Outpatient management following intensive induction chemotherapy for myelodysplastic syndromes and acute myeloid leukemia: a pilot study

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ABSTRACT

Due to infectious and bleeding risks, adults with acute myeloid leukemia or high-risk myelodysplastic syndromes typically remain hospitalized after remission induction chemotherapy until blood count recovery. Here, we explored the medical and financial effects of discharge immediately after chemotherapy completion with close outpatient follow up. Within 12 months, 15 patients fulfilling both medical and logistical criteria were discharged early, whereas 5 patients meeting medical criteria only served as inpatient controls. No patient died. Patients discharged early spent a median of 8 days (range 3-36 days), or 54% of their study time, as outpatients. These patients required less time on intravenous antibiotics (6 *vs.* 16 days; *P*=0.11), received fewer red blood cell transfusions (0.25 *vs.* 0.48 units/day; *P*=0.08), and incurred lower median daily charges ($3,270 *vs.* $5,467; *P*=0.01) than controls. Thus, early discharge of selected patients appears, safe and may reduce cost and resource utilization.
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Key words: acute myeloid leukemia, myelodysplastic syndromes, outpatient management, induction chemotherapy.

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Introduction

Adults with newly diagnosed or relapsed acute myeloid leukemia (AML) or high-risk myelodysplastic syndromes (MDS) commonly receive intensive chemotherapy to achieve disease remission.[1,2] In the United States, many countries in Europe, and elsewhere, these patients typically remain hospitalized "preemptively" until blood count recovery, usually 3-4 weeks after completion of chemotherapy, due to the risk of overwhelming infections and bleeding during pancytopenia.[3] However, highly effective oral prophylactic antimicrobials have been introduced[4] and transfusion support of outpatients has become routine in recent years. As a result, the care of patients with hematologic malignancies treated with other intensive modalities (e.g. autologous or reduced-intensity allogeneic transplantation) is increasingly shifting from inpatient to outpatient settings. Benefits of this shift could include reduced cost, improved quality of life, and possibly reductions in the acquisition of nosocomial infections. Few studies have investigated outpatient management for patients undergoing remission induction chemotherapy for AML.[5-10] We, therefore, conducted a pilot study that allowed discharge of adult AML/MDS patients once induction chemotherapy was completed to explore the safety and potential cost savings of such a strategy.

Design and Methods

Study cohort

Patients aged 18-60 years were eligible if, within the preceding three days, they had begun intensive chemotherapy (e.g. with "7+3" or a regimen of similar or higher intensity) for untreated or relapsed MDS or AML, excluding acute promyelocytic leukemia. Patients with significant hypersensitivities to prophylactic antimicrobials were excluded. The institutional review board approved the study protocol, and participants gave consent in accordance with the Declaration of Helsinki. This study was registered at *www.ClinicalTrials.gov (NCT00844441)*.

Criteria for early hospital discharge

After completion of chemotherapy, patients were re-evaluated and considered eligible for hospital discharge if they fulfilled medical criteria including: ECOG performance status of 0-1, bilirubin 2.5 times or below upper limit of normal (ULN), SGOT and SGPT 1.5xULN or below, serum creatinine 1.5xULN or below, left ventricular ejection fraction 40% or over, no intravenous antimicrobial therapy, no active bleeding, and no refractoriness to platelet transfusions. Once eligibility for medical discharge was determined, patients were screened for logistical criteria: agreeable to close outpatient follow up, and having a reliable caregiver and residency within 30 minutes of the Study Center. Patients meeting both medical and logistical criteria were dis-

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charged. If readmitted, subsequent early hospital discharge was possible if all medical/logistic criteria were again met. Patients who met the medical but not the logistical criteria served as inpatient controls and remained hospitalized until peripheral blood count recovery.

Outpatient management

Patients were discharged on levofloxacin, fluconazole, and acyclovir (or similar medications) and continued until ANC was 0.5×10^9 or over. Patients were seen by an outpatient oncology nurse three times per week and by a physician once weekly. Transfusion thresholds in asymptomatic patients were: hematocrit less than 26% and platelet count less than 10×10^9. Patients with febrile neutropenia were hospitalized for intravenous antibiotics. Patients continued on study until they fulfilled the blood count criteria for complete remission (CR) or CR with incomplete platelet count recovery (CRp),[11,12] received additional chemotherapy, or 45 days had elapsed from day of re-evaluation.

Resource utilization and cost estimates

Information on medical complications and use of medical resources was collected from electronic medical records. Professional and facility charges associated with inpatient and outpatient management were captured using electronic billing information.

Study conduct and statistical analysis

Previous FHCRC data suggested an induction mortality rate of 5% in preemptively hospitalized patients receiving induction chemotherapy (R.B.W, personal communication, September 2008). Therefore, the study was monitored to ensure that the rate of death on study did not exceed 5%. Characteristics and outcomes of discharged patients and inpatient controls were compared with Fisher's exact test (categorical characteristics) and the Wilcoxon-Mann-Whitney test (continuous characteristics) using STATA 11 (StataCorp LP, College Station, TX, USA).

