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Management of disease progression after autologous hematopoietic stem cell transplantation in systemic sclerosis: Results from an international questionnaire-based study

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ABSTRACT

Objective: Autologous stem cell transplantation (AHSCT) is an established treatment in diffuse cutaneous systemic sclerosis (dcSSc). Optimal management of disease progression after AHSCT in dcSSc has not been defined. The aim of this study was to explore the experience and preferences of SSc experts on post-AHSCT management.
Methods: An online questionnaire study was conducted containing 17 questions concerning respondent demographics, definition of SSc progression after AHSCT, diagnostic work-up and treatment preferences.
Results: In total, 69 respondents from 21 countries completed the questionnaire. The majority (89.7 %) works at a university hospital, and were involved in decisions regarding AHSCT in patients with SSc (71 %). Most have 1 to 5 patients who underwent AHSCT under their care. They defined failure to improve after AHSCT as: an increase in mRSS, new onset or worsening of interstitial lung disease (ILD), new onset scleroderma renal crisis (SRC) or inflammatory arthritis. Progression after initial response was defined as: increase in mRSS, new or worsening of ILD, new SRC, inflammatory arthritis, new pulmonary arterial hypertension, digital vasculopathy or impaired physical functioning. The most frequent therapy in case of AHSCT failure was mycophenolate mofetil ($N = 55$, 88.7 %), rituximab ($N = 54$, 87.1 %), nintedanib ($N = 39$, 62.9 %) or/and tocilizumab ($N = 36$, 58.1 %). Combination therapy with more than one of these agents was considered by most respondents ($N = 61$, 88.4 %).

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Conclusion: Our study benchmarks the unique combined experiences of post-AHSCT management among SSc experts. We summarize preferences regarding definition of AHSCT failure and progression after response, as well as approach to diagnostic work-up and treatment.

Introduction

Autologous hematopoietic stem cell transplantation (AHSCT) is increasingly used to treat high-risk and/or progressive diffuse cutaneous systemic sclerosis (dcSSc) [1,2]. It is well established that this treatment approach may induce a significant remission which is retained in a significant number of patients [3,4]. Moreover, impressive long-term benefits of AHSCT on patient survival, skin and lung disease, and quality of life have been demonstrated in two large randomised controlled trials. After AHSCT a sustained response on skin thickening has been reported with up to 86.1 % of patients experiencing an improvement of the modified Rodnan Skin Score (mRSS)[4]. In patients with interstitial lung disease, forced vital capacity increased in 33.3 % of patients and DLCO improved in 11.1 % and stabilized in 52.8 %, with much lower percentages in the control arm. These results have been achieved without administration of routine immunosuppressive medication after AHSCT [3,4]. Similar findings have been reported in (inter) national cohort studies [5,6].

AHSCT is hypothesised to 'reset' the immune system, moving it towards a state of immunotolerance [7]. After transplantation, immunosuppressants are not routinely used for maintenance treatment, as the majority of patients improve and stabilize, without the need for immunosuppressive medication. Studies have reported that around 25 % of patients are treated with various disease modifying anti-rheumatic drugs (DMARDs) for several years post-transplantation [8,9]. This is likely due to several reasons: disease progression after initial response, partial response to AHSCT, and/or new onset of another autoimmune disease [3,8]. In about 10–15 % of patients with an initial response to AHSCT, disease relapse and progression may occur, necessitating immunosuppressive treatment[8,9]. Based on limited literature, disease progression could be considered as an increase in skin fibrosis, new onset or progression of interstitial lung disease (ILD), and/or other SSc manifestations.

To date, no studies or recommendations reported in the literature have investigated the optimal management of disease relapse and progression after AHSCT in patients with SSc. Therefore, our study aimed to explore the collective experience and preferences of SSc experts for post-AHSCT disease management.

Methods

Study design

A Steering Board was assembled which consisted of clinicians with an interest in SSc and AHSCT (JS, GB, YA, NDP, CD, OD, DEF, RF, DK, MK, MCC, MN, AVR, JVL, MH). The resulting group developed a questionnaire-based survey to explore clinicians' perspectives concerning the management of disease progression after AHSCT in patients with SSc.

