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Decitabine Can Be Safely Reduced after Achievement of Best Objective Response in Patients with Myelodysplastic Syndrome

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Abstract

Decitabine is standard therapy in patients with myelodysplastic syndrome (MDS). Current recommendations suggest a dose of 20 mg/m^2 IV daily for 5 days every 4 weeks. However, this therapy is associated with frequent grade 3–4 hematologic toxicity, requiring dose reductions (DR) and/or dose delays (DD). We investigated the outcome of 122 MDS patients who had DD/DR of frontline decitabine therapy. Sixty five patients (53%) had DR by at least 25% or DD (defined as a delay beyond 5 weeks between cycles). Thirty-five patients (29%) underwent DD/DR after achieving best objective response (BOR), 30 patients (25%) before BOR and 57 (54%) had no DD/DR. There was a trend for more durable responses in favor of patients requiring DD/DR after the achievement of BOR (median not reached) (p=0.161). Overall survival rates were significantly higher for patients who had DD/DR after BOR compared to those who had DD/DR prior to BOR or those with no DD/DR (30 v/s 22 v/s 11 months, respectively, p<0.001). Progression-free survival rates also trended higher for those with DD/DR after BOR (median not reached) compared to those who required DD/DR before (median of 15 months) (p=0.285). In conclusion, DD/DR may be safely accomplished once the patient has achieved BOR (preferably complete remission) without impacting outcome. Prospective evaluation of an approach conceiving a loading dose for induction of a best objective response followed by a maintenance schedule is to be considered.

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Authorship

Contribution: H.G., G.G.M., H.K, S.O.B and E.J. designed and performed the research and analyzed the data; H.G., G.G.M., A.M.C. and E.J. analyzed the data; G.G.M., F.R and T.P., provided the analytical tools; and H.G., G.G.M., H.K., G.B, J.C. and E.J. wrote the manuscript.

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Keywords

Decitabine; myelodysplastic syndrome; dose delay; dose reduction

Introduction

Myelodysplatic syndromes (MDS) are a heterogeneous group of hematologic disorders characterized by clonal expansion of a hematopoietic progenitor cell, leading to bone marrow dysfunction, pancytopenia, and a tendency to convert into acute leukemia.[1,2] Methylation plays an important role in the development of these diseases, and hypermethylation can lead to silencing of important tumor suppressor genes and is thought to contribute to MDS pathophysiology.[3] Decitabine is a hypomethylating agent that was shown to improve outcomes of patients with MDS.[4–6]

Decitabine is standard therapy in patients with MDS. Current recommendations suggest a dose of 20 mg/m2 IV daily for 5 days every 4 weeks. However, this therapy is associated with frequent grade 3–4 hematologic toxicity, requiring dose reductions (DR) and/or dose delays (DD).[7] Patients with MDS frequently present with myelosuppression as a result of their disease. This leads to frequent DD and/or DR during decitabine treatment. In the phase II study assessing the decitabine regimen of 20 mg/m^2 IV daily for 5 days, grade 3 or higher neutropenia, thrombocytopenia, febrile neutropenia, and anemia occurred at rates of 31%, 18%, 14%, and 12% of patients, respectively. [8] Thirty-two percent of the administered cycles in that study were delayed primary due to myelosuppression. Most of these delays occurred during the first cycles of treatment. The effect of these DD or DR on response to treatments and patient outcomes are unknown. The aim of the study is to assess the impact of the timing and occurrence of DD and/or DR (DD/DR) of decitabine on the outcome of patients with MDS treated with decitabine at our institution.

