Value of infliximab (Remicade®) in patients with low-risk myelodysplastic syndrome: final results of a randomized phase II trial (EORTC trial 06023) of the EORTC Leukemia Group

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Online Supplementary Appendix

Study design

Main eligibility criteria included: MDS intermediate or good IPSS risk score and FAB type RA, RARS, or RAEB with ≤ 10% bone marrow blasts; no poor cytogenetic characteristics defined as complex abnormalities or involvement of chromosome 7; ≥6 weeks prior to randomization without treatment for MDS other than supportive care only; WHO performance status 0-2; Hb <10 g/dL or RBC transfusion dependent and/or neutrophil count $<1.5\times10^9$/L and/or platelet count $<100\times10^9$/L or platelet transfusion dependent; absence of current or prior history of an opportunistic infection; no severe cardiac or pulmonary dysfunction; serum bilirubin ≤1.5xULN; serum creatinine ≤ 1.5 x ULN; absence of current or prior active or latent tuberculosis infection; and no confirmed pregnancy or nursing women. Patients without cytogenetic data (n=7) were assigned 0.5 points for cytogenetics in the IPSS scoring. Signed written informed consent was obtained according to ICH/GCP and national/local regulations. Eligible patients were randomized prospectively at the EORTC Headquarters in Brussels. Randomization, using a minimization technique, was stratified by center, cytogenetics (good, intermediate, unknown due to failure) and IPSS score (low, intermediate 1, intermediate 2).[14] The study protocol was approved by the EORTC protocol review committee and by the ethical committee of each participating center.

Patients were randomized 1:1 to receive infliximab 3 mg/kg (arm A) or infliximab 5 mg/kg (arm B). Infliximab was injected intravenously on days 1, 15 and then every four weeks until Month 6 (for a total of 8 infusions). No dose modifications were allowed. In case of infectious episodes during the trial period, the injection of infliximab could be delayed for up to a maximum of two weeks. If more than two weeks delay was necessary for the resolution of the event, the study therapy was discontinued.

Reasons to discontinue the treatment included: disease progression (patients responding to study therapy by Month 6 (8th infusion) were scheduled to continue treatment until the first progression has been documented); stable disease by Month 6; adverse event during or within 1 h following the infusion; serum sickness-like reaction; diagnosis of active tuberculosis; exposure to an individual with active tuberculosis; congestive heart failure; serious infection; major protocol violation; patient refusal to continue; lost to follow up; and pregnancy.

Primary end point was the response rate (complete response, partial response and hematologic improvement) as defined by Cheson *et al.*[15] Secondary end points included the definition of toxicity profile of infliximab in MDS patients and the duration of response. Overall and progression-free survivals, although not specifically indicated as secondary end points in the protocol, were also evaluated prospectively.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (available from: *http://ctep.cancer.gov/reporting/ctc.htm*).

Statistical design of the study

Statistical considerations were as follows: P0 (the largest response probability which, if true, implies that the therapeutic activity does not warrant further investigation of the regimen) was 15%; P1 (the lowest response probability which, if true, implies that the therapeutic activity does warrant further investigation of the regimen) was 35%; beta (the accepted probability of rejecting from further trials a regimen with a true response rate at least equal to P1) was 0.05; and alpha (the accepted probability of recommending for further investigation a regimen with a true response rate equal to or lower than P0) was 0.15.

In the original statistical consideration, the Fleming 1-stage design was used for each randomized arm. This implied that a total of 34 patients should have been randomized in each treatment group and that if 7 or less responses were observed the trial should conclude that infliximab (at the given dose level, according to randomization) was not sufficiently active and should not be further investigated in this patient population, while if 8 or more responses were observed, the trial should

conclude that infliximab (at the given dose level, according to randomization) should be further investigated in this patient population.

The protocol was amended on March 2006 due to a drop in the accrual. The protocol was amended from a 1-stage Fleming design to a Simon 2-stage design taking into consideration the same assumptions as in the initial protocol (P0=15%, P1=35%, beta=5%, alpha=15%). This implied entering and evaluating the first 18 patients for each infliximab arm. If 2 or less responses were observed (2 of 18=11.1%), the trial would conclude that infliximab (at the given dose level, according to randomization) should not be further investigated in this patient population, while if 3 or more responses were observed, one should continue the accrual for an 18 additional patients, in the arm(s) which passed the 1st step. In the 2nd step, the total of 36 patients entered in each of the randomized treatment arm(s) which passed the 1st step should be evaluated using these rules: if 7 or less responses were observed (7 of 36=19.4%), conclude that infliximab (at the given dose level, according to randomization) should not be further investigated in this patient population, while if 8 or more responses were observed, conclude that infliximab (at the given dose level, according to randomization) should be further investigated in this patient population.

