Published in final edited form as:

Am J Hematol. 2013 May ; 88(5): 365–369. doi:10.1002/ajh.23410.

Prognostic impact of *RAS* mutations in patients with myelodysplastic syndrome

Aref Al-Kali^{1,2}, Alfonso Quintás-Cardama¹, Raja Luthra³, Carlos Bueso-Ramos³, Sherry Pierce¹, Tapan Kadia¹, Gautam Borthakur¹, Zeev Estrov¹, Elias Jabbour¹, Stefan Faderl¹, Farhad Ravandi¹, Jorge Cortes¹, Ayalew Tefferi², Hagop Kantarjian¹, and Guillermo Garcia-Manero^{1,*}

¹Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas

²Department of Hematology, Mayo Clinic, Rochester, Minnesota

³Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Abstract

RAS is an oncogene frequently mutated in human cancer. *RAS* mutations have been reported in 10–15% of cases of acute myeloid leukemia (AML) but they appear to be less frequent among patients with myelodysplastic syndrome (MDS). The impact of *RAS* mutations in patients with MDS is unclear. We conducted a retrospective study in 1,067 patients with newly diagnosed MDS for whom *RAS* mutational analysis was available. Overall, 4% of patients carried mutant *RAS* alleles. Notably, FLT3 mutations, which were found in 2% of patients, were mutually exclusive with *RAS* mutations. Patients with *RAS* mutations had a higher white blood cell count as well as bone marrow blasts compared with patients carrying wild-type *RAS*. However, no differences were observed between both groups regarding the risk of AML transformation (9% vs. 7%) and overall survival (395 days vs. 500 days, $P = 0.057$). In summary, *RAS* mutations are infrequent in patients with MDS and do not appear to negatively impact their outcome.

Introduction

Processes such as cell proliferation, differentiation, apoptosis, self-renewal, cell cycle checkpoint control, DNA repair and genomic stability underpin the pathogenesis of myeloid malignancies. Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are

© 2013 Wiley Periodicals, Inc.

*Correspondence to: Guillermo Garcia-Manero, Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 428, Houston, TX 77030. ggarciam@mdanderson.org.

Additional Supporting Information may be found in the online version of this article.

Partially presented in abstract form at the 52nd annual meeting of the American Society of Hematology, Orlando, FL Dec 4–7th 2010.

Conflict of interest: Nothing to report

Author Contributions

A.A. provided patient care, collected data, analyzed data, and wrote the manuscript; A.Q. analyzed data and wrote the manuscript; R.L. and C.B.R. performed molecular work and reviewed the manuscript; S.P. performed statistical analysis and reviewed the manuscript; T.K., G.B., Z.E., E.J., S.F., F.R., J.C., and H.K. provided patient care and reviewed the manuscript; G.G.-M. provided patient care, designed research, analyzed data, and wrote the manuscript.

characterized by the presence of an array of cytogenetic aberrations and mutations involving genes that regulate the homeostasis of all the aforementioned processes [1,2] Mutations in a series of genes have been recently described in patients with AML, including *nucleophosmin member 1 (NPM1)* [3], *fms-related tyrosine kinase 3 (FLT3)* [4–6], *KIT* [7], *RAS* [8–11], *CCAAT/enhancer-binding-protein-alpha (C/EBPα)*, *TET2* [12], *mixed-lineage leukemia (MLL)* [13] *isocitrate dehydrogenase 1 and 2 (IDH1/2)* [14,15], and *p53* [9,16]. These gene mutations have not only improved our ability to more accurately predict the prognosis of patients with AML but also have provided novel targets for therapeutic intervention. Unlike AML, where gene mutations are frequently seen, point mutations are rarely present in MDS, with the exception of *TET2*, which can be detected in approximately 20% of cases. Although the prognostic impact of gene mutations has been extensively studied in patients with AML, limited information is available regarding the prognosis of patients with MDS carrying *RAS* mutations [17–25]. *RAS* mutations have been shown to promote cell proliferation and be associated with a higher risk of progression to AML and worse prognosis [20,26,27].

