Leukemia Research Reports 2 (2013) 26–28

Contents lists available at SciVerse ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Brief Communication

Evaluation of early discharge after hospital treatment of neutropenic fever in acute myeloid leukemia (AML)

Victor Chow [a,b,*], Kathleen Shannon Dorcy [b], Ravinder Sandhu [b], Kelda Gardner [b,c], Pamela Becker [a,d], John Pagel [a,b,c], Paul Hendrie [a,c], Janis Abkowitz [a], Frederick Appelbaum [a,b,c], Elihu Estey [a,b,c]

[a] University of Washington School of Medicine, Seattle, USA
[b] Fred Hutchinson Cancer Research Center, Clinical Research Division, Seattle, USA
[c] Seattle Cancer Care Alliance, Seattle, USA
[d] Institute for Stem Cell and Regenerative Medicine, Seattle, USA

ARTICLE INFO

Article history:
Received 30 October 2012
Received in revised form
27 November 2012
Accepted 11 January 2013
Available online 19 March 2013

Keywords:
Leukemia
Neutropenic
Fever
Discharge
Neutrophil

ABSTRACT

Background: Hospital admission for neutropenic fever in patients with AML is a standard practice. However, discharge practices vary once patients become afebrile, with many patients hospitalized until rise in the absolute neutrophil count (ANC) to >500 (ANC recovery). Data to support this practice are sparse. We hypothesized that patients admitted for neutropenic fever, particularly if in complete remission (CR) or about to enter CR following the chemotherapy course associated with neutropenic fever, might be safely discharged earlier (ED). Benefits of ED are less exposure to hospital pathogens, reduced cost, increased availability of beds for patients more in need of urgent care, and potentially, enhanced psychological well-being.

Methods: We identified patients age 18–70 with newly diagnosed AML who were admitted to the University of Washington Medical Center with neutropenic fever between January 2008 and May 2010. We compared subsequent (within 30 days of discharge) deaths, intensive care unit (ICU) admissions, and readmissions for neutropenic fever according to discharge ANC, regarded as a numerical variable using the Mann–Whitney *U* test and as <500 vs >500 using the Fisher Exact test. We used the Mann–Whitney *U* or Spearman correlation to analyze the relation between ANC at discharge and other covariates that might have affected outcome: age, ECOG performance status at admission for neutropenic fever, days inpatient, remission status, and type of infection (pneumonia, gram negative bacteremia, others).

Results: We evaluated 49 patients discharged after admission for neutropenic fever, 26 of whom were discharged with an ANC <500. Thirty five of the patients were in CR or entered CR following the chemotherapy course associated with their neutropenic fever admission. Patients who were discharged with lower ANC were more likely to be readmitted with neutropenic fever (Mann–Whitney U $p=0.03$), although this was not true using ANC categorized as $<$ vs >500 (Fisher Exact $p=0.24$, 95% confidence interval -0.47, 0.11). There was no relation between ANC at discharge and subsequent admission to an ICU (Mann–Whitney U $p=0.50$, Fisher Exact $p=0.64$, 95% confidence interval 0.2, 0.34 using the 500 ANC cut off). One patient died: a 55 year old discharged with ANC 0 after successful treatment of neutropenic fever died 19 days after hospital readmission with fever of unknown origin. *Stenotrophomonas maltophilia* pneumonia and sepsis were discovered 14 days after readmission. Assuming a beta distribution and rates of death of 1/26 for discharge with ANC <500 and 0/23 for discharge with ANC >500, the probability that a discharge ANC with <500 is associated with a higher death rate is 0.019. The number of events was too small for a multivariate analysis. However, patients with better performance status ($<$ ECOG 2) or who spent a shorter time in hospital after admission for neutropenic fever were more likely to be discharged with lower ANC (Fisher exact $p=0.09$ and Spearman $p=0.02$ respectively), while the likelihood of discharge with ANC <500 was unrelated to age, remission status, or type of infection. Thus we examined the relation between ANC and readmission for neutropenic fever separately in patients with better or worse performance status and in patients who spent more or less than the median time (8 days) in hospital after admission for neutropenic fever. This analysis indicated that patients discharged with lower ANC were more likely to be readmitted only if they had

* Corresponding author at: Fred Hutchinson Cancer Research Center, Clinical Research Division, Seattle, USA. Tel.: +1 206 354 1731.
E-mail address: vicachow@u.washington.edu (V. Chow).