Since 36 (2 x 18) patients with a follow up longer than six months (duration of treatment at which time point the response is assessed) were already entered at the time of the amendment, an interim analysis was performed on complete data for all these patients. After the approval of the amendment by the EORTC protocol review committee, the study was closed to accrual to perform the interim analysis for the first stage. The study remained closed after the interim analysis given the demonstrated lack of sufficient efficacy of the two schedules of infliximab evaluated (see below).

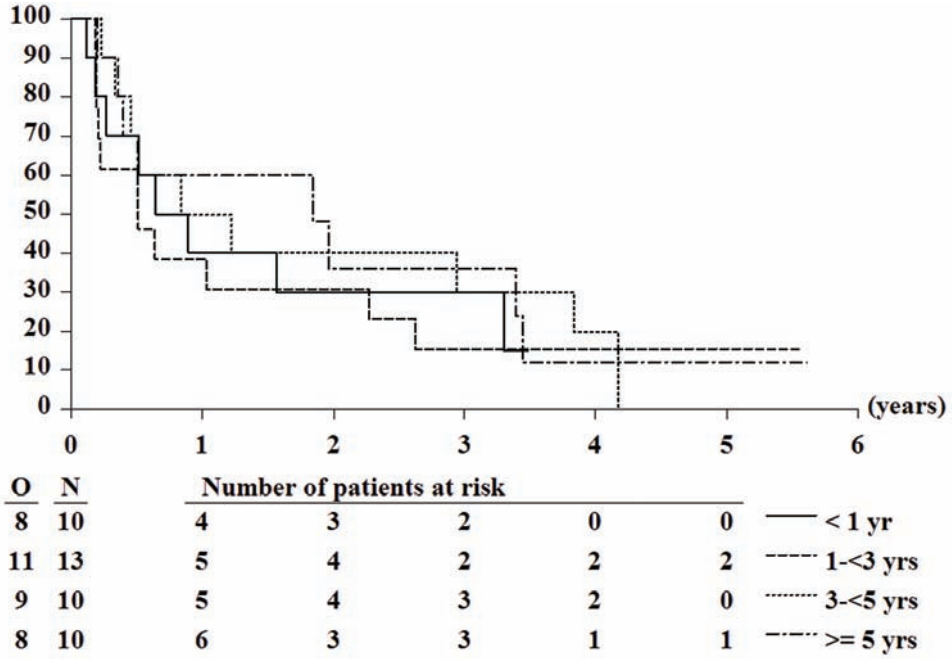
Adherence to protocol treatment

Dose modifications were made in 2 of 22 (9%) patients in the 3 mg/kg group *versus* 1 of 21 (5%) patients in the 5 mg/kg. Delay occurred in 6 of 22 (27%) *versus* 3 of 21 (14%) patients in the 3 mg/kg and 5 mg/kg groups, respectively. Both dose modification and delay in administration occurred in 1 patient in the 3 mg/kg group, *versus* none in the 5 mg/kg group. Delays and/or dose modifications occurred on course 1, 2, 3, 4, 5, 6, 7 and 8 in 1, 4, 3, 4, 3, 4, 1, and 1 patients, respectively. Reasons for delay and/or dose modification included: drug dilution problems (n=5), administrative problems (n=4), infection (n=3), neutropenia (n=1), Quincke's edema (n=1), skin rash (n=1) or other (n=6).

