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A Randomized Study of 2 Dose Levels of Intravenous Clofarabine in the Treatment of Patients With Higher-Risk Myelodysplastic Syndrome

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Abstract

BACKGROUND—Clofarabine is a nucleoside analog with activity in myeloid malignancies. Experience in myelodysplastic syndrome (MDS) is limited.

METHODS—The goal of this study was to evaluate the activity and safety of 2 different doses (15 mg/m² vs 30 mg/m² daily×5 days) of intravenous clofarabine in patients with higher-risk MDS. Fifty-eight patients with a median age of 68 years (range, 25–89) including 15 patients (28%) with secondary MDS and 35 patients (60%) who received prior DNA methyltransferase (DNMT) inhibitors were adaptively randomized between the 2 dose cohorts.

RESULTS—The overall response rate (ORR; based on a modification of International Working Group criteria) was 36% including 26% with complete remission (CR) (ORR, 41% at 15 mg/m² and 29% at 30 mg/m²). Responses were lower in patients who failed DNMT inhibitors (ORR, 17%; CR rate, 14%). The 8-week mortality rate was 19%. Median survival was 7.4 months for all patients, 13.4 months for responders, and 21.7 months for complete responders. Some adverse events, particularly hepatic and renal, were more severe (grade >2) in patients randomized to 30 mg/m² of clofarabine. Myelosuppression and infectious complications were frequent.

CONCLUSIONS—Both the lower and higher doses of clofarabine have comparable clinical activity, but the lower dose appeared less toxic. If these results are confirmed, lower doses of clofarabine, possibly in alternative schedules, should be pursued.

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CONFLICT OF INTEREST DISCLOSURES

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Keywords

myelodysplastic syndrome; clofarabine; nucleoside analogs; DNA methyltransferase inhibitors

INTRODUCTION

myelodysplastic syndrome (MDS) is a heterogeneous group of clonal hematopoietic stem cell disorder, characterized by dysplastic changes in myeloid, erythroid, or megakaryocytic progenitors and cytopenias in 1 or more cell lines.¹ The International Prognostic Scoring System provides a score to assess survival and risk of evolution to acute myeloid leukemia (AML) based on percentage marrow blasts, karyotype, and severity of cytopenias.^{2,3} The risk of progression to AML varies between 10% and 70%, and the median survival times range from 3.5–5.7 years to 0.4–1.2 years for lower-risk and higher-risk patients, respectively.

Given the considerable clinical heterogeneity, therapeutic decisions remain challenging for patients with MDS. Several drugs for MDS therapy have become available, such as lenalidomide for patients with transfusion-dependent 5 q– lower-risk MDS and DNA methyltransferase (DNMT) inhibitors (hypomethylating agents) for patients with a broader range of MDS. Complete remission (CR) rates remain low; responses are transient and mostly do not significantly outlast treatment duration.^{4–6} After patients lose their response to DNMT inhibitors, no therapeutic alternatives currently exist. Hence there is an ongoing need to expand the armamentarium of therapeutic options for patients with MDS.

Clofarabine is a newer generation nucleoside analog, which is similar in its molecular structure to fludarabine and cladribine, but has distinct features that expand its spectrum of activity.⁷ Besides its capacity to effectively inhibit DNA synthesis, it also causes disruption of mitochondrial membrane integrity with resultant release of proapoptotic proteins, and is an effective inhibitor of ribonucleotide reductase. The latter leads to intracellular depletion of natural nucleosides and thus enhanced uptake of the analog during DNA synthesis (self-potential). Furthermore, clofarabine has a higher affinity to deoxycytidine kinase, the rate-limiting enzyme in intracellular nucleoside phosphorylation, and a longer retention time of the triphosphate metabolite than do its predecessors.

Although there is more experience with clofarabine in adults with AML, earlier studies have also suggested clinical activity in MDS.^{8–10} By using an oral formulation of clofarabine at doses between 20 mg/m² and 40 mg/m² (with a bioavailability of around 55%) daily for 5 days, we reported an overall response rate (ORR) of 43% (25% CR rate), including a 30% response rate (10% CR) among patients who failed DNMT inhibitor therapy.¹¹

A commonly used dose of clofarabine in AML is 30 to 40 mg/m² intravenously (IV) daily × 5 days. We hypothesized that in MDS lower-dose schedules may still be as effective and less toxic. The current study tests the hypothesis by comparing lower (15 mg/m²/d × 5) doses of clofarabine to standard dose (30 mg/m²/d × 5) clofarabine.

