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A real-world study of clofarabine and cytarabine combination therapy for patients with acute myeloid leukemia

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Abstract

Clofarabine and cytarabine (Clo + Ara-C) combinations have efficacy in treatment of acute myeloid leukemia (AML). We retrospectively analyzed clinical outcomes of 71 AML patients receiving Clo + Ara-C regimens at the University of Minnesota from 2011 to 2016: 44 patients (62%) had newly diagnosed AML and 27 patients (38%) had relapsed/refractory AML. The median age of patients was 69 years (interquartile range [IQR], 63–75 years). Nearly 60% of the patients had secondary AML, and about half of patients had adverse risk cytogenetics. Objective response rate (ORR) was 42% in all patients with complete remission (CR) rate of 20%. Progression-free survival (PFS) at 2 years was 16% (95% CI 8–27%) and overall survival (OS) at 2 years was 21% (95% CI 11–33%) for all patients. The 30-day mortality rate was 18%. Clo+Ara-C- containing regimens are an acceptable upfront therapy option for patients who are not candidates for “7+3” induction, but do not induce durable remissions.

Keywords

Clofarabine; cytarabine; acute myeloid leukemia; myeloid leukemias and dysplasias; chemotherapeutic approaches; Ara-c

Introduction

Anthracycline and cytarabine-based induction chemotherapy (“7 + 3”) remains the standard of care for first treatment of acute myeloid leukemia (AML) for patients who are fit for

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intensive therapy [1]. Alternative treatment regimens for patients who are elderly or frail include hypomethylating agents or low-dose cytarabine. These less intensive, non-curative treatments have low objective response rates (ORR) of 15–20% [2–4]. However, median overall survival ranges from 7.7 months to 24.5 months with hypomethylating agents, despite similar response rates, which suggests additional disease modifying effects beyond response rates [2,3,5].

Cytarabine's activity in highly proliferative hematologic malignancies has led to development of newer nucleoside analogs including fludarabine, cladribine and clofarabine. Clofarabine, a derivative of cladribine, is a second-generation nucleoside analog with enhanced properties including high lipophilicity, increased cell uptake, greater affinity for key enzymes involved in DNA synthesis, resistance to phosphorolytic cleavage and deamination, and ability to induce direct mitochondrial damage and downregulate anti-apoptotic proteins [6,7]. In-vitro studies demonstrate synergy with cytarabine via clofarabine-induced deoxy-cytidine kinase (dCK) activity, which enhances accumulation of AraC triphosphate intra-tumorally [8].

Initial clinical studies of clofarabine combined with cytarabine (Clo + Ara-C) showed ORR of 60–75% in newly diagnosed patients with AML [9–11]. A study of a younger population of AML and high-risk MDS patients used clofarabine 50 mg/m² and cytarabine 1 g/m² on days 1–5 with ORR 60% and CR of 52% ($n = 60$) [9]. Clofarabine 30 mg/m² has also been combined with cytarabine 20 mg daily for 14 days with ORR 63% and median OS 11.4 months ($n = 70$) [12]. Compared to clofarabine alone, the combination had higher response rate, but no survival advantage. Addition of clofarabine 10 mg/m² to idarubicin and cytarabine induction in newly diagnosed younger and middle-aged AML patients did not improve CR rates or OS, but led to shortened time to CR and delayed hematopoietic recovery [13].

Relapsed/refractory (R/R) AML is a challenging disease to treat with poor outcomes. Regimens such as mitoxantrone and etoposide (ME), fludarabine, cytarabine, idarubicin, and G-CSF (FLAG-IDA), or intermediate-dose cytarabine (IDAC) with or without anthracycline can induce remissions in 25–40% of R/R patients [14]. The randomized CLASSIC I clinical trial in patients with R/R AML reported encouraging overall response rates (ORR; 46% vs. 23%, $p < .01$) with combination Clo+Ara-C as compared to clofarabine monotherapy, although with higher 30-day mortality and no difference in overall survival [15].

In this study, we report on our institutional experience of Clo + Ara-C at the University of Minnesota for treatment of AML in both upfront and salvage settings.

Methods

Patient selection

Patients in this retrospective analysis were adults (≥ 18 years) with diagnosis of non-APL AML receiving Clo + Ara-C chemotherapy at the University of Minnesota from 2011 to 2016. The electronic medical record was queried for patients with diagnosis of AML who received combination of Clo+Ara-C for treatment. Drug dosages and patient characteristics

were verified by review of the medical record. This study was reviewed and approved by University of Minnesota Institutional Review Board.

