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Outpatient care of patients with acute myeloid leukemia: Benefits, barriers, and future considerations

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Abstract

Patients with acute myeloid leukemia (AML) who receive intensive induction or re-induction chemotherapy with curative intent typically experience prolonged cytopenias upon completion of treatment. Due to concerns regarding infection and bleeding risk as well as significant transfusion and supportive care requirements, patients have historically remained in the hospital until blood count recovery—a period of approximately 30 days. The rising cost of AML care has prompted physicians to reconsider this practice, and a number of small studies have suggested the safety and feasibility of providing outpatient supportive care to patients following intensive AML (re-) induction therapy. Potential benefits include a significant reduction of healthcare costs, improvement in quality of life, and decreased risk of hospital-acquired infections. In this article, we will review the currently available literature regarding this practice and discuss questions to be addressed in future studies. In addition, we will consider some of the barriers that must be overcome by institutions interested in implementing an “early discharge” policy. While outpatient management of selected AML patients appears safe, careful planning is required in order to provide the necessary support, education and rapid management of serious complications that occur among this very vulnerable patient population.

Keywords

Acute myeloid leukemia; Chemotherapy; Costs; Infection; Outpatient care; Quality of life

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1. Introduction

The care of patients with acute myeloid leukemia (AML) who receive induction therapy with curative intent has historically required a prolonged hospital stay during the period of profound chemotherapy-induced pancytopenia. Close inpatient monitoring was felt to be necessary because of the frequent transfusion requirements and the risk for serious infectious complications, a major contributor to early death (“treatment-related mortality” [TRM]) after intensive AML therapy [1,2]. Over the past 2 decades, however, TRM rates of AML patients following induction chemotherapy have significantly declined [3,4], a trend that is primarily attributable to improvements in supportive care, including the administration of prophylactic antimicrobials during neutropenia [5] and the availability of more efficacious broad-spectrum antimicrobials for the treatment of neutropenic fever/infection [6,7]. As clinicians and medical support staff have become more comfortable preventing, recognizing, and treating the complications associated with aggressive AML treatment, an interest in moving patient care partially to the outpatient setting has emerged. This is due in large part to an effort to reduce the significant financial costs required to treat AML patients, and as the costs of managing patients with hematologic malignancies have continued to climb [8–11], reducing the expenses incurred by prolonged inpatient hospital stays has become increasingly more attractive. Other motivations stem from the desire to reduce the rates of nosocomial infections and improve patients’ quality of life. Several small case studies have suggested the feasibility and safety of hospital discharge following completion of AML chemotherapy [8–15]. In this review, we will examine the potential benefits of a policy of outpatient supportive care for AML patients following curative-intent remission induction therapy in both academic and community institutions. We will highlight some of the barriers that may be experienced by facilities interested in implementing such a practice, while simultaneously pointing to potential safety issues related to outpatient management. We will also draw attention to various open questions that remain to be addressed in future studies.

2. Previous experience

Studies pioneering outpatient care of complex patients treated with intensive chemotherapy were conducted in the setting of hematopoietic cell transplantation (HCT). Initial studies indicating the safety and cost-effectiveness of outpatient management were published almost 20 years ago, and the benefits of this practice continue to be explored even today [16–19]. For instance, a recent randomized trial of early discharge (n = 66) versus inpatient hospitalization (n = 65) following high-dose conditioning and autologous stem cell rescue from France demonstrated a mean cost reduction of 6% per patient among individuals affected by a variety of non-leukemic malignant diseases with no increased risk of post-transplant adverse events [20]. Implementation of HCT programs that are entirely based on outpatient management has now been undertaken by some centers, with persistent demonstration of cost savings and no adverse effects on mortality. For example, in a retrospective review of cost utilization among 91 multiple myeloma patients receiving outpatient autologous HCT since 2006, Holbro et al. reported an annual cost savings of 740,000 Canadian dollars for the institution (521,126 US dollars referencing the current rate of exchange, January 2016) and no deaths, although a high readmission rate (78%) for

neutropenic fever within 100 days was noted [21]. While transplant centers employ highly specialized physicians and support staff dedicated specifically to the management of HCT patients, the positive experience in this setting led several researchers at academic institutions to begin exploring outpatient alternatives for AML patients after induction chemotherapy as the duration of severe cytopenias is similar.

