

Outpatient intensive induction chemotherapy for acute myeloid leukemia and high-risk myelodysplastic syndrome

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Key Points

- Outpatient intensive induction chemotherapy for newly diagnosed, relapsed, or refractory AML and high-risk MDS is feasible.
- Outpatient induction is safe and does not result in excessive utilization of blood products or other resources.

To improve patient quality of life and reduce health care costs, many conditions formerly thought to require inpatient care are now treated in the outpatient setting. Outpatient induction chemotherapy for acute myeloid leukemia (AML) may confer similar benefits. This possibility prompted a pilot study to explore the safety and feasibility of intensive outpatient initial or salvage induction chemotherapy administration for adults with AML and high-risk myelodysplastic syndrome (MDS). Patients with no significant organ dysfunction and a treatment-related mortality (TRM) score corresponding to a day 28 mortality rate of <5% to 10% were eligible for study. Patients were treated as outpatients with daily evaluation by providers and only admitted to the hospital if mandated by complications. Twenty patients were consented, and 17 were treated. Eight patients received initial induction chemotherapy and 9 received salvage induction chemotherapy. Fourteen patients completed induction chemotherapy administration in the outpatient setting (82.4%; exact 95% confidence interval [CI], 55.8-95.3). Three patients were admitted during the course of chemotherapy administration, 2 for neutropenic fever and 1 for grade 3 mucositis. No patients died within 14 days of the initiation of induction chemotherapy (exact 95% CI, 0-22.9). Results of this pilot study suggest it is feasible to complete outpatient induction chemotherapy in select patients with AML and high-risk MDS. A team including nurses, social workers, medical providers, and pharmacists was key to the successful implementation of outpatient induction.

Introduction

Patients with newly diagnosed, relapsed, or refractory acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS) are often treated with intensive induction chemotherapy with the goal of achieving complete remission.^{1,2} This treatment routinely causes pancytopenia, rendering patients susceptible to life-threatening infections, the leading cause of death in this cohort, and bleeding events.³ Therefore, until recently, standard of care dictated that intensive remission induction, beginning with the receipt of chemotherapy and extending until count recovery (3-4 weeks), preemptively be completed in the inpatient setting.⁴ This established practice imparts significant economic burden; in fact, several studies have concluded that intensive induction (including initial, salvage, and reinduction) and transplantation are the greatest drivers of cost in AML, with inpatient costs accounting for the largest fraction.⁵⁻⁷

Submitted 15 July 2019; accepted 7 January 2020; published online 19 February 2020. DOI 10.1182/bloodadvances.2019000707.

Presented in part at the 59th annual meeting of the American Society of Hematology, Atlanta, GA, 9-12 December 2017.

The study protocol is included as supplemental material available with the online version of this article.

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

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Available data in patients with leukemia suggest that the number of hospital days, transfusions, bleeding events, days on antibiotics, and infections may all negatively affect quality of life.⁸

To reduce health care costs and improve quality of life measures, there has been a trend toward outpatient management of many conditions formerly thought to require inpatient care. Risks of infection and bleeding, the principal barriers to outpatient intensive induction in AML and MDS, are likely reduced by improvements in supportive care. Today, outpatient transfusion support is routine, and effective oral broad-spectrum antimicrobial prophylaxis is available. To date, the feasibility, safety, and potential cost savings of outpatient consolidation chemotherapy for AML and hematopoietic stem cell transplantation in hematologic malignancies have been established and are increasingly common.⁹⁻¹³ Furthermore, several studies (including 2 at our institution) have shown that early discharge after intensive induction chemotherapy is feasible, safe, and reduces daily charges in selected patients.¹⁴⁻¹⁷ In contrast, no studies, to the best of our knowledge, have thus far investigated outpatient administration of intensive induction chemotherapy in patients with AML and high-risk MDS. This prompted conduct of the current pilot study to test the feasibility of outpatient intensive induction chemotherapy for select patients with AML and high-risk MDS and to preliminarily assess its impact on resource utilization.