MATERIALS AND METHODS

Study Group

Patients with a confirmed diagnosis of MDS based on World Health Organization (WHO) or French-American-British (FAB) Group criteria with marrow blasts $\geq 5\%$ or International Prognostic Scoring System intermediate-risk or high-risk status were eligible (Table 1).¹² All patients provided written informed consent according to institutional guidelines. Prior biologic or targeted therapies (eg, hypomethylating agents), or single-agent chemotherapy, with the exception of cytarabine at doses $\leq 1 \text{ g/m}^2$, were permitted. Patients receiving prior intensive multiagent chemotherapy were excluded. Hematopoietic growth factor support was allowed before therapy with clofarabine. Patients were required to have Eastern Cooperative Oncology Group performance status ≤ 2 , and adequate hepatorenal function (serum creatinine $<2 \text{ mg/dL}$; total bilirubin $<2 \text{ mg/dL}$; alanine aminotransferase [ALT] $<3 \times$ upper limit of normal). Patients were excluded for active and uncontrolled infections and other uncontrolled and severe intercurrent illnesses (eg, symptomatic congestive heart failure), and prior treatment with clofarabine. The study was approved by the institutional review board of The University of Texas MD Anderson Cancer Center and was conducted in accordance with the principles of the Declaration of Helsinki.

Treatment and Monitoring

Patients were adaptively randomized to 1 of 2 dose schedules: 15 mg/m^2 versus 30 mg/m^2 IV over 1 hour daily for 5 consecutive days. Courses were repeated every 4 to 8 weeks depending on resolution of toxicities and marrow recovery. In case of persistent disease, subsequent courses were started regardless of counts. In case of CR, continuation of therapy required recovery of neutrophil counts to $0.75 \times 10^9/\text{L}$ and platelet counts to $50 \times 10^9/\text{L}$. Any drug-related nonhematologic toxicities needed to have recovered to grade ≤ 1 before institution of the next course. Therapy was permitted for a maximum of 12 courses, unless patients had no response after ≥ 3 courses, progressed, or relapsed on therapy. Patients with stable disease could remain on therapy if it was thought to be in their best interest. Dose reductions (from 15 mg/m^2 daily $\times 5$ to 10, 7.5, or 5 mg/m^2 daily $\times 5$, and from 30 mg/m^2 to 20, 15, and 10 mg/m^2 , respectively) were implemented for prolonged marrow aplasia (marrow cellularity $\leq 5\%$ without evidence of disease by day ≥ 42), major infections, and any drug-related grade ≥ 3 nonhematologic toxicities. No escalation of clofarabine doses was allowed. Supportive care measures such as antibiotic prophylaxis (eg, levofloxacin, valacyclovir, and itraconazole or voriconazole), hematopoietic growth factors, and transfusions were provided as necessitated for optimal medical care of the patients. Antifungals were withheld on days when clofarabine was given to avoid exacerbation of liver function abnormalities. Inpatient administration of therapy was optional.

Patients were monitored with complete blood count/platelet count at least weekly during course 1 and at various frequencies as mandated thereafter. Creatinine, bilirubin, and ALT were monitored weekly during course 1 followed by once every 2 to 4 weeks while on therapy. Marrow aspiration (including cytogenetics if abnormal at study start) to document remission was required every 1 to 3 courses.

Response Criteria

CR was defined as normalization of blood counts with neutrophils $1 \times 10^9/\text{L}$ and platelet counts $100 \times 10^9/\text{L}$, and marrow blasts $\leq 5\%$. Hematologic improvement was defined as CR with the exception of a lack of platelet recovery to $100 \times 10^9/\text{L}$.¹³

Statistical Design

The primary endpoint of the study is assessment of efficacy of 2 different dose schedules of IV clofarabine as defined by response rate. Secondary endpoints include comparisons of response duration, survival, and toxicity of the patients in each of the 2 dose levels. Patients were randomized to receive either 15 mg/m² or 30 mg/m² using an adaptive procedure that based assignment probabilities on observed results in preceding patients according to the method by Berry.¹⁴ For the first 30 patients, the randomization was balanced with probability of $\frac{1}{2}$ to each of the 2 arms. Beginning with patient 31, and for each subsequent patient, data from all patients with evaluable response versus no response were incorporated using a Web-based data entry screen as provided by the Department of Biostatistics at The University of Texas MD Anderson Cancer Center. Assignment to a treatment was stopped if the probability that patients were assigned to this arm was $\leq 5\%$ or if there was an indication that a response rate of $\geq 20\%$ was not achieved. A treatment would only be selected as superior if there was sufficient evidence of superiority, whereas otherwise the trial would accrue up to a total of 60 patients and would be regarded as inconclusive. Continuous variables are summarized using the mean or median (range). The distribution of time-to-event endpoints (response duration, survival) were estimated using the Kaplan-Meier method. Response duration was calculated from response date to last follow-up. Survival was calculated from start of treatment date until death or last follow-up.