Over time, early hospital discharge of AML patients who receive post-remission “consolidation” chemotherapy has become routine in both academic and community healthcare centers, with several studies suggesting the feasibility and safety, as well as the cost-effectiveness, of this practice [12,15,22,23]. Admittedly, while some consolidation regimens may produce a duration of cytopenias similar to remission induction therapies, the infection risk is likely higher in patients with active leukemia than those who already have achieved remission [24]. Still, much less attention has been paid to the evaluation of outpatient management of AML patients after completion of induction chemotherapy until recently, and only a few studies have so far explored early discharge policies for this more vulnerable patient population. As early as 1995, Ruiz-Argüelles et al. reported on the successful discharge of 24 AML patients after induction chemotherapy [25]. In their cohort, no patients experienced early death although 7 required readmission for neutropenic fever and 4 had severe infectious complications. Less encouraging was the study by Gillis et al. who attempted to selectively discharge patients receiving either induction or consolidation cycles of chemotherapy [26]: only 4 of 33 patients receiving induction or salvage therapy could be discharged after treatment, in contrast to the 46 of 53 patients who were discharged after consolidation therapy. Two Canadian studies and one from Denmark later described more successful outpatient discharge rates in the induction setting with no reported fatalities [12–14]. Consistent with the HCT experience, the most frequent complications experienced by patients in all three studies were related to neutropenic fever/infection, which often required readmission. Despite high rates of readmission in the Canadian study by Allan et al. (1.5 readmissions/patient), the total number of hospital days was reduced by 30% when compared to 9 inpatient controls, as was the use of inpatient IV antibiotic therapy (57% fewer days) [12].

These earlier reports led us to undertake a prospective pilot study at the University of Washington (UW) Medical Center/Seattle Cancer Care Alliance (SCCA), in which we enrolled 39 patients with either AML or high risk myelodysplastic syndrome (MDS) undergoing intensive induction or re-induction chemotherapy between 2009 and 2010 [27]. Fifteen patients met pre-designated medical (particularly, lack of hepatic or renal dysfunction, absence of bleeding or platelet refractoriness, no clinical signs of heart failure, and no need for IV antimicrobials) and logistical (particularly, permanent or temporary residence within 30 min of the study center, willingness to have close clinic follow-up, and availability of a reliable caregiver) criteria and were discharged within 1–3 days of completion of chemotherapy, whereas 5 patients who met medical but not logistical criteria for early hospital discharge served as inpatient controls; the 19 patients who failed to meet the medical criteria for early hospital discharge were taken off study. Consistent with the findings from others, the majority of the 15 discharged patients ($n = 13$) on our study required at least 1 readmission (range 0–2), primarily for neutropenic fever ($n = 16$), but no early deaths (defined as death within 30 days of chemotherapy) occurred in our cohort [27].

Based on the data obtained in our pilot study, we then conducted a larger, comparative, non-randomized phase 2 prospective study, in which we enrolled 178 adults AML or high-risk MDS patients after receipt of induction or re-induction chemotherapy [28]. Within 72 h of chemotherapy completion, patients were reassessed medically and deemed eligible for early discharge if they had an ECOG performance status of 0–1, bilirubin level less than or equal to 3 times the upper limit of normal, glomerular filtration rate at least 25% of the lower limit of normal, and no clinical signs of heart failure or bleeding. Of 136 patients who fulfilled these medical eligibility criteria, 107 patients also permanently or temporarily resided within 60 min travel time to the treating center and had a reliable caregiver, thus meeting logistical criteria for early hospital discharge. The remaining 29 patients who met medical but not logistical discharge criteria served as inpatient controls, an approach that allowed for a comparison of costs, resource utilization and complication rates between the inpatient and outpatient groups. Similar to our pilot study, discharged patients were seen multiple times per week by an oncology nurse and evaluated by a physician or advanced care provider at least once weekly. Four deaths occurred within 30 days of treatment, all of which occurred among patients allocated to the experimental arm of the study, and only discharged patients required ICU care ($n = 9$ [8%] vs. 0 in the control arm, $p = 0.20$). While these outcomes may raise some concern regarding safety of an early discharge policy in selected patients, it is notable that the early death rate on the experimental arm (2.9%) is comparable to the rates seen in contemporary cohorts of adults undergoing induction chemotherapy for newly diagnosed AML (3–4%) [3]. The vast majority of patients discharged early ($n = 93$ [87%]) required readmissions, primarily for neutropenic fever/infection, and a statistically significantly increased incidence of documented bloodstream infections was found in these patients, as we will discuss later.

