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A Phase II Study of the Oral VEGF Receptor Tyrosine Kinase Inhibitor Vatalanib (PTK787/ZK222584) in Myelodysplastic Syndrome: Cancer and Leukemia Group B Study 10105 (Alliance)

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Abstract

Background—Angiogenesis is implicated in the pathophysiology and progression of myelodysplastic syndromes (MDS). Vatalanib (PTK787/ZK222584; Novartis and Schering AG) inhibits receptor tyrosine kinases of vascular endothelial growth factor, platelet derived growth factor and c-Kit. We examined whether vatalanib induces hematological responses in MDS and/or delays progression to acute myeloid leukemia (AML) or death.

Methods—Two cohorts were studied. Vatalanib 1250 mg orally was given once daily (cohort 1) or 750–1250 mg once daily in an intra-patient dose escalating schedule (cohort 2) in 28-day cycles to 155 patients with MDS; 142 patients were evaluable for response and 153 for toxicity.

Results—The median age was 70.5 years; 51% had low risk (International Prognostic Scoring System {IPSS} Low/Intermediate-1) and 32% had high risk (IPSS Intermediate-2/High) MDS. Hematological improvement was achieved in 7/142 (5%) patients; all 7 were among the 47 patients able to remain on vatalanib for at least 3 months (hematological improvement achieved in 15% of these 47 patients). For patients with low risk and high risk MDS, respectively, median progression-free survivals were 15 and 6 months, median times to transformation to AML were 28 and 6 months, and median overall survivals were 36 and 10 months. The most frequent non-hematological adverse events grade ≥2 were fatigue, nausea or vomiting, dizziness, anorexia, ataxia, diarrhea, and pain. Two deaths (one intra-cerebral hemorrhage and one sudden death) were possibly related to vatalanib.

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Conclusions—Vatalanib induces improvement in blood counts in a small proportion of MDS patients. Clinical applicability is limited by side effects.

Keywords

Angiogenesis inhibitors; humans; myelodysplastic syndromes; treatment outcome; vascular endothelial growth factor

Introduction

The myelodysplastic syndromes (MDS) are clonal hematopoietic disorders that mainly affect older adults and are characterized by morphological dysplasia, ineffective hematopoiesis resulting in cytopenias, and an increased propensity to develop acute myeloid leukemia (AML) [1]. Death often results from the consequences of chronic cytopenias or from transformation to AML. Novel, preferably oral, drugs that are capable of both acting on the pathophysiological mechanisms underlying MDS and that can be tolerated by older and sometimes frail patients are needed.

Angiogenesis is critical for the viability, growth, and metastases of solid tumors. Identification of increased microvessel density in MDS and in leukemias suggests that angiogenesis may play an important role in the pathophysiology of hematological malignancies as well [2,3]. Plasma levels of angiogenic growth factors including vascular endothelial growth factor (VEGF) are elevated in MDS [2]. VEGF produced by the malignant clone appears to stimulate both angiogenesis (paracrine effect) and growth of the malignant cell itself (autocrine effect), and its expression has prognostic significance [4]. VEGF and its receptors are expressed by malignant myeloblasts [5–9]. VEGF also stimulates matrix metalloproteinase-induced cleavage and release of inflammatory cytokines and apoptotic mediators, factors that may contribute to the pathophysiology of MDS [10–12]. Finally, VEGF strongly induces endothelial production of cytokines that may stimulate leukemia cell growth, including granulocyte-macrophage colony stimulating factor (CSF), granulocyte-CSF, macrophage-CSF, stem cell factor/kit ligand (SCF/KL), interleukins (IL)-6 and −7, and flt3-ligand [6,8,13,14]. In contrast to leukemic cells, VEGF has no effect on the growth of normal hematopoietic progenitors [9]. Inhibition of VEGF receptor tyrosine kinases (RTKs) and other cytokines including platelet derived growth factor (PDGF) and SCF/KL may therefore have both anti-angiogenic and direct anti-leukemic effects.

Angiogenesis inhibitors have attractive features including a unique mechanism of action, relative lack of resistance and toxicity, and the potential to be combined with chemotherapeutic agents. However, many anti-angiogenic agents previously tested in MDS, including the anti-VEGF antibodies and the VEGF RTK inhibitor SU5416, have disadvantages such as the need for intravenous administration. Further, anti-VEGF antibodies are foreign proteins, and do not have the potential to inhibit other RTKs such as PDGF-R and c-Kit which may be important in the pathogenesis of myeloid malignancies. An RTK inhibitor that is orally administered and well tolerated would therefore be an attractive agent in MDS.