Results and Discussion

We enrolled 39 patients from April 2009 to April 2010. Nineteen of the 39 (48.7%) patients did not meet medical early discharge criteria upon re-assessment after completion of chemotherapy and were thus taken off study. Fourteen of the 19 were ineligible for discharge because they were receiving intravenous antibiotics for uncomplicated neutropenic fever, 2 had liver function abnormalities, one had multi-organ failure secondary to sepsis, one had ongoing bleeding, and one withdrew consent. Five of the 20 medically eligible patients did not meet logistical discharge criteria and remained hospitalized (controls; all 5 patients did not have permanent or temporary local housing), while 15 met both medical and logistical criteria and were discharged after completion of chemotherapy (Table 1).

Thirteen of the 15 patients who were discharged early required readmission prior to peripheral blood count recovery, and 6 patients were readmitted twice while on protocol. Causes for readmission were neutropenic fever (n=16), bleeding (n=2) and nausea/vomiting (n=1). As summarized in Table 2, 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); in other words, 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 patients were hospitalized for a median of 21 days (range 10-21; $P<0.01$ compared to patients discharged early) after completion of chemotherapy before removal from protocol. Our small sample size limited our ability to detect statistically significant differences between the two study cohorts. With this limitation in mind, however, inpatient controls tended to receive longer treatment with IV antibiotics (6 *vs.* 16 days; $P=0.11$) and more red blood cell transfusions (0.25 *vs.* 0.48 units/day; $P=0.08$). No patient required intensive care unit (ICU) care, and no deaths occurred in either group.

Unlike consolidation chemotherapy, after which outpatient management is well accepted by physicians and patients and is cost saving,[13] only a few retrospective and prospective studies have investigated whether selected patients could be safely discharged after completion of induction chemotherapy for AML/MDS.[5-10] Like these previous reports, our data suggest that outpatient management of selected patients with AML/MDS following induction or salvage chemotherapy is feasible and safe.

Table 1. Characteristics of early discharge and inpatient control cohorts.

Parameter	Early Discharge (n=15)	Inpatient Control (n=5)
Median age (range), years	50.8 (19.4-59.6)	49.2 (26.2-54.2)
Sex (male/female), n.	5/10	5/0
Disease, n. (%)		
AML	12 (80.0%)	5 (100%)
MDS (RAEB-2)	3 (20.0%)	0 (0%)
Current disease status, n. (%)		
Untreated	9 (60.0%)	4 (80.0%)
First relapse	6 (40.0%)	1 (20.0%)
Median WBC (range), $\times10^3/\mu L$	4.9 (0-113.8)	2.6 (0.2-45.1)
Median hemoglobin (range), g/dL	9.2 (8.2-11.4)	9.5 (8.1-12.4)
Median platelets (range), $\times10^3/\mu L$	56 (9-166)	28 (10-67)
Median temperature (range), °C#	36.6 (35.8-37.9)	36.3 (35.8-36.6)
Median temperature (range), °C##	37.0 (35.9-37.7)	36.4 (36.3-37.0)
Treatment§		
"3+7" ± gemtuzumab ozogamicin	3 (20%)	2 (40%)
Idarubicin/HiDAC/pravastatin	3 (20%)	2 (40%)
G-CLAC	5 (33.3%)	1 (20%)
FLAM	2 (13.3%)	
MEC/gemtuzumab ozogamicin/cyclosporine	1 (6.7%)	
FLAG/gemtuzumab ozogamicin	1 (6.7%)	
Off study reason at end of study period, n. (%)		
Blood count recovery	6 (40.0%	1 (20.0%)
Additional chemotherapy	4 (26.7%)	1 (20.0%)
IV antibiotics at time of subsequent discharge	4 (26.7%)	0 (0%)
Physician/patient decision	1 (6.7%)	2 (40.0%)*
Regular hospital discharge	0 (0%)	1 (20.0%)

*WBC, total white blood cell count; IV, intravenous. #At the time of study enrollment. ##At the time of re-assessment after completion of chemotherapy. §"3+7" ± gemtuzumab ozogamicin (GO): daunorubicin (45-90 mg/m²) x 3 days + cytarabine 100 mg/m²x7 days GO (6 mg/m²) x 1 day; idarubicin (12 mg/m²) x 3 days/HiDAC (cytarabine 1,500 mg/m²) x 4 days/pravastatin; G-CLAC: G-CSF/clofarabine (25 mg/m²) x 5 days/HiDAC (cytarabine 2,000 mg/m²) x 5 days; FLAM: flavopiridol (50 mg/m²) x 3 days/HiDAC (cytarabine 2,000 mg/m²/72 h) x 1/mitoxantrone (40mg/m²) x 1 day; MEC/GO/cyclosporine: mitoxantrone (6 mg/m²) x 5 days/etoposide (80mg/m²) x 5 days/cytarabine (500 mg/m²) x 5 days/GO (3 mg/m²) x 1 day/cyclosporine; FLAG/GO: fludarabine (30 mg/m²) x 5 days/HiDAC (cytarabine 2,000 mg/m²) x 5 days/GO (3 mg/m²) x 1 day. *In both cases, patients were discharged before peripheral blood count recovery and followed as outpatients by a local oncologist.*

Table 2. Inpatient/outpatient management, resource utilization, and cost estimates of early discharge and inpatient control cohorts.

