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Frequency and Reasons for Return to Acute Care in Leukemia Patients Undergoing Inpatient Rehabilitation:

A Preliminary Report

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Abstract

Objective—To assess the frequency and reasons for return to the primary acute care service among leukemia patients undergoing inpatient rehabilitation.

Design—Retrospective study of all patients with leukemia, myelodysplastic syndrome, aplastic anemia, or myelofibrosis admitted to inpatient rehabilitation at a tertiary referral-based cancer center between January 1, 2005, and April 10, 2012. Items analyzed from patient records included return to the primary acute care service with demographic information, leukemia characteristics, medications, hospital admission characteristics, and laboratory values.

Results—225 patients were admitted a total of 255 times. 93/255 (37%) of leukemia inpatient rehabilitation admissions returned to the primary acute care service. 18/93 (19%) and 42/93 (45%) of these patients died in the hospital and were discharged home respectively. Statistically significant factors ($p < .05$) associated with return to the primary acute care service include peripheral blast percentage and the presence of an antifungal agent on the day of inpatient rehabilitation transfer. Using an additional two factors (platelet count and the presence of an antiviral agent both with a $p < .11$), a Return To Primary (RTP) - Leukemia index was formulated.

Conclusions—Leukemia patients with the presence of circulating peripheral blasts and/or antifungal agent may be at increased risk of return to the primary acute care service. The RTP-Leukemia index should be tested in prospective studies to determine its usefulness.

Keywords

Leukemia; Inpatient; Rehabilitation; Cancer; Complications; Treatment

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This study will be presented as a poster presentation at the European Cancer Rehabilitation and Survivorship Conference, September 17, 2012.

Leukemia and other pre-leukemic cancers (e.g. myelodysplastic syndrome (MDS), aplastic anemia, and myelofibrosis) can lead to significant deconditioning secondary to the disease itself, chemotherapy treatments, and medical complications. Cachexia, nausea, fatigue, and anemia are common among patients receiving chemotherapy.^{1,2} Other common effects of leukemia treatment include myopathy (e.g. steroid and critical care induced) and peripheral neuropathy (e.g. critical care and chemotherapy induced). Consequently, leukemia patients' function can be affected. Many leukemia patients require inpatient rehabilitation to discharge them from the hospital. Rehabilitation is important in this patient population for two other reasons. The first is that survival may be related to a patient's functional status.³ Further treatment eligibility is often dependent upon a patient's functional status. The second is that rehabilitation has implications on quality of life. Studies have shown that rehabilitation can improve function and symptoms such as fatigue, well being, and pain.⁴⁻¹⁰

Often due to medical reasons, rehabilitation inpatients must be transferred back to the primary acute care service. This is to prevent further medical decline of the patient and/or because the patient is no longer able to adequately tolerate therapy as required by inpatient rehabilitation guidelines. These transfers back are undesired. An uninterrupted inpatient rehabilitation stay with consistent therapy participation is preferred and the most efficient way to utilize these rehabilitation resources. Returning to the primary acute care service can lead to interruptions and result in a loss of functional improvements. Several previous studies have identified risk factors for return to the primary acute care service in different patient populations.¹¹⁻¹⁴ Alam et al. reported a transfer rate of 21% back to the primary acute care service for cancer patients on inpatient rehabilitation (compared to 9.7% for matched non-cancer controls).¹⁵ Guo et al. found that 35% of cancer patients in acute inpatient rehabilitation were transferred back to the primary acute care service. They were also able to find several variables with a statistically significant relationship with return to the primary acute care service.¹⁶ Fu et. al. in a preliminary analysis of hematopoietic stem cell transplant patients with a variety of primary cancers including leukemia revealed a 52% rate of return to the primary acute care service.¹⁷

On an inpatient rehabilitation unit, leukemia patients are among the most medically complex. Pancytopenias require frequent blood transfusions. Neutropenia and thrombocytopenia put patients at high risk for infection and bleeding respectively. The purpose of this study is to identify risk factors associated with return to the primary acute care service of leukemia patients undergoing inpatient rehabilitation. This is the first study to concentrate specifically on leukemia patients and analyze risk factors associated with return to the primary acute care service.

METHODS

Subjects

This retrospective study included all patients with a medical history of leukemia, myelodysplastic syndrome, myelofibrosis, or aplastic anemia admitted to the inpatient rehabilitation service at a tertiary referral-based cancer center from January 1, 2005, to April 10, 2012.

