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Pre-transplant Neutropenia Is Associated with Poor Risk Cytogenetic Features and Increased Infection-related Mortality in Patients with Myelodysplastic Syndromes

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ABSTRACT

A retrospective cohort analysis was performed to determine the impact of neutropenia on the outcome of hematopoietic cell transplantation (HCT) in patients with myelodysplasia (MDS). Among 291 consecutive patients, 178 (61%) had absolute neutrophil counts (ANCs) <1500/μL and 113 (39%) had ANCs ≥1500/μL within 2 weeks before HCT. Neutropenic patients more often had poor risk karyotypes (34% vs. 12%, p<0.0001) and high risk IPSS scores (37% vs. 18%, p=0.0006). After HCT, the rate of infections caused by gram-positive bacteria and invasive fungal infections was significantly increased among neutropenic patients (rate ratio [RR] 1.77, p=0.02 and RR=2.56, p=0.03, respectively), while infections caused by gram-negative bacteria were not affected (RR 1.33, p=0.53). The hazards of non-relapse mortality (NRM) [HR=1.62 (1.1-2.4), p=0.01], overall mortality [HR=1.55 (1.1-2.1), p=0.007], and infection-related mortality [HR=2.22 (1.2-4.2), p=0.01] were increased in neutropenic patients, while relapse, engraftment, and graft-versus-host-disease were not affected. After adjusting for cytogenetic risk and marrow myeloblast percentages, neutropenic patients remained at significant hazard for infection-related mortality [HR=1.94 (1.0-3.8), p=0.05], but not for overall mortality or NRM. We propose that intensified strategies to prevent infections should be implemented in MDS patients with pre-existing neutropenia who undergo HCT.

Key Words: neutropenia, MDS, stem cell transplant

INTRODUCTION

Neutropenia has been previously defined as an absolute neutrophil count (ANC) less than two standard deviations below the normal mean of the population, usually <1500/μL. The actual numerical value of neutropenia is dependent upon age, ethnic group, and other genetic and environmental factors [1]. Neutropenia is a frequent problem in patients with Myelodysplastic Syndromes (MDS) and is either a primary result of marrow failure or develops secondary to therapy. Among the International Prognostic Scoring System (IPSS) cohort of 805 patients with primary MDS who had ANC data available, 366 (46%) had ANCs <1500/μL [2]. Patients with neutropenia have an increased risk of developing infections, and the risk and type of infections depend on the severity and duration of neutropenia [3,4]. The ability to assess neutropenia as an isolated risk factor in MDS is limited. The World Health Organization's (WHO) diagnostic schemata do not have a separate classification system based solely upon the type of cytopenia(s) present [5]. While the IPSS does score the number of cytopenias, it does not consider the type or the severity of cytopenias present [2]. Furthermore, patients with MDS may have increased risks of infectious complications above and beyond the severity of neutropenia as they can have both quantitative and qualitative defects in neutrophil function [6]. Other investigators have shown that neutropenic patients with a diagnosis of MDS or acute myeloid leukemia (AML) have increased risks for invasive aspergillosis in comparison to neutropenic patients without these disorders, thus indicating that it is not only the development of neutropenia but also the underlying cause that predisposes neutropenic patients to certain types of infections [7]. In a cohort of 109 patients with MDS who underwent hematopoietic stem cell transplantation (HCT) at the Fred Hutchinson Cancer Research Center (FHCRC), death from infectious complications accounted for 53% of overall mortality [8]. Pre-existing neutropenia likely was a predisposing factor. The increased rate of infection could be secondary to pre-transplant colonization with bacterial or fungal organisms, increased antibiotic resistance

secondary to increased use of pre-transplant antibiotics or due to sustained impairment of immune functions following engraftment.

Given the current lack of information, we performed a retrospective cohort analysis to characterize the effects of pre-transplant neutropenia on post-transplant outcomes. Additionally, we were interested in characterizing associations between neutropenia and other known predictors of survival.

MATERIALS AND METHODS

We performed a retrospective cohort analysis of results in 291 consecutive patients with a diagnosis of MDS or AML with multilineage dysplasia transformed from a prior diagnosis of MDS (tAML). Chronic myelomonocytic leukemia patients were excluded from this analysis. All patients received their allogeneic hematopoietic stem cell transplants (HCT) between January, 1994 and December, 2003 at the Fred Hutchinson Cancer Research Center (FHCRC) or the VA Puget Sound Healthcare System. All patients were enrolled in IRB approved protocols active at time of enrollment. One-hundred-seventy-eight patients (61%) had ANCs <1500/μL (neutropenic cohort) and 113 (39%) had ANCs ≥1500/μL (non-neutropenic cohort) within 2 weeks prior to HCT. Within the neutropenic cohort, there were 137 patients who had an ANC <1000/μL, and 86 patients who had an ANC <500/μL. Patients who received growth factor therapy within 30 days prior to the ANC measurement were excluded from this analysis. Patients who received chemotherapy or other cytoreductive therapy within 30 days prior to measurement of the ANC were excluded because their neutropenia may have been solely due to cytotoxicity rather than their underlying disease. Thirty-three non-neutropenic patients and 32 neutropenic patients received chemotherapy greater than 30 days before measurement of the ANC. In this small number of patients, the median time from chemotherapy to measurement of the ANC was 101 (range: 41-563) and 115 (range: 36-806) days for the non-neutropenic and neutropenic cohorts, respectively. There were no substantial differences between these 2

groups in regards to distribution by median follow-up, median age, gender, or etiology of MDS/tAML (**Table 1**). Additionally, the distribution by WHO diagnostic categories was similar between the two groups. However, patients with neutropenia were more likely to be in the IPSS high risk group (65% vs. 17.7%, p=0.0006) and this was primarily due to the presence of poor risk cytogenetics (33.7% vs. 12.4%, p<0.0001) [2].

