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Does High-Dose Cytarabine Cause More Fungal Infection in Patients With Acute Myeloid Leukemia Undergoing Consolidation Therapy

A Multicenter, Prospective, Observational Study in China

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Abstract: Invasive fungal infection (IFI) remains as a significant cause of morbidity and mortality in patients with acute myelogenous leukemia (AML). Here, we report the subgroup analysis of China Assessment of Antifungal Therapy in Haematological Disease (CAESAR) study to evaluate the risk of IFI in patients with AML in 1st remission receiving high-dose cytarabine (HiDAC) as consolidation. A total of 638 patients with AML in 1st complete remission were selected from the database. Among them, 130 patients received HiDAC alone with total dose of 2–3 g/m^2 × 6 while 508 patients received multiple-agent combination chemotherapy (multiagent chemo group). The patients' characteristics were generally not different but more patients in HiDAC group had peripherally inserted central catheter (61.5% vs 44.5%, $P = 0.002$). The median duration of neutropenia was 8.0 days in both HiDAC (2–20) and multiagent chemo group (2–28). Number of patients with prolonged neutropenia (>14 days) tended to be more in multiagent chemo group but not significant different (16.3% vs 8.8%, respectively). There was no significant difference between 2 groups in persistent neutropenic fever (40.8% vs 33.1%), antifungal treatment (11.5% vs 11.4%), and incidence of proven/probable IFI (4 probable in HiDAC vs 1 proven/4 probable in multiagent chemo, $P = 0.35$) or possible IFI. As to the clinical outcome in terms of duration of hospitalization and death in remission, there was a trend of shorter duration of hospitalization in HiDAC (19 days, 3–70) compare to multiagent chemo group (21 days, 1–367, $P = 0.057$) while no death documented in HiDAC group and only 2 patients died in the multiagent chemo group (0.4%). As to risk factors associated with IFI in all 638 patients, there was a trend of more IFI in patients with severe neutropenia (3.0%, $P = 0.089$) and previous history of IFI (3.85%, $P = 0.086$) while the antifungal prophylaxis was not associated significantly reduced IFI. Overall, our data support the perception that HiDAC alone as consolidation in first remission AML patients was well tolerated and not associated with increased hematological toxicity and IFI than conventional combination chemotherapy. Antifungal prophylaxis may not necessary except for patients with previous history of IFI.

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Abbreviations: AML = acute myeloid leukemia, CAESAR = China Assessment of Antifungal Therapy in Haematological Disease, CR = complete remission, Flud = fludarabine, HiDAC = high-dose cytarabine, IFI = invasive fungal infection, IntDAC = intermediate-dose cytarabine.

INTRODUCTION

Invasive fungal infection (IFI) remains as a significant cause of morbidity and mortality in patients with acute myelogenous leukemia (AML).[1–3] Prolonged neutropenia after chemotherapy is one major risk factor for developing IFI.[4] Neutropenia duration is mainly affected by the age of patients, disease status, and intensity of the chemotherapy. For patients with AML undergoing induction, reinduction, or allogeneic hematopoietic cell transplantation, longer and/or more severe neutropenia puts patients at a higher risk for developing IFI.[4–6]

High-dose cytarabine (HiDAC) is the standard consolidation treatment for adult patients with AML.[7,8] In a retrospective study, HiDAC was considered as the leading cause of increased IFI in patients receiving induction chemotherapy compare to patients with chemotherapy without HiDAC.[9] Another clinical report showed that HiDAC is a major risk factor for the development of hepatosplenic candidiasis.[10] Although there is a strong consensus that HiDAC regimen is a risk factor

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for IFI, and antifungal prophylaxis is warranted and recommended by clinical guidelines, using antifungal prophylaxis after HiDAC as consolidation treatment for AML in remission remains controversial.[11–14] More recently, a retrospective analysis in 27 patients receiving 76 cycles of HiDAC demonstrated that HiDAC as consolidation therapy was associated with low-risk of fungal infection and the incidence of documented IFI, empirical intravenous antifungal use and duration of antibiotic use were not increased.[15]

To illustrate the risk of IFI for patients with AML in 1st remission receiving HiDAC as consolidation therapy, we performed a subgroup analysis in a prospective observational study of 4889 patients (China Assessment of Antifungal Therapy in Haematological Disease study, CAESAR study) focusing on epidemiology, risk factors, and prognosis of IFI receiving chemotherapy for hematological malignancy in China.[16] We compared the incidence of IFI and antifungal use in patients receiving HiDAC regimen with other combination chemotherapy consolidation.