The survey consisted of 17 questions including (but not limited to) clinician demographics, experience with AHSCT in SSc, preferences regarding definition of disease progression, and diagnostic work-up at the time of progression and treatment (Appendix A.1).

The survey invitation was circulated amongst target stakeholders by email among the extensive international EUSTAR network (which includes >200 centers with expertise in SSc), membership of the UK Scleroderma Study Group (UKSSG) and Scleroderma Clinical Trials Consortium (SCTC), and the European AHSCT consortium of the UPSIDE trial [10]. To highlight, the UPSIDE trial is an international trial with 11 participating centres with longstanding experience in SSc and AHSCT in SSc, including multidisciplinary teams with in total 12 rheumatologists.

The survey was launched on the 25th of February and open until the 20th of April 2024. No rewards or incentives were offered for completion of the survey.

Statistical analyses

Data were imported and analysed from the survey platform into SPSS® 25 software (IBM). Descriptive statistics (mean, SD / median, Q1, Q3 for continuous normally/non-normally distributed variables and frequency with percentage for categorical variables) were used. All statistical analyses were performed using SPSS® 25 software (IBM).

Results

Clinician demographics

The survey was completed by 69 respondents and detailed clinician demographics are presented in Table 1. Half (N = 35, 49.3 %) were of self-disclosed female sex, and the median age of the majority (~95 %) of respondents was 31 years or older. Respondents were from 21 countries, most commonly from Italy and USA (both N = 9, 13.0 %), UK and Canada (both N = 7, 10.1 %), and Spain (N = 5, 7.2 %). The majority of respondents were rheumatologists (N = 63, 92.6 %). Years in practice since completion of specialist training varied: 6–10 years (N = 14, 20.6 %). 11–20 years (N = 19, 27.9 %) and 21–30 years (N = 16, 23.5. For the majority (N = 61; 89.7 %) of respondents' clinical practices was based in a University hospital. Most participants reported that they had between taken care of 1 to 5 SSc patients who had undergone AHSCT (N = 29, 44.6 %), and around one-fifth (N = 12, 18.5 %) had >20 transplanted patients.

AHSCT procedures

The majority (N = 49, 71 %) of the respondents reported playing an important role in treatment decision concerning AHSCT. The most frequently used conditioning regimen among respondents was a non-myeloablative conditioning scheme (N = 25, 37.0 %) (with anti-thymoglobulin (N = 21, 83 %), without ATG (N = 4, 17 %)). Myeloablative regimens were used in 28 % (N = 18) of respondents (with ATG (N = 7, 38.9 %), with total body irradiation (TBI) (N = 6, 33.3 %), without TBI (N = 5, 27.8 %)). The conditioning regimen was unknown in N = 22 (31.3 %) of respondents. CD34+ selection was used by half (N = 32, 52.2 %) of respondents, one-third (N = 22, 31.9 %) did not know if CD34+ was used.

Maintenance therapy post AHSCT

Around half (N = 24, 40.7 %) of respondents indicated that routine maintenance immunosuppressive therapy is provided after autologous stem cell transplantation. This percentage was higher in respondents with < 10 transplants (N = 19, 82.6 %) compared to respondents with > 10 transplants (N = 4, 23.5 %). Mycophenolate mofetil was the most commonly prescribed therapy (N = 21, 87.5 %). Less commonly used agents were methotrexate (N = 8, 33.3 %), glucocorticoids (N = 7, 29.2 %), azathioprine (N = 4, 16.7 %) and cyclophosphamide (N = 1, 4.2 %), other treatments, such as rituximab (N = 1, 4.2 %) are infrequently used as maintenance therapies. Reasons not to give maintenance immunosuppressive treatment were: being not considered unnecessary to achieve remission (N = 25, 71.4 %), risk of infection (N = 20, 57.1 %),

Table 1
Systemic sclerosis expert survey respondent characteristics.