Patients and methods

Study group

One hundred twenty-four patients with MDS treated between 11/2003 and 7/2010 with frontline decitabine were retrospectively analyzed for DD/DR. Informed consent was obtained according to institutional guidelines and in accordance with the Declaration of Helsinki.[6] The study has been fully approved by The University of Texas MD Anderson Cancer Center Surveillance Committee. The FAB morphologic classification was used for MDS and CMML diagnosis. Eligibility criteria included (1) age 16 years or older; (2) diagnosis of MDS with intermediate or high risk IPSS, or diagnosis of chronic myelo-monocytic leukemia CMML; [9] normal organ function.[10,11] Patients with prior intensive chemotherapy with cytarabine 1 g/m^2 or more were not eligible. Diagnosis of CMML was based on the typical morphologic picture, unexplained leukocytosis greater than 12×10^9/L lasting for at least 3 months, exclusion of other myeloproliferative disorders, and presence of at least 1×10^9/L monocytes.[11]

Therapy

Patients were randomized to receive decitabine in 1 of 3 schedules: (1) 20 mg/m^2 intravenously [12] over 1 hour daily for 5 days (N=93); (2) 20 mg/m^2 daily for 5 days, given in 2 subcutaneous (SC) doses daily for 5 days (n=14); or [9] 10 mg/m^2 IV over 1 hour daily for 10 days (n=17).[6] All patients received the same decitabine total dose per course, 100 mg/m^2. Courses of decitabine were given every 4 weeks, at least in the first 3 courses, regardless of the counts, as long as (1) there were no significant myelosuppressive, life-threatening complications with a particular course, such as pneumonia severe infection or bleeding, or severe organ damage, and (2) there was evidence of persistent disease. No dose escalations were considered. Dose reductions by 25% to 30%, rounded to 15, 10, 7.5, and 5 mg/m^2, were allowed for grade 3 or 4 nonmyelosuppressive toxicities, for severe myelosuppression-associated complications (infections, bleeding), or for prolonged myelosuppression defined as a hypocellular marrow (5% or less cellularity) without evidence of disease for 6 weeks or more after the start of a course of therapy. Other dose modifications (eg, 50% dose reductions) were occasionally considered for severe complications, if judged in the best safety interest of the patient. Use of erythropoietin and granulocyte–colony-stimulating factor (G-CSF) was allowed as indicated by the clinical condition. In general, erythropoietin at a dose of 40,000 units SC weekly was allowed for red cell transfusion dependence or for a hemoglobin level below 10 g/dL. G-CSF 300 to 480 μg SC was given if the granulocyte count was less than 1×10^9/L in the setting of a febrile episode or documented infection, or in a patient in complete remission (CR) but with granulocyte counts less than 1×10^9/L prior to initiation of the next course of decitabine.

Response criteria and statistical considerations

Response criteria for CR and partial remission (PR) were identical to the ones used for acute myeloid leukemia (AML), but required response durability for at least 4 weeks.[6] CR required normalization of the bone marrow and peripheral counts with 5% or less marrow blasts, a granulocyte count of 1×10^9/L or more, and a platelet count of 100×10^9/L or more, lasting for at least 4 weeks. A PR was similar to CR except for persistent marrow blasts above 5%, but which were reduced by 50% or more. A marrow CR referred to reduction of marrow blasts to 5% or less without normalization of peripheral counts. Response duration was dated from first evidence of response until disease progression.[10] DD was defined as a delay beyond 5 weeks between cycles. Best objective response was determined by International Work Group (IWG) modified response criteria. Survival data was reported from start of therapy and was obtained by Kaplan- Meier survival curves. Overall survival was defined as time from start of therapy till death. Progression free survival was defined as time from start of therapy till progression of MDS or transformation into acute myeloid leukemia(increased blasts to 30% or more in the blood and/or the bone marrow). The curves were compared using the log-rank test.

Results

Patients' characteristics

A total of 124 patients were assessed. For the purpose of this analysis, patients were divided in 3 groups: patients who had no DD/DR, those who had best objective response before

DD/DR and those who had best objective response after DD/DR. Median age at diagnosis was 65 years (range 37–90). Performance status (PS) was 0 or 1 in 98% of the patients. Patients who had best objective response after DD/DR were more likely to have higher baseline hemoglobin (p=0.01) and the number of decitabine cycles was significantly higher for patients who had best objective response before DD/DR (p<0.001). There were no other statistically significant differences in characteristics between the 3 groups of patients. Baseline characteristics are summarized in Table 1.