METHODS

Study Design

As previously reported, the CAESAR study was a multiple-center observational study to evaluate the incidence and treatment outcome of IFI in patients with hematological malignancy.[16] Patients' characteristics including diagnosis, chemotherapy or conditioning regimen, known IFI risk factors, microbiology study, diagnosis of IFI, and antifungal therapy were collected by case report form. The diagnosis of proven, probable, or possible IFI was according to European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group 2008 criteria.[17] The study was conducted in line with the Declaration of Helsinki, International Conference on Harmonization/Good Clinical Practice and study protocol including informed consent were approved by the Ethics Committee from all participating hospitals.

For our study, we set up the following criteria to include patients in the analysis from the CAESAR study database: patients age less than 60, diagnosed with AML in 1st remission receiving consolidation chemotherapy, and consolidation therapy with HiDAC with total dose $\geq 12\,g/m^2$ ($2–3\,g/m^2 \times 6$) alone without any other chemotherapy versus all other consolidation with multiple agents chemotherapy.

Data Analysis

Data analysis were conducted by independent contract research organization as previously reported.[16] Only patients with proven and probable IFI were included for the calculation of IFI incidence. Statistics were based on analysis of variance (ANOVA), Wilcoxon rank-sum test, or χ^2 test. Risk factors analysis for IFI was based on univariate analysis with $P \leq 0.05$ as statistically significant.

RESULTS

Patient Characteristics

A total of 638 patients with 1st remission AML were selected from the database as show in Table 1. Among these patients, 130 patients received HiDAC alone with minimal $12\,g/m^2$ ($2–3\,g/m^2 \times 6$) as consolidation while 508 patients received multiple agent chemotherapy, which included 493 patients with standard-dose cytarabine combined with anthracyclins and 15 patients received fludarabine and intermediate-dose cytarabine ($0.5–2\,g/m^2 \times 5$, Flud + IntDAC, n = 15).

Comparison of HiDAC With Multiagent Chemo

The overall base-line characteristics of patients such as sex, comorbidity, diabetes mellitus, Epstein–Barr virus viremia, CMV viremia, low albumin, and number of previous chemotherapy were nonsignificantly different between 2 groups. The median age in the HiDAC group tended to be higher than the multiagent chemo group (41 vs 36.5, $P = 0.06$) so as patients with history of previous IFI (16.9% vs 11%, $P = .07$), but not statistically significant. Of note, more patients in the HiDAC group had peripherally inserted central catheter than patients with multiagent consolidation (61.5% vs 44.5%, $P = 0.002$) and also for abnormal liver function after chemotherapy (12.3% vs 4.9%, $P = 0.004$) as shown in Table 1. Both factors are considered as risk factors of IFI based on the outcome of original CAESAR study.[16]

The duration of chemotherapy induced neutropenia was similar between 2 groups of patients as shown in Table 1. Median duration of neutropenia was both 8.0 days (2–20) in the HiDAC and multiple-agent chemo group (2–28). Number of patients with prolonged neutropenia (>14 days) tended to be more in patients in multiagent chemo group but not significant different (16.3% vs 8.8%, respectively). As to the neutropenic fever, there was no significant difference between 2 groups (40.8% vs 33.1%).

Overall, 73 patients received antifungal treatment during the inpatient chemotherapy, including 15 (11.5%) in HiDAC group and 58 (11.4%) in the multiagent chemo group. The incidence of IFI was documented as probable in 4 patients in HiDAC group with 1 proven plus 4 probable in multiagent chemo group without statistic difference ($P = 0.35$). Besides, another 8 and 23 patients were identified as possible IFI in HiDAC and multiagent chemo group, respectively, as shown in Table 2.

As to the clinical outcome in terms of duration of hospitalization and death in remission, there was a trend of shorter duration of hospitalization in the HiDAC group (19 days, 3–70) compare to 21 days (1–367) in the multiagent chemo group ($P = 0.06$). There was no death in remission documented in patients in HiDAC group while only 2 patients died in the multiagent chemo group (0.4%) without any statistical difference.

