

# Care Patterns and Barriers to Outpatient Care for Adults With AML Following Intensive Chemotherapy at NCCN Member Institutions

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## Abstract

**Background:** Prolonged hospitalization following intensive (re)induction chemotherapy for acute myeloid leukemia (AML), while standard, is costly and resource intense, limits inpatient bed capacity, and negatively impacts quality of life. Early hospital discharge (EHD) following completion of chemotherapy has proven safe as an alternative at select institutions, but is not widely implemented. **Patients and Methods:** From February 2023 through May 2023, the NCCN Best Practices Committee conducted a survey evaluating AML hospitalization patterns, care models, and barriers to EHD at its 33 member institutions. **Results:** A total of 30 (91%) institutions completed the survey; two-thirds treat >100 patients with AML annually and 45% treat more than half of these with intensive chemotherapy. In the (re)induction setting, 80% of institutions keep patients hospitalized until blood count recovery, whereas 20% aim to discharge patients after completion of chemotherapy if medically stable and logistically feasible. The predominant reasons for the perceived need for ongoing hospitalization were high risk of infection, treatment toxicities, and lack of nearby/accessible housing. There was no significant association between ability to practice EHD and annual AML volume or treatment intensity patterns ( $P = .60$  and  $P = .11$ , respectively). In contrast, in the postremission setting, 87% of centers support patients following chemotherapy in the outpatient setting unless toxicities arise requiring readmission. Survey responses showed that 80% of centers were interested in exploring EHD after (re)induction but noted significant barriers, including accessible housing (71%), transportation (50%), high toxicity/infection rate (50%), high transfusion burden (50%), and limited bed availability for rehospitalization (50%). **Conclusions:** Hospitalization and care patterns following intensive AML therapy vary widely across major US cancer institutions. Although only 20% of surveyed centers practice EHD following intensive (re)induction chemotherapy, 87% do so following postremission therapy. Given the interest in exploring the EHD approach given potential advantages of EHD for both patients and health care systems, strategies to address identified medical and logistical barriers should be explored.

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## Background

Adults with acute myeloid leukemia (AML) typically remain hospitalized following intensive induction therapy while cytopenic due to infection risks, toxicity monitoring, and transfusion needs. However, this care strategy has important shortcomings for patients and health systems due to costs,<sup>1,2</sup> effects on quality of life,<sup>3,4</sup> risk of nosocomial infections, and impact on hospital bed availability. Moreover, high costs associated with recently approved drugs may create reimbursement challenges for hospitals. These negative consequences, along with improvements in supportive care and outpatient care delivery,<sup>5</sup> led investigators at the University of Washington/Fred Hutchinson Cancer Center (UW/FHCC) to develop an early hospital discharge (EHD) care pathway for adults with AML and other high-grade myeloid neoplasms. Therein, patients are discharged within 3 days of completing intensive AML-like (re)induction chemotherapy and are closely followed as outpatients until cytopenias resolve. Building on data from a prospective pilot study (ClinicalTrials.gov identifier: NCT00844441), a prospective phase II trial (NCT01235572) in adults aged up to 75 years demonstrated safety of this approach and substantial reductions in medical resource utilization and care costs.<sup>6,7</sup> A retrospective analysis of 375 EHD patients treated in the 4 years after completion of this phase II trial confirmed

these findings in a larger, medically more diverse cohort of adults treated outside clinical trial settings.<sup>8–11</sup> Given the potential benefits of the EHD approach, we surveyed discharge practices at other major cancer institutions caring for patients with AML to better understand interest in, and barriers to, adopting an EHD approach more broadly.

## Patients and Methods

### Study Sample

Our sample size encompassed one representative of the NCCN Best Practices Committee (BPC) at each of the 33 cancer centers (<https://www.nccn.org/home/member-institutions>) that were members of NCCN at the time of writing (see Table S1 in the supplementary materials, available online with this article). A maximum of one response was accepted from each center. This nonprofit alliance of cancer centers, primarily located in metropolitan areas across the United States, aims to serve patients throughout respective states, including suburban and rural areas. The goal of the NCCN Best Practices Committee (BPC), composed of one member (senior physician, nurse, or administrative leader) from each Member Institution, is to improve the

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effectiveness and efficiency of center operations via sharing best practices. To this aim, the BPC collects data and information, forms working groups, and conducts surveys regarding processes, programs, and policies at NCCN Member Institutions related to relevant topics.