Response to treatment

Response to decitabine treatment is summarized in table 2. Overall, 74 (60%) patients responded, with 53 (43%) achieving a CR, 5 (4%) marrow CR (mCR), and 16 (13%) clinical benefit (CB). We then analyzed responses to treatment vis-a-vis the timing of DD/DR (Table 2). Sixty-five patients (53%) had DR by ≥ 25% or DD for a median of 7 days (range, 1 to 97). Thirty-five patients (28%) had achieved best objective response before DD/DR. In the other 30 patients who had DD/DR, responses continued to improve after DD/DR and best objective response was obtained after DD/DR. Twenty-five (20%) patients had both DD and DR. In the group of 35 patients who had achieved best objective response before DD/DR, 27 (77%) had a CR, 1 (3%) a mCR and 7 (20%) clinical benefit (CB). In the group of 30 patients who had DD/DR before achieving best objective response, 22 (73%) obtained a CR, 2 (7%) a mCR and 6 (20%) CB. DD occurred after a median of 2 courses, with a median of 4 delays per patient (range, 1 to 22). DR occurred after a median of 7 courses (range, 2 to 24) with a median reduction of 25% (Table 2). The median number of courses with DR was 6 (range, 1 to 18). The most common reasons for DD/DR were myelosuppression in 48 patients (74%) and infection in 10 patients (15%). The median number of courses to response was higher for patients who had DD/DR before achieving best objective response (median=3) compared to the other 2 groups of patients (median=2) (p=0.015). The total number of courses delivered for patients who had best objective response prior to DD/DR was higher (median=12) than patients who had DD/DR prior to best objective response (median= 10) or patient who had no DD/DR (median=3) (p<0.001). (Table 2)

Outcome

With a median follow-up of 81 months, the median progression free survival (PFS) and overall survival (OS) for the entire population of patients were 15 and 22 months, respectively. At the last follow-up, 11 (9%) patients are still alive and in CR, 4 of which had received an allogeneic stem cell transplant (ASCT) after achieving CR.

Next, we analyzed the outcomes of the 3 groups of patients based on occurrence and timing of DD/DR as defined above. There was a trend for more durable responses in favor of patients who achieved best objective response prior to DD/DR (median not reached) or patients who had no DD/DR (median not reached) compared to those who required DD/DR before best objective response (median of 16 months) (p=0.161)(Figure 1a). OS rates were significantly higher for patients who had achieved best objective response prior to DD/DR compared to those who had DD/DR prior to best objective response or those with no DD/DR (30 v/s 22 v/s 11 months, respectively, p<0.001) (Figure 1b). PFS rates also trended higher

for those with best objective response before DD/DR (median not reached) and those with no DD/DR (median not reached) compared to those who required DD/DR before best objective response (median of 15 months) (p=0.285) (Figure 1c).

Discussion

In this present analysis, we show that patients with MDS undergoing treatment with decitabine frequently encounter myelosuppression or infections that would lead the treating physician to reduce the dose(s) of decitabine or delay subsequent doses. This is particularly important in MDS since patients are expected to receive multiple courses over months to years especially in the case of favorable response to treatment. The effect of DD/DR was largely unknown and to our knowledge, this is the first report to address the effect of DD/DR on patients' outcomes.

We have demonstrated that, in cases where dose modification is necessary, DR/DD did not have a negative impact on outcome compared to patients who did not. Moreover, patients who achieved best objective response prior to DD/DR had better outcomes as compared to patients who get DD/DR prior to achieving best objective response. There was a trend for better PFS, longer duration of response, as well as a better OS when the treatment modification occurred only after achieving best objective response. This dose optimization is very important in securing a continuous exposure to the drug (median number of cycles given for this group of patients was 12 cycles) and thus a better outcome. The etiology of this phenomenon is likely multifactorial and may partially depend of the pharmacokinetic properties of decitabine. It is now well known that responses to decitabine and hypomethylating agents (HMA) in general are usually gradual in patients with MDS. [13] It may be due to progressive changes in the marrow microenvironment. One hypothesis to explain these differences in outcomes may be that a certain level of the drug is necessary to maintain a therapeutic effect. It was shown that a relatively low dose but better exposure, every 4 weeks for example, optimizes epigenetic modulation (hypomethylation induction, activation of p15INK4B) as well as clinical results. Thus, the level of hypomethylation may become undertherapeutic in case of DD/DR, especially before achieving best objective response, which could explain our findings.

