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Invited review

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.

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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 740,000Canadian 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