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Conflict of interest

No conflict of interest.

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Myelodysplastic syndromes with single neutropenia or thrombocytopenia are rarely refractory cytopenias with unilineage dysplasia by World Health Organization 2008 criteria and have favourable prognosis

The World Health Organization 2008 (WHO 2008) classification of myelodysplastic syndrome (MDS) individualized a new 'refractory cytopenia with unilineage dysplasia' (RCUD) category (Brunning *et al*, 2008) in which two subcategories were added to the previous refractory anaemia (RA) classification (WHO 2001; Brunning *et al*, 2001; Jaffe, 2002), i.e. refractory neutropenia (RN) and refractory thrombocytopenia (RT), defined by dysplasia in only one myeloid lineage, and one or

Table I. Patient characteristics.

	IA		IN		IT		All	
N (%)	1142	(79)	134	(9)	169	(12)	1445	(100)
Sex								
Female	572	(50)	58	(43)	67	(40)	697	(48)
Male	570	(50)	76	(57)	102	(60)	748	(52)
Age								
Median (range)	76	(17–99)	68·4	(30–87)	70·2	(26–92)	74·1	(17–99)
Blood count, median (range)								
Haemoglobin, g/l	89	(30–119)	130	(120–159)	132	(120–186)	91	(30–186)
MCV, fL								
ANC, $\times 10^9$/l	3·4	(1·5–28)	0·89	(0·1–1·49)	2·9	(1·5–32)	3	(0·1–32)
Platelet count, 10^9/l	267	(100–1540)	179	(100–419)	65	(2–99)	232	(2–1540)
Country								
France	266	(23)	77	(57)	87	(51)	430	(30)
Germany	523	(46)	4	(3)	8	(5)	535	(37)
Italy	353	(31)	53	(40)	74	(44)	480	(33)
WHO 2001 diagnosis*								
RA	253	(22)	22	(16)	26	(15)	301	(21)
RARS	233	(20)	0	(0)	2	(1)	235	(16)
RCMD	273	(24)	32	(24)	62	(37)	367	(25)
RCMD-RS	87	(8)	2	(1)		(0)	89	(6)
5q-	71	(6)	3	(2)	4	(2)	78	(5)
RAEB-1	125	(11)	26	(19)	33	(20)	184	(13)
RAEB-2	65	(6)	29	(22)	11	(7)	105	(7)
MDS-U	16	(1)	16	(12)	29	(17)	61	(4)
AML/sAML	19	(1)	4	(2)	2	(1)	25	(1)
WHO 2008 diagnosis*								
N (%)	523	(88)	29	(5)	42	(7)	594	(100)
RA	54	(10)	–		–		54	(9)
RN	–		2	(7)	–		2	(0)
RT	–		–		1	(2)	1	(0)
ICUS	–		–		2	(5)	2	(0)
RARS	107	(20)			1	(2)	108	(18)
RCMD	255	(49)	11	(38)	20	(48)	286	(48)
5q-	39	(7)	1	(3)	1	(2)	41	(7)
RAEB-1	35	(7)	10	(34)	12	(29)	57	(10)
RAEB-2	20	(4)	5	(17)	5	(12)	30	(5)
AML	13	(2)	–		–		13	(2)
IPSS category								
Low/int-1	967	(85)	79	(59)	130	(77)	1176	(81)
Int-2-High	81	(7)	33	(25)	14	(8)	128	(9)
Unknown	94	(8)	22	(16)	25	(15)	141	(10)

5q-, 5q- syndrome; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; IA, isolated anaemia; ICUS, isolated cytopenia of unknown significance; IN, isolated neutropenia; Int-1/Int-2, intermediate 1/2; IPSS, international prognostic scoring system; IT, isolated thrombocytopenia; MCV, mean corpuscular volume; MDS-U, myelodysplastic syndrome, unclassifiable; RA, refractory anaemia; RAEB, refractory anaemia with excess blasts; RARS, refractory anaemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RN, refractory neutropenia; RT, refractory thrombocytopenia; sAML, secondary AML; WHO, World Health Organization.