Also, the better outcomes obtained for patients who had DD/DR only after obtaining best objective response highlights the importance of dose density in the treatment of MDS patients. This phenomenon has been well described in other hematologic malignancies, mainly chronic myeloid leukemia, in which the effect of dose reduction appeared to negatively influence outcomes if done prior to achievement of best objective response. Jain et al have shown that patients with CML treated with high doses of imatinib can be safely dose reduced once they have achieved a major cytogenetic response without having any impact on event free survival or transformation free survival.[14] Similarly, Jabbour et al have shown in their retrospective analysis of the DASISION trial comparing frontline imatinib and dasatinib in CML that timing of first dose reduction and/or interruption appeared to have a potential impact on efficacy.[15] Rates of major molecular response were found to be higher when first dose reduction and/or interruption occurred >6 months after treatment

initiation in both arms. Thus, maintaining dose dense decitabine schedule appears to be linked to better responses and outcomes.

In this analysis, we have shown that patients who had achieved best objective response prior to DD/DR are able to be maintained on treatment for a longer period of time (as documented by the higher number of cycles delivered), likely accounting for the improved outcomes. In our study, patients who achieved best objective response prior to DD/DR received a significantly higher number of cycles (median of 12 cycles), as compared to patients who needed DD/DR prior to best objective response or patients who had no DD/DR (median of 10 cycles and 3 cycles, respectively, $p<0.01$). This correlation between longer exposure and better outcomes has also been described recently by Jabbour et al who demonstrated that patients with DD/DR were able to receiver a greater median number of cycles of decitabine than those without DD/DR.[16] This is in line with the analysis of prognostic factors in patients with MDS by Kantarjian et al, in which they have shown that a longer duration of decitabine treatment improves response rates.[17]

There are few potential limitations in the current analysis. First, this is a retrospective analysis of data previously published about patients with MDS treated with decitabine at a single institution. These results will need to be confirmed in a prospective multicenter setting. Since it is now widely accepted that the 5-day IV schedule (20 mg/m^2) of decitabine has been is optimal, demonstrating a CR rate of 32%, compared with 21% with 5-day subcutaneous schedule and 24% in the 10-day IV schedule[6], an area for further research would be to undertake prospective DD/DR analyses in a broader population of patients treated with this regimen. Second, all patients analyzed in this study have been treated with decitabine. Although azacitidine is also a HMA which has similar activity and mechanism of action to decitabine, our data cannot be extrapolated and applied to DD/DR practices in MDS patients receiving AZA. Third, it is hard to draw conclusions regarding the effects of DD/DR in the SC schedule due to the limited number of patients in this subgroup. We recognize the importance of a subcutaneous schedule for ease-of-delivery and for other maintenance strategies. Thus, additional studies comparing the 5-day IV versus the 5-day SC schedules in larger numbers of patients may be warranted.

In conclusion, decitabine is effective in treating patients with MDS. In the present analysis, we demonstrated that DD/DR may be safely accomplished particularly in patients who have achieved the best objective response without impacting outcome. It is important for treating physicians to recognize that once best objective response is achieved, DD/DR may be warranted to possibly deliver as many cycles as possible and thus prolong survival in case of responders. Prospective evaluation of an approach conceiving a loading dose for induction of a best objective response followed by a maintenance schedule is to be considered for patients with MDS treated with decitabine and HMA in general.