RESULTS

Characteristics of the Study Group

The characteristics of the patients are listed in Table 1. Greater than 80% of the patients were older than 60 years. Approximately $\frac{1}{4}$ of the patients had secondary MDS as defined by a preceding malignancy that was treated with chemotherapy, radiation, or both. About $\frac{2}{3}$ of the patients received some form of prior therapy for the MDS diagnosis, mostly in the form of azacitidine (29%) decitabine (43%), or both (12%). On the basis of the WHO classification, 58% of the patients had a diagnosis of refractory anemia with excess blasts (RAEB)-1 or RAEB-2, and the majority of the patients (78%) had intermediate-2 and high-risk MDS by the International Prognostic Scoring System. Fourteen patients (24%) had blasts between 20% and 29% and therefore carried a diagnosis of AML by WHO and RAEB in transformation (RAEBt) by FAB. Seventeen patients (29%) and 22 patients (38%) had intermediate and poor karyotypes, respectively. Assignment to cytogenetic groups was based on the International Prognostic Scoring System.² There were no statistically significant differences in any of these characteristics between the 2 treatment groups.

Response

All 58 patients have been evaluated for response. CR was achieved in 15 patients (26%) and hematologic improvement in 6 (10%) for an ORR of 36% (Table 2). Responses were similar in both dose cohorts (15 mg/m² vs 30 mg/m²), with no differences in rates of CR and possibly a trend for a better overall response in the group of patients who were treated with clofarabine 15 mg/m². Nine patients had a diagnosis of chronic myelomonocytic leukemia (CMML), and 3 (2 CR, 1 hematologic improvement) responded; the 2 CRs occurred at the 30-mg/m² dose level. Among the 14 patients with a diagnosis of AML (RAEB-t by FAB criteria), 6 patients responded (4 CR and 2 hematologic improvement). In these, all the responses occurred at doses of 15 mg/m² and none at 30 mg/m². The patient numbers in these subgroups are too small to allow for definite conclusions except for the findings that 1) patients with the diagnosis of CMML and AML (with blasts between 20% and 29%) had similar responses as the whole group; and 2) treatment at lower doses was as effective as at higher doses.

Fifteen patients had secondary MDS defined as a prior history of malignancy that had been treated with either chemotherapy, radiation or both. Five patients who had a prior malignancy but did not receive therapy or surgery only were not counted. Their ORR of 40% was comparable to that of the whole group, although all responses occurred at 15 mg/m² and none at 30 mg/m².

A particularly relevant subgroup is patients who have been exposed to prior therapy with DNMT inhibitors and either achieved no response to them or relapsed on them. Six of these 35 patients (17%) responded. Responses were equally divided between the 2 dose cohorts.

In multivariate analysis of factors including cytogenetics, prior exposure to DNMT inhibitors, and dose (15 mg/m² vs 30 mg/m²), prior treatment with DNMT inhibitors resulted in an independently significantly higher nonresponse rate (odds ratio [OR], 8.57; $P=.0001$). This was further confirmed by step forward multivariate analysis on all the baseline characteristics.

Survival, Response Duration, Mortality

Median duration of response was 8.8 months (range, 1–46+ months), and median survival 7.4 months (range, 0–48.2+ months), with no significant differences between the 2 groups with respect to either parameter (Figs. 1 and 2). Among responders, the median survival was 13.4 months (range, 2.3–48.2+ months) and 21.7 months (range, 3.9–48.2+ months) for those who have achieved a CR. The median number of cycles to response was 1 (range, 1–3). The 1-year survival probabilities were 37% overall (37% for patients treated at 15 mg/m²; 38% for patients treated at 30 mg/m²), and the 1-year progression-free survival was 39% (50%; 25%). None of the differences reached statistical significance. Mortality rates at 4 and 12 weeks are summarized in Table 3. Overall, 14 patients (24%) died within the first 12 weeks of therapy, with a trend for lower mortality rates at 15 mg/m² (7 patients [19%]) compared with 30 mg/m² (7 patients [33%]). Deaths were usually related to myelosuppression-associated infectious complications.