*The WHO 2001 cohort corresponds to the patients diagnosed since the beginning of the registries, who were all classified according to the WHO 2001 classification. The WHO 2008 cohort is the subgroup of patients of the WHO 2001 cohort who have been diagnosed after 2008, and for which the WHO 2008 diagnosis was available.

two cytopenias. However, very few reports have addressed the frequency and clinical relevance of RN and RT, and whether these WHO diagnoses apply to patients with a single blood cytopenia, particularly thrombocytopenia or neutropenia.

Among 1910 MDS patients included in its registry before 2010, the Groupe Francophone des Myelodysplasies (GFM) identified 29 cases of isolated neutropenia (IN; absolute neutrophil count $<1{\cdot}5 \times 10^9$/l) and 38 of isolated thrombocy-

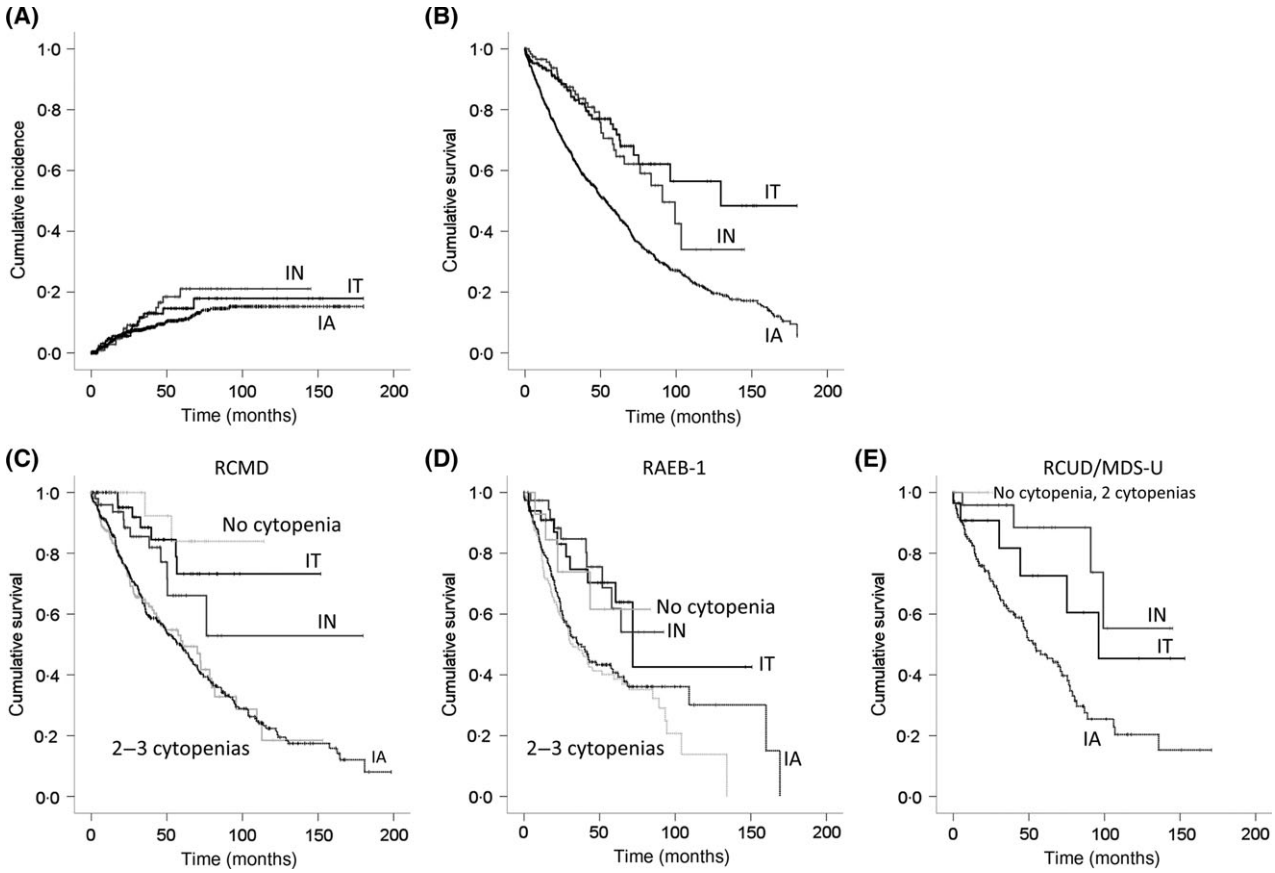

Fig 1. Outcome of patients with an isolated refractory cytopenia (A) Incidence of evolution to acute myeloid leukaemia (AML) in patients without AML at diagnosis. Logrank $P = 0{\cdot}08$. (B) Overall survival. Logrank $P < 0{\cdot}001$. (C) Overall survival of refractory cytopenia with multilineage dysplasia (RCMD) patients according to the type and number of cytopenias. Logrank $P < 0{\cdot}001$. (D) Overall survival of refractory anaemia with excess blasts (RAEB-1) patients according to the type and number of cytopenias. Logrank $P = 0{\cdot}002$. (E) Overall survival of refractory cytopenia with unilineage dysplasia (RCUD) and myelodysplastic syndrome-unclassifiable (MDS-U) according to the nature and number of cytopenias. The 'no cytopenia' and '2 cytopenias' groups curves are superimposed. Logrank $P = 0{\cdot}004$. IA, isolated anaemia (dotted line). IN, isolated neutropenia (dark grey line). IT, isolated thrombocytopenia (solid line). No cytopenias, light grey line. MDS with 2 or 3 cytopenias, light grey dotted line.