Vatalanib (PTK787/ZK222584: 4-chlorophenyl)-(4-pyridin-4-ylmethylphthalazin-1-yl)amine succinate; Novartis Pharmaceuticals, Inc./Schering AG] is an orally bioavailable, selective inhibitor of all three VEGF RTKs (VEGF-R1 [Flt-1], VEGF-R2 [KDR] and VEGF-R3 [Flt-4]), the PDGF receptor (PDGF-R) and c-Kit kinases [15–17]. It does not inhibit other kinases, and has no cytotoxic or anti-proliferative activity on cells that do not express VEGF receptors [17]. Vatalanib inhibits VEGF and PDGF-induced angiogenesis in

animal models [17], and early reports indicated efficacy in several malignancies in humans [18,19]. Based on this rationale, the Cancer and Leukemia Group B (CALGB) conducted a multi-center phase II study to evaluate the efficacy and tolerability of vatalanib as a single agent in MDS.

Patients and Methods

Patient eligibility

Patients diagnosed with primary or therapy-related (secondary) MDS, as defined by the World Health Organization 2001 criteria [20], were eligible for this study. Patients with "low risk" MDS, including those with refractory anemia (RA), RA with ring sideroblasts (RARS), refractory cytopenias with multilineage dysplasia (RCMD), RCMD-RS, MDS-unclassified, or MDS associated with isolated del(5q), were required to have at least one of the following criteria necessitating treatment: hemoglobin <10 g/dL, platelets <50,000/μL, or absolute neutrophil count (ANC) <1,000/μL. Patients with RA with excess blasts (RAEB)-1, RAEB-2, chronic myelomonocytic leukemia (CMML)-1 or −2 were eligible irrespective of blood counts. Enrollment of patients with "high risk" MDS (RAEB-2 or CMML-2) was discontinued for lack of efficacy on November 30, 2006, after enrollment of 32 patients. Peripheral blood smears, bone marrow aspirate and biopsy slides, and cytogenetic studies were obtained prior to initiation of vatalanib and were reviewed centrally. Detailed eligibility criteria are provided in Online Resource 1A. The study was approved by the human subjects committee at each participating institution. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines.

Treatment plan

Vatalanib, manufactured by Schering AG as a 250 mg tablet, was provided by Novartis Pharmaceuticals. The initial cohort of patients enrolled prior to January 15, 2005 (cohort 1) received vatalanib 1250 mg orally once daily on a 28-day cycle. In an attempt to improve drug tolerability, a second cohort of patients was enrolled after January 15, 2005 (cohort 2: dose escalation cohort). For these patients, vatalanib was administered orally at a starting dose of 750 mg daily (dose level −2). If tolerated, the dose was increased to 1000 mg/daily (dose level −1) after 4 weeks, and finally to 1250 mg daily (dose level 0) after another 4 weeks in patients who experienced grade ≤1 toxicity at the time of the next planned dose escalation. Patients were advised to avoid grapefruit and grapefruit juice due to potential interference in the ability of cytochrome P450 3A4 (CYP3A4) to metabolize vatalanib. The starting dose was not reduced for patients with pre-existing cytopenias, but dose modifications were pre-specified for both hematological and non-hematological toxicities grade ≥2. Patients requiring dose reductions below dose level −2 were removed from protocol therapy. In patients achieving hematological improvement or stable disease, treatment was continued until relapse, progression of disease, or unacceptable toxicity. Patients with disease progression or transformation to AML were removed from protocol therapy. All patients were followed for survival.

Patients received supportive care including transfusions of blood products and antibiotics as appropriate. Erythropoietic stimulating agents were prohibited, though myeloid growth factors were permitted for treatment of febrile neutropenia as per the American Society of Clinical Oncology guidelines [21].

Evaluation of response, survival and adverse events

Patients were monitored for toxicity and response as detailed in Online Resource 1B. Response, progression and relapse were assessed using standardized criteria [22].

Transformation to AML was defined as an increase in bone marrow or peripheral blood blasts to ≥20%. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_30).

Statistical Considerations

The primary objectives were (a) to estimate complete and partial remission (CR and PR) and hematological improvement rates, and (b) to evaluate the time to transformation to AML or death. Secondary objectives included determining the duration of response, progression-free and overall survival (PFS and OS), and the safety of vatalanib.

One hundred fifty-five patients were enrolled between December 15, 2003, and April 7, 2008. Of these, the participation of 2 patients was cancelled prior to starting treatment. Based on central CALGB review of pathology (by author RPH), 7 others were determined to have had AML at registration and 4 had diagnoses other than MDS, one of whom was subsequently found to have copper deficiency that can mimic MDS. Two patients began treatment but subsequently withdrew their consent to be followed. Thus, 142 patients were evaluable for response and 153 for toxicity. The total number of patients ultimately enrolled was higher than initially planned, because of the inclusion of a second cohort of patients to whom a dose-escalating schedule of vatalanib was administered in order to examine if drug tolerability, and thus hematological response, might be improved. Statistical methods are detailed in Online Resource 1C.