These results are complemented by a recent study investigating the safety and benefits of early discharge in the pediatric AML population [29]. Getz et al. retrospectively examined data from the Pediatric Health Information System (PHIS) to assess whether resource utilization differed among children discharged within 3 days of chemotherapy completion and those who remained hospitalized for more prolonged periods (median: 15–23 days after completion of chemotherapy). A 116% higher risk of ICU care, as well as increased requirement for vasopressors, oxygen support, and inpatient IV antibiotics was found among patients discharged early. The authors concluded that the increase in inpatient support required by early discharge patients suggests a higher risk of treatment-related complications among this patient group, although the TRM was similar to patients who remained hospitalized [29]. In another study, the Children's Oncology Group (COG) retrospectively examined the clinical course of pediatric AML patients who were discharged early after chemotherapy completion in comparison to those who remained in the hospital [30]. Out of 153 eligible patients, however, early discharge occurred in only 11%. These patients experienced high rates of re-admission (80–100%), though the number of inpatient days was reduced overall. Outcomes of interest included rates of Viridans streptococcal bacteremia, hypoxic episodes, and hypotension, all of which were increased in children who were discharged early (adjusted risk ratio = 1.67, 1.92, and 4.36, respectively). Similar to the other studies, no difference was seen in mortality rates between the two groups [30]. Therefore, while it may be that selected patients with AML can be discharged from the hospital early

after completion of induction chemotherapy and be followed as outpatients during the time of profound cytopenia, the risk of acute toxicity-related complications is not negligible. Careful attention must be paid to ensuring close follow-up for these patients and devising strategies for rapid management should significant medical problems occur.

3. Potential benefits of outpatient management

3.1. Reduction of healthcare costs

A few of the studies discussed above, including our own, have assessed cost savings achieved by an early discharge policy as one of the main outcomes of interest. The impetus for this lays in the fact that inpatient hospital reimbursements have been repeatedly shown to be the major driver of the high cost of AML care [8]. In the study by Ruiz-Argüelles et al., the early discharge of AML patients following completion of induction chemotherapy led to an average savings of 1700 USD per patient [25]. Consistent with this estimate, we found approximate cost savings of 2000 USD charged per patient discharged early compared to inpatient controls in both the pilot and phase 2 studies conducted at the UW/SCCA [27,28]. Efforts to quantify fiscal gains from changes in clinical practice are often hindered by the inherent difficulties in calculating healthcare costs, particularly in the U.S. For example, we utilized hospital “charges” as a surrogate for healthcare cost in our studies. “Charges”, however, do not represent true hospital reimbursement rates, as these differ based on negotiations between healthcare institutions and individual payers. In general, these “charges” will tend to overestimate the true cost of care. Therefore, while providing a reasonable metric by which to make comparisons of healthcare “cost savings”, the “hospital charges” accrued by either discharged patients or inpatient controls cannot be used to estimate the true costs of AML management. In the community setting, where outpatient care is often provided by practices operating independently of the hospital where chemotherapy is administered, quantification of healthcare costs becomes even more complicated, as both the inpatient and outpatient facilities have different “charge” rates and have negotiated separate reimbursement rates with individual payers.