Treatment Administration and Consolidation Therapy

Given the known myelosuppressive nature of clofarabine and according to departmental treatment practice, 78% of the patients were treated in an inpatient facility, with a third of these patients staying for up to a month in a laminar air flow room (protective environment). The remainder of the patients received therapy in the outpatient setting. The decision regarding admitting patients to a laminar air flow room was mainly based on age ≥ 50 years (as has been the practice at The University of Texas MD Anderson Cancer Center for many years with regard to AML/MDS induction therapy). About half of the patients received hematopoietic growth factor support (mainly filgrastim) while on therapy with clofarabine. Almost all patients (83%) received concomitant therapy with prophylactic antibiotics (antifungal, antibacterial, and antiviral). Seventeen patients (29%) received consolidation therapy, which consisted of a median of 2 cycles (range, 1–12). Noncontinuation was mainly because of lack of response in combination with toxicities. Fifteen of these patients were in the 15-mg/m² group. Dose reductions during consolidation became necessary in 10 patients (59%), mostly because of myelosuppression and infectious complications during the preceding cycles of therapy.

Toxicities

Toxicities during the first course of therapy are summarized in Table 4. Almost all patients (n=95) experienced grade ≥ 2 toxicities; this was equal on each treatment arm. They mostly consisted of gastrointestinal adverse events, skin eruptions, and elevations of transaminases and/or bilirubin. Grade >2 toxicities were less frequent. However, there were more patients (52%) with grade 3 elevations of transaminases, bilirubinemia, and creatinine as well as acute renal failure, skin rashes, diarrhea, and mucositis with clofarabine at 30 mg/m² compared with the 15-mg/m² dose group (22%). The 30-mg/m² dose independently predicted for significantly higher rate of any toxicity (grade >2) by step forward multivariate analysis after considering covariates including creatinine, bilirubin, performance status, and prior exposure to DNMT inhibitors (OR, 3.99; $P=.02$). Nine patients (16%) developed elevations of the levels of creatinine, and another 4 patients (7%; 1 receiving the 15 mg/m² schedule and 3 the 30 mg/m² schedule) developed acute renal failure. Although in each of them the surrounding circumstances included infections, sepsis, and the use of nephrotoxic agents (vancomycin, aminoglycosides, amphotericin, furosemide), the outcome of these patients was poor. About 50% of the patients developed at least 1 infectious episode while on therapy.

DISCUSSION

Therapy of patients with MDS has improved substantially over the past few years with the availability of lenalidomide for lower-risk, transfusion-dependent patients and 5q– abnormality, and DNMT inhibitors for most of the remainder. Despite progress, trying to match the biological heterogeneity of MDS with effective therapies still leaves room for improvement. The prognosis remains poor for patients with higher-risk disease and especially those who have failed to respond or have relapsed on DNMT inhibitor therapy. In a study by Jabbour et al, the median survival for these patients was 4.3 months, and the estimated 12-month survival rate was 28%.¹⁵

Clofarabine is a second-generation deoxyadenosine analog with a long track record in the investigational treatment of adults with AML.^{16–18} As earlier studies indicated activity in patients with MDS, several clinical studies have focused specifically on these patients.⁹ Given the availability of an oral formulation of clofarabine (bioavailability of 55%), we reported our experience using 3 different doses (ranging from 20 to 40 mg/m² daily for 5 days) in a similar population of patients with MDS as in the current study.¹¹ The response rate was 43% for all patients and 30% for those failing prior therapy with DNMT inhibitors. A few tentative conclusions could be drawn: 1) clofarabine showed activity in patients with MDS, including poor prognostic groups; 2) lower doses appeared to achieve similar responses as higher doses but with the added benefit of better tolerability; and 3) there still remained questions about optimal dose, schedule, and target population. Although there is ongoing interest in optimizing the oral formulation of clofarabine (see below), the intravenous route remains attractive and has a longer track record above all in patients with AML, and also there is no defined best schedule in MDS.