Results

Patient characteristics

The patient population was 63% male, 94% white, and had a median age of 70.5 years (range, 27 – 91 years) (Table 1). Over 51% were classified as low risk MDS (International Prognostic Scoring System {IPSS}[23] category Low or Intermediate {Int}-1), and 50% were fully active (Eastern Cooperative Oncology Group {ECOG} performance status 0). The most common subtype of MDS was RCMD (25% of patients).

The median time from initial diagnosis of MDS to initiation of protocol therapy was 5 months, and nearly 30% (41 of the 138) patients reporting prior history had previously received therapy for MDS (Table S1, Online Resource 2). Of those reporting, approximately 18% of patients had received chemotherapy and 12% had received radiation therapy for malignancies other than MDS. In the 3 months prior to registration, 20% had had infections, 4% had bleeding requiring transfusions, 12% had received platelet transfusions (median, 3.5 transfusions), and 62% had received red blood cell transfusions (median, 6 units). Peripheral blood counts and bone marrow blast percentages at baseline are shown in Table S2 (Online Resource 3). Approximately 46% of patients had IPSS [23] “good risk” cytogenetics while 25% had “poor risk” cytogenetic abnormalities (Table S3 in Online Resource 4).

Response and survival

Of 73 patients in cohort 1, 20 discontinued treatment due to adverse events and an additional 29 patients declined to continue therapy (Table S4 in Online Resource 5). Fifty-five patients (75%) required dose modification or treatment delay. To improve drug tolerability, the standard dosing regimen (1250 mg daily) administered to cohort 1 was changed to a dose-escalation strategy for cohort 2. Nevertheless, of 69 patients in cohort 2, 24 discontinued treatment due to adverse events and 17 additional patients declined to continue treatment. In this cohort, treatment was modified or delayed in 47 patients (68%). Other reasons for

discontinuation of treatment are listed in Table S4. The dose escalation strategy thus had little impact on the ability of patients to receive a prolonged trial of vatalanib.

Response—Seven patients achieved hematological improvement (Table 2). Of these, 4 were erythroid responses (3 major and 1 minor) and 3 were platelet responses (2 major and 1 minor). No patients achieved improvement in more than one cell line. All 7 patients achieving hematological improvement were among the 47 who were able to receive at least 3 cycles of treatment; no responses occurred in patients who discontinued vatalanib earlier. The hematological improvement response rate was thus 15% in patients who received at least 3 cycles of treatment, and 5% overall. Median duration of response was 6 months (range, 2 – 46 months). No patients achieved partial or complete remission.

Patients who achieved hematological improvement tended to have low risk MDS (Table 3). Five of the 7 patients were in the IPSS Low or Int-1 risk categories, 5 had good risk cytogenetics, and only 1 had RAEB-2. Central pathology review and IPSS assignment could not be performed for 1 patient.

Outcomes—To evaluate PFS and OS, patients in each cohort were stratified into low (IPSS score 0–1: Low or Int-1) and high (IPSS score ≥1.5: Int-2 or High) risk categories. This resulted in the inclusion of 119 patients for whom adequate information was available to assign an IPSS category. Twenty-three patients without IPSS categorization, 7 with AML at enrollment, 4 with diagnoses other than MDS, and 2 whose registration was cancelled, were excluded from survival analyses. Patients were followed for a median of 70.7 months.

Progression-Free Survival: Of 142 patients in the analysis, 40 developed a non-AML progression and 34 experienced transformation to AML. One hundred eighteen patients have died. For patients in cohorts 1 and 2 combined, the median PFS was 15 months and 6 months for all low risk and high risk patients, respectively (Fig. 1A).

Overall survival: For patients in cohorts 1 and 2 combined, the median survival times were 36 months and 10 months for all low risk and high risk patients, respectively (Fig. 1B). The median survival times were 25 and 59 months for low risk patients in cohorts 1 and 2 respectively, and were 13 and 10 months for high risk patients in the two cohorts.

The median time to transformation to AML or death for the 142 MDS patients was 17 months (18 months in cohort 1 and 14 months in cohort 2), and was 28 and 6 months for patients with low and high risk MDS, respectively. The cumulative incidence of transformation to AML or death is shown in Fig. 2. There were no significant differences between dose cohorts for either transformation to AML or death. However, there was a significant difference in transformation to AML between those with high risk and low risk MDS ($p = 0.002$). The difference between the cumulative incidences for death from non-AML causes between patients with high and low risk MDS was not significant.