To our knowledge, all studies of outpatient AML management that have assessed cost outcomes have done so from the perspective of the healthcare institution [25,27,28]. One limitation of this approach is that it does not address the financial costs assumed by the patient and his/her caregiver(s). It is likely that early hospital discharge leads to increased out-of-pocket expenses to cover local housing, transportation to and from the clinic, food, home health, and/or prescription drugs such as oral antibiotics. Prior attempts to understand the financial burden experienced by patients with hematologic malignancies undergoing HCT have suggested that such personal expenses are substantial and, of course, not captured by review of hospital billing records [31]. It is therefore important to consider the “patient perspective” of healthcare savings in future explorations of outpatient AML management if we are to reassure ourselves that the savings garnered by “the system” are not simply being shifted onto the shoulders of patients and their families.

3.2. Quality of life benefits

Studies in the HCT setting suggest that hospitalization poses a significant detriment to quality of life and increases the risk of depression and sleep disturbances [32]. Efficace et al., in an assessment of quality of life factors affecting patients enrolled in clinical trials for leukemia, found that fatigue, increased numbers of blood transfusions, hemorrhages, number of days with fever or on antibiotics, and increased hospitalization days all led to impaired quality of life in their patient population [33]. On this basis, one might intuit that the ability to recover from chemotherapy in one's home environment would lead to improvements in a patient's quality of life. In our own experience, a large portion of the AML patients undergoing induction or re-induction therapy are very interested in the ability of being able to leave the hospital early after completion of chemotherapy. While the phase 2 early discharge trial at our institution was ongoing, we encountered occasional difficulties with enrollment due to the patients' fear of not meeting the requisite logistical criteria. The desire to undergo outpatient care during the duration of pancytopenia was so strong in some patients that they elected to not participate in the trial and pursue outpatient care off-protocol. This observation suggests that conducting a prospective randomized study, while ideal to further evaluate an early discharge policy, could be challenging as patients may be unwilling to enter a randomization that might allocate them to prolonged hospitalization if discharge is an option.

Still, it is possible that for some, the transition from inpatient to outpatient care may be temporarily detrimental to quality of life, especially if it is implemented immediately after the completion of chemotherapy. In fact, many AML patients recovering from induction chemotherapy experience this transition as an uncomfortable shift in responsibility, suddenly requiring them and their caregivers to assume the burden of monitoring symptoms, commuting to appointments, navigating unfamiliar clinics, communicating complex medical information to new providers, and coordinating care with support services. Not surprisingly, this upheaval is particularly challenging for patients who live at greater distance from their cancer center [32]. Furthermore, for early discharge patients, this transition would typically occur after about one week, a time associated with worsening cytopenias and significant decline in health-related quality of life [34], particularly when undergoing intensive chemotherapy [35]. While we suspect that quality of life is improved for patients allowed early hospital discharge, we recognize that this is not a foregone conclusion and recommend that quality of life endpoints be included in randomized trials of early discharge to test this hypothesis.

Maximizing quality of life is an important goal of cancer care, particularly in AML where survival for some high-risk groups is measured in months rather than years [36]. Furthermore, the U.S. Food & Drug Administration (FDA) places a high value on quality of life, accepting quality of life improvement as a primary endpoint in the drug approval process [37]. Nevertheless, few randomized trials in AML have used patient-reported outcomes as endpoints [38]. Though we advocate studying the effects of various outpatient care strategies on quality of life in AML patients, we anticipate several hurdles in this line of research. First, there is no standard instrument to measure quality of life in patients with AML, nor is there an AML-specific instrument. The most commonly used instruments

include the EORTC Quality of Life Questionnaire (QLQ-C30) and the Functional Assessment of Cancer Therapy-General version (FACT-G) [39], but these general measures have not been validated in AML specifically. To compensate for this lack of specificity, some groups have opted to quantify quality of life in AML by administering batteries of multiple instruments, a practice that could lead to patient burn-out and lower adherence rates [40–42]. More recently, the FACT-Leukemia (Leu) subscale, a 17-item addition to the 27-item FACT-G, was created and validated in patients with acute and chronic myeloid and lymphoid leukemias [43]; this instrument has not been widely used. It is unclear which instrument (or combination of instruments) is ideal for measuring quality of life in AML patients. A second hurdle in measuring quality of life in this setting is compliance with repeated questionnaires, as patients are often fatigued and may even demonstrate cognitive impairment related to their disease or treatment [44]. While severity of illness correlates with poor compliance with these instruments in other cancers [45,46], achieving high rates of patients participation with frequent questionnaires is feasible in the post-HCT population [47] and, with optimal study design, could likely be accomplished in newly-diagnosed patients during their transition from inpatient to outpatient care.