### Survey Design

With input from the BPC, 2 physicians at one of the member institutions (FHCC) developed the survey based on a literature review and results from a prior informal email survey that was sent to 45 cancer centers worldwide (described previously<sup>12</sup>). The survey comprised 25 questions (see Supplementary Table S2) divided into 5 general areas: (1) patient characteristics and transplant treatment patterns; (2) cancer center resources; (3) practice patterns following intensive AML (re)induction chemotherapy; (4) practice patterns following postremission AML therapy; and (5) perceived barriers to EHD implementation. As skip logic was applied, the denominator varied between questions (Supplementary Table S2). EHD was defined as aiming to discharge patients after completion of chemotherapy before blood count recovery if medically stable and logistically feasible. The survey was piloted at 2 cancer centers for readability of the questions, structure, and content. The pilot was considered successful, and the survey was then distributed in unchanged fashion via a web-based tool (SurveyMonkey) to one BPC representative at each of the NCCN Member Institutions. Committee members were instructed to review the survey and identify a content expert at their center to complete the survey, in line with the expectation of BPC membership. No incentives were offered.

### Statistical Considerations

Results were summarized using descriptive statistics, including tallies, percents, and visual summaries with histograms and pie charts. Fisher exact was used to evaluate associations between categorical covariates, whereas 2-sample normal approximation proportion tests were used to compare proportions. As we did not expect every center to respond to the survey, we calculated

the precision available if at least 85% of the centers ( $\geq 28$  of 33) responded. Using the normal approximation to a proportion estimate, the 95% confidence interval would have width  $\pm 18\%$  for a rate of 50%, and a width  $\pm 11\%$  for a proportion of 10% or 90%. With 28 responding centers, the power for a  $2 \times 2$  comparison (eg, EHD practice [yes vs no] and a binary volume measure [high vs low]) using Fisher exact test (2-sided) would be 86% if one binary variable had distribution 50/50 and the other variable had a difference in rates of 10% versus 70%. If more centers respond, the power will be larger than calculated. Statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing).