Patients and methods

Preliminary work

Before initiation of this outpatient induction (OPI) study, 12 patients were treated with a combination of clofarabine and high-dose cytarabine with granulocyte colony-stimulating factor^{18,19} in our outpatient clinic (details provided in supplemental Table 1). With institutional review board approval, we retrospectively reviewed the medical records of these outpatient treatments during December 2010 through April 2012. Eight patients had active disease at the time of treatment, and 4 received a combination of clofarabine and high-dose cytarabine with granulocyte colony-stimulating factor for postremission therapy. Eleven of 12 patients were able to receive the full 5-day infusion as an outpatient, and 1 patient received day 5 of chemotherapy as an inpatient. Outcomes are provided in supplemental Table 2. No patient died within the first 30 days from the start of outpatient treatment. It was this experience and safety data that served as the proof of concept for the development of the current OPI clinical trial.

Feasibility study of OPI

We performed a prospective feasibility study to assess if outpatient management during induction chemotherapy was logistically possible and safe. Eligible patients were aged ≥ 18 years with newly diagnosed, relapsed, or refractory AML or high-risk MDS (10%-19% blasts in marrow by morphology) who were planned to receive intensive initial or salvage induction chemotherapy. Criteria were established to minimize the risk of treatment-related mortality (TRM) and complications leading to hospital admission. To be eligible for OPI, all patients were without active infection and had the following: normal chest imaging, adequate cardiac function (left ventricular ejection fraction $\geq 45\%$ by multigated acquisition scan or echocardiogram and no ongoing cardiac issues such as uncontrolled arrhythmias, unstable angina, or congestive heart failure), expected death rate $< 5\%$ to 10% within 28 days of beginning intensive

therapy (TRM score $< 9.21^{20}$), peripheral blast count $< 10 \times 10^9/L$, and fibrinogen level > 100 mg/dL. The TRM score calculator is available at <https://www.fhcrc-research.org/TRM/Default.aspx?GUID=E7232E60-E1C7-428C-8177-B50DD6B5895B>.

Logistical requirements included residence within 30 minutes of our treatment center, dedicated caregiver support, and willingness to return to the treating physician's office for outpatient follow-up once outpatient treatment was completed. Facility requirements mandated that all cases were discussed with the infusion room nursing staff, the facility had the capacity to accommodate all infusions, and outpatient infusion pumps were available if continuous infusion treatment was administered. The University of Washington/Fred Hutchinson Cancer Research Center Cancer Consortium Institutional Review Board approved this protocol, and informed consent was obtained from all study subjects.

Outpatient management

All OPI patients received prophylactic antimicrobial agents such as oral levofloxacin, acyclovir or valacyclovir, and appropriate antifungal agents (posaconazole or voriconazole). OPI patients treated with cytarabine ≥ 1 g/m² received prophylactic prednisolone acetate 1% ophthalmic drops and systemic steroids. They were treated according to the inpatient induction chemotherapy regimen, for which they also provided informed consent, if they were also enrolled on an investigational study. OPI patients were evaluated daily by an advanced practice provider (nurse practitioner or physician assistant) or attending physician while receiving induction chemotherapy. Daily evaluations included: vital signs, weight, complete blood count, platelet count, and serum basic metabolic panel, uric acid, lactate dehydrogenase, magnesium, and phosphate. Physical examination for cerebellar toxicity was performed before administration of each dose of high-dose cytarabine. Prespecified parameters were used to alert advanced practice providers or the attending physician of findings on the daily assessment. The following thresholds were used to trigger transfusion administration: hematocrit $< 26\%$ and platelet count $< 10 \times 10^9/L$. OPI patients were admitted to the hospital for predetermined complications of therapy (eg, temperature $\geq 38.3^\circ C$ or $\geq 38^\circ C$ for > 1 hour if neutropenic or $\geq 38.3^\circ C$ if not neutropenic), significant bleeding, severe organ toxicity, or regimen-related toxicity). After completion of induction, patients were also similarly admitted to the hospital for fever or other medical indications and discharged per our standard early discharge criteria.¹⁵

To support patients on this protocol, patients needed a full-time caregiver, utilization of our center's 7-day per week outpatient laboratory, transfusion and infusion services, and medical provider personnel. Nursing personnel provided support for OPI patients with ongoing education regarding monitoring for fevers and other side effects when residing in local housing and provided reminders to call our 24-hour emergency line.