Comparison of HiDAC With Flud + IntDAC

Based on previous report, HiDAC and use of fludarabine was considered as high-risk for infection and/or IFI,[19] thus though with limited number, we further evaluated the Flud + IntDAC as a single group and compared to HiDAC group as shown in Table 3.

The baseline characteristics of patients such as age, sex, history of IFI, and number of previous chemotherapy were not significantly different between 2 groups. More patients in the Flud + IntDAC group received antifungal prophylaxis as shown in Table 3. Although the duration of neutropenia is not significant in the 2 groups (median 8.0 days in both groups), more patients with Flud + IntDAC presented with profound neutropenia (86.7% vs 35.4%, $P = .003$). As to the incidence of IFI and patient receiving antifungal treatment were not significantly different between 2 groups. Of note, the duration of hospitalization was prolonged in patients with Flud + IntDAC (median 19 vs 26, $P = 0.009$) as shown in Table 4.

TABLE 1. Clinical Characteristics of AML Patients Undergoing Consolidation Chemotherapy in 1st Remission

Parameters		HiDAC (N = 130)	Multiagent Chemo (N = 508)	*P* Value
Age	Median	41.0	36.5	0.056
	Min, max	1.0, 58.0	1.0, 59.0	
Sex	Male	71 (54.6%)	251 (49.4%)	0.33
	Female	59 (45.4%)	257 (50.6%)	
Comorbidity	Yes	23 (17.7%)	115 (22.6%)	0.24
	No	107 (82.3%)	393 (77.4%)	
Diabetes mellitus	Yes	5 (3.8%)	17 (3.3%)	0.79
	No	125 (96.2%)	491 (96.7%)	
Epstein–Barr virus viremia	Yes	—	2 (0.4%)	0.81
	No	22 (16.9%)	96 (18.9%)	
	Not evaluable	108 (83.1%)	410 (80.7%)	
CMV viremia	Yes	—	2 (0.4%)	0.70
	No	22 (16.9%)	99 (19.5%)	
	Not evaluable	108 (83.1%)	407 (80.1%)	
Abnormal liver function	No	112 (86.2%)	480 (94.5%)	0.0044
	ALT 2–5 N	16 (12.3%)	25 (4.9%)	
	ALT ≥5 N	2 (1.5%)	3 (0.6%)	
Central venous line	No	43 (33.1%)	246 (48.4%)	0.0021
	PICC	80 (61.5%)	226 (44.5%)	
	Other	7 (5.4%)	36 (6.1%)	
Low albumin	Yes	13 (10.0%)	40 (7.9%)	0.48
	No	117 (90.0%)	468 (92.1%)	
History of IFI	Yes	22 (16.9%)	56 (11.0%)	0.073
	No	108 (83.1%)	452 (89.0%)	
No of previous chemo*	<=3	64 (49.2%)	238 (46.9%)	0.27
	4–6	52 (40.0%)	186 (36.6%)	
	>6	14 (10.8%)	84 (16.5%)	
Antifungal prophyalxis	Yes	34 (26.2%)	136 (26.8%)	0.91
	No	96 (73.8%)	372 (73.2%)	

The consolidation chemotherapy included 3 to 4 cycles of HiDAC and 3 to 4 cycles of mutliagent regimen according to the Chinese Consensus of AML treatment.[18] ALT = alanine transaminase, AML = acute myeloid leukemia, HiDAC = high-dose cytarabine, IFI = invasive fungal infection, PICC = peripherally inserted central catheter.

* Cycles of induction and consolidation chemotherapy received.

TABLE 2. Clinical Outcome of AML Patients Undergoing Consolidation Chemotherapy in 1st Remission