Parameter	Early Discharge (n=15)	Inpatient Control (n=5)
Inpatient/outpatient management		
Median days on study (range), days	16 (9-44)	21 (10-21)
Median days spent as outpatient (range), days	8 (3-36)	N/A
Median days spent as inpatient (range), days	6 (0-28)	21 (10-21)
Median number of outpatient periods (range), n	2 (1-3)	N/A
Median days spent as outpatient per outpatient period (range), days	6 (1.5-24)	N/A
Median % outpatient/total days (range), %	53.8% (28.6-100%)	0%
Resource utilization		
Median number of days in ICU (range), n	0	0
Median number of days on IV antibiotics (range), n	6 (0-28)	16 (0-19)
Average per day on study	0.46 (0-0.76)	0.82 (0-0.90)
Median number of RBC transfusions (range), n	4 (1-12)	9 (4-12)
As outpatient	0 (0-6)	0
As inpatient	4 (0-12)	9 (4-12)
Average per day on study	0.25 (0.05-0.57)	0.48 (0.19-0.57)
Median number of platelet transfusions (range), n	5 (2-20)	5 (3-15)
As outpatient	3 (0-17)	0
As inpatient	2 (0-16)	5 (3-15)
Average per day on study	0.29 (0.19-0.69)	0.30 (0.18-0.71)
Cost		
Median total billing charges (range), $ dollars	49,229 (32,425-228,684)	114,799 (42,903-148,475)
Median charges per day on study (range), $ dollars	3,270 (1,676-5,667)	5,467 (4,290-7,070)
Median charges per inpatient day on study (range), $ dollars	6,491 (4,350-9,804)	5,379 (4,290-7,070)
Median charges per outpatient day on study (range), $ dollars	1,319 (40-2,822)	N/A

ICU: intensive care unit; IV intravenous; RBC: red blood cell; WBC: total white blood cell count. Note: total billing charges include professional fee and facility charges; information was obtained via electronic billing records.

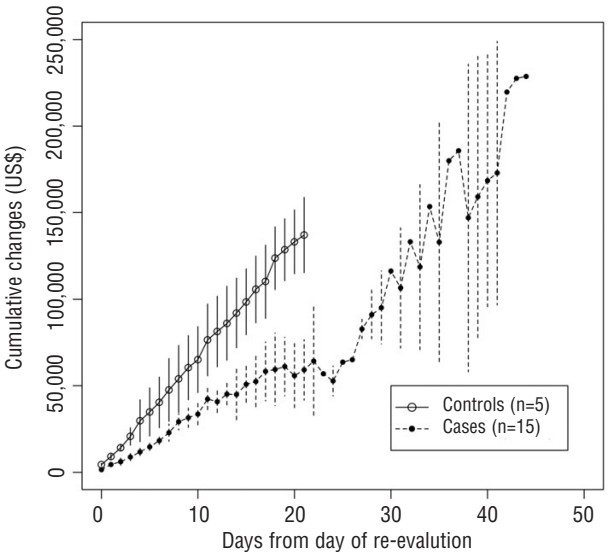

Figure 1. Cumulative charges: cumulating total charges (professional and facility charges) incurred by patients discharged early (cases; n=15) and inpatient controls (controls; n=5). Data are shown as mean and its 95% confidence interval at each time point assuming normal distribution of charges.

Treatment of AML is a significant economic burden for patients, insurance companies, and society.[14-19] Most costs are associated with remission induction treatment, with inpatient cost the largest cost component.[17] Despite the small sample size of our study, the median daily total professional and facility charges were significantly lower for patients discharged early compared to inpatient controls over the study period ($3,270 *vs.* $5,467, P=0.01; see Table 2; cumulative charges for controls and patients discharged early are shown in Figure 1). These results were confirmed using generalized estimating equation (GEE) modeling to account for multiple billing dates per patient (*data not shown*). In contrast, the daily charges per inpatient day were relatively similar between these two groups (P=0.40), suggesting that charges are not substantially higher if readmission is necessary. Although we analyzed charges and not costs, our data suggest that outpatient management of selected patients may significantly reduce financial burden.

In summary, although re-admission is common, early discharge appears safe and may reduce cost and resource utilization. There may be other benefits to early discharge after remission induction chemotherapy. For example, prolonged hospitalizations lead to significant productivity losses and costs due to morbidity.[17,20] Early discharge may facilitate resumption of independent functioning and re-integration into family and professional life after completion of intensive AML/MDS treatment, thus providing another potential opportunity for societal cost savings.

Authorship and Disclosures

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