Study definitions and endpoints

AML was defined as bone marrow or peripheral blood myeloid blast count $\geq 20\%$, or AML with t(8;21), inv(16), or t(16;16) [16]. No patients had acute promyelocytic leukemia. Secondary AML was defined as AML evolved from prior hematopoietic neoplasm. Therapy-related AML was defined as patients with AML who had previously received cytotoxic chemotherapy. Response definitions were based on 2017 European Leukemia Net Recommendations [16]. Complete remission (CR) was defined as bone marrow blasts $<5\%$ by morphology and absence of circulating blasts or extra-medullary disease with hematologic recovery (absolute neutrophil count $\geq 1.0 \times 10^9/\text{L}$, platelet count $\geq 100 \times 10^9/\mu\text{L}$). CR with incomplete count recovery (CRi) was defined as meeting criteria for CR without hematologic recovery. ORR was defined as CR+CRi. Persistent disease (PD) was defined as not meeting criteria for CR or CRi. Death from indeterminate cause was defined as death occurring before completion of therapy, death <7 days following its completion, or death ≥ 7 days after completion of therapy with no blasts in the blood, but no bone marrow examination available. Death in aplasia was defined as death ≥ 7 days after completion of therapy while cytopenic, with aplastic or hypoplastic bone marrow obtained within 7 days of death, and without evidence of PD.

Newly diagnosed disease included patients without prior leukemia-directed therapy with or without need for re-induction at day 14 for PD. Relapsed disease was defined as relapse after at least one line of induction therapy, with exclusion of PD at day 14 after “7 + 3” induction therapy receiving re-induction with Clo + Ara-C. Refractory disease was defined as failure to attain CR following at least two courses of induction therapy. PD included $>5\%$ blasts by morphology on day 14 bone marrow biopsy after “7 + 3” induction therapy.

Toxicity data were obtained retrospectively by medical chart review and as per Common Terminology Criteria of Adverse Events (CTCAE) version 4.0. Fungal infection was defined as possible, probable, or proven by EORTC/MSG criteria [17]. Charlson Comorbidity Index (CCI) was used for comorbidity assessment [18].

Primary endpoint of the study was ORR. Secondary endpoints were disease-free survival, overall survival, adverse events, and 30-day mortality. Subgroup analysis included de novo versus therapy-related/secondary AML, white blood cell (WBC) count <30 or $\geq 30 \times 10^9$ cells/L, newly diagnosed versus R/R disease, dosage of Clo + Ara-C, and re-induction at day 14 of primary treatment versus primary induction.

Statistical analyses

Statistical comparisons of categorical factors were completed with the chi-square or Fisher's exact test, if expected cell counts were too small. Continuous factors were compared by general Wilcoxon rank test for non-parametric data. Unadjusted estimates of overall and progression-free survival (PFS) were calculated by Kaplan–Meier curves [19]. Comparisons were completed with the log-rank test. All reported p-values were two-sided. SAS 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Patient characteristics

A total of 71 adult patients were identified as receiving treatment with Clo + Ara-C for AML: 44 patients (62%) had newly diagnosed AML and 27 patients (38%) had R/R AML (Table 1). The median age of patients was 69 years (IQR 63–75), with age of R/R patients significantly younger as compared to newly diagnosed patients (median age 60 [IQR 49–71] vs. 71 years [IQR 66–76], $p < .01$). CCI scores were similar in newly diagnosed and R/R groups, with 18% of all patients having high scores of 8. Nearly 60% of all patients had secondary AML, and about half of patients had adverse cytogenetics (similar in newly diagnosed and R/R populations). Of those with molecular testing, molecular studies showed 18% (10 of 55) FLT3/*ITD* mutation, 12% (6 of 51) NPM1 mutation and 3% (1 of 32) CEBPA biallelic mutation. Ten patients received Clo+Ara-C as re-induction for PD at day 14 after upfront “7+3” induction therapy. This group had high rate of therapy-related/secondary AML (80%) and adverse cytogenetics (60%). Of R/R patients, 13 patients (48%) had 3 prior therapies and 15 patients (56%) had prior allogeneic transplantation. Median follow-up of all patients was 17 months (range, 10–33 months).