In the current study, we therefore compared, in an adaptively randomized fashion, clofarabine IV 15 mg/m² versus 30 mg/m², daily ×5. We report an ORR of 36% (including a CR rate of 26%), an 8-week mortality rate of 19%, and a median overall survival of 7.4 months (13.4 months for responding patients). Responses in patients who have failed DNMT inhibitors were lower (17%). There is no large-scale experience of response rates to second-line therapy of patients who have failed DNMT inhibitor therapy, partly because of a lack of standard practice and hence a variety of different therapies that are being applied (if any). The lower response rate in this situation, however, is in keeping with our previous experience of oral clofarabine.¹¹ The side effect profile was consistent with previous reports. Although more patients were randomized to the lower-dose arm, the study was open until accrual was complete, and was not stopped prematurely, as the statistically defined stopping rules were not met. This means that the trial remained inconclusive regarding determination of a superior dose schedule. Nevertheless, from a clinical point of view, a few observations are important. As has also been shown in previous trials, lower doses (at least down to 15 mg/m²/dose) can achieve at least similar response rates as higher doses. In the multivariate analysis, more important than dose, however, was prior treatment with DNMT inhibitors. Dose had a bigger impact with respect to toxicities grade >2. Lower doses were better tolerated. Although the distribution of grade 2 toxicities did not differ much, there were more patients suffering from grade >2 adverse events with respect to renal insufficiency and elevations of transaminases and/or hyperbilirubinemia. Even at lower doses, clofarabine retains its myelosuppressive properties, and as a consequence, myelosuppression-related infections remain a major concern, and patients need close follow-up throughout their treatment course, although the treatment can be delivered on an outpatient basis.

The current study continues not to provide a definitive answer as to the definition of an optimal dose and schedule, nor does it answer the question of whether there is any advantage to the IV schedule over the oral formulation. Both appear comparable at equitoxic doses. The choice of an optimal dose and schedule remains problematic for a variety of reasons, including differences of pharmacokinetics between IV and oral administration of clofarabine, differences in toxicities because of patient selection and exposure to prior DNMT inhibitors, and distribution of patients with secondary versus primary MDS.

Although there is a trend to reduce the dose of clofarabine with the main purpose to decrease toxicity, there are also concerns that too low a dose (eg, $<15 \text{ mg/m}^2$) may sacrifice response. Unpublished data from an ongoing trial at The University of Texas MD Anderson Cancer Center suggest that a flat dose of 10 mg orally daily for 5 days may not be effective enough to pursue. Other investigators have taken a similar approach to us. Sekeres et al reported on 22 assessable patients with mainly higher-risk MDS who received 55 mg, 35 mg, or 25 mg of a fixed dose of oral clofarabine daily for 5 days every 4 weeks.¹⁹ The preliminary conclusion was that 55 mg was too toxic (2 of 4 patients died within 30 days), and that 25 mg had an acceptable safety (no induction deaths) and response profile (4 of 10 patients achieved a marrow remission). Unfortunately, there are no preclinical models, and trial designs are primarily made based on clinical empiricism. As DNMT inhibitors and clofarabine together might be more active, another ongoing study is evaluating a DNMT inhibitor alternating with clofarabine in patients with higher-risk MDS. Other schedules of clofarabine including lower doses given over a prolonged time >5 days are also being evaluated. Although currently no specific recommendation regarding an optimal schedule of clofarabine in MDS is possible, there is sufficient activity to warrant further clinical trials. Any promising lead from smaller single-institution trials should be validated and confirmed in larger multicenter clinical studies.

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Figure 1.
Remission duration is shown.

Figure 2.
Survival is shown.

Table 1**Patient Characteristics**

Characteristic	All	15 mg/m²	30 mg/m²
No.	58	37	21
Age			
Median, y	68	68	65
Range, y	25–89	25–89	34–83
60 years (%)	49 (84)	31 (84)	18 (86)
Male sex, No. (%)	38 (66)	24 (65)	14 (67)
Marrow blasts			
Median, %	12	14	10
Range, %	2–28	2–28	5–27
Marrow blasts ≥20%, No. (%)	7 (12)	6 (16)	1 (5)
Secondary MDS, No. (%)	15 (28) ^a	10 (31) ^b	5 (20) ^c
Prior radiation therapy	6 (11) ^a	3 (9) ^b	3 (15) ^c
Prior chemotherapy	13 (24) ^a	9 (28) ^b	5 (20) ^c
Prior radiation and chemotherapy	5 (9) ^a	2 (6) ^b	3 (15) ^c
Prior MDS therapy, No.			
Median	1	1	1
Range	0–3	0–3	0–2
Previous MDS therapy, No. (%)			
Azacitidine	17 (29)	14 (38)	11 (52)
Decitabine	25 (43)	11 (30)	6 (29)
Azacitidine and decitabine	7 (12)	3 (8)	4 (19)
Other ^d [+DNMT inhibitors]	11 (19)	10 (27)	1 (5)
WHO classification, No. (%)			
RA	1 (2)	1 (3)	0
RAEB-1	12 (21)	5 (14)	7 (33)
RAEB-2	22 (37)	15 (41)	7 (33)
CMML	9 (16)	6 (16)	3 (14)
AML	14 (24)	10 (26)	4 (20)
IPSS, No. (%)			
Int-1	9 (16)	8 (22)	1 (5)
Int-2	23 (40)	11 (30)	12 (57)
High	22 (38)	16 (43)	6 (29)
Other [CMML, AML]	4 (7)	2 (5)	2 (10)
IPSS cytogenetic group, No. (%)			
Intermediate	17 (29)	10 (27)	7 (33)
Poor	22 (38)	12 (32)	10 (48)

Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; DNMT, DNA methyltransferase; Int, intermediate; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; RA, refractory anemia; RAEB, refractory anemia with excess blasts; WHO, World Health Organization.

Cytogenetic subgroups were defined as established by Greenberg et al (good: normal, del (5q) only, del (20q) only, -Y only; intermediate: +8, single miscellaneous, double abnormalities; poor: complex or chromosome 7 abnormalities).²

DNMT inhibitor = azacitidine, decitabine.

^a Of 54 patients with available information.

^b Of 32 patients with available information.

^c Of 20 patients with available information.

^d Including farnesyltransferase inhibitors, lenalidomide, valproic acid, suberoylanilide hydroxamic acid, MGCD-0103 (benzamide histone deacetylase inhibitor).

Table 2**Response**

Patients	Dose, mg/m²	No.	CR, No. (%)	HI, No. (%)	All, No. (%)
All patients	15	37	10 (27)	5 (14)	15 (41)
	30	21	5 (24)	1 (5)	6 (29)
	All	58	15 (26)	6 (10)	21 (36)
With prior DNMT inhibitors	15	22	3 (14)	1 (5)	4 (19)
	30	13	2 (15)	0	2 (15)
	All	35	5 (14)	1 (3)	6 (17)
With secondary MDS	15	10	2 (20)	4 (40)	6 (60)
	30	5	0	0	0
	All	15	2 (13)	4 (27)	6 (40)

Abbreviations: CR, complete response; DNMT, DNA methyltransferase; HI, hematologic improvement; MDS, myelodysplastic syndrome.

Table 3

Mortality Rates at 4 and 12 Weeks of Therapy

Dosage	No.	4 Weeks, No. (%)	12 Weeks, No. (%)
15 mg/m ²	37	5 (14)	7 (19)
30 mg/m ²	21	3 (14)	7 (33)
All patients	58	8 (14)	14 (24)

Table 4**Toxicities**

Toxicity	15 mg/m ² (n=37)		30 mg/m ² (n=21)	
	2, No. (%)	>2, No. (%)	2, No. (%)	>2, No. (%)
Any	35 (95)	8 (22)	20 (95)	11 (52)
Nausea	23 (62)	1 (3)	12 (57)	1 (5)
Skin rash	14 (38)	2 (5)	6 (29)	2 (10)
Transaminase elevations	12 (32)	1 (3)	8 (38)	6 (29)
Diarrhea	10 (27)	—	5 (24)	1 (5)
Vomiting	9 (24)	—	7 (33)	1 (5)
Hyperbilirubinemia	6 (16)	1 (3)	4 (19)	2 (10)
Headache	5 (14)	1 (3)	4 (24)	—
Creatinine increase	2 (5)	1 (3)	3 (14)	3 (14)
Mucositis	4 (11)	1 (3)	—	1 (5)
Constipation	3 (8)	—	2 (10)	—
Pruritus	3 (8)	—	—	1 (5)
Myalgia/bone pain	2 (5)	—	1 (5)	1 (5)
Fatigue	2 (5)	—	—	1 (5)
Edema	2 (5)	—	1 (5)	—
Acute renal failure	—	1 (3)	—	3 (14)
Congestive heart failure	1 (3)	—	—	1 (5)
Weakness	1 (3)	—	—	1 (5)
Prolonged myelosuppression ^a	—	1 (3)	—	1 (5)
Intracranial hemorrhage	—	1 (3)	—	—
Tremor	1 (3)	—	—	—
Sensory neuropathy	1 (3)	—	—	—
Anorexia	1 (3)	—	—	—
Lower gastrointestinal bleeding	—	—	—	1 (5)

Toxicities during first course only.

^aNo recovery of counts and marrow cellularity by day 42.