RESEARCH LETTER

blood advances

TO THE EDITOR:

Invasive fungal infections after CLAG-M/CLAG chemotherapy for acute myeloid leukemia and high-grade myeloid neoplasms

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Invasive fungal disease (IFD) is a major treatment complication in patients with acute myeloid leukemia (AML) and other high-grade myeloid neoplasms.[1,2] CLAG-M (cladribine, high-dose cytarabine, granulocyte–colony-stimulating factor/filgrastim, and mitoxantrone) is a contemporary (re)induction chemotherapy regimen with encouraging response rates and clinical outcomes.[3-7] However, because of the inclusion of cladribine and use of higher doses of cytarabine, CLAG-M is associated with increased myelosuppression, which may result in a higher risk of infection.[8]

With current management strategies, the overall IFD rate in this patient population ranges between 13% and 18%[9-11] and is associated with significant morbidity, mortality, and expense.[1,2,12,13] Although mold-active antifungal prophylaxis (M-PPX) has an established role in prevention of IFD, its use is recommended based on more traditional chemotherapy regimens,[1,2,14] and with evolving leukemia treatment strategies, the specific benefits of M-PPX require re-evaluation.[12]

In this retrospective, single-site cohort study, we examine the incidence and patterns of IFD during treatment with CLAG-M/CLAG, and compare these with IFD patterns following 7 + 3/HiDAC ([cytarabine and anthracycline]/[high-dose cytarabine]) regimens. We identified proven/probable and possible IFDs (as per a modified 2008 EORTC/MSGERC definitions;[15]supplemental Material) after chemotherapy cycles in adults aged ≥18 years with newly diagnosed (ND) or relapsed/refractory (R/R) AML or other high-grade myeloid neoplasms. Patients were treated between 2006 and 2018 at the Fred Hutchinson Cancer Center/University of Washington. End points were captured either up to 180 days from the start of cycle 1, 90 days from the start of the patients' last chemotherapy cycle (up to 5 cycles), or until hematopoietic cell transplant, last clinical visit, or death, whichever occurred first. The study was approved by the Fred Hutchinson Cancer Center Institutional Review Board. Chemotherapy treatment details and definitions are described in the supplemental Material. Standard primary antifungal PPX consisted of fluconazole 200 mg daily (non–M-PPX) during severe neutropenia before

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The full-text version of this article contains a data supplement.

Table 1. Demographics

	CLAG-M ND	CLAG-M R/R	7 + 3	Total
n	195	137	115	447
Age, median (range), y	62.2 (18.6-84.4)	57.0 (19.3-82.6)	57.1 (20.2-78.8)	59.4 (18.6-84.4)
Female, n (%)	83 (43)	60 (44)	50 (43)	193 (43)
Ethnicity, n (%)				
Hispanic or Latino	4 (2)	2 (1)	4 (3)	10 (2)
Not Hispanic or Latino	187 (96)	114 (83)	39 (34)	340 (76)
Unknown	4 (2)	21 (15)	72 (63)	97 (22)
Race, n (%)				
White	162 (83)	114 (83)	84 (73)	360 (81)
Black/African American	9 (5)	2 (1)	4 (3)	15 (3)
Asian	15 (8)	10 (7)	8 (7)	33 (7)
American or Alaskan Native/Pacific Islander	7 (4)	8 (6)	13 (11)	28 (6)
Unknown/mixed	2 (1)	3 (2)	6 (5)	11 (2)
Primary disease, n (%)				
AML	154 (79)	109 (80)	104 (90)	367 (82)
Myelodysplastic syndrome	29 (15)	23 (17)	11 (10)	63 (14)
Other	12 (6)	5 (4)	0 (0)	17 (4)
Secondary disease, n (%)	71 (36)	39 (28)	27 (23)	137 (31)
Performance status, n (%)				
0	35 (18)	22 (16)	2 (2)	59 (13)
1	152 (78)	94 (69)	92 (80)	338 (76)
2	6 (3)	16 (12)	16 (14)	38 (9)
3	2 (1)	4 (3)	3 (3)	9 (2)
Treatment-related mortality score, median (range)	3.0 (0.0-96.0)	0.1 (0.0-84.0)	20.0 (0.0-93.0)	3.0 (0.0-96.0)
No. of prior therapies, n (%)				
0	137 (100)	0	115 (100)	252 (56)
1	0	39 (28)	0	39 (28)
2	0	57 (42)	0	57 (42)
≥3	0	41 (30)	0	41 (30)
Prior hematopoietic cell transplant, n (%)	0	36 (26)	0	36 (8)
Active graft-versus-host disease at baseline, n (%)	0	2 (1)	0	2 (0.4)
Baseline absolute neutrophil count, median (range)	2.0 (0.0-95.1)	1.7 (0.0-92.0)	0.8 (0.0-25.8)	1.6 (0.0-95.1)
Baseline peripheral blasts, median (range)	3.0 (0.0-96.0)	0.1 (0.0-84.0)	20.0 (0.0-93.0)	3.0 (0.0-96.0)
Year to initiate therapy, n (%)				
2006-2010	0	0	71 (62)	71 (16)
2011-2014	43 (22)	61 (45)	41 (36)	145 (32)
2015-2018	152 (78)	76 (55)	3 (3)	231 (52)
Cycle 2 chemotherapy, n (%)	150 (77) [130 FF]	70 (51) [58 FF]	88 (77) [77 FF]	308 (69) [265 FF]
7 + 3 reinduction	0	4 (3)	11 (10)	15 (3)
CLAG-M reinduction	35 (18)	33 (24)	3 (3)	71 (16)
CLAG consolidation	97 (50)	16 (12)	2 (2)	115 (26)
HiDAC consolidation	13 (7)	7 (5)	64 (56)	84 (19)
Other	5 (3)	10 (7)	8 (6)	23 (5)
Days after cycle 1, median (interquartile range)	40 (37-47)	44 (36-56)	43 (34-49)	42 (36-49)
Cycle 3 chemotherapy, n (%)	60 (31) [44 FF]	21 (15) [14 FF]	64 (56) [47 FF]	145 (32) [105 FF]
7 + 3 reinduction	0	0	4 (3)	4 (1)

