Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome

Barbara Deschler,[1] Gabriele Ihorst,[2] Uwe Platzbecker,[3] Ulrich Germing,[4] Eva März,[1,5] Marcelo de Figuerido,[1,5] Kurt Fritzsche,[5] Peter Haas,[1] Helmut R. Salih,[6] Aristoteles Giagounidis,[7] Dominik Selleslag,[8] Boris Labar,[9] Theo de Witte,[10] Pierre Wijermans,[11] and Michael Lübbert[1]

[1]University of Freiburg Medical Center, Freiburg, Germany; [2]Institute of Medical Biometry, Medical Informatics and Center of Clinical Trials, Albert-Ludwigs University of Freiburg, Freiburg, Germany; [3]University of Dresden Carl Gustav Carus, Dresden, Germany; [4]University of Düsseldorf, Düsseldorf, Germany; [5]Department of Psychosomatic Medicine and Psychotherapy, University of Freiburg Medical Center, Germany; [6]University Hospital Tübingen, Germany; [7]St Johannes-Hospital Duisburg, Germany; [8]AZ St Jan, Brugge, Belgium; [9]University Hospital Zagreb, Croatia; [10]Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; and [11]Haga Hospital, The Hague, The Netherlands

 doi:10.3324/haematol.2012.067892

Online Supplementary Design and Methods

Patient treatment and study participation

Of the 195 patients, 16 participated in a randomized phase III EORTC study (06011; NCT00043134) of low-dose decitabine *versus* best supportive care for elderly patients with intermediate- or high-risk MDS (and received decitabine), 56 patients receiving decitabine were treated within the non-randomized AML Study 00331; NCT00866073 and one patient was treated within a phase II study on combination therapy with 5-azacytidine, valproic acid. Forty-nine were treated within the toxicity-reduced conditioning protocol FBM (fludarabine, BCNU and melphalan), 6 patients underwent induction chemotherapy within a randomized phase III trial (AML-17; NCT00052299) of the EORTC and the GIMEMA (gemtuzumab ozogamycin combined with standard intensive chemotherapy *versus* standard intensive chemotherapy alone for induction/consolidation in patients aged 61-75 years with previously untreated AML), and 2 patients were treated within the AMLSG 10-07 (NCT00783653) phase I/II clinical study of SU11248 combined with standard chemotherapy with cytosine arabinoside and daunorubicin in patients with FLT3-mutated AML over 60 years of age (*Online Supplementary Tables S1 and S2*).

Comparative investigations with results of EORTC and German MDS Study Group phase III data (trial 06011)

Investigating the prognostic value in an independent patient cohort, data of 233 patients who were included in a randomized phase III EORTC trial for elderly MDS patients were assessed. Data of 151 patients were fully evaluable for performance status and EORTC QLQ-C30 'fatigue'. Of these, 14 patients were excluded because they were initially included in our study. Therefore, data of 137 patients were available for statistical calculations (*Online Supplementary Table S3*).

EORTC patients were comparable regarding gender and survival; they were, however, younger than patients in the CGA/QOL trial with a median age of 70 (BSC) and 69 (decitabine) years as compared to 75 (BSC) and 74 (hypomethylating agents) years. All patients had an ECOG performance status of 2 or below (equal to Karnofsky Index ≥70). Activities of daily living (ADL) were not assessed. Cox's proportional hazards model was used to determine the independent prognostic importance of several factors, particularly performance status and fatigue to obtain HR estimates and corresponding 95% confidence intervals (CI) in the independent control group (n=137) (*Online Supplementary Table S4*).

A similarly strong prognostic value of 'performance status' was observed in the independent cohort while patient-reported QOL/'fatigue' did not show the same impact on survival. We found several possible reasons for this discrepancy. One of these could be the better performance status of the selected EORTC trial patients (as ECOG performance of >2, equivalent to a Karnofsky Index of <70, was an exclusion criterion) compared to the BSC and HA groups in our study, making them comparable to our IC patients in which 'fatigue' was of no strong prognostic importance either. In addition, in the EORTC trial, 25-30% of patients switched from BSC or HA to IC after progression.[1] In other words, the prognostic value of 'fatigue' may be more pronounced in patients with a compromised performance status. Other reasons could be that EORTC trial patients were pre-selected MDS patients only and, finally, the EORTC QOL questionnaire was not included in a structured assessment, making comparisons difficult.

References

1. Yeo W, Mo FK, Koh J, Chan AT, Leung T, Hui P, et al. Quality of life is predictive of survival in patients with unresectable hepatocellular carcinoma. Ann Oncol. 2006;17(7):1083-9.

Online Supplementary Table 1. Differences between treatment groups.