The reported incidence of *RAS* mutations ranges widely between 2 and 48% [17–25] However, most large cohorts have reported the presence of *RAS* mutations in approximately 10% of patients [28] In addition, *N-RAS* has been found mutated and constitutively activated in 10% of patients with AML, whereas *K-RAS* is mutated in 5% of patients and *H-RAS* is rarely mutated in AML [29,30] The *RAS* proto-oncogene belongs to the small GTPase family and exists in three distinct isoforms, *N-RAS*, *K-RAS*, and *H-RAS* [30] Most oncogenic *RAS* mutations found in human cancers, including AML, occur at codons 12, 13, and 61. However, mutations at alternate codons have also been reported [30,31] *RAS* regulates the growth and differentiation of many cell types [32]. *RAS* mutations constitutively activate the *RAS* signaling pathway by increasing the intracellular levels of *RAS* GTP, which in turn activates the *RAS*/Raf/MEK and the *RAS*/PI3K signaling pathways via interaction with many effectors including Raf proteins, phosphoinositide-3-OH kinase, and RalGDS. In mice, oncogenic *N-RAS* or *K-RAS* has been shown to be sufficient to induce AML or a myeloproliferative disorder that resembles chronic myelomonocytic leukemia (CMML) [33–35]. This phenomenon has been shown to take place in hematopoietic stem cells rather than in the common myeloid progenitor [36].

DNA hypomethylating agents constitute standard therapy for patients with MDS. The impact of *RAS* mutational status on response to these agents is unknown [37,38]. In this report, we describe the incidence and type of *RAS* mutations in 1,067 evaluable patients with MDS diagnosed at The University of Texas MD Anderson Cancer Center and we analyze the impact of these mutations on prognosis in the context of a variety of MDS therapies, including DNA hypomethylating agents.

Patients and Methods

A retrospective review was done to identify all patients newly diagnosed with MDS at MD Anderson between 2000 and 2009. The analysis followed institutional guidelines. The diagnosis of MDS was based on the French American British classification [39]. Response rate was coded based on the modified International Working Group criteria [40].

RAS, *FLT3* [tyrosine kinase domain (TKD) or internal tandem duplication (ITD)], *KIT*, and *JAK2* gene mutational status was assessed by PCR on bone marrow aspirates as previously described [5,26,41]. Cytogenetics were assessed on at least 20 metaphases of each cell type obtained from bone marrow aspirates as previously described [41]. The International Prognostic Scoring System (IPSS) was calculated for each patient [42]. Overall survival (OS) was calculated by the Kaplan- Meier method, while the *t*-test was used to estimate differences between two groups (*RAS* mutated vs. wild type).

Results

Patient characteristics

A total of 1,075 patients with MDS were diagnosed and treated at our institution over the last 10 years. *RAS* mutational analysis was available in all but eight patients. Forty-three (4%) of 1,067 patients were found to carry a *RAS* mutation. In the *RAS* mutated group, the median age was 66 years with 27/43 (63%) being males. The white blood cell count was higher in the *RAS* mutated group (median $6.8 \times 10^9/\text{dL}$) compared to the wild type group ($3.2 \times 10^9/\text{dL}$) ($P < 0.001$ by Mann-Whitney median test). A similar trend was observed regarding bone marrow blast burden (9% vs. 5%, $P < 0.001$). Most patients carrying *RAS* mutations had high-risk MDS [RAEB, RAEB-t, and CMML; 38 (88%) patients]. The rates of leukemic transformation were similar in the *RAS* wild-type and the *RAS* mutated groups (7% vs. 9%, $P = 0.61$). Patient characteristics are shown in Table I.

