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Early infectious complications among patients treated with induction compared to hypomethylating therapy for acute myeloid leukemia

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Letter to the Editor

The lethality of acute myeloid leukemia (AML) is often associated with infectious complications, caused either by direct disruption of normal hematopoiesis by the disease or by marrow suppression during its treatment [1, 2]. Conventional upfront therapy frequently incorporates cytarabine and an anthracycline to induce remission, a common example being ‘7+3’ induction chemotherapy. Induction causes profound cytopenias and may carry unacceptably high treatment-related morbidity and mortality among certain populations, such as those with advanced age, significant comorbidity, or compromised functional status. In the last decade, the hypomethylating agents (HMAs) 5-azacytidine and decitabine have emerged as tolerable and effective therapies for less robust patients [3, 4]. Although HMAs are felt to be better tolerated than conventional induction for these populations [4, 5, 6, 7], few studies have directly compared these strategies in terms of safety and tolerability.

Infectious complications are an important consideration for the tolerability of AML therapy, particularly given the rate of infection with standard induction. It is known that bacterial and fungal infections predominate [8, 9, 10], although the spectrum of these complications can vary according to choice and extent of antimicrobial prophylaxis [8, 9, 10], baseline immune status [2], and local flora. Less is known regarding how infectious complications may differ according to initial treatment with HMA therapy versus induction. We performed a retrospective cohort study of patients with newly diagnosed AML to compare the incidence and timing of infectious complications among those receiving HMA versus conventional 7+3 therapy.

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We identified adults aged 18 or older, newly diagnosed with AML, seen at Massachusetts General Hospital (MGH) between January 1, 2010 and June 30, 2014, and initially treated with either '7+3'-based induction ('induction' group) or HMA therapy ('HMA' group). We excluded patients with acute promyelocytic leukemia, those initially treated at a different institution, and those receiving supportive care alone or experimental treatments without an induction or HMA component. We collected relevant patient data from the electronic medical record. Secondary AML was defined as AML in a patient with a prior myeloid neoplasm or prior exposure to chemotherapy or radiotherapy. Cytogenetic risk was documented per the National Cancer Research Institute Adult Leukaemia Working Group [11]. This study was approved by the institutional review board prior to initiation.

Febrile neutropenia (FN) was defined as temperature over 38.0°C (100.4°F), with an absolute neutrophil count of less than 500/mm³, regardless of culture data. Bacteremia and fungemia were identified by blood culture data and clinical findings. Pneumonias were identified by culture or imaging data, as per Infectious Diseases Society of America guidelines [12]. Cellulitis, neutropenic colitis or typhlitis, and mucositis were diagnosed per the judgment of the treating physician based on clinical data. *Clostridium difficile* colitis and urinary tract infection (UTI) were diagnosed per the treating physician according to stool and urine cultures. Grade IV infections were defined using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 [13]. Patients were considered at risk for infectious complications starting at the day of treatment initiation. Time to infection was calculated from day 1 of AML treatment to documentation of infection. Patients were censored at death, date last known alive (LKA), date of salvage therapy, or on the date of hematopoietic cell transplantation (HCT). The primary outcome was 30-day and 60-day infectious event rates.

Continuous and ordinal variables were compared using Wilcoxon and Fisher's exact test, as appropriate. The cumulative incidence of infection was performed with the method of Fine and Gray using SAS 9.2, with death considered a competing risk (Cary, NC, USA). Incidence rate ratios (IRR) were calculated as the number of events/person-years at risk and compared between groups using Stata 9.1 (College Station, TX, USA). Significance was defined at $p < 0.05$.