Respondent characteristics		N (%) of survey respondents ($n = 69$)
Female sex		35 (49.3 %)
Age (Median)	*18–30 years*	4 (5.8 %)
	31–49 years	29 (42.0 %)
	50–70 years	33 (47.8 %)
	> 70 years	3 (4.3 %)
Country		
Australia		2 (2.9 %)
Brazil		1 (1.4 %)
Canada		7 (10.1 %)
Croatia		1 (1.4 %)
Denmark		1 (1.4 %)
France		4 (5.8 %)
Germany		3 (4.3 %)
Hungary		1 (1.4 %)
India		1 (1.4 %)
Israel		4 (5.8 %)
Italy		9 (13.0 %)
Japan		1 (1.4 %)
Netherlands		4 (5.8 %)
Norway		1 (1.4 %)
Portugal		1 (1.4 %)
Serbia		2 (2.9 %)
Spain		5 (7.2 %)
Switzerland		4 (5.8 %)
Turkey		1 (1.4 %)
United Kingdom		7 (10.1 %)
United States of America		9 (13.0 %)
Speciality		
Rheumatology		63 (92.6 %)
Haematology		1 (1.5 %)
General (internal) medicine		2 (2.9 %)
Other		2 (2.9 %)
Time since completion of specialist training (years)	0–5	7 (10.3 %)
	6–10	14 (20.6 %)
	11–20	19 (27.9 %)
	21–30	16 (23.5 %)
	>30	12 (17.6 %)
Type of hospital	University	61 (89.7 %)
	General hospital	4 (5.9 %)
	Private practice	3 (4.4 %)
Number of SSc patients with AHSCT under respondents care	None	11 (16.9 %)
	1–5	29 (44.6 %)
	6–10	7 (10.8 %)
	10–20	6 (9.3 %)
	>20	12 (18.5 %)

increased risk of malignancy ($N = 5$, 14.3 %), interference with effect of AHSCT ($N = 5$, 14.3 %), or other reasons such as lack of evidence for post-AHSCT maintenance treatment ($N = 3$, 4.2 %).

SSc disease progression after AHSCT

Failure to improve post-AHSCT

Respondents defined *failure to improve* after AHSCT as stable mRSS (i.e. no clinically meaningful worsening or improvement in mRSS) ($N = 26$, 42.6 %) or clinically meaningful worsening of skin thickening (e.g., mRSS $\geq$ 25 % or greater or $\geq$ 5 units compared to baseline) ($N = 51$, 83.6 %), new ILD (clinical diagnosis according to the clinician) ($N = 45$, 73.8 %) or clinically meaningful progression of ILD (e.g., decrease of $\geq$ 10 % in the predicted % FVC) ($N = 50$, 82.0 %), stable ILD (i.e. no worsening or improvement in ILD) ($N = 9$, 14.8 %), new pulmonary arterial hypertension (PAH) ($N = 24$, 39.3 %), new onset of scleroderma renal crisis ($N = 34$, 55.7 %), new onset of inflammatory arthritis ($N = 34$, 55.7 %), worsening of digital vasculopathy (e.g. recurrent digital ulcers or gangrene) ($N = 28$, 45.9 %), worsened physical functioning due to SSc (e.g. increase of > 0.4 in the HAQ-DI score) ($N = 28$, 45.9 %), or other reasons such as cardiac involvement ($N = 1$, 1.4 %) or myositis ($N = 1$, 1.4 %). Respondents with < 10 transplants more often selected stable ILD ($N = 8$, 19.5 % vs $N = 1$, 5.9 %), new onset of PAH ($N = 18$, 43.9 % vs $N = 5$, 29.4 %) compared to respondents with > 10 transplants.

Progression after initial response to AHSCT

Respondents defined *progression after initial response to AHSCT* as increase of mRSS ($N = 54$, 88.5 %), new ILD ($N = 48$, 78.7 %) or worsening of ILD ($N = 48$, 78.7 %), new PAH ($N = 34$, 55.7 %) (PAH present prior to AHSCT is generally an exclusion criteria), new onset of scleroderma renal crisis ($N = 42$, 60.9 %), new onset of inflammatory arthritis ($N = 39$, 56.5 %), worsening of digital vasculopathy ($N = 32$, 52.5 %), worsened physical functioning due to SSc ($N = 31$, 50.8 %), or other reasons such as cardiac involvement ($N = 2$, 2.9 %), gastrointestinal symptoms ($N = 3$, 4.3 %), or myositis ($N = 2$, 2.9 %). Respondents with < 10 transplants more often selected new onset of PAH ($N = 26$, 63.4 % vs $N = 6$, 35.3 %) compared to respondents with > 10 transplants.