Treatment

The most common dosing regimen used in 53 patients (75%) was intravenous (IV) clofarabine 20 mg/m² daily on days 1–5 and subcutaneous (SQ) cytarabine 20 mg twice daily on days 1–10 (“5 + 10”) [10]. This regimen was more commonly used in newly diagnosed patients (84% vs 59%, $p = .02$) than in R/R patients. Other regimens ($n = 18$, 25%) included IV clofarabine with dose ranging from 20 to 60 mg/m² on days 1–5 or days 2–6 and IV cytarabine with dose ranging from 0.5 to 2 g/m² on days 1–5 or days 2–6 (Table 1).

Response to clofarabine and cytarabine chemotherapy

The ORR to Clo + Ara-C chemotherapy was 42% ($n = 30$) for all patients with CR rate of 20% ($n = 14$, Table 2). In newly diagnosed patients, ORR was 50% ($n = 22$) and CR rate was 27% ($n = 12$). In R/R patients, ORR was 29% ($n = 8$) and CR rate was 7% ($n = 2$).

Nine patients died during the course of Clo+Ara-C chemotherapy: cause of death included disseminated fungal infection ($n = 4$), bacterial sepsis ($n = 3$), and respiratory failure ($n = 2$). They were considered not evaluable for disease response, but included in the analysis.

For “5 + 10” regimen of Clo + Ara-C, ORR was 42% with 19% CR rate: 46% ORR and 24% CR in 37 newly diagnosed patients and 38% ORR and 6% CR in 16 R/R patients. For other Clo + Ara-C-containing regimens ($n = 18$), ORR was 44% with 22% CR rate: 71% ORR (5 of 7) and 42% CR (3 of 7) in newly diagnosed patients and 27% ORR (3 of 11) and 9% CR (1 of 11) in R/R patients.

Of 11 patients who had re-induction with Clo + Ara-C at day 14, ORR was 73% ($n = 8$) and CR rate was 36% ($n = 4$). Ten of these patients were newly diagnosed and had received “7 + 3” as initial induction prior to receiving Clo + Ara-C for residual leukemia at day 14,

whereas 1 patient had R/R AML and had received mitoxantrone and etoposide as induction on day 1. The median time from primary induction (day0) until re-induction with Clo+Ara-C was 16 days (range, 13–26 days). There were no cases of chemo-therapy-induced aplasia.

ORR was not significantly different in de novo versus therapy-related/secondary AML subgroups (53% vs. 34%, $p = .09$), adverse vs. favorable/intermediate cytogenetics (35% vs. 49%, $p = .26$), WBC <30 or $30 \times 10^9/L$ (41% vs. 47%, $p = .78$), or age <70 years or ≥ 70 years (38% vs. 47%, $p = .43$). For patients with FLT3/*ITD* mutation, ORR was 50% (5 of 10). In those treated with Clo + Ara-C after post-allogeneic transplantation relapse, ORR was 33% (13% CR).

Clinical outcomes of responders

Median time to objective response was 28.5 days (range, 20–74 days) for all patients.

Median duration of response among patients achieving CR or CRi ($n = 30$) was 5.1 months (range, 4 days to 52 months), similar in newly diagnosed and R/R patients (4.1 vs. 5.7 months, $p = .13$).

A total of 16 patients (22%) had consolidation with allogeneic transplantation following Clo + Ara-C. Of transplanted patients, 15 patients received one cycle of Clo + Ara-C and one patient received two cycles of induction with Clo + Ara-C to achieve CR/CRi prior to transplant. Forty-three percent ($n = 7$) of transplanted patients had adverse cytogenetics. Ten patients were alive at last follow-up, and seven remain in remission. Of eight transplanted patients who died, cause of death was relapse ($n = 4$), infection ($n = 1$), graft-versus-host disease ($n = 1$), and intracranial hemorrhage ($n = 1$). Of patients who had objective response to Clo + Ara-C but did not receive allogeneic transplant ($n = 17$), 11 were alive at last follow-up, with seven in remission.