Procedure

Approval for this study was obtained from the institutional review board (IRB). A waiver of informed consent was granted by the IRB in compliance with federal and institutional guidelines. An experienced rehabilitation medicine specialist reviewed medical records for medical and demographic information. Data collected could be divided among demographic information, leukemia characteristics, medications, laboratory values, and hospital

admission characteristics. Demographic information included age, gender, race, marital status, insurance type, and date of death (if applicable). Leukemia characteristics included type of leukemia, most recent bone marrow leukocyte blast count percentage, and last peripheral leukocyte blast count percentage. In addition, if the patient had received a bone marrow transplant in the past and whether the patient relapsed was recorded. Medication data included the presence of antibacterial agents, antiviral agents, and antifungal agents. Laboratory values consisted of peripheral white blood cell count, platelets, creatinine, prealbumin, and albumin on the day of transfer to inpatient rehabilitation. Hospital admission characteristics included the patient's location prior to admission, reason for hospitalization, reason for transfer to inpatient rehabilitation, if the patient had returned to the primary acute care service, and reason for transfer back to the primary acute care service (if applicable). Reasons for hospitalization and transfer back to the primary acute care service were categorized based on the root cause. For example, a patient who was admitted with shortness of breath that was later found to be due to a pneumonia was categorized under infection not under respiratory.

Analyses included examining variable frequencies and conducting nonparametric statistical tests on the variables described above which included demographics, leukemia characteristics, medications, hospital admission characteristics, and laboratory values. Due to unequal sample sizes and distribution characteristics, non-parametric tests were used. Using logistic regression analysis, we were able to identify variables for a preliminary model based on medically related variables and the probability of a leukemia patients' return to the primary acute care service. The resulting model was termed the Return to Primary – Leukemia (RTP – Leukemia) index.

RESULTS

225 patients with these diagnoses were admitted a total of 255 times to inpatient rehabilitation. Table 1 lists displays the distribution of patients and inpatient rehabilitation admissions. The age of the patients ranged from 20 to 92 years.

Table 2 lists the outcomes of patients who returned to the primary acute care service. The main reasons for return to the primary acute care service were infection 33/93 (36%), mental status changes 16/93 (17%), cardiac 11/93 (12%), functional decline 9/93 (10%), completed rehabilitation but not safe medically to discharge 6/93 (7%), further leukemia treatment 5/93 (5%), and gastrointestinal 4/93 (4%). 19/33 (58%) of the patients who returned to the primary acute care service due to infection were originally admitted to the hospital for an infection. However, only 38/106 (36%) of patients initially admitted to the hospital for infection returned to the primary acute care service.

Table 3 lists selected demographic variables of our study population. No statistically significant relationships were found with demographic characteristics and return to the primary acute care service.

Table 4 lists selected clinical variables of the study population. With respect to clinical and laboratory variables, two variables, peripheral blast count and the presence of an antifungal agent, were found to independently have a $p < .05$ association with return to the primary acute care service.

Two other factors, platelets and the presence of an antiviral agent, independently had $p < .11$. Using the four factors with $p < .11$ (i.e. peripheral blast count, platelet count, the presence of an antifungal agent, and the presence of an antiviral agent), a probability model was created. We used logistic regression analysis to create the proposed RTP-Leukemia index. Table 5

presents the results of this analysis. Cut points for the variables were their clinical accepted normal limits.

Table 6 presents the RTP-Leukemia index. The four clinical variables were incorporated into the index. For each of the 4 variables, the patient can receive a score of 0 or 1. Antiviral and antifungal agent were dichotomized into not present = 0 and present = 1. Platelet count was dichotomized into greater than 140,000 per microliter (μL) = 0 and less than 140,000/ μL = 1. 140,000/ μL is the lower limit of the normal clinical range. Peripheral blast percentage was dichotomized into 0% = 0 and greater than 0% = 1. The presence of any leukocyte blasts in the peripheral blood stream is abnormal. Summing the score of the 4 variables results in a RTP-Leukemia index score. Each patient would have a score ranging from 0 to 4. Table 6 also demonstrates the number of patients with each score that returned to the primary acute care service and the probability of return to the primary acute care service with each score. A Wald test for the overall index revealed a p .0052.

Figure 1 is the logistic curve of the regression analysis and return probabilities across the entire RTP-Leukemia index range.