	KI (range)	ADL (range)	Fatigue (range)	HCT-CI	Age	Hb
BSC	Mean: 65.53±17.3 Median: 70 (20-90)	Mean: 79.6±27.7; Median: 95 (20-100)	Mean: 53.39±33.9 Median: 53 (0-100)	Mean: 2.9±1.8; Median: 3	Mean: 74.9±5.6 Median: 75.2	Mean: 8.9±1.37
DAC	Mean: 77.06±14.6 Median: 80 (30-80)	Mean: 93.1±12.46; Median: 100 (55-100)	Mean: 58.9±33.9 Median: 66.6 (0-100)	Mean: 2.12±1.8 Median: 2	Mean: 73.9±5.2 Median: 74.17	Mean: 8.8±1.28
IC/HCT	Mean: 74.5±11.3 Median: 80 (40-90)	Mean: 97.6±9.3; Median: 100 (25-100)	Mean: 47.6±28.4 Median: 44.3 (0-100)	Mean: 2.68±2.16 Median: 2	Mean: 68.28±4.3 Median: 68	Mean: 9.3±1.58
P value Kruskal-Wallis	0.0005	0.000	0.1056	0.0598	0.000	0.2073

Online Supplementary Table 4. Cox's proportional hazards model was used to determine the independent prognostic importance of several factors, particularly performance status and 'fatigue' to obtain HR estimates and corresponding 95%CIs in the independent control group (n=137, 06011 trial).

Parameter	Hazard Ratio (95%CI)	*p* value
ECOG PS: 2 *vs.* 0	2.70 (1.36 , 5.36)	0.005
Poor risk cytogenetics *vs.* low risk	2.13 (1.37, 3.34)	0.0009
BM blasts: > 20% *vs.* ≤20%	2.05 (1.28, 3.30)	0.003
ECOG PS: 1 *vs.* 0	1.96 (1.18 , 3.23)	0.009
Unkown cytogenetics *vs.* low risk	1.20 (0.64 , 2.22)	0.59
EORTC C30 fatigue: ≥50 *vs.* <50	1.04 (0.69, 1.56)	0.86

A similarly strong prognostic value of "performance status" was observed in the independent cohort while patient-reported QOL/fatigue did not show the same impact on survival. We found several reasons for this discrepancy: One reason for this could be the better performance status of the selected EORTC trial patients (as ECOG performance of >2 (equivalent to a Karnofsky Index of <70) was an exclusion criterion) compared to our study's BSC and HA groups making them rather comparable to our IC patients in which fatigue was of no strong prognostic importance either. In addition, in the EORTC trial, 25-30% of patients switched from BSC or HA to IC after progression.[1] In other words, the prognostic value of fatigue may be more pronounced in patients with a compromised performance status. Further aspects may be that EORTC trial patients were pre-selected MDS patients only, and finally, the EORTC QOL questionnaire was not included in a structured assessment, making comparisons difficult.

Online Supplementary Table 2. Associations between risk assessment score variables with established MDS/AML-related risk factors (Fisher's Exact Test).

Karnofsky Index <80%	Poor risk cytogenetics/IPSS	1.000
Fatigue ≥50	Poor risk cytogenetics/IPSS	0.5402
ADL (Barthel Index) <100	Poor risk cytogenetics/IPSS	0.8308
Karnofsky Index <80%	Bone marrow blasts >20%	0.5566
Fatigue ≥50	Bone marrow blasts >20%	0.1054
ADL (Barthel Index) <100	Bone marrow blasts >20%	0.6877

Online Supplementary Table 3. Results of independent patient cohort. Patients' demographics and clinical characteristics (06011 trial).

	Patient Demographics and Clinical Characteristics					
Demographic or clinical characteristic	BSC (n= 75)		DAC (n=62)		Total (n=137)	
	No. of patients	%	No. of patients	%	No. of patients	%
Age, years						
Median	70		69		70	
Range	60-85		60-90		60-90	
Sex						
male	45	60	38	61.3	83	60.6
female	30	40	24	38.7	54	39.4
ECOG performance status						
0	17	22.7	16	25.8	33	24.1
1	46	61.3	36	58.1	82	59.9
2	12	16	19	16.1	22	16.1
IPSS						
int-1	7	9.3	6	9.7	13	9.5
int-2/high	68	90.7	56	90.4	124	90.6
EORTC C30 QOL fatigue						
<50%	39	52	35	56.5	74	54
≥50%	36	48	27	43.5	63	46

Investigating the prognostic value in an independent patient cohort, data of 233 patients that were included in a randomized phase III EORTC trial for elderly MDS patients were assessed. Data of 151 patients were fully evaluable for performance status and EORTC QLQ-C30 fatigue. Of those, 14 patients were excluded because they were initially included in our study. Thus, data of 137 patients remained for statistical calculations. EORTC patients were comparable regarding gender and survival; yet were younger than patients in the CGA/QOL trial with a median age of 70 (BSC) and 69 (decitabine) years as compared to 75 (BSC) and 74 (hypomethylating agents) years. All patients had an ECOG performance status ≤2 (equal to Karnofsky Index ≥70). Activities of daily living (ADL) were not assessed.