Causes of death were similar for patients in both cohorts. The majority (65%) of deaths were related to MDS or AML. In two patients, death was possibly attributable to vatalanib (intra-cerebral hemorrhage in one, and sudden death in the other patient). The remaining deaths were unrelated to MDS or to vatalanib.

Toxicity

Of 155 patients enrolled, 153 were evaluable for toxicity. Adverse events of CTCAE grade ≥2 and incidence ≥5% and at least possibly related to vatalanib are shown in Table 4. Hematological adverse events of grades 3 and 4 were experienced by 24% and 33% patients in cohort 1, and by 19% and 34% patients in cohort 2, respectively. Non-hematological

adverse events of grades 3 and 4 occurred in 52% and 11% patients in cohort 1, and 38% and 5% patients in cohort 2, respectively. Two patients suffered grade 5 adverse events at least possibly related to vatalanib. Overall, the most frequent non-hematological grade 3 and 4 adverse events in both cohorts combined were constitutional (fatigue, 23% and 3%, respectively), gastrointestinal (nausea, 10% and 0%; vomiting, 5% and 0%), or neurological (dizziness, 6% and 2%; pain, 5% and 0%). Grade 3 and 4 febrile neutropenia occurred in 7% and 0% patients, respectively, ataxia in 3% and 1%, and proteinuria in 1% and 0%. Fewer patients in cohort 2 experienced grade 2–4 fatigue (45% vs 59% in cohort 1), nausea (21% vs 44%), vomiting (16% vs 29%), dizziness (14% vs 30%), or ataxia (6% vs 17%). However, this reduction in adverse events did not have a meaningful impact on the ability of patients in cohort 2 to remain on vatalanib since the proportion of patients who were able to receive at least 3 cycles of treatment (33%) remained the same as in cohort 1.

Discussion

In this large phase 2 study, vatalanib monotherapy had minimal efficacy in MDS. Hematological improvement was noted in only 5% of all patients, and was limited to those able to take vatalanib for at least 3 months. In this subset, hematological improvement was observed in 15% patients. Despite a dose escalation strategy aimed at prolonging patients' ability to receive vatalanib, only 33% of patients in either cohort received at least 3 cycles of therapy. This is likely to have negatively influenced the probability of achieving a response. Three of the 7 responders had RCMD, and 4 of 7 had normal cytogenetics, though responses were also observed in other subtypes of MDS. The most frequent lineage that responded to vatalanib was erythroid (in 4 of 7 responders). Two of the seven patients (29%) achieving hematological improvement had received one prior line of therapy for MDS. Multi-lineage responses were not seen in any patients. Although stable disease was observed in several patients, the median survival times of 36 months and 10 months, respectively, in low and high risk patients suggest that vatalanib monotherapy does not alter the natural history of MDS.

In a previous phase 1 study, vatalanib (500–1000 mg twice daily) was administered alone or in combination with induction chemotherapy to 63 patients with poor prognosis *de novo*, refractory, relapsed, or secondary AML, or advanced MDS [24]. The maximum tolerated dose (MTD) was 750 mg twice daily. Seven (11%) patients withdrew from that study. In contrast to our study, no responses were observed with vatalanib monotherapy, though 2 patients achieved stable disease for 10 and 14 months, indicating only modest clinical activity even when combined with chemotherapy.

Recent studies, published after initiation of our trial, suggest that the tolerability and efficacy of single-agent vatalanib is quite variable in patients not only within a disease modality, but also across a spectrum of diverse malignancies. Jahan et al reported the results of a CALGB phase 2 trial examining the safety and activity of a 1250 mg once daily dose of vatalanib in 47 patients with untreated malignant mesothelioma [25]. Toxicity was acceptable and grade 3–4 adverse events were infrequent (2–15%), but efficacy was modest (6% PR). Why vatalanib was better tolerated by patients with mesothelioma than our patients with MDS in cohort 1 when administered at an identical dose remains unclear. In patients with gastrointestinal stromal tumor, vatalanib was generally well tolerated at 1250 mg/day, although temporary dose reductions were required by the majority; the drug induced PR in 4% patients [26]. Similarly, vatalanib (300–1200 mg/day) was tolerable, and induced stable disease in 48% patients with liver metastases from various malignancies [27]. In patients with myelofibrosis with myeloid metaplasia, dose-limiting toxicities were observed at 750 mg twice daily; 3% patients achieved CR, and 17% demonstrated improvement in hemoglobin level or splenomegaly [28].