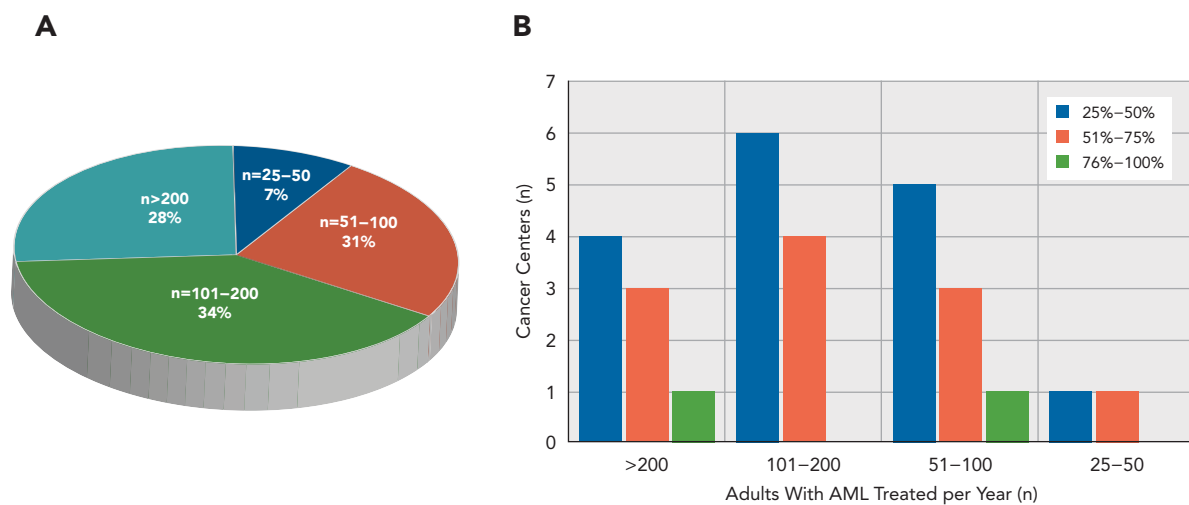
## Results

### Patient Population

Of the entire sample size of 33 NCCN Member Institutions, 30 (91%) completed the survey between February 23, 2023, and May 15, 2023, with responses to some questions missing from 1 to 2 centers. All treat adults with AML, including with allogeneic hematopoietic cell transplantation (HCT). Population sizes of the cities of these institutions range from approximately 21,000 to  $>8$  million, with 50% being mid-sized cities with populations between 200,000 and 1 million.<sup>13</sup> Across the 30 institutions, the number of adults treated for newly diagnosed or relapsed AML varies substantially (Figure 1A), with approximately two-thirds treating  $>100$  patients with AML annually. Only 2 (7%) of the centers treat 75% to 100% of their patients with AML with intensive induction chemotherapy (defined as 7 + 3, high-dose cytarabine [HiDAC] alone, or HiDAC-containing regimens with/without additional drugs), 11 (38%) treat 51% to 75% of their patients intensively, and 16 (55%) treat 25% to 50% of their patients with intensive therapy. There was no association between the proportion of patients treated intensively and patient volume ( $P = .99$ ; Figure 1B).

### Institutional Resources

All 30 centers have outpatient infusion clinics that are open weekdays during daytime hours ( $\sim 7$  AM–5 PM), with 14 (47%) also



**Figure 1.** (A) Number of adults with newly diagnosed and relapsed/refractory AML treated at each center per year and (B) proportion of patients with AML at each center treated with intensive chemotherapy, by AML volume. Abbreviation: AML, acute myeloid leukemia.

capable of providing infusion support during weekday evening hours (~5 PM–10 PM). Only 1 institution has an infusion center open overnight (10 PM–7 AM); 13 (43%) institutions have infusion centers with similar hours on weekends and weekdays, whereas 17 (57%) have reduced hours/availability on weekend days. For holidays, 17 (57%) institutions have similar infusion center availability on holidays as on weekends, whereas 6 (20%) have reduced hours compared with regular weekends.

Most centers ( $n=23$ ; 77%) typically obtain platelets or packed red blood cells for patients without specific transfusion restrictions within 4 hours; at 6 (20%) it takes 4 to 12 hours and at 1 center it takes 12 to 24 hours. Likewise, 24 (80%) centers can administer intravenous antimicrobials in the outpatient setting within 1 hour of ordering, whereas it takes 1 to 2 hours at 5 (17%) centers; at 1 center, outpatient intravenous antimicrobials cannot be administered.