FF, fungal free.
*Defined as initiation by day 14 of the cycle.
†Excluding patients with IFD in previous cycles.

Table 1 (continued)

	CLAG-M ND	CLAG-M R/R	7 + 3	Total
CLAG-M reinduction	2 (1)	3 (2)	4 (3)	9 (2)
CLAG consolidation	13 (7)	2 (1)	2 (2)	17 (4)
HiDAC consolidation	37 (13)	6 (4)	46 (40)	89 (20)
Other	8 (4)	10 (7)	8 (6)	26 (6)
Days after cycle 1, median (interquartile range)	93 (82-111)	96 (79-117)	83 (71-94)	89 (76-104)
M-PPX*, n (%)				
Cycle 1	118 (59)	69 (50)	14 (10)	196 (44)
Posaconazole	111 (57)	51 (37)	2 (2)	164 (37)
Voriconazole	2 (1)	18 (13)	10 (9)	30 (7)
Cycle 2*,† (% of FF cycle 2), n (%)	87 (67)	40 (69)	14 (18)	141 (53)
Posaconazole	78 (60)	32(55)	1 (1)	111 (42)
Voriconazole	9 (7)	8 (14)	12 (16)	29 (11)
Cycle 3*,† (% of FF cycle 3), n (%)	25 (57)	11 (79)	7 (15)	43 (41)
Posaconazole	25 (57)	9 (64)	2 (4)	36 (34)
Voriconazole	0	2 (14)	5 (11)	7 (7)

FF, fungal free.
*Defined as initiation by day 14 of the cycle.
†Excluding patients with IFD in previous cycles.

2014; subsequently, M-PPX with oral posaconazole 300 mg daily or voriconazole 4 mg/kg every 12 hours were recommended.

Cumulative incidence (CI) probabilities of time-to-first IFD were estimated and compared between cohorts at day 90 (D90) after the start of the cycle, treating death as a competing risk, and Gray's test was used for comparisons; curves were shown through D180 for illustrative purposes. Cox proportional hazard regression models were used to evaluate the association between IFD and predefined risk factors.[16,17] Factors associated with $P < .20$ in univariable analysis were considered for inclusion in multivariable models. All reported P values are 2-sided. SAS version 9.4 TS1M3 (SAS Institute Inc, Cary, NC) was used.

We identified 447 adults matching our inclusion criteria, consisting of 195 and 137 patients who were ND and R/R, respectively, and receiving CLAG-M, and 115 patients who were ND and receiving 7 + 3 (Table 1). Consistent with the later time period in which CLAG-M was used relative to 7 + 3, M-PPX was used in the majority of the CLAG-M cohort compared with the minority of the 7 + 3 cohort, with the remaining individuals for each cohort prescribed with fluconazole PPX (Table 1).