In Fig. 1 criteria for failure to improve post-AHSCT and progression after initial response to AHSCT are summarized.

Diagnostic strategy in disease progression post AHSCT

Concerning the diagnostic work-up in case of disease progression post-AHSCT, most respondents ($N = 49$, 80.3 %) would consider testing the autoantibody profile. All respondents would test characteristic SSc-specific antibodies (e.g., anticentromere, anti-Scl-70, anti-RNA polymerase III), around two-thirds would test for other SSc-specific autoantibodies (e.g., anti-Th/To, Anti-NOR90, Anti-U11/12 RNP) ($N = 34$, 70.8 %)/ or autoantibodies associated with myositis overlap (e.g., anti-PM-Scl) ($N = 30$, 62.5 %), and half would test for other CTD-related autoantibodies (e.g., anti-Ro52) ($N = 27$, 56.3 %). Furthermore, 55 % ($N = 33$) of the respondents reported that screening for underlying malignancy would be performed in the context of disease progression after AHSCT.

Treatment approaches

Among the 62 clinicians who answered this specific question regarding treatment of progression or failure, the most frequently chosen therapeutic options in case of AHSCT failure were: mycophenolate mofetil ($N = 55$, 88.7 %), rituximab ($N = 54$, 87.1 %), nintedanib ($N = 39$, 62.9 %), tocilizumab ($N = 33$, 57.9 %). Azathioprine and IVIG were suggested more often in respondents with < 10 transplants ($N = 8$, 20.0 % vs $N = 1$, 5.9 % and $N = 22$, 55.0 % vs $N = 5$, 29.4 % respectively), and tocilizumab in respondents with >10 transplants ($N = 12$, 70.6 % vs $N = 21$, 52.5 %).

<50 % of respondents would choose intravenous immunoglobulins ($N = 30$, 48.4 %), cyclophosphamide ($N = 23$, 37.1 %), glucocorticoids ($N = 23$, 37.1 %), JAK inhibitors ($N = 20$, 32.3 %), second AHSCT ($N = 17$, 27.1 %), cyclosporin ($N = 11$, 17.7 %), azathioprine ($N = 11$, 17.7 %), methotrexate ($N = 10$, 16.1 %), tacrolimus ($N = 10$, 16.1 %), abatacept ($N = 9$, 14.5 %), hydroxychloroquine ($N = 8$, 12.9 %), leflunomide ($N = 4$, 6.5 %) and allogenic HSCT ($N = 4$, 6.5 %) (Fig. 2). When asked to choose the top three preferred therapies after failure of AHSCT the majority of respondents confirmed mycophenolate mofetil ($N = 50$, 81.9 %), rituximab ($N = 42$, 68.8 %) and tocilizumab ($N = 31$, 50.8 %). Combination therapy would be considered by most ($N = 61$, 88.4 %) respondents. The three most frequently chosen drugs considered for combination therapy were mycophenolate mofetil (MMF) ($N = 50$, 82 %), rituximab $N = 44$, 72.1 %) and tocilizumab ($N = 29$, 47.5 %).

Discussion

Our study explored experience regarding post-AHSCT disease management among SSc experts and summarized preferences regarding definitions of AHSCT failure and progression after response, including the diagnostic work-up and treatment for patients with dcSSc. To our

A. Failure to improve after AHSCT
- increase of mRSS* (83.6%)
- new ILD (73.8%)
- worsening of ILD (82.0%)
- new scleroderma renal crisis (55.7%)
- new onset inflammatory arthritis (55.7%)

B. Progression after initial response
- increase of mRSS* (88.5%)
- new ILD (78.7%)
- worsening of ILD (78.7%)
- new renal crisis (60.9%)
- new inflammatory arthritis (56.5%)
- new PAH (55.7%)
- worsening of digital vasculopathy (52.5%)
- worsened physical functioning (50.8%)

Fig. 1. Proposed criteria for failure to improve (A) and progression after initial response (B) to autologous hematopoietic stem cell transplantation in patients with systemic sclerosis.
The criteria selected by > 50 % of respondents. Increase in mRSS: mRSS ≥ 25 % or greater or ≥ 5 compared to baseline. Abbreviations: ILD: interstitial lung disease; mRSS: modified Rodnan skin score; PAH: pulmonary arterial hypertension.