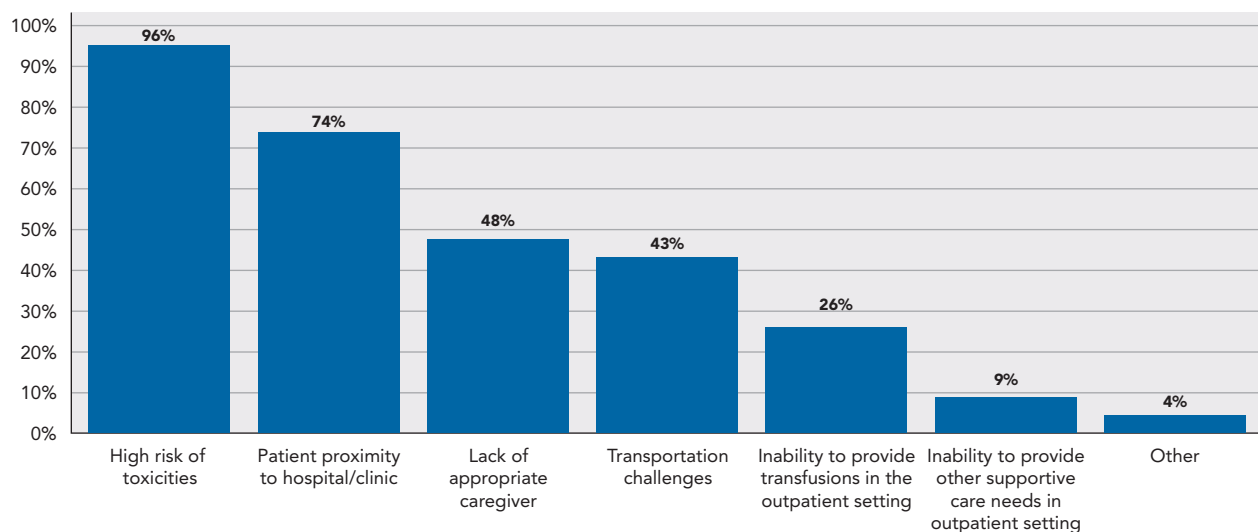
Availability for urgent same-day evaluations varies across institutions, with an advanced practice provider (APP; ie, nurse practitioner or physician assistant) available at 20 (67%) institutions, a physician available at 3 (10%), and either an APP, a physician, or a registered nurse available at 4 (13%); at only 3 (10%) institutions, urgent same-day evaluations are not available. Similarly, the approach to evaluate an outpatient neutropenic patient reporting fever varies across institutions and depends on the contact time. Specifically, if fevers are reported during weekday daytime hours, 13 (43%) centers initially evaluate patients in the outpatient clinic, with subsequent hospital admission if necessary; 13 (43%) refer patients directly to the emergency department (ED), whereas 4 (13%) centers directly admit patients to an inpatient hematology/oncology ward. If fevers are reported outside of regular daytime clinic hours, 24 (83%) centers refer the patient to the ED for evaluation, 2 (7%) conduct the initial evaluation in the outpatient clinic, and 3 (10%) directly admit the patient to the inpatient hematology/oncology unit. If an outpatient with AML requires hospital admission for neutropenic fever (with stable hemodynamics), 11 (37%) institutions typically have an inpatient bed available >75% of the time; at 4 (13%), a bed is available 51% to 75% of the time, at 7 (23%) a bed is available 26% to 50% of the time, and at 6 (20%) a bed is available <25% of the

time. For 2 (7%) centers, direct admissions are not possible, and patients are always directed to the ED.

### Practice Patterns Following Intensive (Re)Induction Chemotherapy

Following intensive induction or reinduction chemotherapy, 24 of 30 (80%) institutions keep patients hospitalized until blood count recovery, whereas 6 (20%) aim to discharge patients early if medically stable and logistically feasible. We did not find a significant association between the center's AML patient volume or treatment intensity patterns and EHD practice ( $P=.60$  and  $P=.11$ , respectively). Centers following EHD strategies tended to be in midsize cities (population 50,000–500,000). Factors contributing to continued inpatient care are summarized in Figure 2, with main reasons being high risk of fever, infection, toxicities from chemotherapy felt to require inpatient monitoring (96%), and limited accessible housing nearby the center (74%). For the centers practicing EHD after completion of (re)induction, dedicated hospital/clinic-associated housing is available in 5. Five institutions also discharge some patients home, and 4 sometimes use local hotels. The timing of discharge varies across institutions, with 4 discharging immediately after completion of chemotherapy and 2 discharging only if a day 14 bone marrow evaluation indicates no immediate additional chemotherapy is indicated. In 4 other centers, patients may be discharged at later time points but before blood counts are fully recovered, defined variably as an absolute neutrophil count (ANC) >500/ $\mu\text{L}$  or >100/ $\mu\text{L}$  without fever or need for antibiotics, and either not requiring platelet transfusions, needing platelets transfusion no more than once weekly, or platelets being >20,000/ $\mu\text{L}$ .