As of 5/1/2012, 12% and 27% of patients were alive from the return to the primary acute care service and those that did not return to the primary acute care service groups respectively ($p=.0056$, $\chi^2=7.664$). Of the patients that are deceased, the mean days from inpatient rehabilitation admission to death were 102 and 217 days (median 63 and 161) ($p<.0001$, $\chi^2=28.9649$) for return to the primary acute care service and those that did not return to the primary acute care service groups respectively.

A program to have a general internal medicine hospitalist from the leukemia service follow leukemia rehabilitation inpatients was begun at our institution in April of 2009. Patients were seen by the hospitalist every weekday to manage their medical care. Prior to the initiation of this program, 38% (66/174) of leukemia inpatient rehabilitation admissions during this study period were transferred back to the primary acute care service. After initiating the program the transfer rate fell to 33% (27/81) ($\chi^2=.504$, $p=.4776$).

DISCUSSION

The purpose of this study is to identify risk factors associated with return to the primary acute care service among leukemia rehabilitation inpatients. Our analysis revealed several factors associated with return to the primary acute care service. This is the first study to perform such an analysis on leukemia patients.

The internal medicine hospitalist did not result in a significant change in return to primary acute care service. This suggests that the physiatrist was as effective at determining patients who needed to be returned to the primary acute care service as the internist. Return to the primary acute care service patients were medically less stable. Patients who did return to the primary acute care service were less likely to be alive (12% versus 27%) and they did not live as long (mean days until death of 102 versus 207) as their counterparts that did not return to the primary acute care service.

Hematopoietic cancer patients can be a medically challenging group of patients to treat. The results of this study and the proposed RTP-Leukemia index could be useful to a consulting physiatrist considering an appropriate rehabilitation plan for a leukemia inpatient. The RTP-Leukemia index scores of 0 and 1 had a return to the primary acute care service probability of 17.65%. However, a RTP-Leukemia index score of 4 had a return to the primary acute care service probability of 49.52%.

It is not surprising, that patients with a higher peripheral blast count percentages are at increased risk of medical complications and thus return to the primary acute care service. A high blast count percentage from either the peripheral blood or bone marrow indicates the leukemia is active and a worse prognosis.¹⁸ Circulating peripheral blast counts are not used for leukemia diagnosis under the World Health Organization (WHO) or the French-American-British (FAB) cooperative group criteria. Bone marrow blast counts continue to be the relied upon standard.^{19,20} Though not as accurate, the circulating peripheral blast counts can give the clinician an idea of the status of their bone marrow. Also they can be performed more frequently requiring a simple blood draw versus the painful and more complex bone marrow biopsy. A significant relationship was found with peripheral blast count percentage but not the last bone marrow blast count percentage. Peripheral blast counts were from blood draws on the day of admission to rehabilitation. The dates of the last bone marrow biopsies was quite varied. The average days from the biopsy until inpatient rehabilitation admission was 39 days.

The presence of antifungal and antiviral agents and their association with return to the primary acute care service are interesting. These agents are often used prophylactically and to treat active infections. One might expect these agents to lower the risk of infection and thus reduce return to the primary acute care service. A possible explanation for our findings could be that they were used in patients with leukopenia or were continued for active treatment of an infection while on the primary acute care service. The leukopenia or the recent infection could put them at risk for more complications while on rehabilitation. Infection was the most common reason for return to the primary acute care service in our study population. It is also important to note that the majority of patients (57%) who returned to the primary acute care service due to infection were admitted initially to the hospital for infection treatment. Perhaps they were very susceptible to infections or the original infection had not resolved.

If otherwise appropriate, patients at higher risk for return to the primary acute care service should not be declined from inpatient rehabilitation. These patients cannot remain on the acute care service if they do not meet acute care criteria. Placement in a skilled nursing facility or long term acute care facility would result in less physician care and may be far from the nearest intensive care unit or oncologist.

Comparison to Prior Studies

Rates of return to the primary acute care service of 21% and 35% have been reported in the literature looking at cancer rehabilitation patients.^{15,16} The limitation of these studies is that they looked at a diverse population of cancer rehabilitation inpatients as a whole and were not specifically looking at one type of cancer population. The rate of return of 37% is close to Guo et al. (35%) study of cancer rehabilitation patients as whole. The top three reasons for transfer from inpatient rehabilitation back to the primary acute care service were respiratory distress, wound complications, and tumor progression. Factors associated with transfer back to the primary acute care service were a low albumin level, an elevated creatinine level, and presence of tube feeding or Foley catheter.¹⁶ The presence of tube feeding or Foley catheter were not analyzed in our study. However, albumin and creatinine were evaluated. No statistically significant relationships were found with these variables in our population.

