Outpatient Management Following Intensive Induction or Salvage Chemotherapy for Acute Myeloid Leukemia

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Keywords
Acute myeloid leukemia, early hospital discharge, health care cost, intensive chemotherapy, outpatient management, quality of life

Abstract: Adults with newly diagnosed or relapsed acute myeloid leukemia (AML) commonly receive intensive chemotherapy to achieve disease remission. In the United States and many other countries, it is standard practice that these patients remain hospitalized "preemptively" until blood count recovery, owing to the risk for overwhelming infections and bleeding during pancytopenia. This care policy requires hospitalization for an average of 3 to 4 weeks after completion of chemotherapy. However, highly effective oral prophylactic antimicrobials are now available, and transfusion support of outpatients has become routine in recent years. As a result, the care of patients with hematologic malignancies treated with intensive modalities is increasingly shifting from inpatient to outpatient settings. Benefits of this shift could include the reduced need for medical resources (eg, transfusions or intravenous antimicrobial therapy), improved quality of life (QOL), decreased rates of nosocomial infections, and lower costs. Increasing evidence indicates that select AML patients undergoing intensive remission induction or salvage chemotherapy can be discharged early after completion of chemotherapy and followed closely in a well-equipped outpatient facility in a safe and cost-effective manner. Further demonstration that the current approach of preemptive hospitalization is medically unjustified, economically more burdensome, and adversely affects health-related QOL would very likely change the management of these patients throughout this country and elsewhere, resulting in the establishment of a new standard practice that improves cancer care.

Introduction

In 2013, an estimated 14,590 individuals in the United States will be confronted with a new diagnosis of acute myeloid leukemia (AML),[1] a cancer of immature hematopoietic cells that leads to proliferation and accumulation of abnormal myeloid cells that do not differentiate normally.[2,3] A large number of patient- and disease-specific characteristics, most importantly cytogenetic and molecular

abnormalities of the leukemia cells, have been identified that help in prognostication and the prediction of therapeutic outcomes. Overall, however, despite aggressive therapies, most patients will eventually die of their disease, as a consequence of impaired normal hematopoiesis, organ infiltration by tumor cells, or treatment-related toxicities.[4-7]

Typically, patients with AML receive intensive chemotherapy to induce complete remission (CR) as the first step toward cure.[4-7] A CR—conventionally defined as the presence of less than 5% blasts in the bone marrow together with the recovery of peripheral blood counts and absence of extramedullary disease[5]—can be achieved in 60% to 80% of newly diagnosed AML patients who are younger than 60 years of age, and in up to 50% of patients aged greater than 60 years. However, disease relapse affects the majority of patients who initially achieve a CR. While different therapeutic options are currently available for relapsed/refractory AML, high-intensity salvage chemotherapy remains a mainstay of therapy, and is aimed to re-induce remission.[4-7] Thus, patients are frequently treated with high-dose chemotherapy regimens throughout the course of their disease.

Improvements in Administering Intensive Chemotherapy for AML Patients

It is well known that the risk of serious complications or early death as a complication of treatment-related toxicities varies considerably among AML patients. For example, in patients treated on SWOG trials between 1991 and 2003, the day-30 mortality was less than 5% in some patient subsets but 50% or higher in others.[8] However, despite the fact that curative-intent induction and salvage treatment regimens for AML have remained relatively unchanged for several decades,[4-7] Othus and associates recently demonstrated a decline in treatment-related mortality rates following intensive induction chemotherapy over the last 20 years, with significantly lower rates in patients treated between 2006 and 2009.[9] Although various selection biases cannot be fully excluded, this observation strongly suggests that major improvements have been made in the supportive care of AML patients undergoing curative-intent chemotherapy. Chief among these is likely the introduction of more potent antibiotics, particularly antifungals. Many of these can be administered orally and are well tolerated.[10] Below, we discuss how the availability of these drugs may render superfluous the need for inpatient management of AML during remission induction therapy.