For consideration of EHD, 5 of the 6 centers practicing EHD use formal checklists for both medical and logistical criteria (Table 1) and 1 uses informal criteria. All centers with formal EHD criteria require patients to live close by (defined variably as within 60 minutes of the treatment center, able to get to appointments locally, or housing at the institution hotel), caregiver availability, and ability of the center to support the frequency of blood products needed. For all centers, 25 (83%) centers did not change discharge practices following the COVID-19 pandemic, whereas



**Figure 2.** Predominant reasons for keeping patients with acute myeloid leukemia hospitalized following induction.

**Table 1.** Formal Discharge Criteria for Early Hospital Discharge (N=5)

Formal Discharge Criteria	n (%)
Ability to live close to clinic <sup>a</sup>	5 (100)
Availability of caregiver	5 (100)
Blood product frequency need	5 (100)
Fever/Infection status	4 (80)
Type of chemotherapy regimen	3 (80)
Performance status	2 (60)
Age	2 (40)
Organ function criteria	1 (40)
Other <sup>b</sup>	1 (20)

<sup>a</sup>Defined as <60 minutes at 2 institutions, no specific distance at 1 but “patient needs to be able to get to appointments and receive transfusions.”

<sup>b</sup>Housing at the institution hotel.

3 (10%) now discharge patients early more frequently and 2 (7%) discharge patients early less frequently.

### Practice Patterns Following Postremission Chemotherapy

We next examined how centers deliver care following postremission (“consolidation”) therapy, defined as HiDAC-based regimens, and why differences exist between postinduction and postremission settings. Most centers (n=21; 70%) deliver chemotherapy inpatient and discharge patients after completion of chemotherapy if medically and logistically feasible, 5 (17%) additional centers administer chemotherapy outpatient and continue outpatient supportive care unless toxicities arise requiring admission, 3 (10%) centers deliver chemotherapy inpatient and provide inpatient supportive care through some level of blood count recovery, and 1 center follows another approach (not detailed). The discrepancy seen in frequency of EHD practice in the induction versus postremission settings (20% vs 87%;  $P<.001$ ) may be attributed to several factors (Figure 3), with the predominant reason being perceived higher supportive care needs after (re)induction than postremission therapy (eg, laboratory monitoring, nursing and provider needs). Also noted as considerations were the need for assessment of disease response to determine whether reinduction is

needed, and the lack of an established local oncologist at the time of diagnosis/induction.

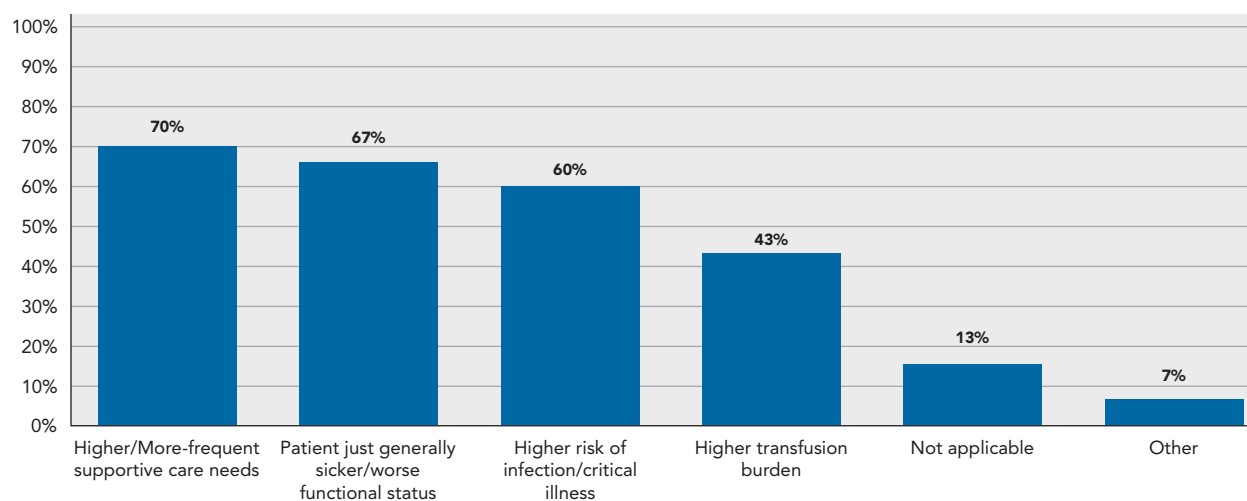
### Barriers to EHD Implementation

Survey responses showed that 80% of centers were interested in participating in a clinical trial piloting EHD at their institution, but most noted barriers to implementation (Table 2). The most common obstacle was affordable housing near the center (70%) and transportation, with 50% of centers describing challenges for patients to come to clinic multiple times weekly for monitoring/supportive care due to geography or weather. In addition to possible barriers listed in the survey, institutions identified additional hurdles, including the need to “change the culture” at the institution, caregiver challenges, availability of oncology triage clinic with only limited hours, lack of same-day access to “urgent” care, limited weekend transfusion support, and the need for increased resources dedicated to the outpatient leukemia clinic.