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Clinical practice points

- Decitabine is standard treatment for MDS patients
- Myelosuppression is frequently encountered during decitabine treatment and leads to dose delays or reductions (DD/DR)
- DD/DR can be accomplished without impacting outcome particularly if done after obtaining best objective response
- A strict regimen of “induction” (with no DD/DR) followed by maintenance with less strict criteria for DD/DR may lead to better outcomes and must be investigated in prospective trials

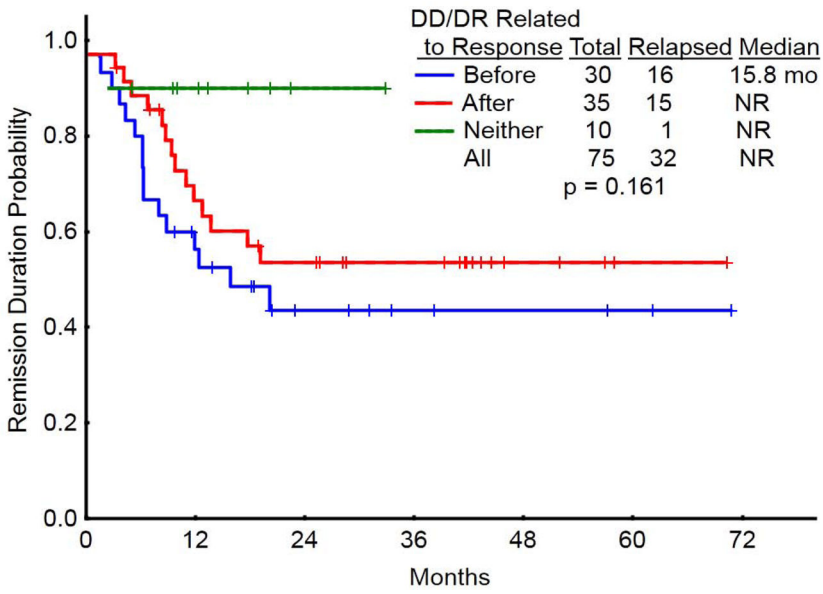

Figure 1.

Response Duration, DD/DR Before BOR vs. After BOR v/s no DD/DR

DD, dose delay; DR, dose reduction; BOR, best objective response; mo, months.