The D90 CI of proven/probable IFD for the entire chemotherapy course was 20% in the CLAG-M cohort (n = 332) and 12% in the 7 + 3 cohort (n = 115; $P = .171$; Figure 1; supplemental Table 1). Among the ND CLAG-M and R/R CLAG-M cohorts, there were no differences in proven/probable IFD at D90 (CI, 18% vs 22%, respectively; $P = .239$). When cohorts were stratified based on the use of M-PPX, the D90 CI of proven/probable IFD was significantly higher in CLAG-M without M-PPX than that of 7 + 3 without M-PPX (CI, 28% vs 11%, respectively; $P = .007$); there was no significant difference between groups receiving M-PPX (CI, 7.5% vs 0%, respectively; $P = .646$). For subsequent cycles, the CI of proven/probable IFD did not significantly differ by cohort or subsequent chemotherapeutic regimen, ranging from 16% to 20% in the CLAG-M cohort and 15% to 17% in the 7 + 3 cohort, regardless of whether the second cycle was a reinduction or consolidation regimen (supplemental Figures 2 and 4). Complete response status did not significantly affect IFD rate; however, there was a nonsignificant trend of increased IFD rate after resistant leukemic disease (supplemental Figure 6). The D90 CI of all categories of IFD (ie, proven/probable/possible IFD) was similar in the CLAG-M and the 7 + 3 cohort (33% vs 30%; supplemental Figures 1, 3, and 5). When cohorts were stratified based on M-PPX usage, the D90 CI of proven/probable/possible IFD was significantly higher in CLAG-M without M-PPX than that in 7 + 3 without M-PPX (CI, 42% vs 23%, respectively; $P = .004$).

In total, there were 19 proven, 72 probable, and 75 possible first IFDs identified. The median time to proven/probable IFD after CLAG-M cycle 1 was 19 days (interquartile range, 12-23), and median time after cycle 2 was 21 days (interquartile range, 18-30; supplemental Tables 1 and 2). The majority (91%) of proven/probable IFDs occurred during a period of neutropenia (absolute neutrophil count <500 cells per μL). *Aspergillus* species was more common in the CLAG-M without M-PPX cohort, accounting for 90% of cases, compared with 46% in the CLAG-M with M-PPX cohort ($P < .001$; supplemental Table 1). The overall improvement of proven/probable IFD was 86% (n = 78/91), with response sustained in 55% (n = 50/91) until the censor date. Therapeutic drug monitoring was performed in 88 of 200 (44%) patients receiving M-PPX. Among 25 of these patients with proven/probable IFD, 6 had therapeutic drug monitoring within 14 days before the IFD diagnosis and all were therapeutic (supplemental Table 1).

The use of M-PPX as a time-dependent covariate was the only variable significantly associated with the development of a proven/probable IFD by D90 in univariable (hazard ratio, 0.40; 95% confidence interval, 0.23-0.72; $P = .002$) and multivariable analysis (hazard ratio, 0.25; 95% confidence interval, 0.13-0.47; $P < .001$; supplemental Tables 3 and 4).