Thirty-four (79%) out of 43 *RAS* mutation carriers had an *N-RAS* mutation. *RAS* mutations were not detected in RARS, RCMD-RS, or MDS-U, while only one of the patients with RA had an *N-RAS* mutation. Eighteen (2%) of 1027 patients carried *FLT3* mutations (ITD or TKD), which did not overlap with *RAS* mutations. The *JAK2*^{V617F} mutation was detected in nine of 37 patients with *RAS* mutations, including two of three patients with 5q- syndrome. *RAS* mutations were detected at 4% in patients with diploid cytogenetics and those carrying cytogenetic abnormalities (19/511 and 24/556, respectively). *RAS* mutations clustered in patients with CMML [12 out of 80 (15%) patients] compared to other MDS groups (4%). Of note, no cases of myeloproliferative CMML (WBC count $13 \times 10^9/\text{dL}$) [27] were found. Five of 68 patients with wild type *RAS* transformed into AML while no transformations were observed among patients in the *RAS* mutated group ($P = 0.33$). Most patients in both groups had diploid cytogenetics. Additional information regarding distribution of mutations based on WHO classification, cytogenetics and CMML and clinical outcomes are shown in Supporting Information Tables SI–SIII.

Impact of *RAS* mutations on response to therapy

Next, we evaluated the impact of *RAS* mutations in response to MDS-directed therapy. Patients with MDS carrying wild type *RAS* alleles achieved similar response rates compared to their *RAS* mutated counterparts (42% vs 43%) (2 5). A complete response (CR) was attained by five of 14 (36%) patients with mutated *RAS* compared to a CR rate of 40% observed in the cohort of 236 patients harboring wild type *RAS* ($P 0.74$). When analyzing response rates in relation to the type of MDS therapy, patients with mutated *RAS* did not appear to achieve significantly different response rates compared to those carrying wild-type

RAS alleles after therapy with hypomethylating agents (40% vs. 41%), clofarabine (67% vs. 46%), or cytarabine-based therapy (25% vs. 59%) (Supporting Information Table SIV). However, the small number of patients with mutated *RAS* treated with each type of therapy was too small to draw any definite conclusions.

Impact of *RAS* mutations on survival

Importantly, in spite of no apparent differences regarding response rates, a trend towards a worse OS was observed among patients in the *RAS* mutated group compared to that of patients harboring wild type *RAS* (395 days vs. 500 days, $P = 0.057$) (Table II and Fig. 1). Furthermore, the presence of *RAS* mutations was associated with a trend towards a shorter OS across all MDS subgroups compared with their wild type counterparts (Fig. 2). That trend was statistically significant among patients with RCMD carrying *RAS* mutations ($P = 0.00045$). However, the importance of this finding is undermined by the small number of patients with RCMD carrying *RAS* mutations included in the analysis. No differences regarding OS were observed between patients with CMML carrying *RAS* mutations and those carrying wild type *RAS* alleles (728 days vs. 687 days, $P = 0.44$).