2213-0489/$ - see front matter
http://dx.doi.org/10.1016/j.lrr.2013.01.001

spent more than 8 days in hospital or if they were performance status <2.
Conclusions: Our results suggest that an ANC of 500 is an excessively high cut off for discharge following hospitalization for neutropenic fever. The rate of rise of the ANC, as well as its absolute value, may also play a role.

1. Introduction

Patients with acute myeloid leukemia (AML) are at increased risk for developing serious infections after receiving cytotoxic chemotherapy[4]. Admission to hospital and administration of broad spectrum antibiotics is thus standard should patients develop fever while neutropenic (NF)[5,7]. However, discharge practices vary once such patients become afebrile, with many patients remaining hospitalized until rise in their absolute neutrophil count (ANC) to $>500/\mu L$ (ANC recovery). There are several reasons to question this practice. First, today's antibiotics are probably more effective than those available when the practice was initiated. Second, Bodey et al. noted that at a given neutrophil count <1000 infections were less common in patients in remission than in those not[2]. Third, keeping patients in hospital until ANC recovery increases their exposure to hospital-acquired infections and may decrease psychological well-being. Finally, this policy increases costs and/or decreases the availability of beds for patients more in need of urgent care[1,3,8]. These considerations motivated us to retrospectively compare rates of re-admission, admission to ICU, and death (from the event prompting re-admission) according to discharge ANC in patients discharged from hospital after apparent successful treatment of NF. Here we report our results.

2. Materials and methods

After obtaining IRB approval we reviewed the medical records (accessed electronically) of 144 patients given chemotherapy for newly-diagnosed AML at the University of Washington/Seattle Cancer Care Alliance (UW/SCCA) between January 2008 and May 2010. Essentially all 144 received "3+7" or "more intense" regimens, particularly those containing ara-C at a daily dose $\geq 1\ g/m^2$. Forty-nine of the 144 were admitted because of NF (a single oral temperature $\geq 38.3\ ^\circ C$ or a temperature $\geq 38\ ^\circ C$ for ≥ 1 h unrelated to transfusion and accompanied by an ANC of $<500/\mu L$, or $>500/\mu L$ with a predicted decline to $<500/\mu L$, in accordance with 2010 Infectious Disease Society of America criteria).[6] For each of the 49, this admission was the first for NF. Patients were included regardless of whether they were receiving induction or post-remission therapy and regardless of whether or not they were in complete remission (CR). Thirty-five of the 49 (71%) were thought to be in CR or were shown to be in CR at the next marrow exam.

We classified ANC at discharge after seemingly successful treatment of NF in two ways. First we used the actual ANC on day of discharge and employed the Mann–Whitney test to compare distribution of discharge ANC count in (a) patients who were or were not re-admitted to hospital for NF within 30 days of discharge, (b) patients who were or were not admitted to ICU within 30 days of discharge, and (c) patients who died vs those who survived these 30 day after discharge. Second we categorized the discharge ANC as $<$ vs >500 (a commonly used criterion for discharge) and used the Fisher exact test to compare the rates of the above outcomes according to whether the ANC was below or above this level. In general patients were discharged on levofloxacin or ciprofloxacin and fluconazole. Exceptions were patients in whom an organism had been isolated from blood; such patients were typically discharged on antibiotics appropriate for that organism, e.g. vancomycin for coagulase negative staph.

We also examined the relation between discharge ANC and the following: age, performance status (PS) [0–2 vs 3–4] as evaluated at initial admission for NF, CR status (yes/no), and cause of the NF—pneumonia, gram negative bacteremia (GNB), other (including fever of unknown origin) prompting the initial admission for NF. These relations were analyzed using Spearman correlation, Mann–Whitney, or Fisher exact depending on whether covariates were numerical (e.g. age) or binary (e.g. ANC $<$ vs >500, performance status 0–2 vs 3–4).