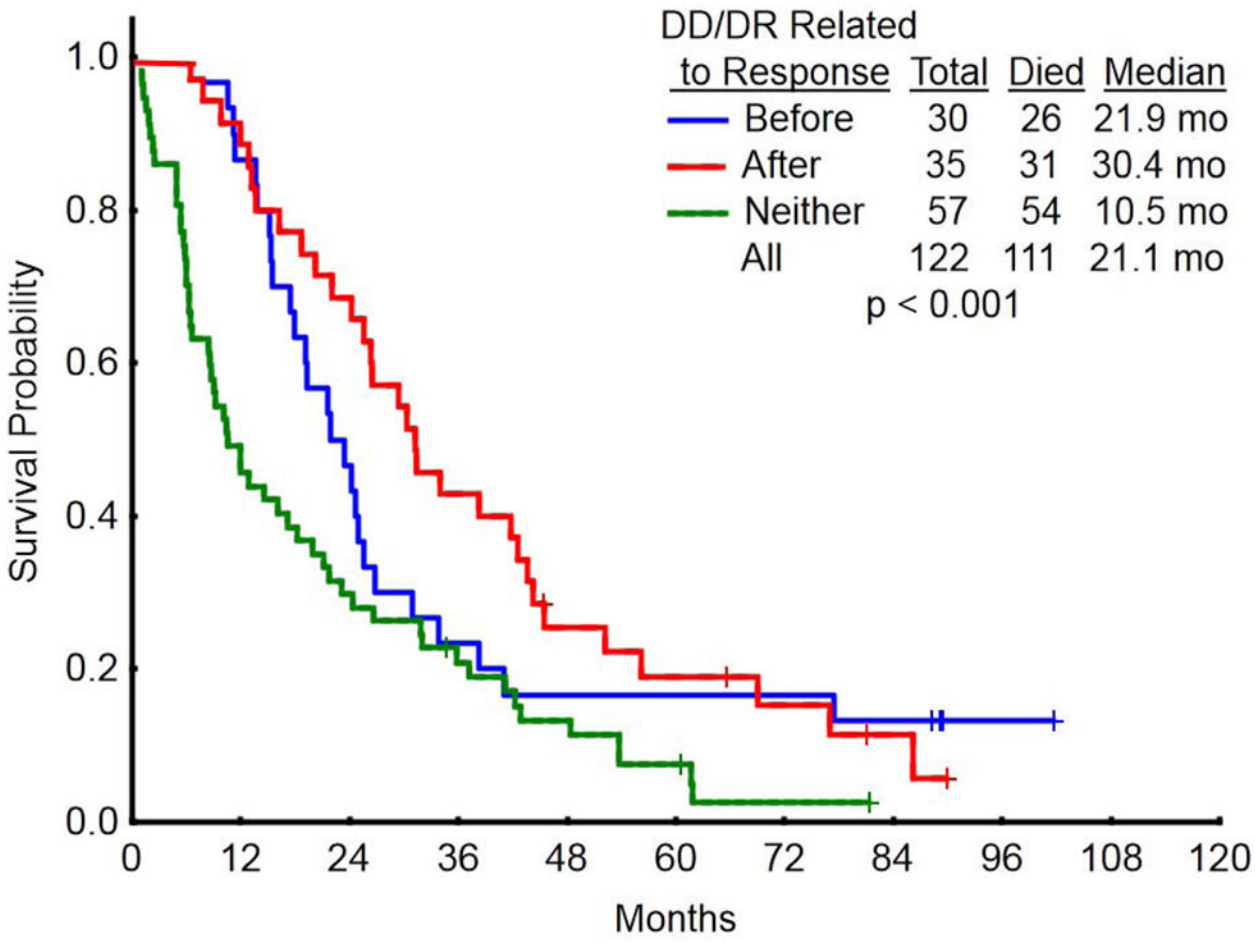

Figure 2.

Overall survival: DD/DR Before BOR vs. After BOR v/s no DD/DR

DD, dose delay; DR, dose reduction; BOR, best objective response; mo, months.

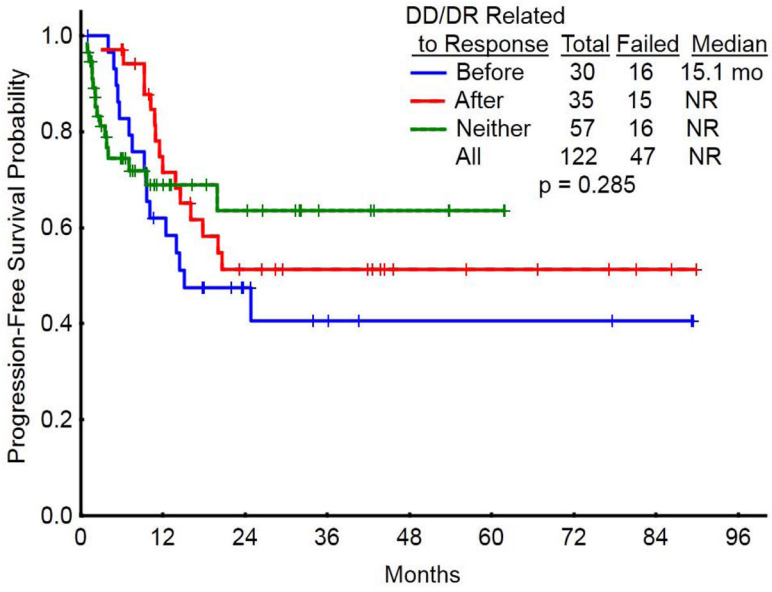

Figure 3.

Progression free survival: DD/DR Before BOR vs. After BOR v/s no DD/DR

DD, dose delay; DR, dose reduction; BOR, best objective response; mo, months.