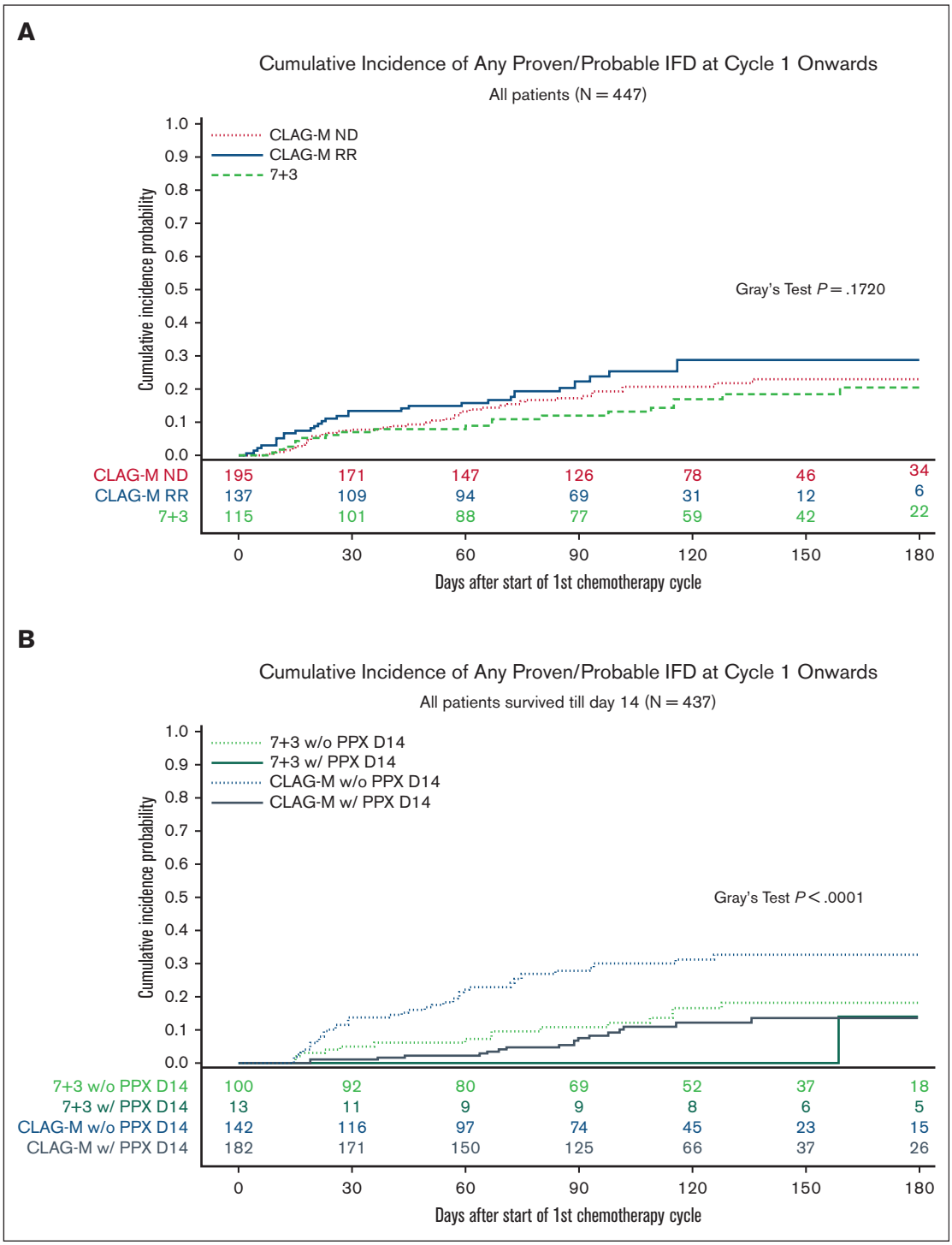

Figure 1. CI of proven/probable IFD at cycle 1 onwards. CI of proven/probable IFD from cycle 1 (including subsequent cycles) until day 180 or specified end point, for ND CLAG-M vs R/R CLAG-M vs 7 + 3 (A) and CLAG-M vs 7 + 3 with and without M-PPX (B) (shown as PPX D14). Numbers below the curves indicate patients at risk. Death was treated as a competing risk event. *P* values are from Gray test comparing cohorts.

This study demonstrates that there is a relatively high risk of developing an IFD with the intensive, contemporary chemotherapy regimen, CLAG-M (and subsequent chemotherapy) compared with a historical control cohort receiving a 7 + 3 regimen. However, a key finding of the study was that the use of M-PPX mitigated the IFD risk, allowing the use of the more intensive CLAG-M regimen without a significantly higher incidence of IFD.

The duration of neutropenia for CLAG-M/CLAG has previously been reported by this study group, with a median time to neutrophil

recovery >500 cells per μL of 26 and 30 days, respectively.[3,8] This is considerably longer that what is reported for more traditional AML regimens[18] and is a key risk factor for IFD.[19]

Despite a reduced rate of overall IFD and significantly less *Aspergillus* infections with the use of M-PPX, difficult to treat non-*Aspergillus* fungal organisms such as *Fusarium* species and mucormycosis were more prevalent (54% vs 10% in patients not receiving M-PPX).

Current guidelines and recommendations for IFD PPX are primarily based on more traditional chemotherapy regimens such as 7 + 3, with the majority of evidence to guide practice being large studies incorporating such regimens.[1,2,14] Therefore, large cohort studies such as this are of particular importance to demonstrate the IFD risk using contemporary, high-intensity AML therapies. This study was limited by the extended timeframe to incorporate historical controls, which resulted in variation in practices over time, subsequently limiting some comparisons, such as the low numbers of patients receiving 7 + 3 with M-PPX. Despite this, our results show that without M-PPX, patients treated with CLAG-M have a higher risk of developing IFD than those receiving 7 + 3. However, the use of M-PPX appears to mitigate this difference and is a critical aspect of supportive care for this patient population. These data support the use of M-PPX in all patients receiving CLAG-M/CLAG as standard of care.

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Contribution: J.L., J.A.H., R.B.W., A.B.H., and C.S.W. designed the study and interpreted the results; H.X., J.L., C.S.W., and J.A.H. analyzed the data and created the figures; A.B.H., E.L.C., E.M.H., L.E.K., C.S.W., and J.A.H. collected data; J.L. and J.A.H. drafted the manuscript; and C.S.W., A.B.H., H.X., E.L.C., K.G.S., E.M.H., G.-S.C., L.E.K., W.M.L., M.G., S.C.-A.C., D.C.M.K., M.A.S., M.B., D.N.F., C.L., S.A.P., and R.B.W. contributed to the writing and revision of the manuscript and approved the final version.

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