We identified 172 consecutive patients treated for AML, of whom 125 received induction and 47 received HMA therapy (Supplemental Table I). Those receiving induction were younger (58 vs. 75 years, $p < 0.0001$), and fewer had secondary AML (33% vs. 62%, $p = 0.001$). As expected, a greater proportion of induction patients achieved either complete remission (CR) or complete remission with incomplete peripheral blood count recovery (CRi) (82% vs. 38%, $p < 0.0001$), and underwent subsequent HCT (58% vs. 11%, $p < 0.0001$). Of those receiving induction therapy, 93% received antibacterial prophylaxis usually with a quinolone, and 94% received antifungal prophylaxis with fluconazole. Among HMA patients, 51% received antibacterial (typically a quinolone) and 38.3% received antifungal (fluconazole) prophylaxis. Patients in the induction group were neutropenic for a median duration of 27 days during the 60-day study period, compared with 15 days in the HMA group (range 0–60 days for both groups, $p = 0.042$). 28% of HMA patients did not experience an ANC drop below 500/mm³ in the first 60 days of treatment.

Induction patients had a greater 30-day and 60-day cumulative incidence of febrile neutropenia compared to those undergoing HMA therapy (83% vs. 34% at 30 days; 87% vs. 40% at 60 days, $p < 0.0001$) (Figure 1, Supplemental Table II). These findings are consistent with prior studies reporting that approximately 30% of AML patients on decitabine or azacitidine developed febrile neutropenia during the course of their treatment [6, 14]. In our study, HMA patients also experienced a longer time to infection than those receiving induction therapy (Figure 1). [Table I and Figure 1 near here]

As anticipated, there was a higher rate of bacteremia in the 7+3 therapy group at both 30 and 60 days (30 days: IRR 3.0, $p = 0.025$; 60 days: IRR 2.4, $p = 0.022$). Of those patients who developed bacteremia after initiation of 7+3 induction, the most commonly isolated organism in culture was vancomycin-resistant enterococci (VRE) at 40%. Additionally, 6.7% of induction patients who developed bacteremia grew methicillin-resistant *Staphylococcus aureus* (MRSA). In comparison, patients receiving HMA therapy were far less likely to develop a multidrug-resistant bloodstream infection, with only one case of VRE and no cases of MRSA. This difference in rates of multidrug-resistant infections likely reflects the lower rate of febrile neutropenia and consequently less antibiotic use in patients in the HMA group.

The rate of all colitis was also higher among patients undergoing induction (IRR 10. at 60 days, $p < 0.0001$), as was the rate of infectious C. Diff colitis specifically (IRR 12, $p = 0.0026$). The rates of all pneumonia and specifically fungal pneumonia were comparable in the two groups at 30 days, but became significantly higher in the induction group by 60 days (PNA: IRR=3.1 $p < 0.001$; Fungal PNA: IRR=3.85, $p = 0.028$) (Table I). The most common pathogen for pneumonia in the induction group was *Aspergillus* at 26.7% (Supplemental Table III).

Despite the less aggressive nature of HMA treatment, UTI and cellulitis were more common in this group in the first month of treatment compared to the induction group (Table I). HMA patients had a higher rate of UTI at 30 days and a trend towards more UTI at 60 days (30 days: IRR 0.23, $p = 0.0037$; 60 days: IRR 0.71, $p = 0.47$). The rate of cellulitis was also greater in the HMA group at the 30 days (30 days: IRR 0.26, $p = 0.015$; 60 days: IRR 0.80, $p = 0.63$).

In prior studies, the majority of hospitalizations or emergency department visits among AML patients receiving therapy were due to neutropenic fever or infection [15]. We found that 36% of patients receiving HMA therapy were admitted at least once for an infection during the 60 day follow-up period, compared to 8.0% of patients receiving induction therapy ($p < 0.0001$). Despite this, patients receiving HMA still spent less overall time hospitalized when compared to the induction group, who typically remain in the hospital for the duration of their induction cycle (11 days vs. 34 days, $p < 0.0001$). 8.0% of patients in the induction group had a grade IV infectious complication, compared with 6.4% in the HMA group (IRR 1.26, $p = 0.77$). All grade IV infections in this study resulted in admission to an intensive care unit.