In contrast, other studies reported that vatalanib at the same dose as in the current study (1250 mg/day) was difficult to tolerate. Only 44% of patients with melanoma tolerated this dose; 37% never tolerated this dose, and 19% required dose reduction [29]. Clinical efficacy was modest (3% PR). Vatalanib was discontinued (usually for adverse events) in 25% patients with advanced non-small cell lung cancer; the PR rate was 4% [30]. Similarly, vatalanib-related toxicities required discontinuation in 48% patients with multiple myeloma; efficacy was modest (5% PR) [31].

The types of adverse effects observed in our study were similar to those reported in other trials of vatalanib cited above, albeit with varying frequency and severity. In cohort 2 we used a dose-escalation strategy, starting at 750 mg/day (the minimum biologically active dose [27] and 50% of the MTD [24]), to examine if tolerance to the toxic effects of vatalanib might develop. Although adverse events were somewhat less frequent, vatalanib remained difficult to tolerate even at lower starting doses. Consistent with this observation, we found no correlation between drug exposure and toxicity [32]; detailed pharmacokinetic results from the current study will be reported separately. Previous studies found that most grade 3–4 adverse events were not dose-related [27], with the possible exception of light-headedness, fatigue, and vomiting at 1000 mg twice daily [33]. As in our study, patients with multiple myeloma found it difficult to tolerate a dose-escalation regimen [31]. Since all responses observed in the current study occurred in patients able to tolerate vatalanib for at least 3 months, its efficacy may be enhanced by strategies that improve tolerability since anti-angiogenic therapy likely needs prolonged, continuous administration. However, vatalanib is not being developed further because of its inability to improve survival in advanced colorectal cancer in a randomized placebo-controlled trial when combined with chemotherapy [34,35].

The modest efficacy of vatalanib appears to be remarkably similar to that of other anti-angiogenic agents in MDS. The anti-VEGF antibody bevacizumab administered to 21 patients with RAEB-1 or −2 was well tolerated, but response (major erythroid hematological improvement [transfusion independence]) that lasted 3 months was seen in only one (5%) and reduction in bone marrow blast percentage in 3 patients, despite a biological effect on angiogenesis (reduction in plasma VEGF levels and marrow microvessel density) in 80% of patients [36]. Similarly, SU5416, a small molecule RTK inhibitor of VEGF-R2, Flt-3 and c-Kit, administered to 22 patients with high grade MDS (RAEB or RAEB in transformation {RAEB-T}), induced a PR in one patient (5%) with RAEB-T and unfavorable cytogenetics, resulting in a reduction in bone marrow blasts from 28% to 8%, event-free survival of 11 months, and OS of >16 months [37]. As we observed with vatalanib, 3 of 4 patients (1 MDS and 3 AML) who responded to SU5416 required at least 2 months of treatment before achieving a response.

Other drugs such as thalidomide, lenalidomide, arsenic trioxide and the matrix metalloprotease inhibitor AG3340 (Prinomastat™) that act only partly by inhibition of angiogenesis/VEGF signaling have demonstrated higher activity in MDS. However, it remains unclear to what extent efficacy and toxicity of these multi-functional agents are related to their anti-angiogenic activity versus their effects on other pathways.

In summary, this and other studies with vatalanib in various hematological malignancies and solid tumors demonstrate a consistent theme, i.e. a low response rate and poor tolerability as a single agent, and lack of survival benefit even when combined with chemotherapy in phase III trials. Our study also indicates that toxicity from vatalanib is not necessarily dose-dependent. Finally, the modest and remarkably similar single agent activity of vatalanib and other anti-angiogenic agents suggests that although angiogenesis is increased and may play a role in pathogenesis and progression of MDS, inhibition of this pathway alone is not

