use mobilization without cyclophosphamide with good results. Harvesting stem cells has also been debated. CD 34+ selection used by some centers was not found to affect the outcome of HSCT [24]. Regarding conditioning, the place of cardioprotective chemotherapy in patients with cardiac risk factors has not been evaluated in a randomized clinical trial and there is still a debate about the role of total body irradiation that may increase the risk for hematological malignancies (in the SCOT trial two of the 7 TRM were diagnosed with myelodysplastic syndrome). Post-HSCT care involves the question of whether and what immunosuppressive therapy should be reinitiated after HSCT and should it be used routinely or only if signs of relapse occur. Several markers have been suggested to predict non-response or a relapse, as lack of seroconversion of ANA and increase of T and B cell counts (as seen in patient 1) [Figure 2], yet these markers are not absolute.

Last, the three RCTs compared HSCT to cyclophosphamide that have fallen from grace recently. Currently, new regimens including combination therapies as MMF and rituximab, MMF and pirfedinone (SLS3), and MMF with nintedanib (SENSCIS trial) are often used and should be compared to HSCT.

CONCLUSIONS

HSCT is a novel, efficacious therapy that brings new hope and new expectations for the treatment of severe progressive SSc. A careful selection of patients in the right window of opportunity has already reduced greatly TRM and morbidity and will be further improved using a genetic approach and precision medicine. We have presented the first Israeli experience of HSCT treatment for five patients with SSc, an important step to the medicine in Israel.

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Capsule

Ethnicity reflected in tumor genomes

In the United States, African Americans are more likely to develop and succumb to lung cancer than European Americans. Several factors likely contribute to this racial disparity, including the possibility that disease biology differs between the two groups. Tumor genome sequencing can shed light on this hypothesis. Through targeted sequencing of 129 tumors, **Mitchell** and co-authors found somatic mutations in the *PTPRT* and *JAK2* genes in more than 30% of lung adenocarcinomas from African Americans versus 10% of tumors from European Americans. The proteins encoded by *PTPRT* and *JAK2* function in cellular signaling pathways implicated in cancer. Whether identification of these mutations will lead to new therapies is unclear, but the study broadly supports the idea that tumor biology may differ across racial groups.

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Eitan Israeli

Capsule

Predicting transmission risk for de novo mutation

The reduction in sequencing costs and the increase in prediction accuracy make individual assessment of genetic risk from mutations more attractive and valuable. After examining mutation rates in blood and sperm, **Breuss** and colleagues surveyed families in which a child has been diagnosed with autism spectrum disorder. The authors found a small set of individuals in which a mosaic of potentially causative mutations was observed in the father's blood or sperm. Differential mutational processes seem to govern when the genetic variants arise. Screening for paternal mosaicism might help determine the risk of autism in future children of fathers that carry a de novo mutation.

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Eitan Israeli

"We make a living by what we get, but we make a life by what we give"

Winston Churchill (1874–1965), British statesman, Prime Minister of the United Kingdom, won the Nobel Prize in Literature in 1953 for his overall lifetime body of work