An important consideration is how earlier transitions to outpatient care might affect the quality of life of direct caregivers. Studies in the HCT population suggest that caregivers may develop significant disturbances in quality of life due to alterations in family dynamics, daily routine, and the stress of providing both physical and emotional support [48]. Another study of quality of life in patients undergoing HCT and their caregivers found that quality of life declines significantly for both parties during hospitalization, and that for caregivers, the primary effects on quality of life were in physical and mental functioning, and the percentage meeting criteria for depression nearly tripled from baseline during their loved one's hospitalization [32]. These data argue against the notion that caregivers are significantly “burdened” by providing the majority of supportive care in the home, though other interpretations are possible. To our knowledge, this effect has not been studied among caregivers of leukemia patients outside of the HCT setting. Whether any conclusions from HCT data can be extrapolated to patients with AML pre-HCT remains unstudied outside the pediatric setting. As quality of life improvement might be one of the most important arguments to support the further development of outpatient care strategies for AML patients undergoing intensive (re)induction chemotherapy, more extensive studies will be necessary to assess the impact on quality of life of patients as well as caregivers, ideally with optimized and validated tools.

3.3. Infection risk

One of the pervasive arguments against prolonged hospitalization after induction chemotherapy is that longer hospitalizations lead to increased exposure to hospital-acquired and often multidrug-resistant organisms. Still, almost all studies of out-patient AML management report high readmission rates for neutropenic fever [12,13,25,27,28], and there is no definitive data to suggest that a policy of early discharge indeed reduces the risk of serious infections. On the one hand, in a study by Halim et al. [49], the rates of septicemia were reduced from 22% to 13% after their institution began to shift care of AML patients to the outpatient setting. Their patients received prophylactic oral antibiotics during the period

of profound neutropenia. Interestingly, among those who did develop bacteremia, there was a notable shift from gram-negative to gram-positive infections, which was largely attributed to gram-negative coverage provided through prophylactic ciprofloxacin [49]. Contrasting with the reduction in septicemia in the Halim study, the pediatric study by Miller *et al.* showed an increased risk of Viridans streptococcal bacteremia (a pre-designated outcome of interest) among children discharged early after AML treatment when compared to an inpatient control population [30]. Likewise, in our phase 2 study, we noted a higher proportion of patients experiencing a documented bloodstream infections compared to inpatient controls (37% *vs.* 14% $p = 0.04$). Similar to the study by Halim *et al.*, the majority of positive blood cultures among patients discharged early in our study involved gram-positive organisms (28 gram-positive *vs.* 8 gram-negative infections). This finding may represent the influence of gram negative antibiotic prophylaxis, but also highlights the need for thorough teaching of patients and caregivers about the importance of sterile handling of indwelling catheters. Interestingly, despite the increased frequency of bacteremias among discharge patients in our study, these same patients required fewer overall days of IV antibiotics. This result may be explained by differences in the management of culture negative neutropenic fever, as no difference in antibiotic duration was noted between the discharged and control patients with documented infections. This observation that overall use of IV antibiotics is reduced among patients discharged early is consistent with findings from another study, although direct comparisons between the 2 studies are limited as culture data were not reported in the study by Allan *et al.* [12].