Progression-free survival and overall survival

Median PFS from first dose of Clo+Ara-C was 1.2 months (3.4 months for newly diagnosed and 1.1 months for R/R patients) and median OS was 5.9 months (6.3 months for newly diagnosed and 4.8 months for R/R patients). PFS probability at 2 years was 16% in all study patients: 24% in newly diagnosed patients and 7% in R/R patients ($p = .02$, 95% CI 8–27%) (Figure 1(b)). Overall survival probability at 2 years was 21% in all patients (Figure 1(a)): 30% in newly diagnosed patients and 9% in R/R patients ($p = .12$, 95% CI 11–33%). Primary causes of death were relapse (70%, $n = 35$), followed by infection (22%, $n = 11$) and other causes (8%, $n = 4$). Among patients with objective response (CR + CRi) to Clo + Ara-C, there was no difference in OS or PFS among those who were transplanted vs. not transplanted (Figure 1(c,d)).

Toxicities

Adverse effects from induction therapy are shown in Table 3. Infectious complications included bacterial infection in 68% ($n = 48$), invasive fungal infection in 15% ($n = 11$), and viral infection in 4% ($n = 3$). Grade III–IV organ toxicities included hepatotoxicity (20%, $n = 14$), gastrointestinal (GI) toxicity (18%, $n = 13$), cardiotoxicity (14%, $n = 10$), nephrotoxicity or electrolyte abnormalities (44%, $n = 31$; 14 patients with nephrotoxicity, 11

patients with hypophosphatemia, four patients with hypokalemia, two patients with hyperkalemia, one patient with hyponatremia), neurotoxicity (13%, $n = 9$), respiratory toxicity (23%, $n = 16$), and other organ toxicity (24%, $n = 17$). Other grade III–IV organ toxicities included malnutrition ($n = 8$), skin ($n = 2$), thrombosis ($n = 1$), and anaphylaxis ($n = 1$).

Invasive fungal infections consisted of aspergillus ($n = 1$) with ($n = 4$), zygomycetes ($n = 1$), candida ($n = 1$), rhodotorula ($n = 1$), and acremonium majority of infections localized (seven patients with pneumonia, one with skin infection, one with sinusitis) and two disseminated infections. Ten of 11 patients with probable or proven fungal infections received Clo+Ara-C for newly diagnosed AML. Fungal prophylaxis was most commonly voriconazole ($n = 5$), followed by fluconazole ($n = 3$), and micafungin ($n = 1$). Two patients had fungal infection diagnosed at time of AML, so were not on prophylaxis prior to treatment. Patients who had undergone prior allogeneic transplantation ($n = 15$) had similar rates of grade III–IV toxicity, with 31% nephrotoxicity or electrolyte abnormalities, 27% hepatotoxicity, 53% bacterial infections, 20% GI toxicity, 20% other toxicity, 13% respiratory toxicity, 7% viral infections, and no severe cardiotoxicity, neurotoxicity, or probable/proven invasive fungal infections. Clo + Ara-C chemotherapy was associated with 30-day mortality rate of 17% ($n = 12$) in all study patients: 20% (9 of 44) in newly diagnosed patients and 11% (3 of 27) in R/R patients.

Discussion

In these patients with newly diagnosed and R/R AML, we report our experience of treatment with combination Clo + Ara-C. Our patient population was elderly and with aggressive disease biology as indicated by high rates of secondary AML, adverse cytogenetics and WBC counts $>30 \times 10^9/L$ at time of treatment. Prior studies have shown that “7 + 3” remains the best induction option for elderly patients with good performance status, but a significant proportion of elderly patients with AML may not be fit for intensive therapy or have cardiomyopathy limiting anthracycline use [20]. With ORR 50% and CR rate of 27%, Clo+Ara-C combination therapy may be best suited for those who have had reached lifetime dose of anthracycline or with preexisting cardiomyopathy precluding use of “7 + 3.”

We observed a similar 30-day mortality rate (17%) as other studies of Clo + Ara-C [10–12,21]. Chemotherapy-related toxicities and early death rate with Clo + Ara-C are not clearly more favorable than those reported for newly diagnosed elderly patients treated with “7 + 3” regimens [22,23]. Newly diagnosed patients in our study had higher 30-day mortality than R/R patients (20% vs. 11%), likely due to patient selection with older age and more comorbidities in newly diagnosed group.

Other studies have shown that single agent clofarabine in newly diagnosed elderly patients with secondary AML, high blast count, and adverse cytogenetics who were not fit for intensive therapy has both acceptable efficacy (46% ORR, 38% CR) and low toxicity (30-day mortality of 10%) [24]. The decision to add Ara-C to clofarabine should consider performance status of patients, as increase in toxicity may reduce any gains in disease response [15]. Other less-intensive regimens such as azacitidine have reported early death

rate of 10%, and may preferred for patients with low bone marrow blast count and poor performance status [3]. Decitabine given in a 10-day schedule has shown efficacy in *TP53* mutated AML and MDS, a particularly aggressive molecular subtype of disease [25].