### Hospital Resource Utilization Following Other Chemotherapy Regimens and HCT

Finally, the survey queried hospitalization practices following HCT and other types of non-HCT treatments, which may require more intensive monitoring or may cause profound myelosuppression, as seen with standard induction regimens, but for which reimbursement may be variable if dispensed in the hospital. For initiation/ramp-up of venetoclax, for instance, 6 (20%) centers always hospitalize patients, 6 (20%) never hospitalize patients during treatment initiation, and 18 (60%) sometimes do so, depending on clinical and logistical parameters. There was no statistically significant association between hospitalization for ramp-up and AML volume ( $P=.65$ ) or EHD practice for intensive therapy ( $P=.57$ ).

Administration of CPX-351 was handled differently across institutions as well, with 11 (37%) administering the drug inpatient and patients remaining hospitalized until cytopenias resolve, 3 (10%) administering the drug outpatient with patients then hospitalized for monitoring during their cytopenic period, and 4 (13%) administering the drug outpatient and patients

**Figure 3.** Factors that underlie the difference in hospitalization practices following induction and postremission chemotherapy.

**Table 2.** Perceived Barriers to Early Hospital Discharge Implementation (N=24)

Barrier	n (%)
Housing: location and affordability	17 (71)
Transportation to clinic multiple times weekly too challenging	12 (50)
Toxicity/Infection rate too high (limited bed availability if readmission necessary)	12 (50)
Transfusion burden too high to support in outpatient setting	12 (50)
Supportive care burden: patients require more visits (with RNs and providers) than center capacity	10 (42)
No urgent evaluation possible in outpatient clinic	3 (13)
Caregiver challenges	1 (4)
Need to change the culture	1 (4)

remaining outpatient unless a complication arises; 6 (20%) centers use a mix of strategies depending on clinical, demographic, and treating physician variables, and 5 (17%) centers do not use CPX-351. Half of the centers practicing EHD for conventional AML induction chemotherapy administer CPX-351 in the outpatient setting or give the drug in the hospital and discharge patients after chemotherapy, whereas the other half uses a mix of inpatient/outpatient strategies. In terms of post-HCT hospitalization practices, of the centers that responded, 24 (83%) hospitalize patients for 3 to 4 weeks, 3 (10%) for 2 to 3 weeks, and 2 (7%) for >4 weeks after myeloablative conditioning. Following reduced-intensity/nonmyeloablative conditioning, of the centers that responded, 18 (64%) hospitalize patients for 3 to 4 weeks, 8 (29%) for 2 to 3 weeks, and 2 (7%) for <2 weeks. Shorter post-HCT hospitalization (2–3 weeks) for myeloablative conditioning was more likely to occur in centers that practice EHD ( $P=.005$ ), but there was not a significant association between EHD practice and shorter post-HCT hospitalization with reduced intensity/nonmyeloablative conditioning ( $P=.65$ ).

## Discussion

Discharge early from the hospital offers many potential benefits for health care systems and patients alike. Nonetheless, in a national survey of 30 of the 33 NCCN Member Institutions, we found only 6 (20%) centers use some form of EHD strategy following AML (re)induction chemotherapy, whereas, in the postremission setting, 87% of centers either discharge patients after chemotherapy or deliver chemotherapy in the outpatient setting altogether unless toxicities/complications arise. Despite much interest in the approach, major (albeit potentially addressable) barriers to EHD exist, including local housing availability, transportation, and high supportive care needs.