Numerous factors have been identified that are associated with adverse treatment outcome, including age and covariates that may serve as surrogates for the biologic (rather than chronologic) age of a patient. These include performance status, organ function parameters (eg, bilirubin, fibrinogen, albumin, creatinine), degree of cytopenias, and disease characteristics. Such factors formed the basis for several scoring systems initially aimed at recognizing patients at high risk for treatment-related mortality with intensive induction chemotherapy,[11-14] and may need to be critically reassessed in light of improved supportive care measures. Nonetheless, they offer an empiric approach in identifying subsets of AML patients who will likely do well following intensive chemotherapy.

Inpatient Care as Standard for Patients Undergoing Intensive Chemotherapy for Newly Diagnosed or Recurrent AML

AML patients are routinely hospitalized for intensive chemotherapy regimens, which usually entail continuous infusions that are easier to deliver in the hospital. Moreover, as these patients often present with fever and/or infections or bleeding at initial diagnosis or disease relapse, they may require hospital admission independent from their anti-AML treatment. Despite improvements in supportive care, however, it remains standard practice to keep patients preemptively in the hospital for the additional 3 to 4 weeks required for recovery of normal blood counts. This permits close monitoring for treatment-related toxicities and complications of cytopenias, such as bleeding and infection, with infection being the principal cause of death in this disease.[15] An informal poll of physicians in private practice in Washington and physicians at the VA Puget Sound Health Care System in Seattle, Washington, suggests that a similar policy is in place in the community setting as well. This is the case even in patients who do not require intensive supportive therapy when chemotherapy is completed; such patients constitute the majority of those younger than 75 years. In contrast, AML patients receiving consolidation therapy are routinely discharged from the hospital after completion of chemotherapy, although it is often as intense or more intense than induction therapy and produces a similar degree and duration of cytopenias. Subsequent outpatient care is not only feasible, but also well accepted by patients and cost effective.[16-19] This contrasting approach may reflect the observation that infection at any given neutrophil count is less common in patients in remission than in those with active disease.[20-22] Nevertheless, it is arguable whether the difference in infection rates is sufficient to justify such a dramatic difference in practice standards and warrant preemptive hospitalization in many cases, particularly those predicted to be at very low risk of experiencing serious side effects of treatment-related mortality.

Quality of Life for AML Patients Undergoing Intensive Chemotherapy

Along with life expectancy, quality of life (QOL) is among the most important considerations for patients with AML. Its significance is highlighted by the fact that improvement in QOL can serve as a primary endpoint in the regular drug approval process in the United States.[23] The need to include QOL measures has motivated efforts to formally include patients' perspectives on QOL. To date, the lack of validated measures of QOL for patients with AML and methodologic limitations have hampered the use of this endpoint, and only very few randomized studies have utilized QOL endpoints in AML.[24] The measure most frequently used has been the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).[24] Not surprisingly, the available evidence suggests that QOL is greatly impaired in AML patients, particularly immediately after diagnosis and during therapy.[25] Affected domains include physical, psychological and emotional, as well as sexual function.[25] Factors such as fatigue, number of blood transfusions, hemorrhages, days with fever, days on antibiotics, and days spent in the hospital can adversely affect a patient's QOL.[24]

Economic Burden of AML Therapy

Several studies have addressed the economics of AML.[25-34] For example, in a study reviewing Medicare claims for 2657 patients with AML, the largest cost driver was hospital reimbursement (84% of costs), followed by physician payments (7% of costs), outpatient hospital/clinic payments (4% of costs), and home health care payments (2% of costs).[25,30] Similarly, a longitudinal study of 275 older patients with AML treated at 28 US hospitals from 2000 through 2003 showed that these patients incurred substantial hospital charges ($113,118 [~$145,000 in 2012 $US] for a mean length of stay of 23 days).[31] Although comparable data are not readily available for younger patients in the United States, experience suggests that hospitalization accounts for a disproportionate share of their costs as well. Several European studies from France, Germany, Sweden, and the Netherlands also highlighted the high cost of AML therapy. Consistent with the US data, these studies have demonstrated that the vast majority of costs are associated with induction and reinduction/relapse treatment, with inpatient costs driven by length of hospital stay as the single largest cost component during therapy.[25,28,29,32-34] Thus, it is evident that the resource-intense nature of AML therapy renders these diseases disproportionately expensive, and such treatments are a significant economic burden for patients, insurance companies, and society.