3. Results

Table 1 shows some characteristics of the 49 patients. Thirteen (27%) patients were re-admitted, all for NF. The rate of readmission increased as the discharge ANC became lower ($p=0.03$). However the ANC 500 cut-off point did not clearly distinguish patients who were and were not re-admitted (Table 1). Nor was there a relation between the ANC at discharge (actual value or <500 vs >500) and subsequent need for ICU admission. One patient died within 30 days of discharge. She was a 55 year old who was discharged afebrile with ANC of 0 after a hospital stay of 21 days; the cause of this fever was not determined. She was readmitted with fever the next day while her ANC remained 0. She was intermittently febrile and 14 days after re-admission blood cultures grew *Stenotrophomonas maltophilia* leading to her death, at which time her ANC remained 0. This history suggests that the infection that led to her death was acquired in the hospital.

Table 1
Patient characteristics.

	Discharge ANC $<500/\mu L$	Discharge ANC $>500/\mu L$	
Patients	$N=26$	$N=23$	
Median ANC @ discharge	0.13 (range 0–0.45)	1.47 (range 0.61–13.57)	
Median age (yrs)	55 (range 20–67)	51 (range 18–70)	
ECOG performance status @ admission for NF			
0–2	22 (84.6%)	16 (69.6%)	
3–4	4 (15.4%)	7 (30.4%)	
Median # days inpatient prior to initial discharge			
	7 (range 3–60)	10 (range 4–57)	
In/Entering CR			
YES	16 (61.5%)	19 (82.6%)	
NO	10 (38.5%)	4 (17.4%)	
Infections prompting first NF admission			
Pneumonia	3 (11.5%)	3 (13%)	
GNB	3 (11.5%)	2 (8.7%)	
Other	20 (77%)	18 (78.3%)	
Re-admission	9 (35%)	4 (17%)	($p=0.24$)
Re-admission to ICU	2 (8%)	3 (13%)	($p=0.64$)
Death	1 (4%)	0	

4. Discussion

We were interested in knowing whether patients who were discharged before ANC recovery did well because they were younger, had better PS, or more likely to be in CR than patients who were not discharged before ANC recovery. However while patients with better PS (but not age) were more likely to be discharged than other patients, better PS was not associated with fewer re-admissions. Likewise patients in CR were not less likely to be re-admitted. Thus 9 of the 35 patients (26%) who were in CR or shown to be in CR at their next marrow after initial NF were readmitted for a subsequent NF within 30 days of discharge vs 4 of the 14 patients who were not in CR. The contrast between this finding and Bodey et al.'s[2] likely reflects the development of better antibiotics and correspondingly less need for reliance on normally functioning neutrophils (as in patients in CR).

A point made by Bodey et al. that still seems true however is that the trend in neutrophil count is a better predictor than a cutoff value such as 500. Specifically, only 3 of the 22 patients (14%) whose neutrophil count increased by 500 or more between initial admission for NF and discharge were subsequently re-admitted vs 10 of 27 patients (37%) with less of an increase ($p=0.10$). If we used 50 rather than 500 as the criterion of a rise, readmission rates were 7/37 (19%) for those with such an increase vs 6/12 (50%) for those without ($p=0.06$).

Our results call into question the practice of keeping patients admitted for NF in the hospital after successful treatment of the NF. They also suggest the ANC 500 cut-off point is of limited use, although the trend of the ANC should be taken into consideration.

Funding

Victor Chow was funded by the American Cancer Society 2010 Summer Fellowship in Clinical Cancer Research. All other authors have no funding sources to disclose.

References

1. Bennett CL, Calhoun EA. Evaluating the total costs of chemotherapy-induced febrile neutropenia: results from a pilot study with community oncology cancer patients. *The Oncologist* 2007;**12**:478–83.
2. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Annals of Internal Medicine* 1966;**64**:328–40.
3. Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer* 2005;**103**:1916–24.
4. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia. *Cancer* 2004;**100**:228–37.
5. Dale DC. Advances in the treatment of neutropenia. *Current Opinion in Supportive and Palliative Care* 2009;**3**:207–12.
6. Freifeld A, Bow E, Sepkowitz K, Boeckh M, Ito J, Mullen C, et al. Clinical guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2011;**52**:e56–93.
7. Innes H, Marshall E. Outpatient therapy for febrile neutropenia. *Current Opinion in Oncology* 2007;**19**:294–8.
8. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 2006;**106**:2258–66.