Discussion

Gene mutations have been intensely investigated in myeloid neoplasms, particularly in patients with AML. However, their importance in patients with MDS has not been completely defined. In the present study, *FLT3* and *RAS* mutations were infrequently found (less than 10% of patients) in MDS compared to a reported incidence of approximately 35% for *FLT3* mutations among patients with AML. Several gene mutations have been found to be predictive of OS among patients with AML and have been incorporated into models to refine the prognosis of patients with intermediate cytogenetics. However, none of the molecular markers used in AML are currently included in prognostic models for MDS. We herein report the largest cohort of patients with MDS assessed for the presence of *RAS* mutations to date. *RAS* mutations were infrequently detected, being present in only 4% of patients, which is not dissimilar to the mutational frequencies previously reported in two other relatively large studies (over 200 patients) of patients with MDS in which *RAS* mutations were found in 6.3 and 9% of patients, respectively [18,28]. As previously reported [28], *RAS* mutations were more frequent in patients with CMML, with an incidence of 12%. The use of next-generation sequencing technology has allowed the detection of *N-RAS* and *K-RAS* mutations in 22 and 12% of patients with CMML, respectively [43], suggesting that *RAS* mutations in CMML are more frequent occurrences than previously appreciated. Interestingly, none of the patients with CMML in our series were hyperproliferative (i.e., WBC count $>12 \times 10^9/\text{dL}$), in contrast with previous reports [27,44]. Gelsi-Boyer et al. [45], reported an incidence of *RAS* mutations of 46% in patients with myeloproliferative CMML but none in patients with myelodysplastic CMML. However, patients carrying *RAS* mutations had a higher WBC than those with wild type *RAS* (6.8 vs. 3.2) as well as a higher bone marrow blast burden (9% vs. 5%) which translated into a higher risk MDS category in the *RAS* mutated group compared to the wild type group (89% vs. 59%). This is in keeping with previous series reporting a higher incidence of *RAS* mutations among patients with high-risk MDS [28]. Interestingly, no *RAS* mutations were detected in low risk MDS with

ringed sideroblasts (RARS or RCMD-R). Similar to previously reported series, mutations at codon 12 of *N-RAS* were the *RAS* mutations more frequently detected (24 of 43 cases), followed by mutations at codon 12 of *K-RAS* (nine of 24 cases) [20,46]. Typically, *RAS* mutations clustered preferentially in patients with diploid cytogenetics. *FLT3* mutations (ITD and TKD) were uncommon, being detected in only 2% of cases, and they did not overlap with *RAS* mutations.

No apparent difference was observed regarding response to therapy according to *RAS* mutational status, with overall response rates in the wild type and mutated *RAS* groups of 42 and 43%, respectively. Importantly, the presence of *RAS* mutations did not appear to impair the ability of responding to any type of therapy employed in the management of patients with MDS (e.g., hypomethylating agents, clofarabine, or cytarabine-based therapy). For instance, around 40% of all CRs were attained by patients that received therapy with hypomethylating agents (i.e., azacytidine and decitabine) in both groups. However, solid conclusions regarding the impact of *RAS* mutations in therapy response could not be confidently drawn given the small number of patients in the *RAS* mutated group. Importantly, *RAS* mutational status did not impact significantly patient survival in any of the MDS categories evaluated, although a trend was observed towards worse OS among patients with *RAS* mutated MDS as a whole, which was statistically significant only among patients with RCMD. However, this latter group only included three patients. Of note, despite the relatively high incidence of *RAS* mutations observed among patients with CMML, the former did not appear to impact significantly OS compared with the cohort of patients with CMML carrying wild-type *RAS* alleles.

In summary, *RAS* mutations are infrequent events in patients with MDS that identify a specific subset of patients with higher WBC count and bone marrow blast burden. The presence of *RAS* mutations does not appear to significantly impact response or OS compared with their wild type counterparts. However, the use of agents specifically targeting an overactivated *RAS* pathway (e.g., MEK inhibitors), such as in cases of *RAS* mutations, might selectively improve the outcomes of this subset of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by grant RP100202 from the Cancer Prevention & Research Institute of Texas, the Ruth and Ken Arnold Fund (GGM), the MD Anderson Cancer Center Leukemia SPORE grant CA100632, and the MD Anderson Cancer Center Support Grant (CCSG) CA016672.