Potential Benefits of Outpatient Management After Intensive Chemotherapy for Active AML

The established practice of prolonged hospitalization after induction chemotherapy for AML is potentially harmful. For example, it is well known that hospital-acquired (nosocomial) infections are more difficult to treat than infections acquired outside of the hospital. Moreover, the recent refusal of Medicare to recompense hospitals for iatrogenic errors has drawn attention to the fact that hospitals may not be as safe as previously believed.[35] Furthermore, it is conceivable that early discharge of patients following completion of chemotherapy is associated with improved QOL. Obviously, an improvement in QOL measures is most compelling if the intervention (early discharge) does not affect response rates and survival.

Together with increasing attention to costs, these considerations have boosted the desire to change the management of AML from the inpatient to the outpatient setting during much of induction/reinduction therapy. Awareness of the potential benefits of outpatient management has coincided with improvements in supportive care to accomplish this goal. Perhaps foremost among these are an increased ability to deliver transfusions in the outpatient setting and, as mentioned before, new, oral, broad-spectrum antimicrobials with high activity against organisms like *Pseudomonas* and *Aspergillus (*which are commonly responsible for fatal infections during neutropenia in AML). When administered prophylactically, they reduce morbidity and mortality from infection in AML.[36] Employing prophylactic oral antibiotics, Halim and colleagues reported a decrease in the incidence of septicemia from 22% to 13%, which was associated with a shift from inpatient to outpatient management.[37] In fact, very limited data suggest that early hospital discharge may reduce the number of days on intravenous antibiotics relative to inpatient care.[18] Nevertheless, effective inpatient antibiotics are available for outpatients who develop infections or neutropenic fever while on prophylactic therapy.

There may be additional benefits to early discharge after remission induction chemotherapy, as prolonged hospitalizations are associated with a decreased ability to resume independent functioning after discharge, leading to significant productivity losses and costs owing to morbidity.[25,38] Early discharge may thus facilitate resumption of independent functioning and reintegration into family and professional life after completion of AML treatment, and provide another potential opportunity for societal cost savings.

Exploration of Outpatient Management Strategies After Induction or Salvage Chemotherapy for AML

Unlike consolidation chemotherapy, only a few retrospective and noncontrolled prospective studies have