Resource utilization

Resource utilization data were obtained from the electronic medical record for the duration of the chemotherapy administration.

Safety monitoring, definitions, and statistical analysis

The study was monitored to assure that there was not an excess probability of admission to the hospital during receipt of outpatient chemotherapy (predictive probability < 0.10) or death within 14 days

of initiating chemotherapy (predictive probability >0.9) based on the “predictive probabilities” tool (MD Anderson Cancer Center Department of Statistics).

Intensive induction chemotherapy days were limited to those days when chemotherapy infusions were administered, excluding priming only (ie, growth factor) days. Resource utilization data were collected for 30 days after the initiation of induction chemotherapy or until receipt of new chemotherapy if before day 30. Sixty-day mortality data were collected. The following criteria were established for determination of feasibility of OPI: >50% of patients completed chemotherapy without requiring admission and <5% of treated patients died within 14 days of starting induction.

Results

Between 1 October 2013 and 14 May 2018, twenty patients with newly diagnosed AML, relapsed or refractory AML, or high-risk MDS were enrolled before receipt of induction chemotherapy. Seventeen patients were treated and constitute the OPI cohort. Of those not treated, 2 were unable to be scheduled in the outpatient department, and 1 was found to have bilateral paraspinal soft tissue extramedullary disease prompting admission. The consented patients represent 29%, and the treated patients, 24%, of potential eligible patients seen at our center during this time frame.

Patient characteristics are summarized in Table 1. The OPI cohort had a median TRM score of 1.59 (range, 0-8.001) with a corresponding TRM (death with 28 days) probability ranging from 1% to 5% to 10%.²⁰

Two OPI patients received new chemotherapy before day 30 of the induction period; resource utilization data collection was stopped on the day of new chemotherapy receipt (day 17 and day 18, respectively).

Hospital admissions and early death

Fourteen OPI patients completed induction chemotherapy in the outpatient setting (82.4%; exact 95% confidence interval [CI], 55.8-95.3). Three patients required inpatient admission: 2 for neutropenic fever and 1 for grade 3 mucositis. All 3 patients requiring admission received the remaining doses of induction chemotherapy as inpatients.

Within the 30 days of starting induction chemotherapy, 2 (11.8%) patients were never admitted to the hospital, and 12 (70.6%) patients required hospital admission after completion of chemotherapy. Patients spent a median of 11 days inpatient (mean, 11 days; interquartile range, 10 days; range, 0 to 27 days), with a median of 1 period of hospitalization (range, 0-3). Reasons for admission included neutropenic fever, sepsis, altered mental status, mucositis, and chest pain, as well as other typical expected occurrences.

No OPI patient died within 14 days of initiating chemotherapy. Two OPI patients (11.8%) died within 60 days of the initiation of induction chemotherapy, 1 due to transition to palliative care before assessment of disease response (Table 2).

Intensive care unit level of care, resource utilization

During receipt of the induction chemotherapy regimen, no OPI patients required intensive care unit (ICU) admission. Two (11.9%) OPI patients required ICU level of care within 30 days,

Table 1. Patient characteristics

Parameter	Outpatient induction (N = 17)
Age, median (range), y	53 (19-72)
Male/female, n	10/7
TRM score, median (range)	1.6 (0-8.0)
Treatment days, median (range)	5 (4-5)
New chemotherapy within 30 d, n (%)	2 (12)
Disease, n (%)	
AML	15 (88)
MDS (EB-2)	2 (12)
Disease status, n (%)	
New diagnosis	8 (47)
Relapsed or refractory	9 (53)
Regimen, n (%)	
IAP	2 (12)
GCLAM	7 (41)
D-GCLAM	2 (12)
GCLAC	3 (18)
D-MEC	3 (18)
Year, n (%)	
2010-2013	1 (6)
2014-2017	16 (94)
HCT day 1, median (range), %	28 (23-40)
PLT count day 1, median (range), ×10 ⁹ /L	71 (12-1108)