References

1. Kelly LM, Gilliland DG. Genetics of myeloid leukemias. *Annu Rev Genom Hum Genet.* 2002; 3:179–198.
2. Garcia-Manero G. Myelodysplastic syndromes: 2012 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2012; 87:692–701. [PubMed: 22696212]
3. Falini B, Mecucci C, Tiacci E, et al. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. *N Engl J Med.* 2005; 352:254–266. [PubMed: 15659725]

4. Frohling S, Schlenk RF, Breitruck J, et al. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: A study of the AML Study Group Ulm. *Blood*. 2002; 100:4372–4380. [PubMed: 12393388]
5. Beran M, Luthra R, Kantarjian H, et al. FLT3 mutation and response to intensive chemotherapy in young adult and elderly patients with normal karyotype. *Leuk Res*. 2004; 28:547–550. [PubMed: 15120929]
6. Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. *Blood*. 2002; 100:1532–1542. [PubMed: 12176867]
7. Paschka P, Marcucci G, Ruppert AS, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): A Cancer and Leukemia Group B Study. *J Clin Oncol*. 2006; 24:3904–3911. [PubMed: 16921041]
8. Bacher U, Haferlach T, Schoch C, et al. Implications of NRAS mutations in AML: A study of 2502 patients. *Blood*. 2006; 107:3847–3853. [PubMed: 16434492]
9. Stirewalt DL, Kopecky KJ, Meshinchi S, et al. FLT3, RAS, and TP53 mutations in elderly patients with acute myeloid leukemia. *Blood*. 2001; 97:3589–3595. [PubMed: 11369655]
10. Beaupre DM, Kurzrock R. RAS and leukemia: From basic mechanisms to gene-directed therapy. *J Clin Oncol*. 1999; 17:1071–1079. [PubMed: 10071302]
11. Radich JP, Kopecky KJ, Willman CL, et al. N-ras mutations in adult de novo acute myelogenous leukemia: Prevalence and clinical significance. *Blood*. 1990; 76:801–807. [PubMed: 2200539]
12. Delhommeau F, Dupont S, Della Valle V, et al. Mutation in TET2 in myeloid cancers. *N Engl J Med*. 2009; 360:2289–2301. [PubMed: 19474426]
13. Whitman SP, Ruppert AS, Marcucci G, et al. Long-term disease-free survivors with cytogenetically normal acute myeloid leukemia and MLL partial tandem duplication: A Cancer and Leukemia Group B study. *Blood*. 2007; 109:5164–5167. [PubMed: 17341662]
14. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med*. 2009; 361:1058–1066. [PubMed: 19657110]
15. Marcucci G, Maharry K, Wu YZ, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: A Cancer and Leukemia Group B study. *J Clin Oncol*. 28:2348–2355. [PubMed: 20368543]
16. Bowen D, Groves MJ, Burnett AK, et al. TP53 gene mutation is frequent in patients with acute myeloid leukemia and complex karyotype, and is associated with very poor prognosis. *Leukemia*. 2009; 23:203–206. [PubMed: 18596741]
17. Nakagawa T, Saitoh S, Imoto S, et al. Multiple point mutation of N-ras and K-ras oncogenes in myelodysplastic syndrome and acute myelogenous leukemia. *Oncology*. 1992; 49:114–122. [PubMed: 1574246]
18. Paquette RL, Landaw EM, Pierre RV, et al. N-ras mutations are associated with poor prognosis and increased risk of leukemia in myelodysplastic syndrome. *Blood*. 1993; 82:590–599. [PubMed: 8329714]
19. Mitani K, Hangaishi A, Imamura N, et al. No concomitant occurrence of the N-ras and p53 gene mutations in myelodysplastic syndromes. *Leukemia*. 1997; 11:863–865. [PubMed: 9177441]
20. Padua RA, Guinn BA, Al-Sabah AI, et al. RAS, FMS and p53 mutations and poor clinical outcome in myelodysplasias: A 10-year follow-up. *Leukemia*. 1998; 12:887–892. [PubMed: 9639416]
21. Bowen DT, Frew ME, Hills R, et al. RAS mutation in acute myeloid leukemia is associated with distinct cytogenetic subgroups but does not influence outcome in patients younger than 60 years. *Blood*. 2005; 106:2113–2119. [PubMed: 15951308]
22. Kosmider O, Gelsi-Boyer V, Cheok M, et al. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). *Blood*. 2009; 114:3285–3291. [PubMed: 19666869]
23. Langemeijer SM, Kuiper RP, Berends M, et al. Acquired mutations in TET2 are common in myelodysplastic syndromes. *Nature genetics*. 2009; 41:838–842. [PubMed: 19483684]
24. Kosmider O, Gelsi-Boyer V, Slama L, et al. Mutations of IDH1 and IDH2 genes in early and accelerated phases of myelodysplastic syndromes and MDS/myeloproliferative neoplasms. *Leukemia*. 2010; 24:1094–1096. [PubMed: 20376084]