Undoubtedly, more effective prevention of neutropenic fever/infection would maximize the time AML patients could spend as outpatients. New generations of oral, broad-spectrum antimicrobials may perhaps contribute to this goal. It is interesting to speculate that measures that minimize clinic visits might be an alternative strategy to accomplish this goal. Current outpatient management requires frequent clinic visits and extended stays in blood draw areas, examination rooms, and infusion suits. Maneuvers that allow home care rather than clinic care (*e.g. via* use of tele-monitoring devices, home blood draws, *etc.*) could reduce the amount of time spent in clinic environments, reduce exposure to health care-associated infections, reduce hospitalization readmission rates, and improve outcomes, including patients' quality of life – a hypothesis that would be directly amenable to testing.

4. Barriers to implementation of outpatient management

It is worth noting that the majority of the studies reported in this review, including our own, were conducted at large academic centers. Many large academic institutions are currently managing a significant portion of their AML patients in the outpatient setting during post-remission therapy, an approach that has been found to be safe and feasible in pediatric patients as well as younger and older adults [12–15,49–51]. If encouraging results in the literature are to support an overall change in practice for patients following (re-)induction therapy, however, potential barriers to implementation at smaller academic and community practice hospitals need to be recognized and addressed. For most centers treating adults with newly diagnosed or relapsed/refractory AML, inpatient management has been routine for many years, and changing such routines will require time for adjustment. When we introduced the pilot study at the UW/SCCA, there were significant concerns, particularly

expressed by nursing staff, that the reduced contact with very ill patients would allow too little time for education regarding the expected complications of intensive AML chemotherapy. In addition, there was apprehension on the part of physicians, nursing, and other hospital staff that patients and caregivers would not be able to recognize signs of impending complications and seek proper emergency care [52]. Over time, these fears were alleviated as experience with this care strategy increased. Provision of outpatient patient education and support, outpatient care following (re)induction chemotherapy, and rapid stabilization and triage of patients requiring readmission has now become routine at the UW/SCCA even in the absence of a clinical trial.

The potential to improve patients' quality of life and simultaneously limit healthcare costs may be substantial in community practice. However, resource utilization by these patients (e.g. transfusions, outpatient visits, and need for a well-equipped emergency department) may be the primary obstacles to providing outpatient supportive care in this setting. Even large academic centers must strategically plan for an influx of patients with frequent infusion needs [52], and close communication and planning with emergency department and admitting hospital staff must occur in order to allow for prompt treatment of infections during the period of profound neutropenia [22,52,53]. The ability of facilities to provide these services may be lacking in smaller communities and institutions. In addition, various socioeconomic and geographic characteristics of a region may present barriers that prevent patients and their caregivers from being able to secure regular home care and housing within a reasonable distance from the hospital. One important focus of future studies is to better define patient characteristics that would portend poor outcome or compliance in the outpatient setting. This may, however, be challenging: in our phase 2 study, we evaluated numerous factors such as patient age, regimen intensity, and disease status, but none was useful as predictor of a patient's total readmission time. It is certainly possible that our ability to detect a difference was limited by the relatively limited cohort size [28], and there may be multiple more patient-specific factors in addition to these that might have a greater influence.

5. Conclusion

The desire to provide optimal care for patients with AML has driven the medical community to explore not only better treatment options but also better forms of supportive care to improve both survival and quality of life of affected individuals while simultaneously reducing personal and societal financial burden. Increasing evidence suggests that maximizing outpatient management of patients with newly diagnosed or relapsed/refractory AML might be one step toward the goal of optimized supportive care. Still, although the published literature regarding a move toward outpatient management of these patients is largely supportive, high readmission rates, increased infections, and the possibility of increased ICU utilization reported by some studies emphasize the need for caution. It is therefore imperative that facilities considering moves toward outpatient AML management have strategies in place to quickly and effectively manage the complications that occur.

There remains significant room for ongoing research in the area of outpatient management of AML patients. In particular, future studies will be required to determine the most

appropriate measures of cost assessment, both from the perspective of the healthcare system and the patient. Quality of life, while often difficult to measure, is an essential outcome to be considered in any future exploration of outpatient AML management. In addition, there remains ample room to investigate improved measures of care provision (prevention of infections, management of neutropenic fever, maximizing of home care) and appropriate selection of patients for early hospital discharge.

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