R/R patients treated with Clo+Ara-C had poor outcomes with ORR of 30% and median PFS of only 1.1 months. In this heavily pre-treated population, about half who had relapsed AML after allogeneic transplantation, the rates of therapy response are expected to be low. Our results are comparable to those reported in the Clo + Ara-C arm of the CLASSIC 1 trial which treated a similar patient population with respect to adverse cytogenetics and age ($n = 320$) [15]. Other groups have used various doses of Clo+Ara-C for R/R AML, with reported ORR ranging from 39% to 61%, CR rate of 33–46%, and median OS of 6–9 months [11,21,26,27].

One setting that Clo + Ara-C may be beneficial for is re-induction therapy for persistent leukemia on day 14 after initial “7 + 3” induction ($n = 10$). This strategy was effective and tolerable soon after initial induction, with no cases of chemotherapy-induced aplasia. Changing chemotherapy regimens at day+14 has not been shown to be superior to re-inducing with 7+3, but may be preferred for patients who are reaching their maximal lifetime anthracycline dose, such as those with therapy-related AML [28].

The high relapse potential in high-risk AML remains a challenge. Despite 42% of patients achieving CR or CRi, durable remissions are rare as evidenced by low 2-year OS and PFS with Clo + Ara-C (21% and 16%, respectively). Although almost half of responding patients received consolidation with allogeneic transplantation, they did not have significant improvement in PFS and OS compared to those who did not receive transplant. This observation is likely due to our small numbers of patients, as it has been previously demonstrated in larger studies that allogeneic transplantation improves survival for intermediate and adverse risk AML in first remission [29]. However, neither chemotherapy nor alloHCT consolidation preserve durable remissions for the majority of patients with high-risk AML. In elderly alloHCT recipients, we previously reported that disease risk index is the most important prognostic factor for relapse and survival [30]. Elderly patients who achieve CR and/or receive alloHCT should be encouraged to enroll in clinical trials of maintenance and consolidation strategies whenever possible.

Clo + Ara-C-containing regimens may be considered an acceptable alternative to “7 + 3” as upfront therapy in elderly patients who are not candidates for “7 + 3,” but remissions are not durable. Induction mortality rate is comparable to that of “7 + 3,” so we would not consider it a less toxic alternative for frailer patients. We show that this regimen can be used safely and effectively as day-14 re-induction chemotherapy for PD. For R/R AML, Clo+Ara-C can induce remission in about one-third of patients including those with aggressive cytogenetic and molecular subtypes, but remissions are short-lived for most patients, emphasizing the need for novel molecular and immunotherapy treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) OS at 2 years (b) PFS at 2 years (c) OS among CR/CRi at 2 years post-remission (d) PFS among CR/CRi at 2 years post-remission. R/R indicates relapsed/refractory.

Table 1.

Patient characteristics.

	Diagnosis			p-Value
	Total	New diagnosis	Relapsed/refractory	
N	71	44	27	
Age				<.01
25–59	15 (21%)	2 (5%)	13 (48%)	
60–69	22 (31%)	16 (36%)	6 (22%)	
70	34 (48%)	26 (59%)	8 (30%)	
Median (IQR)	69 (63–75)	71 (66–76)	60 (49–71)	<.01
Gender: male	46 (65%)	30 (68%)	16 (59%)	.44
Charlson Comorbidity Index				.10
2–3	21 (30%)	10 (23%)	11 (41%)	
4–7	37 (52%)	23 (52%)	14 (52%)	
8	13 (18%)	11 (25%)	2 (7%)	
AML type				.43
De novo	30 (42%)	17 (39%)	13 (48%)	
Therapy related/secondary	41 (58%)	27 (61%)	14 (52%)	
Cytogenetics				.84
Favorable	3 (4%)	2 (5%)	1 (4%)	
Intermediate	32 (45%)	21 (48%)	11 (41%)	
Adverse	34 (48%)	20 (45%)	14 (52%)	
Missing	2 (3%)	1 (2%)	1 (4%)	
Molecular				
CEBPA				.21
No	32 (45%)	20 (45%)	12 (44%)	
Yes	1 (1%)	0	1 (4%)	
Missing	38 (53%)	24 (55%)	14 (52%)	
NPM1				.27
No	45 (63%)	27 (61%)	18 (67%)	
Yes	6 (8%)	5 (11%)	1 (4%)	