In the 6 centers practicing EHD, the ability to do so is supported by many complex variables. In general, these centers have infusion centers with long operating hours, robust outpatient resources with quick access to transfusion support, and short times between ordering and administration of intravenous antimicrobials, and they can perform urgent same-day evaluations. On the other hand, they do not necessarily have rapid access to inpatient beds, with only 4 of the 6 centers expecting bed availability for direct admission most of the time. Notably, EHD was not practiced at any of the centers located in cities with a population >1 million, possibly reflecting the availability of affordable/accessible local housing as a barrier to EHD implementation. Furthermore, there was no association between

ability to use EHD and AML patient volume or treatment intensity patterns. There was, however, an association between shorter post-HCT hospitalizations following myeloablative conditioning and centers that practice EHD ( $P=.005$ ), likely reflecting more robust outpatient clinical services on a broader institutional scale.

In an informal survey of AML experts from the United States, Europe, Asia, and Australia we conducted in 2018, we found a large discrepancy between EHD practice following induction chemotherapy (3/35 [9%] institutions) versus postremission therapy (32/35 [91%]).<sup>12</sup> This pattern was confirmed in this current survey, with 20% of institutions practicing EHD following (re)induction, but 87% of centers supporting outpatient care in the postremission setting. At least partly underlying this difference are higher perceived complication rates and care needs following (re)induction therapy. In contrast, however, in a retrospective study of 375 EHD patients treated at a single institution over a 4-year period, there were no differences in requirements for laboratory monitoring, transfusion needs, or ICU care (if readmitted) after EHD following induction and postremission therapy, despite the fact that patients had a worse functional status during (re)induction compared with postremission therapy. These findings held true even when restricting analysis to a matched subset of patients who underwent EHD after both induction and postremission therapy to limit potential selection bias.<sup>10</sup> These data argue against the notion of substantially greater risks or care needs for patients discharged early following initial induction compared with postremission therapy, potentially allowing implementation of EHD care more broadly. Such retrospective comparisons are, however, intrinsically problematic and potentially flawed. Ultimately the question of to what degree EHD is feasible and safe is best addressed by a prospective randomized trial of appropriate sample size.

Most centers noted significant barriers for establishing an EHD care strategy. Undoubtedly, an appropriate infrastructure,<sup>7</sup> availability of vital resources, and staff training are essential to the implementation of an EHD care strategy.<sup>14,15</sup> Shifting care from the inpatient to the outpatient setting will stress outpatient resources and health care providers. Due to a preexisting, well-functioning HCT service at UW/FHCC that regularly cares for patients in the outpatient department, there was access to an infrastructure felt to support EHD of intensely treated patients with AML when the EHD program was started; this program has significantly expanded and formalized since then. This experience, in conjunction with the results of this survey, indicates that these resources can be divided into institution-related and non-institution-related components. Institution-related elements include an infusion center with extended daily and weekend/holiday hours, an outpatient pharmacy, an infusion area that can deliver intravenous antimicrobials rapidly, access to a blood bank with large transfusion capacity and rapid product release, multidisciplinary expertise in management of acute complications of AML therapy, and openness to changing a long-established care practice. Non-institution-related elements critical for successful EHD include accessible local housing for patients, access to transportation, and availability of a caregiver. Some institutions may be able to address the latter issues, such as through developing strategies for dedicated outpatient clinic-associated housing, while acknowledging complexities such as city size, cost, and weather.

Several limitations of our study need acknowledgment, including the possibility of recall bias and inability to confirm the accuracy of the answers provided by the answering physicians. It is also unknown whether the expert completing the survey was the provider with the most knowledge on the survey topic. Furthermore, many questions had a section that allowed for written-in answers, reflecting a nuance of practice that was not always easily categorizable for analysis. Finally, the survey only queried physician opinions and not those of other providers or stakeholders. Ideally, a prospective randomized trial would test whether inpatient or outpatient care following induction chemotherapy best serves patients, their families, and the health care system.

## Conclusions

Together, our findings show that only a minority of centers practice EHD and suggest that a majority have interests in doing so but face perceived implementation barriers. The recent pandemic and current inpatient bed shortage, along with a more general trend in oncology of moving care from the inpatient to the outpatient setting, makes this an ideal time to explore such changes in care patterns for patients with AML treated with intensive therapy.

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