topenia (IT; platelet count $<100 \times 10^9$/l), with monocytes $<1 \times 10^9$/l. After a review based on WHO 2008 criteria, the main diagnosis was refractory cytopenia with multilineage dysplasia (RCMD; 37·3%), followed by refractory anaemia with excess blasts, type 1 (RAEB-1; 34·3%) and RAEB-2 (11·9%), while only 3 patients were classified as RCUD (2 RN and 1 RT). An additional cytopenia developed in 20·4% of IN and 40·2% of IT within 3 years ($P = 0{\cdot}12$).

To confirm the rare occurrence of WHO 2008 RN and RT diagnoses, a cooperative study between the GFM, German (Düsseldorf) and Italian Fondazione Italiana per le Sindromi Mielodisplastiche (FISM) MDS registries was conducted, analysing patients with isolated anaemia (IA, defined by haemoglobin level <120 g/l) in addition to those with IN and IT. The three multicentre registries prospectively collected the same minimal data set from records of consenting MDS patients after obtaining Institutional Review Board/ethics committee approval in each individual centre.

Among the patients included in the 3 registries at 1 May 2012, 1445 MDS with a single cytopenia were identified (79% IA, 9% IN, 12% IT; Table I). Median age was 76, 68·4 and 70·2 years in the IA, IN and IT groups, respectively ($P < 0{\cdot}001$, ANOVA test).

The most frequent WHO 2001 diagnosis in the whole 1445 group and in the 3 IA, IN and IT subgroups was RCMD (representing 25%, 24%, 24% and 37% of the patients, respectively), followed by RA (16% of IA), RAEB-2 (22% of IN) and RAEB-1 (20% of IT). MDS unclassifiable (MDS-U) was diagnosed in 1% of IA, 12% of IN and 18% of IT. The International Prognostic Scoring System (IPSS) category (Greenberg *et al*, 1997) was Low/Int-1 (81%), Int-2/High (9%) and undetermined (10%) due to missing or failed cytogenetics.

In the 594 patients diagnosed with single cytopenia after 2008 and thus also classified by WHO 2008 criteria, the most frequent diagnosis was still RCMD (48% of all patients, 49% IA, 38% IN, and 48% IT), followed by refractory anaemia with ringed sideroblasts (RARS) for IA (20%), and RAEB-1 for both IN (34%) and IT (20%). RA accounted for only 10% of patients with IA, RN for 2 (7%) of 29 IN, and RT

for 1 (2%) of 42 IT. Additionally, 2 idiopathic cytopenia of unknown significance were diagnosed in the IT group.