D-GCLAM, combination of decitabine priming with cladribine, high-dose cytarabine, and mitoxantrone with granulocyte colony-stimulating factor; D-MEC, decitabine priming with mitoxantrone, etoposide, and cytarabine; EB-2, excess blasts-2; IAP, idarubicin, high-dose cytarabine, and pravastatin; GCLAC, combination of clofarabine and high-dose cytarabine with granulocyte colony-stimulating factor; GCLAM, combination of cladribine, cytarabine, and mitoxantrone with granulocyte colony-stimulating factor; HCT, hematocrit; MEC, mitoxantrone, etoposide, and cytarabine; PLT, platelet; TRM, treatment-related mortality.

for a maximum of 8 days spent in the ICU. During the days of induction chemotherapy, OPI patients received a median of 1 unit of red blood cells (RBCs) and a median of 0 platelet transfusions. They did not require intravenous antibiotics. During the first 30 days following OPI, the patients had an average of

Table 2. Hospital admissions during induction chemotherapy period and 30-day follow up period

Variable	Outpatient induction (N = 17)
Admitted during induction chemotherapy, n (%; 95% CI)	
No	14 (82.4; 55.8-95.3)
Yes	3 (17.7; 4.67-44.2)
Reasons for admission, n	
Neutropenic fever	2
Mucositis	1
Admitted after induction chemotherapy within 30 d, n (%)	12 (70.6)
Not admitted within 30 d, n (%)	2 (11.8)
Death within 14 d, n (exact 95% CI)	0 (0-22.9)
Death within 60 d, n (exact 95% CI)	2 (2.06-37.7)

7.5 ± 3.9 RBC transfusions (median, 6; range, 2-17), 7.6 ± 5.1 platelet transfusions (median, 6; range, 1-18), and 12.8 ± 8.4 days of antibiotics (median, 12 days; range, 0-29 days).

Discussion

Traditionally, due to significant TRM associated with pancytopenia and chemotherapy toxicity, patients with AML and high-risk MDS are preemptively hospitalized for intensive induction chemotherapy beginning with receipt of chemotherapy and extending until count recovery; this practice remains the standard of care throughout the United States and abroad. However, with significant improvements in supportive care, including a multidisciplinary support structure, routine outpatient transfusion programs, and effective broad-spectrum antimicrobial agents, there has been an objective decrease in TRM over time.^{21,22} These improvements enable early hospital discharge after completion of chemotherapy administration. The feasibility, safety, and potential cost saving of outpatient consolidation chemotherapy administration and early discharge after both outpatient consolidation and induction chemotherapy administration in patients meeting logistical criteria have been established.^{12,14,15} Furthermore, one study concluded that it was both feasible and safe to administer an outpatient “semi-intensive” induction program (up to 3 sequential cycles of semi-intensive chemotherapy consisting of cytarabine 200 mg/m² per day continuous infusion for 7 days, filgrastim starting the day before chemotherapy, and either fludarabine 25 mg/m² per day for 4 days or idarubicin 20 mg/m² per day for 3 days). Although admission rates during receipt of chemotherapy were not reported, only 13% of patients were managed exclusively as outpatients throughout the sequential induction cycles.²³

No studies have yet focused on outpatient administration of intensive induction chemotherapy. Although patients with active disease have higher infectious complication rates independent of degree of bone marrow suppression,^{4,24} we suspected that with effective supportive care, patient morbidity and mortality would not be significantly increased by an outpatient approach; furthermore, we recognized that TRM varies widely among patients and suspected that patients at relatively low risk for adverse effects could safely receive OPI.²⁵ Here we investigated an OPI strategy in select patients with newly diagnosed AML, relapsed or refractory AML, or high-risk MDS. In this pilot study, 14 of 17 OPI patients (82.4%; exact 95% CI, 56.6-96.2) received induction chemotherapy exclusively in the outpatient setting, and no patients died within 14 days of the initiation of induction chemotherapy (exact 95% CI, 0-22.9). This outcome suggests that it is feasible to administer OPI chemotherapy in select patients meeting specific disease-related, health-related, and logistical requirements.