	Diagnosis			p-Value
	Total	New diagnosis	Relapsed/refractory	
Missing	20 (28%)	12 (27%)	8 (30%)	.11
FLT3-ITD				
No	45 (63%)	26 (59%)	19 (70%)	
Yes	10 (14%)	3 (7%)	7 (26%)	
Missing	16 (23%)	15 (34%)	1 (4%)	NE
New diagnosis				
New	44 (62%)	44 (100%)	0	
Prior RX (1–2 regimens)	14 (20%)	0	14 (52%)	
Prior RX (3 regimens)	13 (18%)	0	13 (48%)	.40
Prior AlloHCT	15 (21%)	0	15 (56%)	
WBC at diagnosis				
<30 × 10 ⁹ /L	54 (76%)	32 (73%)	22 (81%)	
30 × 10 ⁹ /L	17 (24%)	12 (27%)	5 (19%)	.85
Median (range)	6.8 (0.3–164)	6.9 (0.8–136.0)	6.7 (0.3–164.0)	
Dosing regimen				
IV Clof 20 mg/m ² , SQ Cyt 20 mg (.5 + 10 ⁶)	53 (75%)	37 (84%)	16 (59%)	.02
Other	18 (25%)	7 (16%)	11 (41%)	
IV Clof 40–60 mg/m ² D1–5, IV Cyt 0.5–1g/m ² (D2–6)	12 (17%)	7 (16%)	5 (19%)	
IV Clof 20–30 mg/m ² D1–5, IV Cyt 1–2g/m ² (D2–6)	6 (8%)	0	6 (22%)	
Months of follow-up				
Median (range)	17 (1–54)	17 (1–53)	12 (9–54)	

AML: acute myeloid leukemia; WBC: white blood cell; IQR: interquartile range.

Table 2.

Disease outcomes.

Factors	N	All (%)	New (%)	R/R (%)
N	71		44	27
Day 28 response				
CR	14	(20%)	12 (27%)	2 (7%)
CRi	16	(22%)	10 (23%)	6 (22%)
Relapse	32	(45%)	15 (34%)	17 (63%)
Death from indeterminate cause	8	(11%)	6 (14%)	2 (7%)
Death in aplasia	1	(1%)	1 (2%)	0
AML disease response by subgroup	N	Frequency (%) (% CR, CRi)		p-Value
Age				.43
<70	37	14 (38%)		
70	34	16 (47%)		
Cytogenetics				.26
Favorable/intermediate	35	17 (49%)		
Adverse	34	12 (35%)		
Diagnosis				.09
New	44	22 (50%)		
R/R ^a	27	8 (30%)		
Prior transplant				.43
No	56	25 (45%)		
Yes	15	5 (33%)		
Clof/Cyt dose regimen				.83
5 + 10	53	22 (42%)		
Other	18	8 (44%)		

AML: acute myeloid leukemia; CR: complete remission; CRi: CR with incomplete count recovery; R/R: relapsed/refractory.

Table 3.

Induction complications.

	All patients	Frequency (%)	New	Frequency (%)	R/R	Frequency (%)	p-Value
Renal toxicity (Gr III—IV)	14	(20%)	11	(25%)	3	(11%)	.15
Electrolyte (Gr III—IV)	17	(24%)	13	(30%)	4	(15%)	.16
Cardiotoxicity (Gr III—IV)	10	(14%)	8	(18%)	2	(7%)	.30
Neurotoxicity (Gr III—IV)	9	(13%)	9	(20%)	0		.01
Respiratory (Gr III—IV)	16	(23%)	13	(30%)	3	(11%)	.07
Hepatotoxicity (Gr III—IV)	14	(20%)	8	(18%)	6	(22%)	.68
GI toxicity (Gr III—IV)	13	(18%)	10	(23%)	3	(11%)	.34
Other (Gr III—IV)	17	(24%)	13	(30%)	4	(15%)	.16
Bacterial infection	48	(68%)	34	(77%)	14	(52%)	.03
Fungal infection (probable/proven)	11	(15%)	10	(23%)	1	(4%)	.04
Viral Infection	3	(4%)	2	(5%)	1	(4%)	.86

R/R: relapsed/refractory.