Parameters		HiDAC	Multiagent chemo	*P* Value
Duration of ANC−<−500, days	<7	20 (35.1%)	70 (30.8%)	0.36
	7–14	32 (56.1%)	120 (52.9%)	
	>14	5 (8.8%)	37 (16.3%)	
	Median	8	8	
	Min, max	2, 20	2, 28	
Persistent fever	Yes	53 (40.8%)	168 (33.1%)	0.12
	No	77 (59.2%)	340 (66.9%)	
Antifungal treatment	Yes	15 (11.5%)	58 (11.4%)	1.00
	No	115 (88.5%)	450 (88.6%)	
IFI diagnosis	Proven	—	1 (0.2%)	0.35
	Probable	4 (3.1%)	4 (0.8%)	
	Possible	8 (6.2%)	23 (4.5%)	
	No	118 (90.7%)	480 (94.5%)	
Death	No	130 (100.0%)	506 (99.6%)	1.00
	Yes	—	2 (0.4%)	
Days of hospitalization	Median	19	21	0.057
	Min, max	3, 70	1, 367	

AML = acute myeloid leukemia, ANC = absolute neutrophil count, HiDAC = high-dose cytarabine, IFI = invasive fungal infection.

TABLE 3. Comparison of HiDAC Vs. Flud + IntDAC

		HiDAC (N = 130)	Flud + IntDAC (N = 15)	*P* Value
Age	Median	41.0	41.0	0.89
	Min, max	1.0, 58.0	14.0, 58.0	
Sex	Male	71 (54.6%)	9 (60.0%)	0.78
	Female	59 (45.4%)	6 (40.0%)	
No of conso-chemo	1–2	20 (15.4%)	3 (20.0%)	0.086
	3–4	71 (54.6%)	10 (66.7%)	
	5–6	25 (19.2%)	1 (6.7%)	
	7–10	14 (10.8%)	—	
	>10	—	1 (6.7%)	
Previous IFI	Yes	22 (16.9%)	2 (13.3%)	1.00
	No	108 (83.1%)	13 (86.7%)	
Prophylaxis	Yes	34 (26.2%)	8 (53.3%)	0.037
	No	96 (73.8%)	7 (46.7%)	
Duration of (ANC < 500, day)	<7	20 (35.1%)	2 (15.4%)	0.31
	7–14	32 (56.1%)	9 (69.2%)	
	>14	5 (8.8%)	2 (15.4%)	
	Total	57 (100.0%)	13 (100.0%)	
	Median	8	8	0.44
	Min, max	2, 20	6, 16	
Neutropenia	ANC >= 1000	57 (43.8%)	2 (13.3%)	0.0031
	500 <= ANC < 1000	8 (6.2%)	—	
	100 <= ANC < 500	19 (14.6%)	—	
	ANC < 100	46 (35.4%)	13 (86.7%)	

ANC = absolute neutrophil count, HiDAC = high-dose cytarabine, IFI = invasive fungal infection, IntDAC = intermediate-dose cytarabine.

Risk Factors Associated With IFI in Complete Remission (CR)1 AML

Based on our database, we further analyzed risk factors associated with IFI in all patients with CR1 AML receiving consolidation chemotherapy as shown in Table 5. There was a trend of more IFI occurred in patients with severe neutropenia after consolidation (3.0%, $P = 0.09$) and patients with previous history of IFI (3.85%, $P = 0.09$). The duration of neutropenia and the cycles of chemotherapy received by patients were not associated with increased incidence of IFI. Moreover, it seems that the antifungal prophylaxis did not reduce significantly the incidence of IFI (1.07% vs 2.35%, $P = 0.26$) as shown in Table 5.

TABLE 4. Clinical Outcome of HiDAC Compare to Flud + IntDAC

		HiDAC (N = 130)	Flud + IntDAC (N = 15)	*P* Value
Persistent fever	Yes	53 (40.8%)	6 (40.0%)	1.00
	No	77 (59.2%)	9 (60.0%)	
Antifungal treatment	Yes	15 (11.5%)	3 (20.0%)	0.40
	No	115 (88.5%)	12 (80.0%)	
IFI therapy	Empyrical	7 (53.8%)	2 (66.7%)	1.00
	Pre-emptive	5 (38.5%)	1 (33.3%)	
	Target	1 (7.7%)	—	
	Total	13 (100.0%)	3 (100.0%)	
	No	117	12	
IFI diagnosis	Probable	4 (33.3%)	1 (100.0%)	0.38
	Possible	8 (66.7%)	—	
	Total	12 (100.0%)	1 (100.0%)	
	Miss	118	14	
Death	No	130 (100.0%)	15 (100.0%)	1.00
	Yes	0	0	
Hospitalization	Median	19	26	0.0088
	Min, max	3, 70	7, 80	

Flud = fludarabine, HiDAC = high-dose cytarabine, IFI = invasive fungal infection, IntDAC = intermediate-dose cytarabine.