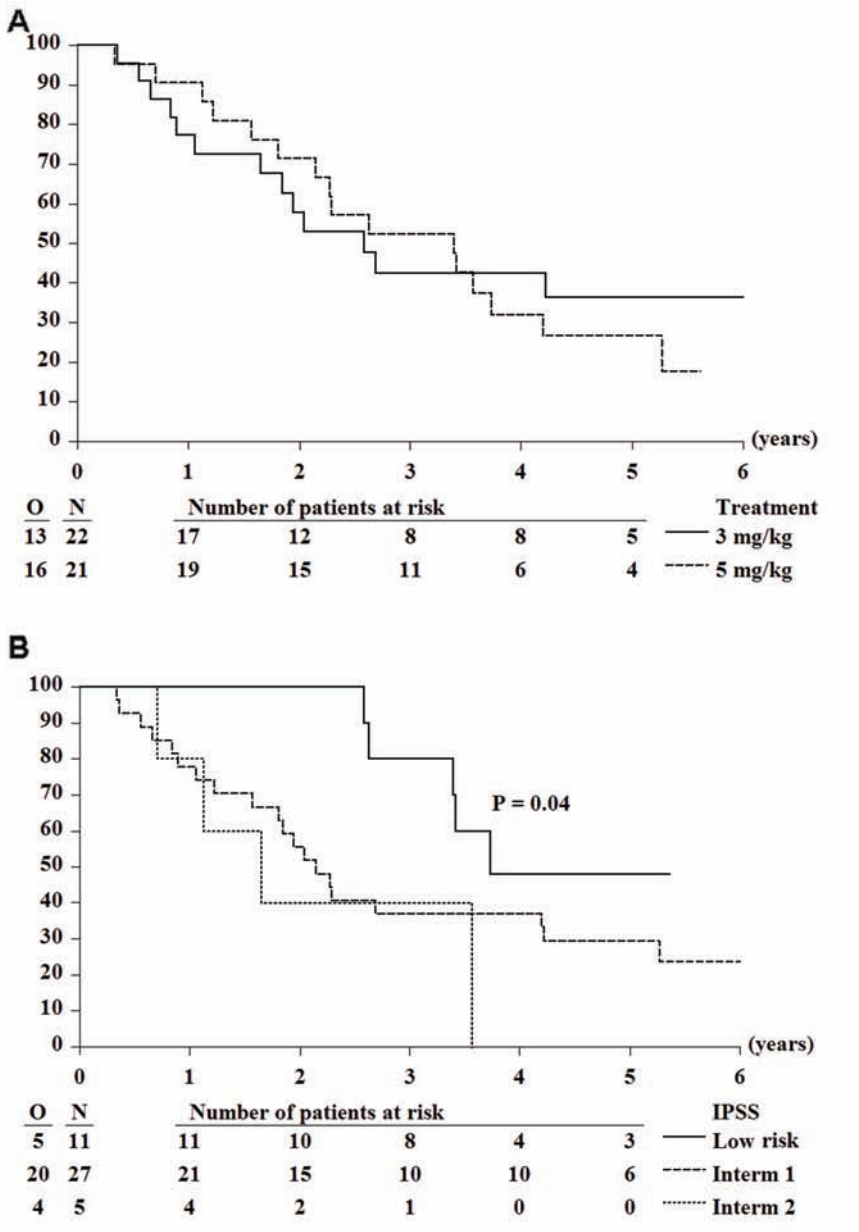
Online Supplementary Table S1. Grade ≥ 3 adverse events* by treatment arm.

	Treatment arm	
	3 mg/kg (n=22) N (%)	5 mg/kg (N=21) N (%)
Allergic reaction/hypersensitivity:		
Grade 4	1 (4.5)	0 (0.0)
Hypertension		
Grade 3	2 (9.1)	0 (0.0)
Hypotension		
Grade 3	1 (4.5)	0 (0.0)
Cardiac general-other		
Grade 3	3 (13.6)	0 (0.0)
Grade 5	1 (4.5)	0 (0.0)
Fatigue		
Grade 3	1 (4.5)	2 (9.5)
Grade 4	2 (9.1)	0 (0.0)
Constitutional symptoms-other		
Grade 3	1 (4.5)	1 (4.8)
Dermatology		
Grade 3	0 (0.0)	2 (9.5)
Nausea		
Grade 3	0 (0.0)	1 (4.8)
Gastrointestinal-other		
Grade 3	0 (0.0)	2 (9.5)
Grade 4	1 (4.5)	0 (0.0)
Infection		
Grade 3	6 (27.3)	4 (19.0)
Grade 4	1 (4.5)	0 (0.0)
Grade 5	2 (9.1)	0 (0.0)
Neurology		
Grade 3	0 (0.0)	2 (9.5)
Pain		
Grade 3	3 (13.6)	1 (4.8)
Grade 4	1 (4.5)	0 (0.0)
Dyspnea		
Grade 3	0 (0.0)	2 (9.5)
Grade 4	2 (9.1)	0 (0.0)
Pulmonary/upper respiratory-other		
Grade 3	2 (9.1)	0 (0.0)
Grade 4	2 (9.1)	0 (0.0)
Acute infusion reaction/cytokine release syndrome		
Grade 4	1 (4.5)	0 (0.0)
Maximal of all adverse events		
Grade 0	1 (4.5)	3 (14.3)
Grade 1	1 (4.5)	4 (19.0)
Grade 2	8 (36.4)	5 (23.8)
Grade 3	7 (31.8)	9 (42.9)
Grade 4	3 (13.6)	0 (0.0)
Grade 5	2 (9.1)	0 (0.0)

Graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Available from: http://ctep.cancer.gov/reporting/ctc.html.



Online Supplementary Figure S1. Progression-free survival from randomization according to time from MDS diagnosis to randomization.



Online Supplementary Figure S2. Overall survival from randomization according to infliximab (A) dosage arm or (B) IPSS score. *P* value given by the Wald test (Cox's model).