The International Prognostic Scoring System prognosticates survival of MDS patients using cytogenetics, platelet, hemoglobin, bone marrow blast count, and absolute neutrophil count.²¹ Some of these variables were looked at in our study. Platelet count had a relationship of $p=.1065$ with respect to return to the primary acute care service in our study.

Study Limitations

Unfortunately, we were unable to analyze functional measures and return to the primary acute care service due to an insufficient number of patients with complete functional scores. The presence of an indwelling catheter such as a feeding tube or Foley catheter has been found to be associated with return to the primary acute care service in cancer patients but was not evaluated in this study. Future research should assess whether there is a relationship with these variables and return to the primary acute care service. The presence of an antifungal and antiviral agents and their relationship with return to the primary acute care service may be influenced by hospital medical care protocols. Multicenter studies would be useful to minimize the influence of these hospital specific care practices.

There are some limitations to the RTP-Leukemia Index. The RTP-Leukemia model established is preliminary. Validation studies in a prospective series are needed to confirm the results. The highest probability the RTP-Leukemia index was able to achieve was only approaching 50% return to the primary acute care service. More prognostic factors associated with return to the primary acute care service or more sophisticated/discriminating models would be useful in future studies to enhance probabilities. The value in the RTP-Leukemia index may not be in predicting which patients will return to the primary acute care service but which patients would be unlikely to require return to the primary acute care service. Patients with few or none of the factors might be candidates for rehabilitation at a free standing rehabilitation facility. A patient with a RTP-Leukemia index score of 0 or 1 had a probability of 82.35% of not requiring transfer to the primary acute care service.

CONCLUSIONS

Leukemia patients can be a challenging population of rehabilitation inpatients. The presence of circulating peripheral blasts and an antifungal agent on the day of inpatient rehabilitation admission may be associated with increased return to the primary acute care service. The RTP-Leukemia Index should be tested in prospective validation studies to determine its usefulness.

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Logistic Regression Curve for the Proposed RTP-Leukemia Index Range (0-4)

Figure 1.
Logistic Regression Curve for the Proposed RTP-Leukemia Index Range (0-4)

Table 1

Distribution of Number of Patients and Inpatient Rehabilitation Admissions

Inpatient Rehabilitation Admissions Frequency	Number of patients	Number of admissions to Inpatient Rehabilitation
Once	199	199
Twice	23	46
Three Times	2	6
Four Times	1	4
Total	225	255

Table 2

Patient Outcomes after Return to the Primary Acute Care Service

Discharged Directly Home	42/93 (45%)
Died in the Hospital	18/93 (19%)
Transferred Back to Inpatient Rehabilitation	10/93 (11%)
Transferred to Hospice	10/93 (11%)
Transferred to a Sub-Acute Facility	10/93 (11%)
Transferred to an Outside Acute Care Hospital	3/93 (3%)
Total	93/93 (100%)

Table 3

Chi-Square Analysis of Select Demographic Variables on the Day of Inpatient Rehabilitation Transfer and Return to the Primary Acute Care Service

Variable	Did the Patient Return to the Primary Acute Care Service?		Chi-Square Analysis
	No	Yes	
Age	63.6±15.0	64±13.1	$p = 0.9518$
Gender			$p = 0.1586$
Male	100 (67.1)	49 (32.9)	
Female	62 (58.5)	44 (41.5)	
Race			$p = 0.6242$
White	124 (62.3)	75 (37.7)	
Black	16 (61.5)	10 (38.5)	
Hispanic	14 (73.7)	5 (26.3)	
Asian	7 (70)	3 (30)	
Native American	1 (100)	0 (0)	
Marital status			$p = 0.2392$
Married	118(61.5)	74 (38.5)	
Divorced	14 (60.9)	9 (39.1)	
Widowed	17 (81.0)	4 (19.0)	
Single	13 (72.2)	5 (27.8)	
Separated	0 (0)	1 (100)	
Insurance type			$p = 0.5760$
Medicare	97 (66.0)	50 (34.0)	
Private Insurance	50 (58.8)	35 (41.2)	
Self-Pay	6 (60.0)	4 (40.0)	
Indigent Free	4 (57.1)	3 (42.9)	
Medicaid	4 (100)	0 (0)	
County Hospital District	1 (50)	1 (50)	

NOTE. Values are mean ± SD or n (%).