TABLE 5. Risk Factors Associated With IFI in Patients With AML CR1

Risk Factors		No Patients	IFI (n)	IFI (%)	*P* Value	RR (95% CI)
Cycles of chemotherapy	>=5	231	2	0.87	0.59	
	3–4	243	5	2.06		2.38 (0.47–12.13)
	1–2	163	2	1.23		1.42 (0.20–9.96)
Neutropenia	500 <= ANC < 1000	45	0	0.00	0.089	
	ANC < 100	233	7	3.00		—
	100 <= ANC < 500	95	1	1.05		—
	ANC >= 1000	265	1	0.38		—
Duration of ANC < 500, day	>14	42	0	0.00	0.52	
	7–14	152	5	3.29		—
	<7	90	1	1.11		—
Previous IFI	No	560	6	1.07	0.086	
	Yes	78	3	3.85		3.59 (0.92–14.06)
Prophylaxis	No	468	5	1.07	0.26	
	Yes	170	4	2.35		2.20 (0.60–8.11)

AML = acute myeloid leukemia, ANC = absolute neutrophil count, CI = confidence interval, CR = complete remission, HiDAC = high-dose cytarabine, IFI = invasive fungal infection, RR = risk ratio.

DISCUSSION

Chemotherapy with HiDAC in AML as a risk factor for IFI and the benefit of antifungal prophylaxis after HiDAC remains undetermined.[12,15] The concern of IFI risk mostly derived from early randomized studies in patients with previously untreated AML receiving induction therapy with high-dose versus standard-dose Ara-C combined with anthracyclins, which demonstrated that HiDAC in induction therapy was associated with increased toxicity in terms of profound and prolonged neutropenia and potentially higher incidence of IFI.[20,21]

In our study, though more patients in the HiDAC group present high-risk features such as peripherally inserted central catheter and history of IFI,[16] the overall infectious episode in terms of persistent fever after chemotherapy, the incidence of IFI, and overall antifungal treatment were not different from patients in the multiagent chemo group. Our data support the 2 previous European studies, which demonstrated the low-risk of IFI in patients receiving HiDAC as consolidation without antifungal prophylaxis.[22,23] It is well established that neutropenia is the dominant risk factor for IFI and particularly prolonged duration of severe neutropenia ($ANC < 0.1 \times 10^9$/L) for more than 3 weeks is key high risk factor of IFI.[19,24,25] Of note, in our study, only 35% of patients in the HiDAC group had severe neutropenia while most patients (91.2%) had neutropenia less than 14 days, which was not different from multiagent chemo group and other previous studies. The limited number of patients with severe neutropenia and/or with prolonged duration of neutropenia in the HiDAC group observed in the analysis may explain partially the low risk of IFI in our study.[12,19] Another possible reason is the impact of remission status on the risk of IFI. It has been shown that failure to enter remission but not neutropenia was independent risk factor for IFI following remission-induction for AML.[26] The CAESAR study also demonstrated that the incidence of IFI was significantly higher in patients receiving chemotherapy for induction therapy (4.95%) compare to patients in remission (1.00%, $P < 0.001$).[16] This dominant impact of remission status on risk of IFI is highlighted by our data which showed that all potential risk factors such as severe neutropenia, duration of neutropenia, and previous IFI documented in the original CAESAR study lost significance in patient with AML in their 1st remission.

Moreover, when we evaluated the toxicity of consolidation chemotherapy in terms of clinical outcome such as duration of hospitalization and death in remission, our data demonstrated that HiDAC was comparable to multiagent consolidation chemotherapy. Therefore, we may conclude that HiDAC has low to moderate toxicity in patients with AML in remission and HiDAC consolidation is overall well tolerated with related low risk of IFI.

It is believed that increased number of HiDAC cycles is associated with increased risk of cumulative toxicity.[27] Actually no clinical studies demonstrated increased mortality and even the frequency of neutropenic fever, the duration of neutropenia, and neutropenic fever were also not increased by the HiDAC cycle number as in consolidation.[15,28–31] Although it is impossible to illustrate the risk of IFI in patients with multiple cycles of HiDAC, we analyzed the possible correlation of the risk of IFI with increased cycles of consolidation chemotherapy in all patients with 1st remission AML and showed that overall there was no increased risk of IFI along with increased chemotherapy cycles in these patient (as shown in Table 5).

