Validation of the Revised Myeloma Comorbidity Index and other comorbidity scores in a multicenter German study group multiple myeloma trial

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Supplements

Methods

Patient population and study design

This prospective study, done in 284 consecutive MM patients at the time of initial diagnosis or first presentation at 5 German Study Group Multiple Myeloma (DSMM) centres (Freiburg, Würzburg, Ulm, Jena, Leipzig), was registered at the German Clinical Trials Register (www.clinicaltrials.gov) (DRKS-00003868). The primary objective was to validate the R-MCI[1] in a multicentre MM cohort. Secondary objectives included the distribution of the R-MCI as compared to the International myeloma working group (IMWG) frailty score[2] and Charlson Comorbidity Index (CCI) (Suppl. Table 1). The analysis was carried out according to the guidelines of the Declaration of Helsinki Principles and Good Clinical Practice. All patients gave their written informed consent for institutional-initiated research studies and analyses of clinical outcome studies conforming to the institutional review board guidelines.

Assessment

The comorbidities assessed in the R-MCI are depicted in Suppl. Table 2, and the IMWG and CCI comorbidities in Suppl. Table 1. Cytogenetics were assessed as followed: del(17p13), del(13q14), t(4;14), t(14;16); t(14;20), hypodiploidy, c-myc and chromosome 1 aberrations were defined as unfavorable, and t(11;14), hyperdiploidy and a normal karyotype as favorable cytogenetics. Genetic abnormalities were detected by fluorescence in situ hybridization (FISH). Renal function was determined via estimated glomerular filtration rate (eGFR by MDRD) and lung disease via lung function test. Pulmonary obstruction and/or restriction were distinguished with the aid of parameters such as forced expiratory volume in one second (FEV_1) and Tiffeneau-Pinelli index (FEV_1/FVC). Pulmonary obstruction was graded through the impairment of the FEV_1: a FEV_1 of ≥80% was scored as mild, <80-50% as moderate and <50% as severe. The KPS was defined as normal (100%), mildly (90%), moderately (80%) or more substantially impaired (≤70%). Frailty and disability were assessed in order to get a more precise determination of patients' physical condition. The Fried definition for frailty was utilized in adaptation (as described in the manuscript text, Table 1A and http://www.myelomacomorbidityindex.org/en_calc.html), which takes into account the added presence of weakness, poor endurance, low physical activity and slow gait speed.[3,4] The assessments of the Freiburg cohort were performed by an oncogeriatrically trained staff member (SMD) and was identically performed throughout the study period. Patient characteristics included age, stage, creatinine, bone marrow infiltration and cytogenetics (Table 1A+B).

Statistical analysis

The R-MCI was assessed and compared to the IMWG and CCI. These scores were also applied in order to compare fit vs. frail patients. Data were analyzed using GraphPadPrism V5.03 and SAS 9.2 (SAS Institute Inc. USA).

References

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Supplementary Table 1. International comorbidity scores: IMWG, CCI and revised Myeloma Comorbidity Index (MCI)

	Revised MCI (Weighted)	IMWG-frailty score	CCI (Weighted)
References	Engelhardt 2017[1]	Palumbo 2015[2]	Charlson 1987[5]
Factors	- Moderate-severe lung disease [1] - Severe renal disease [1] - Reduced KPS: 80-90% [2] ≤70% [3] - Age >60 - ≤70y [1] Age >70y [2] - Moderate-severe frailty [1] - Unfavorable cytogenetics [1] :	- Age >76 - ≤80y [1] Age >80y [2] - ADL ≤4 [1] - IADL ≤5 [1] - CCI ≥2 [1]	- Myocardial infarction [1] - Congestive heart failure [1] - Peripheral vascular disease [1] - Cerebrovascular disease [1] - Dementia [1] - Chronic pulmonary disease [1] - Connective tissue disease [1] - Peptic ulcer disease [1] - Mild liver disease [1] - Mild diabetes [1] - Hemiplegia [2] - Moderate-severe renal disease [2] - Diabetes with end organ damage [2] - Tumor without metastases (exclude if >5y from diagnosis) [2] - Leukemia [2] - Lymphoma [2] - Moderate-severe liver disease [2] - Metastatic solid tumor [6] - AIDS [6]
Number of factors	6	4 (33 questions)	18
Max. points	9	5	33 (+1 per decade from an age of 50)

Abbreviations: CCI, Charlson Comorbidity Index; IMWG, International myeloma working group; KPS, Karnofsky Performance Status; pts, patients; R-MCI, revised myeloma comorbidity score; y, years.
Scoring rules:
a) R-MCI/IMWG/CCI: Addition of present comorbidities, sum score

Supplementary Table 2. Revised myeloma comorbidity score (R-MCI): multivariate with inclusion, definitions and weighting

R-MCI risk factors determined via multivariate analysis[1]	**Definition**	**Score**
1. Renal disease ($eGFR_{MDRD}$)[a]	≥90 60-89 <60	0 0 1
2. Lung disease	No/mild Moderate/severe	0 1
3. KPS	100% 80-90% ≤70%	0 2 3
4. Age (years)	<60 60-69 ≥70	0 1 2
5. Frailty	No/mild Moderate Severe	0 1 1
6. Cytogenetics	Favorable Unfavorable Unavailable	0 1 0
Σ=sum score **Fit (R-MCI 0-3)** **Intermediate-fit (R-MCI 4-6)** **Frail (R-MCI 7-9)**		**Max. 9** **Group allocations**

Abbreviations:
KPS, Karnofsky Performance Status; $eGFR_{MDRD,}$ estimated glomerular filtration rate by MDRD (Modification of Diet in Renal Disease).
[a]eGFR calculated as MDRD 186 × (serum creatinine level [mg/dl]) $^{-1.154}$ × (age [y]) $^{-0.203}$ × (0.742 if female, 1.21 if black person)