investigated whether selected patients could be safely discharged after completion of induction chemotherapy for AML.[18,37,39-42] In 1995, Ruiz-Argüelles and colleagues reported on 24 adult patients who received standard induction chemotherapy with cytarabine and adriamycin (7+3 regimen) and were discharged from 3 institutions in Mexico after completion of chemotherapy to remain at home or in a nearby hotel, provided they had no fevers or obvious infections and had a very good performance status.[39] While rehospitalizations for infections were necessary in 7 patients, no fatalities occurred, and it was estimated that outpatient management saved $1700 (~$2600 in 2012 $US) per patient. One year later, Gillis and associates reported a prospective study on 29 adult AML patients who received a total of 86 induction or consolidation courses at Hadassah University Medical Center in Jerusalem, Israel.[40] After 50 of these treatment cycles, patients were discharged early and followed as outpatients. However, outpatient management was feasible after only 4 of the 33 induction or salvage therapy cycles but in 46 of the 53 consolidation cycles, indicating that, in unselected patients, an early discharge policy might be difficult to implement. More encouraging was a retrospective analysis on 19 consecutive adult AML patients who received induction chemotherapy with the 7+3 regimen between 1996 and 1998 in Toronto, Canada.[18] Ten of these 19 patients were able to be discharged with 10 days of initiating induction chemotherapy. All but 1 patient required readmission (an average of 1.5 readmissions per patient, mainly for episodes of neutropenic fever). Nevertheless, no fatalities occurred, and patients discharged early had 30% fewer in-hospital days than inpatient controls and 57% fewer days of inpatient antibiotic therapy, while transfusion requirements were comparable. In another Canadian study, 70 adult patients were prospectively evaluated after receiving various types of induction chemotherapy for newly diagnosed AML (n=61), relapsed/refractory AML (n=8), or both (n=1), between 2001 and 2002 at the Vancouver General Hospital and British Columbia Cancer Agency.[41] Determining eligibility based on a set of medical criteria (absence of fever, use of prophylactic antimicrobials, hemodynamic stability, resolution of coagulopathy, absence of serious comorbidities), as well as logistic criteria (availability of accommodation within 60 minutes of treatment center, availability of suitable caregiver), patients were discharged after 25 of these 71 induction therapy courses; only 9 patients required readmissions for neutropenic fever, and no fatalities occurred. Finally, in a study conducted at the National University Hospital in Copenhagen, Denmark, 60 patients with acute leukemia (50 of whom had AML) were enrolled between 2004 and 2007 as candidates for outpatient treatment if they lived within a 120-km radius from the hospital and had a caregiver available at night; patients with severe infections and/or refractoriness to platelet transfusions were not treated in the outpatient setting.[42] After 48 of the total 73 induction or reinduction courses, patients were discharged after completion of chemotherapy and followed as outpatients, with no readmission after 19 of these. A median of 8 and 6 days were spent at home with an absolute neutrophil count of 0.5×10^9/L and a platelet count of less than 20×10^9/L. Similar to the other studies, readmissions were primarily for neutropenic fevers, and no fatalities were observed.

At our institution, we conducted a pilot study (NCT00844441) to explore discharge of adult AML patients (excluding acute promyelocytic leukemia) once induction chemotherapy was completed.[43] In our study, we also included patients with high-grade myelodysplastic syndromes (ie, >10% blasts in the bone marrow), as these diseases clinically and biologically resemble AML, and patients who undergo intensive AML-like induction therapies have similar outcomes to AML patients.[44,45] Patients aged 18 to 60 years were eligible if they had begun intensive chemotherapy for untreated or relapsed disease within the preceding 3 days. After completion of chemotherapy, patients were reevaluated and considered eligible for hospital discharge if they fulfilled medical criteria including: Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; adequate liver, kidney, and cardiac function; no intravenous antimicrobial therapy, no active bleeding, and no refractoriness to platelet transfusions. Once eligibility for medical discharge was determined, patients were screened for logistic criteria: being amenable to close outpatient follow-up, having a reliable caregiver, and residing within 30 minutes of the study center. Patients meeting both medical and logistic criteria were discharged. If readmitted, subsequent early hospital discharge was possible if all medical/logistic criteria were again met. Patients who met the medical but not the logistic criteria served as inpatient controls and remained hospitalized until peripheral blood count recovery. Patients were discharged on antimicrobial prophylaxis that was continued until the absolute neutrophil count (ANC) was at least 0.5×10^9/L. Patients were seen by an outpatient oncology nurse 3 times per week and by a physician once weekly. Transfusion thresholds in asymptomatic patients were: hematocrit <26% and platelet count $<10 \times 10^9$/L. Patients with febrile neutropenia were hospitalized for intravenous antimicrobials. Patients continued on study until recovery of peripheral blood counts (ie, ANC $>0.5 \times 10^9$/L and self-sustained platelet count $>20 \times 10^9$/L), they required additional chemotherapy, or 45 days had elapsed from the time of reevaluation. To determine resource utilization and estimate cost, pertinent information was collected from medical records and

electronic billing information (to capture professional and facility charges). Since previous data from our center suggested an induction mortality rate of 5% in preemptively hospitalized patients receiving induction chemotherapy, the study was monitored to ensure that the rate of death during the study did not exceed 5%.