The dose of cytarabine consolidation remains to be determined, though 2–3 g/m^2 was mostly used in clinical setting. The recent Medical Research Council AML15 Trial demonstrated that in consolidation, there was no important difference between cytarabine given at the 3 or 1.5 g/m^2 dose level in terms of relapse risk and overall survival. Although there were modest differences in hematologic toxicity, significantly more supportive care and hospitalization was deployed in the 3 g/m^2 cytarabine group. These may imply that cytarabine at 1.5 g/m^2 regimen can achieve similar clinical outcome with even lower incidence of profound cytopenia and potential risk of IFI.[32]

It is reported that adding chemotherapy such as etoposide to HiDAC causes more significant gastrointestinal damage, which was implicated as the major factor leading to substantially increased rate of IFI.[9] More recently, fludarabine with HiDAC with or without idarubicin (FLAG ± Ida) has been used as salvage chemotherapy in relapse/refractory AML and also

occasionally as consolidation.[33] Fludarabine is considered as a powerful immunosuppressant and fludarabine with HiDAC is associated with a prolonged inhibition effect on lymphopoiesis and myelosuppression, which suggests that this regimen may place patients in high-risk category of IFI.[19] In a retrospective report of 112 courses in 76 patients, 121 episodes of fever were documented, which 45% were classified as pyrexia of unknown origin and 18 were due to proven or probable pulmonary aspergillosis giving an incidence of 16%.[19] In another retrospective analysis, the overall incidence of infection and IFI was not significantly increased compared to conventional induction therapy.[34] In our analysis, though few patients received fludarabine and intermediate-dose Ara-C as consolidation therapy, a more severe neutropenia and prolonged hospitalization were observed. Although no difference of IFI in terms of proven, probable or possible, and actual antifungal treatment was documented, which partly due to limited number of patients in the Flud + IntDAC group and much higher number of patients received antifungal prophyalxis (53.3% vs 26.2% in HiDAC group), our data still suggested that adding fludarabine to IntDAC or HiDAC is associated with significant hematological toxicity which may be associated to potential risk for infection including IFI.

The benefit of antifungal prophylaxis after HiDAC consolidations remains undetermined. In an early randomized study in neutropenic cancer patients, fluconazole prophylaxis was effective in patients with AML who were undergoing induction therapy with cytarabine plus anthracycline-based regimens but risk of failure of antifungal prophylaxis was significantly less for patients in postremission consolidation.[35] Similarly, in our series, there is also no benefit of antifungal prophylaxis in patients receiving consolidation chemotherapy. Moreover, a previous study demonstrated that there was no difference in IFI between patients with AML undergoing HiDAC consolidation with or without fluconazole prophylaxis ($P = 0.47$).[15] Based on the low incidence of IFI with HiDAC in patients in remission, we may speculate that there is limited benefit of antifungal prophylaxis in this setting, thus do not require antifungal therapy except for patients with previous history of IFI.

The obvious limitations of this study were the observational nature, variation of chemotherapy such as dose of cytarabine or different anthrancyclins used and reliance on diagnostic information that was mainly based on participating hospital procedure and partly incomplete. Another interesting issue concerning the use of colony-stimulation factors was not included in the initial CEASAR study. In the Cochrane systemic review, adding G-CSF does not adversely influence all-cause mortality, CR, or relapse rates in patients with AML, and the benefit is limited to reduction of neutropenic and febrile days.[36] More recently, a randomized study in recipients of allogeneic stem cell transplantation demonstrated that prophylactic GM-CSF rather than G-CSF was associated with lower incidence of IFI-related mortality.[37] Although it is a common practice in clinical setting to use G-CSF as a part of supportive care after induction and consolidation chemotherapy in patients with AML in China, the exact role of G-CSF in the prevention or treatment of IFI is remained to be determined. Nevertheless, comparable with previous published studies, our data do support the perception that HiDAC alone was not associated with increased hematological toxicity and high risk of IFI as consolidation therapy particularly compare to other multiple-agent chemotherapy.

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