The slow pace of accrual was believed to be due to the initial limitation of enrollment to only younger patients and to only initial induction therapy; in time, it was expanded to include all ages and both initial or salvage induction. In addition, there were times during which scheduling of multiagent, multiple-day regimens was restricted, which was later improved by adoption of new scheduling paradigms.

As noted in the Results, the mean number of transfusions was 7.5 for RBC and 7.6 for platelets during the first 30 days of induction. Other studies have reported a slightly higher mean of 10 RBC transfusions (threshold hemoglobin 8 g/dL, similar to our threshold) for patients with acute leukemia undergoing induction chemotherapy²⁶ and a lower number of 2.68 platelet transfusions for patients

undergoing treatment of AML with standard-dose intensity regimens receiving prophylactic platelet transfusions for platelet count <10 × 10⁹/L,²⁷ as is our practice. The latter study was performed in Germany, and it is possible that the standard intensity of the regimens reported there may be somewhat less than the intensity of the regimens here, which in many cases include high-dose cytarabine as the reason for the lower number of platelet transfusions needed. The number of platelet transfusions during the time of OPI chemotherapy administration was only 0.47, and thus the number of transfusions during the period of outpatient chemotherapy administration does not account for the difference.

It was not the intent of this initial feasibility study to fully compare the TRM of OPI chemotherapy vs that of inpatient induction chemotherapy, as such an investigation would require treating a large number of patients in the outpatient setting. It was reassuring, however, that only 1 patient (5.88%) died within 30 days of initiating OPI chemotherapy.

Previous studies have shown that length of time spent inpatient both increases cost and has adverse effects on quality of life.^{8,14,15} We therefore sought to determine if the number of inpatient days could be reduced with OPI. We identified a small cohort of patients who were not admitted during the month of induction but we did not conduct formal quality of life studies. Although we anticipate that remaining as an outpatient may improve quality of life for patients with adequate support residing close to medical care, this topic will need to be formally addressed in a future trial. It is critical to highlight the need for an effective multidisciplinary approach to outpatient care. Significant system changes had to be implemented to facilitate close clinical follow-up and effective symptom triage, to provide comprehensive psychosocial support, and to ensure that the patients with AML received education for care of central venous lines, effects of chemotherapy (including risk of infection and bleeding), and medication management. In fact, at our institution, the previous studies of early discharge after induction prompted nurse-led workgroups to help tackle these critical components of outpatient care. Furthermore, because this protocol was resource-intensive with daily evaluations, laboratory draws, infusions, and transfusions, logistical challenges such as scheduling multiple infusions and transfusions were encountered. Effective solutions required input from physicians, nurses, and pharmacists. The need for outpatient clinic services 7 days a week may prevent these procedures from being performed in all centers. We conclude that effective implementation of an outpatient intensive induction chemotherapy program should include an anticipatory interprofessional team-based approach that includes nursing, social work, medical providers, and pharmacists.

Acknowledgment

This research was funded in part through the National Institutes of Health, National Cancer Institute Cancer Center Support Grant P30 CA015704 to the Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium.

Authorship

Contribution: F.L.M. generated the first draft; P.S.B. the last draft of the manuscript; and all authors contributed to the acquisition, analysis, or interpretation of the data for this article, revised the manuscript critically, approved the final version for publication, and agreed to be accountable for the results presented.

Conflict-of-interest disclosure: Institutional research funding was received from AbbVie, Amgen, Bristol-Myers Squibb, Glycomimetics, Invivoscribe, Novartis, Pfizer, Secura Bio, and Trovogene for other studies for which P.S.B. is the Principal Investigator. P.S.B. is on the Medical Advisory Board for Accordant Health Services/Caremark. The remaining authors declare no competing financial interests.

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