Between April 2009 and April 2010, we enrolled 39 patients. Nineteen of the 39 patients did not meet medical early discharge criteria after completion of chemotherapy and were removed from the study. Five of the 20 medically eligible patients did not meet logistic discharge criteria and remained hospitalized (controls; all 5 patients did not have permanent or temporary local housing), while 15 patients met both medical and logistic criteria and were discharged after completion of chemotherapy. Thirteen of the 15 patients who were discharged early required readmission prior to peripheral blood count recovery, with 6 patients being readmitted twice while on protocol. Causes for readmission were neutropenic fever (n=16), bleeding (n=2), and nausea/vomiting (n=1). The patients who were discharged early spent a median of 8 days (range, 3-36 days) as outpatients over a median of 2 outpatient periods (range, 1-3). The median total number of days spent in the hospital was 6 (range, 0-28). Patients who were discharged early spent a median of 53.8% (range, 28.6%-100%) of the time from discharge until removal from study as outpatients. In contrast, the 5 inpatient controls were hospitalized for a median of 21 days (range, 10-21 days; $P<.01$ when compared with patients discharged early) after completion of chemotherapy before being removed from the protocol. No patient required intensive care unit (ICU)-level care, and no deaths occurred in either group. Despite the small sample size of our pilot study, the median daily total professional and facility charges were significantly lower for patients discharged early compared with inpatient controls over the study period ($3270 vs $5467; $P=.01$). In contrast, the daily charges per inpatient day were relatively similar between these 2 groups ($P=.40$), suggesting that inpatient charges are not substantially higher if readmission is necessary. Thus, although we analyzed charges and not costs, our data suggest that outpatient management of selected patients is safe and may significantly reduce financial burden.[43]

Nursing Implications of Outpatient Management Following Intensive AML Chemotherapy

Historically, when the AML patient remained hospitalized for several weeks following remission induction chemotherapy, the nursing focus was on ensuring patient safety. This was accomplished by routinely taking vital signs and doing physical assessments, monitoring for subtle signs of infection and bleeding, and providing supportive care measures (eg, administering medications to control nausea and pain). During this time, the nurse spent time educating the patient about not only the side effects of chemotherapy, but how to prevent infection and care for the central venous catheter, and when to seek emergency care. In addition, social work resources were available for emotional and financial support.

Discharging a patient at the conclusion of induction chemotherapy significantly shortens the time available for initial and reinforced education and places increased responsibility on the patient and caregiver for the monitoring of side effects and the timely recognition (or prevention) of infections so that emergency care is appropriately sought. At our institution, the members of the inpatient nursing staff who traditionally cared for AML patients during their most vulnerable phase of therapy were concerned that the patient would not have sufficient time to understand the nature of their disease, the importance of preventive care measures, and the need for immediate medical attention at minimal signs or symptoms of a cytopenia-associated complication. On the other hand, the members of the outpatient nursing staff who would be following these patients did not have a clinic schedule or structure available to care for these patients in the early phase after completion of induction or salvage chemotherapy, as they traditionally had only assumed care responsibilities after peripheral blood count recovery in such cases. These concerns, along with the need for the patient to acquire the skills necessary to care for central venous catheters and have sufficient time to grasp the implications of the disease in their entire breadth (including the psychosocial and financial aspects), led the clinical nurse specialist to form workgroups to design a program for implementation of an early discharge practice. Questions to address included: How often will patients be seen while neutropenic and/or thrombocytopenic, and who would see them? What would the laboratory monitoring entail? Where will patients be seen when presenting with fevers? If patients with fevers present to the emergency department, how do we ensure they are triaged quickly to receive antibiotics? How will social workers know to initiate central venous catheter referrals earlier than what has so far been the standard? As soon as these issues were identified, subgroups were formed to work on each of these questions and concerns. Inpatient nursing staff worked to identify key items necessary in patient education for safe patient discharge and easy reference for the patient. Outpatient nursing and the social work team identified triage routes for patients with fevers and the myriad of possibilities for central venous catheter care. The principal investigator and a study nurse leading the initial pilot study exploring an early discharge policy identified the need to educate the emergency department staff about the neutropenic AML