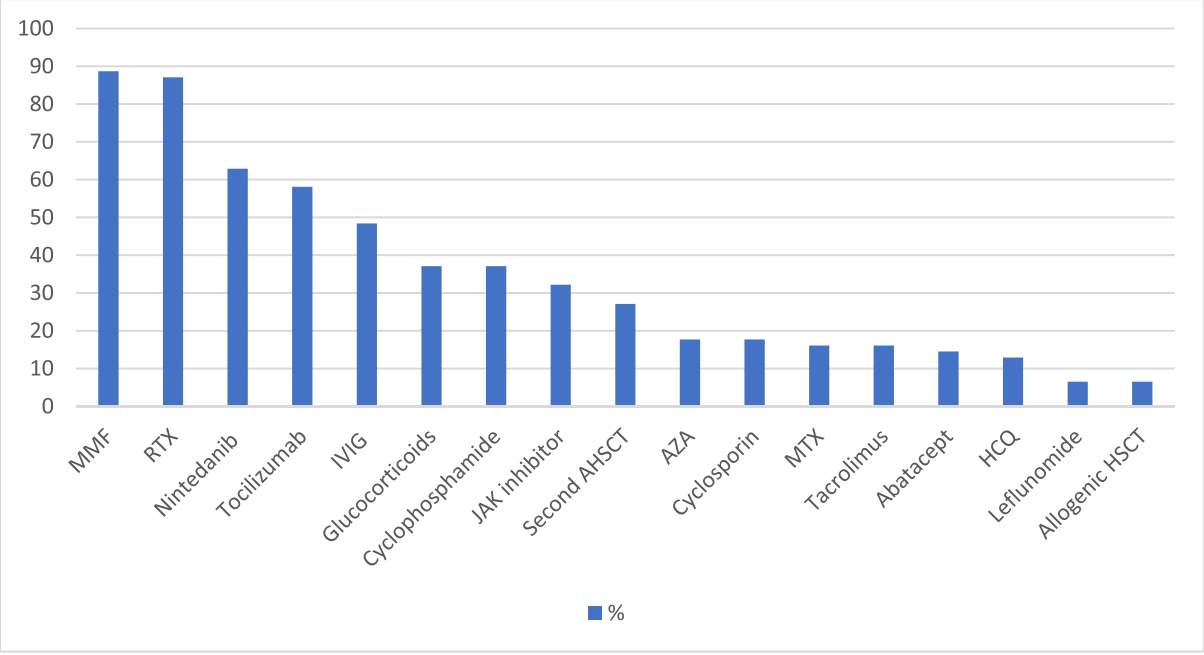

Fig. 2. Preferred treatment in case of failure to improve after autologous hematopoietic stem cell transplantation.
Abbreviations: AZA: azathioprine, (A)HSCT: (autologous) hematopoietic stem cell transplantation, HCQ: hydroxychloroquine, IVIG: intravenous immunoglobulins, JAK: Janus Kinase, MMF: mycophenolate mofetil, MTX: methotrexate, RTX: rituximab.

knowledge, ours is the first study to explore and benchmark the current clinical practice and opinion of experts in SSc concerning post-AHSCT management, including failure and progression.

These data clearly show that there are significant differences in routine practice by experienced clinicians in terms of the currently used conditioning regimens and CD34 selection, which may also affect post-transplant strategies. Use of disease modifying anti-rheumatic drugs (DMARDs) as maintenance therapy after AHSCT also widely varies across respondents. In fact, around half (43.5 %) administer DMARD therapy, most commonly mycophenolate or methotrexate, routinely after AHSCT. However, it is not currently known whether this is a superior approach to no maintenance therapy. Conversely, the main reasons reported for not using DMARDs following AHSCT were it being deemed unnecessary for achieving remission and the risk of infection (71.4 % and 57.1 % of respondents, respectively). Moreover, it was thought that immune reconstitution might be (negatively) suppressed by the use of immunosuppressive therapies as regenerated and regulatory functions of immune cells may be inhibited [11,12]. The effectiveness of various post-transplant treatments is currently being investigated in two uncontrolled observational multicentre studies (NCT03444805 and

NCT01413100) [13,14].