The rates of death attributable to infection within the first 30 and 60 days of treatment were not significantly different in the two groups. At 30 days, the incidence of death due to infection was 2.4% in the induction group and 2.1% in the HMA group (IRR 1.1, $p = 0.98$). At 60 days, 4.0% of patients in the induction group had died as a consequence of an infectious complication, compared with 2.1% of the HMA group (IRR 1.9, $p = 0.63$).

The variation in infectious complications, seen in this study, may stem from differences in the depth of immunosuppression caused by the relative intensity of the therapeutic regimens, the breakdown of protective mucosal and skin barriers, and variations in concurrent antimicrobial prophylaxis and treatment. There may also be differences in risk for specific categories of infection – for example, the older age of HMA patients may reflect why those treated with HMA were more prone to cellulitis and UTI. Prophylaxis during AML treatment is now pervasive, and can be tailored to the flora of the particular region and hospital [16]. At our institution, those receiving induction typically received antifungal and antibacterial prophylaxis at a higher frequency than HMA patients ($p < 0.0001$). Despite this, the cumulative incidence of febrile neutropenia, bacteremia, and colitis remained higher among induction patients, as did early and serious infectious complications from these conditions, including infections with multidrug-resistant organisms.

In summary, we found that among those with newly diagnosed AML, induction chemotherapy is associated with significantly higher rates of early and serious infectious complications, when compared to patients receiving HMA therapy. HMA treated patients were hospitalized for an infectious event more frequently, but patients receiving 7+3 induction spent significantly more time hospitalized overall. The lower likelihood of developing a life-threatening infection following HMA therapy compared to traditional induction therapy is an important consideration in the treatment of AML.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

A. Cumulative incidence of febrile neutropenia in the induction and HMA treatment groups over 60 days from the initiation of treatment. **B.** Cumulative incidence of bacteremia in the two groups over the same time period.

Table I:

Incidence Rates (IR) and Incidence Rate Ratios (IRR) of infectious events at 30 and 60 days in patients receiving induction vs. HMA therapy. Incidence rates are per 1000 person-days. IRR represents the ratio of the 7+3 group IR to the HMA group IR. Infections with significantly greater rates in the induction group are shaded in yellow, while those with significantly greater rates in the HMA group are shaded in grey.

Incidence Rate Ratios (IRR) of Infectious Events								
	30 days				60 days			
	7+3 IR	HMA IR	IRR (95% CI)	p-value	7+3 IR	HMA IR	IRR (95% CI)	p-value
Febrile Neutropenia	72	15	4.8 (2.8, 8.9)	<0.0001	52	9.5	5.5 (3.4, 9.5)	<0.0001
Bacteremia	9.0	3.0	3.0 (1.0, 11)	0.025	4.7	1.5	2.4 (0.93, 8.1)	0.022
MRSA	0.28	0	-	0.73	0.13	0	-	0.73
VRE	3.5	0.74	4.7 (0.70, 201)	0.096	1.7	0.36	4.8 (0.71, 205)	0.091
Fungemia	1.1	0	-	0.27	0.55	0.13	4.1 (0.40, 201)	0.21
Pneumonia	7.2	6.5	1.1 (0.48, 2.9)	0.83	4.8	1.6	3.1 (1.5, 6.8)	0.00080
Fungal PNA	2.3	1.5	1.5 (0.31, 15)	0.63	1.6	0.41	3.9 (1.0, 21)	0.028
Cellulitis	1.7	6.4	0.26 (0.074, 0.85)	0.015	1.2	1.6	0.80 (0.29, 2.1)	0.63
Colitis	7.1	1.5	4.8 (1.19, 42)	0.012	4.1	0.40	10. (3.1, 52)	<0.0001
<i>C. diff</i> colitis	2.0	0	-	0.10	1.5	0.13	12 (1.7, 497)	0.0026
UTI	2.0	8.5	0.23 (0.075, 0.68)	0.0037	1.1	1.6	0.71 (0.25, 1.9)	0.47