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Table 1

Patients characteristics

Parameter	Value	BOR after DD/DR N (%)	BOR prior to DD/DR N (%)	No DD/DR, N (%)	Overall, N (%)	P value
N. of patients		30 (25)	35 (29)	57 (46))	122 (100)	
Arm of study	10 × 10mg/m2 IV	6 (20)	2 (6)	9 (16)	17 (14)	0.34
	5 × 20 mg/m2 IV	19 (63)	29 (83)	43 (75)	91 (75)	
	5 × 20 mg/m2 SC	5 (17)	4 (11)	5 (9)	14 (11)	
Follow up	Median (months)	89	73.3	60.5	81.3	<0.01
Age	Median (range)	64 (44–82)	65 (51–78)	66 (37–90)	65 (37–90)	0.98
Sex	Male	20 (66)	28 (80)	38 (66)	86 (70)	0.34
	Female	10 (34)	7 (20)	19 (34)	36 (30)	
PS	0	20 (67)	22 (63)	22 (39)	64 (52)	0.003
	1	8 (27)	13 (37)	35 (61)	56 (46)	
	2	2 (6)	0 (0)	0 (0)	2 (2)	
BM blasts	Median (range)	8 (2–26)	8 (0–20)	11 (2–25)	10 (0–26)	0.30
WBC (10^9 /L)	Median (range)	2.9 (91–66)	3.6 (1–90)	3.0 (1–62)	3.1 (1–90)	0.47
Hb (g/dl)	Median (range)	9.8 (7–12)	9.0 (6–15)	8.6 (6–13)	9.0 (6–15)	0.01
ANC (10^9 /L)	Median (range)	0.7(0.1–46)	1.3 (0.1–48.1)	1.2(0–27)	1.1 (0–48)	0.11
Plt (10^9 /L)	Median (range)	52 (9–253)	62 (4–413)	56 (3–822)	57 (3–822)	0.88
Cytogenetics	Diploid	12 (40)	17 (49)	19 (33)	48 (39)	0.48
	Xme 5 or 7 abnormality	8 (27)	8 (23)	22 (39)	38 (31)	
	Other	10 (33)	10 (28)	16 (28)	36 (30)	
IPSS (excluding CMML)	INT-2 and High	19 (63)	15 (42)	41 (72)	75 (61)	0.09
	Int-1 and low	5 (17)	10 (29)	7 (12)	22 (19)	
	N/A	6 (20)	10 (29)	9 (16)	25 (20)	

Parameter	Value	BOR after DD/DR N (%)	BOR prior to DD/DR N (%)	No DD/DR, N (%)	Overall, N (%)	P value
Secondary v/s de novo	De novo	22 (73)	23 (66)	41 (72)	86 (70)	0.76
	Secondary	8 (27)	12 (34)	16 (28)	36 (30)	
Growth factor support	ESA	15 (50)	14 (40)	31 (54)	60 (49)	0.41
	G-CSF	6 (20)	2 (6)	12 (21)	20 (16)	0.13
Number of courses	Median(range)	10 (2–23)	12 (1–24)	3 (1–17)	7 (1–24)	<0.01

DD, dose delay; DR, dose reduction; BOR, best objective response; N, number of patients; IV, intravenous; SC, subcutaneous; PS, ECOG performance status; BM, bone marrow; WBC, white blood cell count; Hb, hemoglobin; ANC, absolute neutrophil count; plt, platelet count; Xme, chromosome; IPSS, international prognostic scoring system; Int-2, Intermediate 2; Int-1, intermediate 1; N/A, not available; ESA, erythropoietin stimulating agent; G-CSF, granulocyte-colony stimulating factor.

Table 2

Best responses and timing of DD/DR

Parameter		BOR after DD/DR (N=30) N (%)	BOR prior to DD/DR (N=35) N (%)	No DD/DR N (%)	Overall N (%)	P value
Best response	CR	22 (73)	27 (77)	4 (7)	53 (43)	<0.001
	mCR	2 (7)	1 [9]	2 (4)	5 (4)	
	CB	6 (20)	7 (20)	3 (5)	16 (13)	
# Courses to response	Median (range)	3 (1–8)	2 (1–9)	2 (1–3)	2 (1–9)	0.015
Duration of response (months)	Median (range)	16 (1–70)	NR (0.2–70)	NR (2–33)	NR (0.2–70)	0.161
PFS	Median (range)	15 (0.9–89)	NR (3 –90)	NR (0.7–62)	NR (0.7–90)	0.29
OS	Median (range)	22 (8–102)	30 (6–90)	10 (0.8–81)	21 (0.8–102)	<0.001

DD, dose delay; DR, dose reduction; BOR, best objective response; N, number of patients; CR, complete remission; mCR, marrow complete remission; CB, clinical benefit; #, number; PFS, progression free survival; OS, overall survival.