25. Boultonwood J, Perry J, Pellagatti A, et al. Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. *Leukemia*. 2010; 24:1062–1065. [PubMed: 20182461]
26. Kadia T, Kornblau SM, Kantarjian H, et al. Clinical Characterization and Proteomic Consequences of Mutated Ras in Acute Myeloid Leukemia. *ASH Annual Meeting, New Orleans Abstracts*. 2009; 114:330.
27. Ricci C, Fermo E, Corti S, et al. RAS mutations contribute to evolution of chronic myelomonocytic leukemia to the proliferative variant. *Clin Cancer Res*. 16:2246–2256. [PubMed: 20371679]
28. Bacher U, Haferlach T, Kern W, et al. A comparative study of molecular mutations in 381 patients with myelodysplastic syndrome and in 4130 patients with acute myeloid leukemia. *Haematologica*. 2007; 92:744–752. [PubMed: 17550846]
29. Valk PJ, Verhaak RG, Beijnen MA, et al. Prognostically useful gene-expression profiles in acute myeloid leukemia. *N Engl J Med*. 2004; 350:1617–1628. [PubMed: 15084694]
30. Tyner JW, Erickson H, Deininger MW, et al. High-throughput sequencing screen reveals novel, transforming RAS mutations in myeloid leukemia patients. *Blood*. 2009; 113:1749–1755. [PubMed: 19075190]
31. Le DT, Shannon KM. Ras processing as a therapeutic target in hematologic malignancies. *Curr Opin Hematol*. 2002; 9:308–315. [PubMed: 12042705]
32. Schubbert S, Shannon K, Bollag G. Hyperactive Ras in developmental disorders and cancer. *Nat Rev*. 2007; 7:295–308.
33. Zhang J, Wang J, Liu Y, et al. Oncogenic Kras-induced leukemogenesis: Hematopoietic stem cells as the initial target and lineage-specific progenitors as the potential targets for final leukemic transformation. *Blood*. 2009; 113:1304–1314. [PubMed: 19066392]
34. Braun BS, Tuveson DA, Kong N, et al. Somatic activation of oncogenic Kras in hematopoietic cells initiates a rapidly fatal myeloproliferative disorder. *Proc Natl Acad Sci USA*. 2004; 101:597–602. [PubMed: 14699048]
35. Parikh C, Subrahmanyam R, Ren R. Oncogenic NRAS rapidly and efficiently induces CMML- and AML-like diseases in mice. *Blood*. 2006; 108:2349–2357. [PubMed: 16763213]
36. Sabnis AJ, Cheung LS, Dail M, et al. Oncogenic Kras initiates leukemia in hematopoietic stem cells. *PLoS Biol*. 2009; 7:e59. [PubMed: 19296721]
37. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study. *Lancet Oncol*. 2009; 10:223–232. [PubMed: 19230772]
38. Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood*. 2007; 109:52–57. [PubMed: 16882708]
39. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol*. 1982; 51:189–199. [PubMed: 6952920]
40. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006; 108:419–425. [PubMed: 16609072]
41. Hirsch-Ginsberg C, LeMaistre AC, Kantarjian H, et al. RAS mutations are rare events in Philadelphia chromosome-negative/bcr gene rearrangement-negative chronic myelogenous leukemia, but are prevalent in chronic myelomonocytic leukemia. *Blood*. 1990; 76:1214–1219. [PubMed: 2205309]
42. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997; 89:2079–2088. [PubMed: 9058730]
43. Kohlmann A, Grossmann V, Klein HU, et al. Next-generation sequencing technology reveals a characteristic pattern of molecular mutations in 72.8% of chronic myelomonocytic leukemia by detecting frequent alterations in TET2, CBL, RAS, and RUNX1. *J Clin Oncol*. 2010; 28:3858–3865. [PubMed: 20644105]
44. Onida F, Beran M. Chronic myelomonocytic leukemia: Myeloproliferative variant. *Curr Hematol Rep*. 2004; 3:218–226. [PubMed: 15087071]