sufficient to induce clinical improvement. Simultaneous modulation of other pathophysiological mechanisms will likely be required to achieve more frequent and robust clinical benefit in MDS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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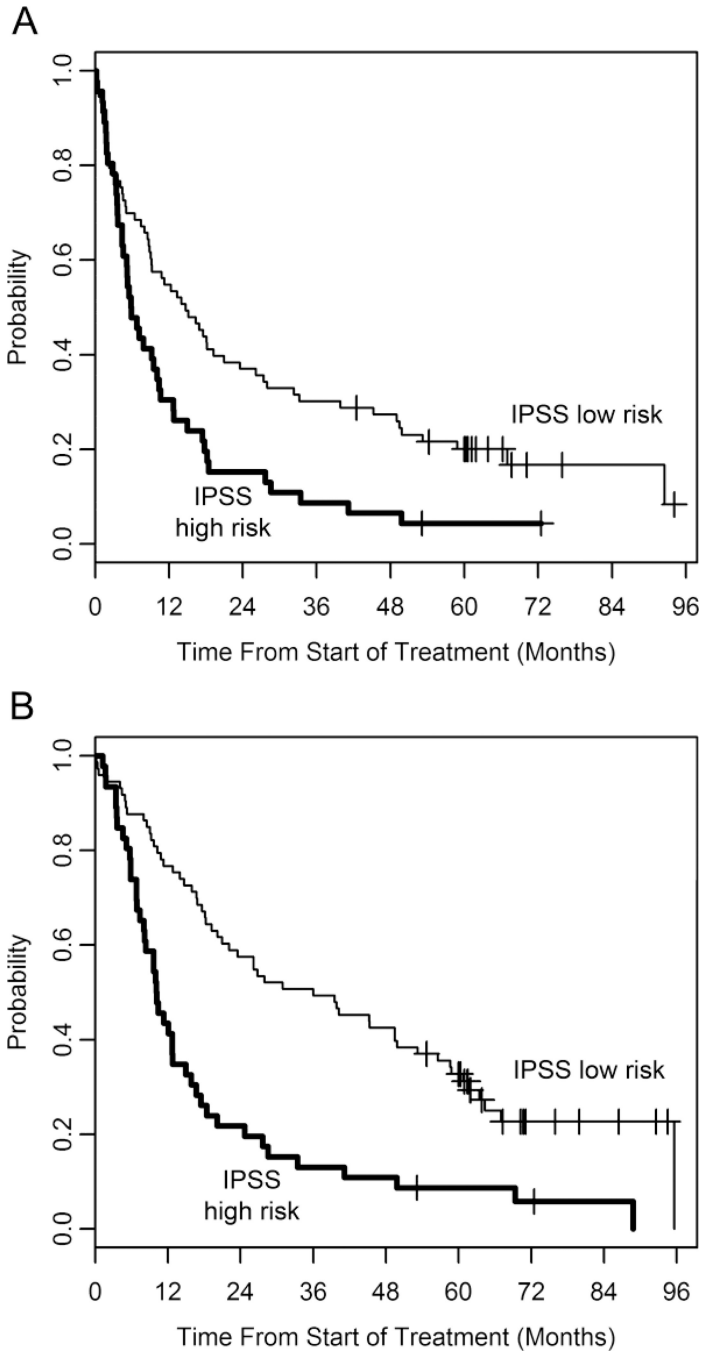

Figure 1. Progression-free survival and overall survival

Progression-free survival (A) and overall survival (B) for patients in dose cohorts 1 and 2 combined were estimated from the start of vatalanib treatment, according to the Kaplan-Meier method. Significance of differences between patients in the International Prognostic Scoring System (IPSS) low risk (Low or Intermediate {Int}-1; score 0–1) and high risk (IPSS Int-2 or High; score ≥1.5) groups was determined using the log-rank test ($p < 0.002$ for progression-free survival and $p < 0.0001$ for overall survival).