Table. Logistic Implications of Outpatient Management Following Intensive Induction or Salvage Chemotherapy for AML

Implementation Issue	Resolution
Outpatient Management	
After hours care	Establishment of call procedures and with specific identification of steps for patient referral and flow during after hours
Emergency care	ED alerted of potential increased number of pancytopenic patients at risk for sepsis and bleeding Generation of patient wallet card with relevant study information to present on arrival to ED to expedite triage and time to intervention Identification of a "sepsis pack" (antimicrobial cocktails) for rapid delivery in OPD prior to transport to hospital
Clinical management in outpatient clinic	Assessed by nurse and/or primary provider 3 times per week Assessed by attending physician once weekly Lab monitoring 3 times weekly or more frequently if needed Symptomatic patient—triage in infusion area with direct admission to inpatient leukemia ward if appropriate, or referral to the ED for further work-up
Education	Continuing of patient and family education by outpatient clinic nursing to reinforce patient education Creation and provision of quick reference guide (who to call and when to call)
Psychosocial support	Social worker referral for all newly diagnosed patients
Inpatient Management	
Outpatient CVC care	Referral to social worker at time of CVC placement to identify home infusion resources Emphasis on formal CVC care education and reinforcement
Education	Establishment of education roadmap and checklist Establishment of written discharge instructions
Handoffs	Identification of OPD attending physician Inpatient resident physician tasked with setting up OPD appointments

AML, acute myeloid leukemia; CVC, central venous catheter; ED, emergency department; OPD, outpatient department.

patient. The clinical nurse specialist served as a resource to each group. The outcomes are summarized in the Table.

Once the pilot study of early discharge following completion of induction chemotherapy was launched, further issues were identified that required just-in-time adjustments. For example, as outpatients required review of laboratory results 7 days per week but individual clinic schedules were only available 5 days per week, the infusion room (which was open 7 days per week) became available for laboratory reviews and symptom management triage. Moreover, as these patients required frequent transfusions of packed red blood cells and/or platelets, support with fluids, and replacement with electrolytes, it was quickly recognized that available slots in the infusion room became a limiting factor—in large part because of our institution's large transplant patient population—and required cooperation and prioritization of scheduling of transfusions/supportive care between programs.

Conclusion

While the curative-intent induction and salvage treatment regimens for AML have changed little over the last several decades, supportive care has significantly improved in this time frame and now enables a more flexible management of AML patients. For example, highly effective oral prophylactic antimicrobials are now available, and transfusion support of outpatients has become routine in recent years. As increasing evidence indicates, such advancements may allow selected patients—most notably those without significant comorbidities, social support system, and residence that is located closely to an outpatient clinic—to be discharged early after completion of intensive remission induction or salvage chemotherapy and to be managed as outpatients with close follow-up in well-equipped and well-staffed outpatient facilities, although specific outpatient support and readmission procedures will need to be put in place in individual institutions to ensure maximal patient safety.

It is noteworthy that published data on this care strategy are still relatively sparse, and additional studies on larger cohorts of patients are warranted to investigate whether early outpatient management can be implemented safely; such studies are currently ongoing (eg, NCT01235572). In addition, defining the elements necessary for optimal outpatient management remains an area for active research. Further demonstration that the current approach of pre-

emptive hospitalization is medically unjustified, economically more burdensome, and adversely affects health-related QOL would very likely change the management of these patients throughout this country and elsewhere, and establish a new standard practice that improves cancer care.

Acknowledgment:

Supported by a grant from the National Cancer Institute/ National Institutes of Health (NCI/NIH; P30-CA015704-35S6 to Dr Walter).

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