In contrast to oncology studies, in the setting of AHSCT in SSc, there is currently a lack of consensus for definition and standardisation of outcomes with respect to response, disease progression and relapse after treatment [15]. Previous clinical trials have used criteria for progression including death, increase in mRSS, drop in lung function parameters, body weight, kidney function and physical functioning [3,16]. In cohort studies, simplified criteria have been used. For example, a large Dutch longitudinal cohort study defined disease progression as progression of skin and lung involvement or the necessity of immunosuppressive treatment therapy [8]. A further Brazilian cohort study used similar criteria for progression, but also added the new onset of scleroderma renal crisis [9]. In line with these previous studies, worsening of skin and lung disease were the most important criteria for progression after transplantation identified by the respondents. New onset of renal and joint involvement was also suggested, as were vascular complications and impairment of physical functioning.

The preferred or prioritised immunosuppressive therapies in case of progression were mycophenolate, rituximab, nintedanib and tocilizumab. It is well known that mycophenolate and nintedanib are commonly used in SSc, while rituximab and tocilizumab are increasingly used in certain settings, but are not typically part of 'standard of care' in dcSSc patients in all countries [17,18]. A second AHSCT would be considered in one-third (27.1 %) of respondents, assuming based on an appropriate reassessment of patients fitness, which has been successfully reported in case reports for refractory patients [19,20]. Use of allogeneic HSCT is limited in this context and should be applied to highly refractory and selected cases [21]. Recently other innovative cellular therapies, such as mesenchymal stromal cells (MSC) and chimeric antigen receptors T cells (CART) have been successfully adopted in refractory autoimmune diseases and may represent additional treatment options [22]. Although the abovementioned therapies have been studied in trials in SSc, there has been no study reporting on the optimal agent in the post-transplant setting in progressive dcSSc. Unfortunately, such a study will likely be challenging to conduct, including because of the low frequency of progression after AHSCT. This will necessitate a multicentre design with a large group of patients, a control arm and long follow-up. Therefore, we currently rely on expert opinion and shared experiences.

A key strength of our study is the worldwide response to the survey which gives a broad view of experience across countries. However, an inherent limitation of our work is the relatively low number of respondents which also hampers comparison within the group, especially the low number of respondents with large experience in AHSCT. Furthermore, we did observe some differences in respondents with lower experience (<10 patients) of transplant compared to the highly experienced group. This limitation was to be expected as AHSCT requires state of the art facilities and experienced multidisciplinary teams, and is therefore not currently offered in most SSc centres. In conclusion, ours is the first effort to specifically investigate post-AHSCT management in SSc. While AHSCT has shown to provide great benefits in patients with rapidly progressive dcSSc and is therefore increasingly performed across the world, not much is known about post-transplantation management. Our findings provide a comprehensive overview of the current treatment strategies utilised by SSc experts in the context of AHSCT, and could strongly support clinicians by informing their real-world patient management. Furthermore, these data can be used as a starting point for further discussions and the development of consensus criteria for disease progression after AHSCT, and the conduct of much-needed future studies on optimal treatment post-AHSCT.

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CRediT authorship contribution statement

Julia Spierings: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Giulia Bandini:** Writing – review & editing, Software, Data curation. **Yannick Allanore:** Writing – review & editing. **Nicoletta Del Papa:** Writing – review & editing. **Christopher P Denton:** Writing – review & editing. **Oliver Distler:** Writing – review & editing. **Daniel E. Furst:** Writing – review & editing. **Raffaella Greco:** Writing – review & editing. **Dinesh Khanna:** Writing – review & editing. **Masataka Kuwana:** Writing – review & editing. **Marco Matucci-Cerinic:** Writing – review & editing. **Mandana Nikpour:** Writing – review & editing. **Anna van Rhenen:** Writing – review & editing. **Jacob M van Laar:** Writing – review & editing. **Michael Hughes:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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