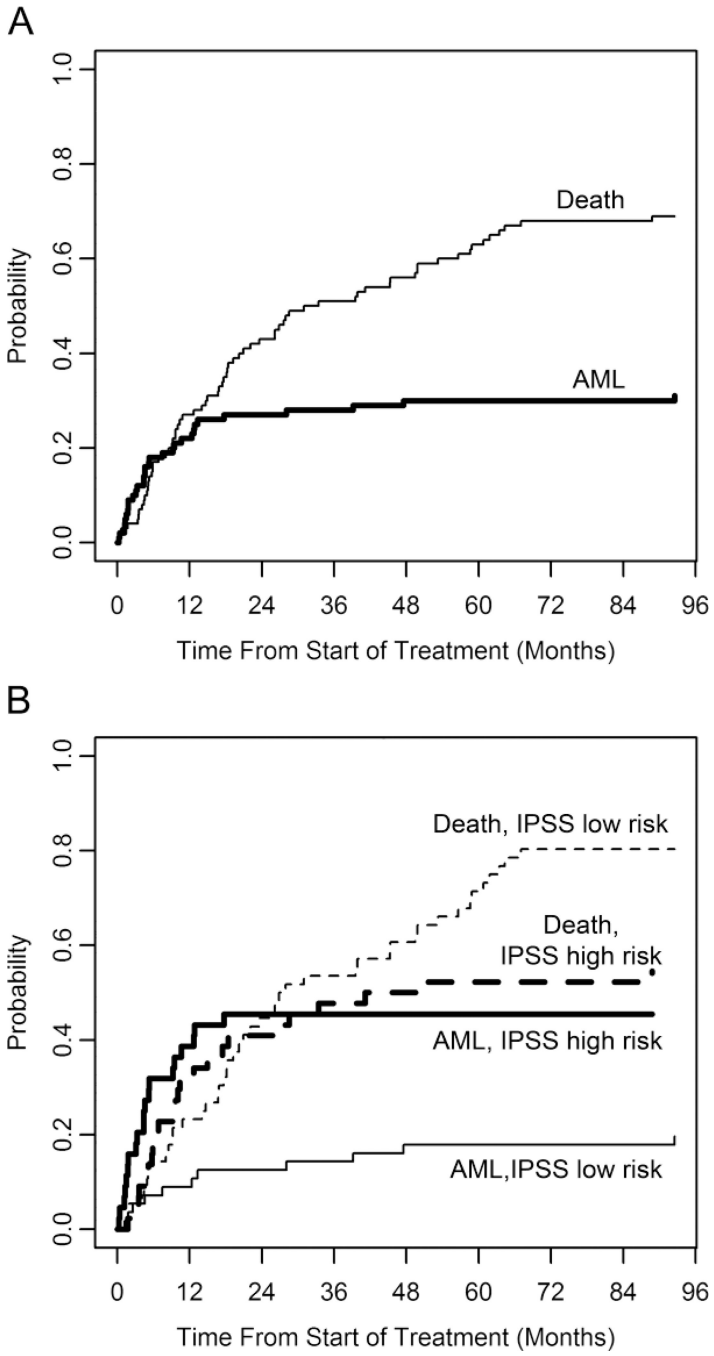

Figure 2. Cumulative incidence of transformation to acute myeloid leukemia or death

The cumulative incidence of acute myeloid leukemia (AML) or death for patients in dose cohorts 1 and 2 combined was estimated from the start of vatalanib treatment using a competing risk model as described in Methods.

A: Cumulative incidence of transformation to AML or death for all patients.

B: Cumulative incidence of transformation to AML or death by International Prognostic Scoring System (IPSS) low risk (Low or Intermediate {Int}-1; score 0–1) and high risk (IPSS Int-2 or High; score ≥1.5) groups.

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Table 1

Patient Demographics and Baseline Characteristics (n=142)

		Cohort 1		Cohort 2		Combined	
		n	**%**	**n**	**%**	**n**	**%**
Gender	Female	27	37	25	36	52	37
	Male	46	63	44	64	90	63
Race	White	67	92	66	96	133	94
	Black	4	5	0	0	4	3
	Other	2	3	3	4	5	4
Age	Median	73		69		71	
	Range	27 – 91		49 – 87		27 – 91	
Diagnosis	CMML-1	8	11	2	3	10	7
	CMML-2	1	1	2	3	3	2
	Isolated del(5q)	2	3	1	1	3	2
	MDS-U	4	5	5	7	9	6
	MPD/MDS	0	0	1	1	1	1
	RA	1	1	2	3	3	2
	RAEB-1	8	11	13	19	21	15
	RAEB-2	12	16	18	26	30	21
	RARS	8	11	8	12	16	11
	RCMD	23	32	13	19	36	25
	RCMD-RS	6	8	4	6	10	7
IPSS Category	Low	17	23	9	13	26	18
	INT-1	31	42	16	23	47	33
	INT-2	13	18	25	36	38	27
	High	2	3	6	9	8	6
	Inevaluable	10	14	13	19	23	16
ECOG Performance Status	(0) Fully Active	35	48	36	52	71	50
	(1) Symptomatic	34	47	31	45	65	46

	Cohort 1		Cohort 2		Combined	
	n	%	n	%	n	%
(2) Ambulatory	4	5	2	3	6	4

Abbreviations: CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MDS-U, MDS unclassifiable; MPD, myeloproliferative disorder; RA, refractory anemia; RAEB, RA with excess blasts; RARS, RA with ring sideroblasts; RCMD, refractory cytopenias with multilineage dysplasia; RCMD-RS, RCMD with ring sideroblasts; IPSS, International Prognostic Scoring System; Int, Intermediate; ECOG, Eastern Cooperative Oncology Group.

Table 2

Response to treatment (n=142)

		Cohort 1	Cohort 2	Combined
		n (%)	n (%)	n (%)
Hematological improvement type	HI-E Major	2 (3)	1 (1)	3 (2)
	HI-E Minor	0 (0)	1 (1)	1 (1)
	HI-P Major	1 (1)	1 (1)	2 (1)
	HI-P Minor	1 (1)	0 (0)	1 (1)
	None	69 (95)	66 (96)	135 (95)
Hematological improvement type among those receiving ≥3 complete cycles of treatment	HI-E Major	2 (8)	1 (4)	3 (6)
	HI-E Minor	0 (0)	1 (4)	1 (2)
	HI-P Major	1 (4)	1 (4)	2 (4)
	HI-P Minor	1 (4)	0 (0)	1 (2)
	None	20 (83)	20 (87)	40 (85)
Duration of hematological improvement in months	Median	8	2	6
	Range	2 – 46	2 – 30	2 – 46

Abbreviations: HI, hematological improvement; HI-E, HI erythroid; HI-P, HI platelets.