Median follow-up of the whole 1445 patient cohort was 31·6 months. After exclusion of the 25 patients with acute myeloid leukaemia (AML) at diagnosis, the probability of AML evolution at 2 years was 10·9%, 21·1% and 14·6% for IA, IN, and IT, respectively, with no significant difference (Log rank $P = 0{\cdot}08$, Fig 1A). Overall survival of the IA group was significantly shorter than that of the IN and the IT groups (median 53·4, 91 and 129 months, respectively $P < 0{\cdot}001$, Fig 1B), reflecting the unfavourable prognosis of isolated anaemia, which was independent of age and IPSS in multivariate analysis (data not shown).

Results of this large collaborative study show that the most frequent WHO 2008 diagnoses in patients with IN or IT are RCMD and RAEB-1, while RCUD is very rare. In a report from the Düsseldorf group, RN and RT accounted for only 9% and 6%, respectively, of RCUD cases, with no prognostic difference between RT, RN and RA (Maassen *et al*, 2013).

Although generally classified as relatively poor prognosis RCMD or RAEB-1 subtypes, IN and IT had a low rate of AML progression (8·9% at 3 years) and relatively prolonged survival (82·2% at 3 years), comparable to the 75% survival at 3 years previously described for RCUD in the Pavia cohort (Cazzola, 2011). On the other hand, Verburgh *et al* (2007) reported a median survival was 109 months in patients with a single cytopenia and unilineage marrow dysplasia, whereas it was poorer in patients with multilineage dysplasia regardless of the number of cytopenias.

Overall survival of IN and IT was significantly better than that of IA, although IA patients did not have a higher rate of AML progression. This observation confirms the poor prognostic significance of anaemia in lower risk MDS, at least when red blood cell transfusion is present (Cazzola & Malcovati, 2005). By comparison with the whole RCMD group of the GFM registry, patients with IT or IN and a RCMD diagnosis had better survival than those with two or more cytopenias ($P < 0{\cdot}001$), and was similar to that of patients with IA (Fig 1C). The same observation was true for RAEB-1 ($P = 0{\cdot}002$, Fig 1D). For WHO 2008 RCUD and WHO 2001 MDS-U, IT and IN had a longer survival than IA ($P = 0{\cdot}004$, Fig 1E), but patients with 2 cytopenias were too few ($n = 5$) for further comparison.

Our study therefore questions the frequency of RCUD, a category introduced by WHO 2008 classification for patients with one dysplastic lineage and one or 2 cytopenias, as most patients with a single cytopenia were classified as RCMD. The good prognostic value of a single cytopenia is already taken into account by both the IPSS (Greenberg *et al*, 1997) and its revised version (Greenberg *et al*, 2012) for clinical decision-making. Further molecular studies of these particular forms of MDS may help understand their significance.

Altogether, our results show that WHO 2008-defined RN and RT (and to a lesser extent RA), are rare in MDS patients with IN, IT and IA, and that MDS patients with a single cytopenia, especially IN and IT, are mostly classified as RCMD using WHO 2008 criteria. If confirmed in non-Caucasian groups, these results would encourage RCUD and RCMD to be merged together in future WHO classifications.

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Author contribution

E.G. coordinated the clinical part of the study, reviewed and analysed the data, contributed patients and wrote the paper. V.A. coordinated the morphological part of the study, reviewed and analysed the data, and wrote the paper. A.S. and V. Santini coordinated the Italian contribution, reviewed the data and revised the manuscript. A.C. analysed the data, wrote the manuscript. I.S., and V. Siguret performed the centralized bone marrow smear review, reviewed the manuscript. P.F contributed patients, wrote the paper. U.G. coordinated the German contribution, reviewed the data and revised the manuscript. All other authors contributed patients, revised the paper and approved the final version of the manuscript.

Conflict of interest

None of the authors have a conflict of interest relative to the subject of the paper.

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