SUPPLEMENTARY APPENDIX

Use of immunosuppressive therapy for management of myelodysplastic syndromes: a systematic review and meta-analysis

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Supplementary Table 1: Methodological quality assessment based on Downs and Black checklist

Study (year of publication)	Reporting (items 1-10; max. 11 points)	External validity (items 11-13; max. 3 points)	Internal validity; bias (items 14-20; ma. 7 points)	Internal validity; confounding (items 21-26; max. 6 points)	Power (item 27; max. 1 point)	Total
Molldrem, JJ et al (2002)(28)	8	1	5	2	0	16
Steensma, DP et al (2003)(33)	8	1	5	1	0	15
Killick, S. et al (2003)(34)	8	1	5	0	0	14
Stadler, M et al (2004)(35)	11	1	5	4	0	21
Komrokji, R et al (2014)(16)	8	2	5	1	0	16
Yamada, T et al (2003)(29)	8	2	5	3	0	18
Ogata, M et al (2004)(52)	7	1	4	0	0	12
Ishikawa, T et al (2007)(41)	9	1	5	1	0	16
Yazji, S. et al (2003)(30)	8	1	4	1	0	14
Saunthararajah, Y et al (2003)(21)	6	1	4	0	0	11
Broliden, PA et al (2006)(36)	8	1	5	1	0	15
Garg, R. et al (2009)(37)	9	1	4	1	0	15
Xiao, L et al (2012)(13)	7	1	5	0	0	13
Passweg, JR et al (2011)(18)	11	1	5	5	1	23
Kadia, TM. Et al (2012)(17)	9	1	5	1	0	16
Deeg, HJ et al (2004)(31)	8	1	3	1	0	13
Scott, BL et al (2010 (1))(38)	7	1	5	1	0	14
Deeg, HJ et al (2002)(20)	7	1	5	1	0	14
Platzbecker, U et al (2005)(39)	8	1	5	1	0	15
Remacha, AF et al (2010)(40)	6	1	5	1	0	13
Scott, BL et al (2010 (2))(32)	7	1	4	0	0	12
Sloand, EM et al (2010)(19)	9	2	5	2	1	19

Supplementary methods:

Date sources and search strategy: This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [24]. MEDLINE via PubMed, Ovid EMBASE, the COHRANE registry of clinical trials (CENTRAL), and the Web of Science electronic databases were searched with no language restriction from inception through September 2018, using the following combination of free-text terms linked by Boolean operators: ("MDS" OR "myelodysplasia" OR "myelodysplastic syndrome") AND ("IST" OR "immunosuppressive therapy" OR "immunosuppression" OR "ATG" OR "anti-thymocyte globulin" OR "tacrolimus" OR "cyclosporine" OR "sirolimus" OR "prednisone" OR "prednisolone" OR "steroids" OR "etanercept" OR "alemtuzumbab").

All relevant articles, irrespective of language, year of publication, type of publication, or publication status, identified via the above search strategy were included in the initial screening step. Additionally, we performed a gray literature search through 1) manual hand search of bibliographies of all identified studies and 2) conference proceedings and abstracts of the following annual meetings: American Society of Hematology, American Society of Clinical Oncology, European Hematology Association and European Society of Medical Oncology.

Study selection and endpoints: According to a formulated search strategy, two reviewers (MS and JPB) independently screened the titles and abstracts of all retrieved studies for eligibility and removing any duplicate records. In a second step, full texts of the potentially eligible studies were reviewed for the final eligibility for

qualitative and quantitative syntheses. There was no disagreement with the the two reviewers regarding the inclusion of any of the studies. As per the MOOSE guidelines, the study selection process was illustrated in a flow diagram (**Figure 1**).

Prospective cohort studies or clinical trials involving human subjects of all ages investigating the use of IST for the treatment of MDS were included. IST was defined as receipt of one or a combination of the following drugs: rabbit and horse ATG, CsA, sirolimus, mycophenolate mofetil and monoclonal antibodies (etanercept, alemtuzumab). We excluded studies that 1.) lack information on either ORR or CR rate, 2.) review articles, editorials, and correspondence letters that did not report independent data, 3.) case series and studies reporting outcomes on fewer than five patients and 4.) retrospective studies given the significant biases involved.

The primary outcomes were ORR and CR rate. Secondary outcomes included rates of HI-E, TI, and AML progression. ORR was defined as the composite rate of achieving a CR, partial remission (PR) and HI-E, which were defined based on the 2006 modified International Working Group (IWG) response criteria for MDS [25].

Data extraction: Two investigators (MS and JPB) extracted data from the selected studies using a standardized data-extraction form, and a third investigator (SG) performed a cross-check for data accuracy. Information abstracted from the selected publications included data relating to study characteristics (study design, patient selection, follow up duration, and number of patients), patient characteristics (age, sex, MDS French-American-British (FAB) and World Health Organization (WHO) type, IPSS category, cytogenetics), treatment characteristics (type, dosing and

treatment schedule of IST used) and measures of effect (response rates and rate of progression to AML).

Quality assessment: The quality of each study was assessed by two authors (MS and JPB) using the modified Down and Black checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions [26]. The Downs and Black checklist contain 27 items in the subcategories of reporting (items 1-10; max. 11 points), external validity (items 11-13; max. 3 points), internal validity/bias (items 14-20; max. 7 points), internal validity/confounding (questions 21-26; max. 6 points), and power (question 27; max. 1 point) for a maximum score of 28 points. As several studies were not reporting information on various components of the checklist, we did not assign quality levels to a defined score range. Quality assessments for individual studies are provided in **Table 1**.

Statistical analysis: Random-effects models were used to pool ORR, rates of CR, HI-E, TI, and progression to AML. All effect sizes underwent logarithmic transformation prior to pooling under a random effects approach using an inverse variance weighting approach. We decided to use random effects model for pooling our effect size as a priori given the inherent heterogeneity in the study design as we were pooling multiple categories of IST across various study designs (observational and clinical trials). In case of AML progression, event rates were pooled after incorporating the person years of follow-up. Heterogeneity of studies included in the meta-analysis was determined using Cochran Q and I^2 indices with a view to further exploring significant heterogeneity (defined as $I^2 > 60\%$) with sensitivity analyses [27]. Subgroup analyses were planned based on the type of IST used. Subgroups

examined were studies reporting the use of ATG, ATG + CsA, ATG + Etanercept, CsA and other IST regimens (Sirolimus, Etanercept, Alemtuzumab and MMF).

Sensitivity analysis was performed for the overall summary effects by removing one study and re-running the meta-analysis for every study in the analysis. All statistical analyses were performed with Comprehensive Meta-Analysis (CMA 2.2, Biostat).