Table 3

Characteristics of patients achieving hematologic improvement (n=7)

		Cohort 1	Cohort 2	Combined
		n	N	N
Diagnosis	CMML-1	1	0	1
	RAEB-1	0	1	1
	RAEB-2	0	1	1
	RCMD	2	1	3
	RCMD-RS	1	0	1
IPSS category	INT-2	0	1	1
	INT-1	3	1	4
	Low	1	0	1
Cytogenetic abnormalities				
	Isolated 20q-	1	0	1
	Normal	3	1	4
	t(8;13)(q11.2;p11.1)	0	1	1

Abbreviations: CMML, chronic myelomonocytic leukemia; RAEB, refractory anemia with excess blasts; RCMD, refractory cytopenias with multilineage dysplasia; RCMD-RS, RCMD with ring sideroblasts; IPSS, International Prognostic Scoring System; Int, Intermediate.

Table 4

Adverse events (n=153)*

	Cohort 1: n=79				Cohort 2: n=74			
Event	**Grade 2–5 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 2–5 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Fatigue (asthenia, lethargy, malaise)	47 (59%)	20 (25%)	22 (28%)	5 (6%)	33 (45%)	20 (27%)	13 (18%)	0 (0%)
Hemoglobin	36 (46%)	11 (14%)	22 (28%)	3 (4%)	30 (41%)	13 (18%)	13 (18%)	4 (5%)
Nausea	35 (44%)	24 (30%)	11 (14%)	0 (0%)	16 (22%)	12 (16%)	4 (5%)	0 (0%)
Platelets	35 (44%)	10 (13%)	8 (10%)	17 (22%)	23 (31%)	3 (4%)	7 (9%)	13 (18%)
ANC	30 (38%)	3 (4%)	11 (14%)	16 (20%)	25 (34%)	3 (4%)	8 (11%)	14 (19%)
Dizziness	23 (29%)	15 (19%)	6 (8%)	2 (3%)	11 (15%)	7 (9%)	3 (4%)	1 (1%)
Vomiting	23 (29%)	19 (24%)	4 (5%)	0 (0%)	12 (16%)	9 (12%)	3 (4%)	0 (0%)
Anorexia	14 (18%)	11 (14%)	3 (4%)	0 (0%)	5 (7%)	4 (5%)	1 (1%)	0 (0%)
Ataxia	13 (16%)	7 (9%)	4 (5%)	2 (3%)	5 (7%)	4 (5%)	1 (1%)	0 (0%)
Pain	9 (11%)	5 (6%)	4 (5%)	0 (0%)	8 (11%)	5 (7%)	3 (4%)	0 (0%)
Proteinuria	9 (11%)	9 (11%)	0 (0%)	0 (0%)	3 (4%)	2 (3%)	1 (1%)	0 (0%)
Diarrhea	8 (10%)	7 (9%)	1 (1%)	0 (0%)	10 (14%)	7 (9%)	3 (4%)	0 (0%)
Febrile neutropenia	7 (9%)	0 (0%)	7 (9%)	0 (0%)	4 (5%)	0 (0%)	4 (5%)	0 (0%)
ALT	6 (8%)	4 (5%)	2 (3%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	2 (3%)
Dyspnea	6 (8%)	4 (5%)	2 (3%)	0 (0%)	3 (4%)	3 (4%)	0 (0%)	0 (0%)
Hypertension	6 (8%)	4 (5%)	2 (3%)	0 (0%)	2 (3%)	2 (3%)	0 (0%)	0 (0%)
Infection (documented clinically or microbiologically)	6 (8%)	5 (6%)	1 (1%)	0 (0%)	2 (3%)	0 (0%)	2 (3%)	0 (0%)
WBC	5 (6%)	2 (3%)	2 (3%)	1 (1%)	4 (5%)	3 (4%)	1 (1%)	0 (0%)
AST	2 (3%)	1 (1%)	1 (1%)	0 (0%)	6 (8%)	2 (3%)	3 (4%)	1 (1%)

*Grades 2–5, and possibly, probably, or likely related to treatment and experienced by at least 5% of all patients.

Abbreviations: ANC, absolute neutrophil count; ALT, alanine aminotransferase; WBC, white blood cell count; AST, aspartate aminotransferase.