Table 4

Chi-Square Analysis of Select Clinical Variables on the Day of Inpatient Rehabilitation Transfer and Return to the Primary Acute Care Service

Variable	Did the patient return to the primary acute care service?		Chi-Square Analysis
	No	Yes	
Presence of Antibiotic			$p = 0.1635$
Yes	144 (62.3)	87 (37.7)	
No	18 (75.0)	6 (25.0)	
Presence of Antifungal			$p = 0.0132$
Yes	117 (59.7)	79 (40.3)	
No	45 (76.3)	14 (23.7)	
Presence of Antiviral			$p = 0.0615$
Yes	110 (60.8)	71 (39.2)	
No	52 (70.3)	22 (29.7)	
Leukemia Type			$p = 0.8722$
AML	63 (61.8)	39 (38.2)	
MDS/aplastic anemia	25 (61.0)	16 (39.0)	
CLL	24 (64.9)	13 (35.1)	
ALL	25 (73.5)	9 (26.5)	
CML	12 (60.0)	8 (40.0)	
APL	5 (62.5)	3 (37.5)	
Myelofibrosis	4 (80.0)	1 (20.0)	
LGL	0 (0.0)	1 (100.0)	
Myeloproliferative Disorder	1 (50.0)	1 (50.0)	
Burkitt Leukemia	0 (0.0)	1 (100.0)	
AML & ALL Biphentotypic	1 (100.0)	0 (0.0)	
PLL	0 (0.0)	0 (0.0)	
Length of stay prior to rehabilitation transfer(days)	25.4±22.0	27.2±22.9	$p = 0.5282$
Albumin(g/dL)	2.8±0.5	2.8±0.5	$p = 0.2433$
Prealbumin(mg/dL)	18.5±8.7	18.1±8.9	$p = 0.4232$
Creatinine(mg/dL)	1.0±0.6	1.0±0.6	$p = 0.8404$
Platelet Count(K/μL)	76.9±114.2	52.6±98.1	$p = 0.1065$
Peripheral white blood cell count(K/μL)	6.4±9.6	5.4±8.1	$p = 0.3498$
Peripheral blast percentage	5.1±7.7	19.0±25.3	$p = 0.0096$
Bone marrow blast percentage	13.0±26.0	15.6±26.8	$p = 0.9480$

NOTE. Values are n (%) or mean $\pm$ SD.

Abbreviations: AML, Acute Myelogenous Leukemia; ALL, Acute Lymphocytic Leukemia; CML, Chronic Myelogenous Leukemia; CLL, Chronic Lymphocytic Leukemia; PLL, Prolymphocytic Leukemia; APL, Acute Promyelocytic Leukemia; LGL, Large Granular Lymphocytic Leukemia; MDS, Myelodysplastic Syndrome; K, thousand; μ L, microliter; mg, milligram; g, gram; dL, deciliter.

Table 5
Logistic Regression Analysis for Leukemia Patients' Return to Primary Acute Care Service

Factor	Frequency*	%	β	SE	Wald (χ^2)	p	OR [95% CI]
Antiviral Present	162	63.52	.259	.139	3.46	0.0626	1.680 [0.97, 2.93]
Antifungal Present	179	70.19	.374	.152	6.01	0.0116	2.11 [1.17, 3.92]
Peripheral Blast >0%	79	30.98	.046	.140	0.11	0.7382	1.09 [0.73, 0.63]
Platelet< 140 K/uL	227	89.02	.411	.240	2.93	0.0865	2.27 [0.94, 6.38]

* Clinical cut points used in classifying patients into categories: K/uL, thousand per microliter;

Table 6

Proposed Return to Primary-Leukemia Index

RTP-Leukemia Index**	Did the patient return to the primary acute care service?	Probability of return to primary acute care service by BMT-Leukemia Index
0 (7)	0 (0%)	0.1765
1 (34)	7 (21%)	0.1765
2 (68)	25 (37%)	0.3144
3 (107)	44 (41%)	0.4015
4 (39)	17 (44%)	0.4952

* Wald test for the overall index = 7.824 ($p = <.0052$); Unit Odds Ratios (per unit change in regressor) = 0.683, CI [0.515, 0.894]

** Antiviral not present = 0; present = 1

Antifungal not present = 0; present = 1

Platelet count 140,000 per microliter (μL) or GREATER = 0; LESS 140 K/ μL than = 1

Peripheral Blast Percentage EQUAL to 0% = 0; GREATER than 0 % = 1

Abbreviations: RTP-Leukemia, Return to Primary – Leukemia Index