45. Gelsi-Boyer V, Trouplin V, Adelaide J, et al. Genome profiling of chronic myelomonocytic leukemia: Frequent alterations of RAS and RUNX1 genes. *BMC Cancer*. 2008; 8:299. [PubMed: 18925961]
46. van Kamp H, de Pijper C, Verlaan-de Vries M, et al. Longitudinal analysis of point mutations of the N-ras proto-oncogene in patients with myelodysplasia using archived blood smears. *Blood*. 1992; 79:1266–1270. [PubMed: 1536950]

Figure 1.
OS status for all patients with MDS.

Figure 2.

OS of different MDS subtypes, according to *RAS* mutational analysis. A) RCMD, refractory anemia with multilineage dysplasia; B) RAEB, refractory anemia with excess blasts; C) RAEB-T, refractory anemia with excess blasts in transformation; D) CMML, chronic myelomonocytic leukemia.

TABLE I

Patient and Disease Characteristics According to *RAS* Mutational Status

MDS	<i>RAS</i> -wild type	<i>RAS</i> -mutated	All patients
No.	1,024	43	1,067
Age, median	68	66	68
Range	18–94	26–84	18–94
Sex (No. [%])			
Male	676 (66)	27 (63)	703 (66)
Female	348 (34)	16 (37)	364 (34)
AML	73 (7)	4 (9)	77 (7)
WBC ($\times 10^9/L$)			3.3
Median range	3.2 0.3–72.2	6.8 0.7–66.4	0.3–72.2
Hemoglobin (g/dL)			9.8
Median range	9.8 3–17.5	9.4 6.3–13.2	3–17.5
Platelets ($\times 10^9/L$)			73
Median range	75 1–1,040	51 1–382	1–1,040
Bilirubin	0.6	0.6	0.6
Creatinine	1	1	1
BM blasts (%)	5	9	5
FAB (No. [%])			
RCMD-R	47 (5)	0	47 (4)
RCMD	165 (16)	3 (7)	168 (16)
RARS	50 (5)	0	50 (5)
RAEB-T	87 (8)	8 (19)	95 (9)
RAEB	453 (44)	18 (42)	471 (44)
RA	123 (12)	1 (2)	124 (12)
MDS-U	18 (2)	0	18 (2)
CMML	68 (7)	12 (28)	80 (7)
5q-	13 (1)	1 (2)	14 (1)
IPSS (No. [%])			
High	142 (14)	9 (21)	151 (14)
Int-2	269 (26)	13 (30)	282 (26)
Int-1	389 (38)	15 (35)	404 (38)
Low	201 (20)	4 (9)	205 (19)
UN	23 (2)	2 (5)	25 (2)

No.: number of patients, FAB: French American British, IPSS: international prognostic scoring system, UN: unknown.

TABLE IIOverall Survival According to *RAS* Mutational Status

MDS subtype	<i>RAS</i> wild-type	<i>RAS</i> mutated	<i>P</i> value
MDS	500	395	0.057
RCMD	700	150	0.0045
RAEB	450	325	0.13
RAEB-T	375	125	0.27
CMML	687	728	0.44

Overall survival is reported in days.