All patients included in this analysis received myeloablative HCT conditioning. In most patients this consisted of busulfan (Bu), prescribed dose 16 × 1 mg/kg, dose-adjusted to achieve target steady state levels of 600-900 ng/mL (tBu), plus cyclophosphamide (Cy), 2 × 60 mg/kg (**Table 1**) [8]. The remaining patients were conditioned with tBu combined with fludarabine, 4 × 30 mg/m^2; Cy 2 × 60 mg/kg plus 12-14.4 Gy total-body irradiation (TBI); tBu, Cy 2 × 60 mg/kg plus 12 Gy TBI; Bu (7 mg/kg) plus 12 Gy TBI; or myeloablative doses of radiolabeled I^{131} [9-13]. Stem cells were infused within 24 hours of completion of TBI or within 36-48 hours of the last dose of chemotherapy. All recipients received T-replete grafts. There were no differences between the two cohorts in regards to donor source, donor HLA-matching, and stem cell source. ABO incompatible grafts underwent red blood cell depletion or plasma reduction depending on pre-transplant recipient/donor ABO isoagglutinin titers.

The majority of the neutropenic patients (84%) and non-neutropenic patients (70%) received intravenous methotrexate and cyclosporine for graft versus host disease (GVHD) prophylaxis [14]. Acute GVHD was diagnosed and graded according to consensus criteria [15]. Chronic GVHD was diagnosed as clinically limited or extensive (requiring immunosuppressive therapy) using previously published criteria [16,17].

Infection Surveillance and Prophylaxis

All patients were monitored for the onset of infections during the first 100 days after HCT. Monitoring included bacterial and fungal blood cultures and chest radiographs when

patients developed a fever (>38.3°C orally). Additionally, all patients receiving ≥0.5 mg/kg of corticosteroid therapy were monitored with weekly bacterial and fungal blood cultures and chest radiographs. For *Pneumocystis jiroveci* prophylaxis all patients received trimethoprim/sulfamethoxasole as first line therapy, dapsone as second line therapy [18], or atovaquone as third line therapy from time of engraftment until 6 months after HCT or until 6 weeks after all immunosuppressive medications had been discontinued. All patients received fluconazole or itraconazole for prevention of candidiasis from time of conditioning until day 75 after HCT [19]. Prophylactic systemic antibiotics with levofloxacin or ceftazidime [20] were initiated in all patients when their ANCs fell below 500/μL.

Definitions of Endpoints

The day of onset of infection was defined as the day the diagnostic test was performed [21]. Invasive fungal infections were defined by the National Institutes of Health Mycosis Study Group/European Organization for Research and Treatment of Cancer consensus criteria [22]. Bacterial infections were defined as positive blood, bronchial lavage (lower respiratory tract), or urine cultures. The day of engraftment was defined as the first of 3 consecutive days on which the ANC remained greater than 500/μL. Evidence of graft rejection was sought in patients who failed to reach ANCs of 500/μL by day 28, and in patients with sustained declines in counts after initial recovery. All patients had marrow evaluations scheduled on days 28, 56, 84 (±3 days), and one year after HCT, and subsequently as clinically indicated. Relapse was defined as post-transplant reappearance of dysplastic cells by flow cytometry, morphologic evidence of dysplastic myeloblasts, or the reappearance of cytogenetic abnormalities identified pre-transplant [23,24]. In patients with morphologic, hematologic, or cytogenetic evidence of relapse, relapse rather than graft rejection was considered to be the cause of failed engraftment. In patients with relapse, relapse was listed as the primary cause of death regardless of other associated events. In patients with GVHD requiring immunosuppressive

therapy who subsequently died with infections, GVHD was considered the cause of death. Multiorgan failure was identified as the cause of death when it occurred in the absence of relapse and was thought not to be primarily due to preceding GVHD or infection. Graft rejection was considered the cause of death if patients had documented loss of graft function after day 28 post-transplant without evidence of relapse or GVHD. Infections were considered causes of death when they occurred in the absence of GVHD, relapse, graft failure, and graft rejection. The coding of death was performed by reviewing autopsy and other medical documents by a single investigator (B.L.S.) who was blinded to the cohort assignment.

Statistical Analysis

Results were analyzed as of December, 2006. Overall survival and progression-free survival were estimated using the Kaplan-Meier method. Cumulative incidence curves for relapse-related mortality, non-relapse mortality, and infection-related mortality were estimated according to methods described by Gooley *et al.* [25]. Deaths were treated as competing events in the analyses of engraftment, GVHD, and progression. Unadjusted and adjusted rate ratios for infection during the first 100 days post-transplant were estimated using Poisson regression. Rates of bacterial infections were adjusted by use of TBI and CMV recipient serostatus + vs. – [26]. Rates of invasive fungal infections were adjusted by age > 40 years and matched related donor vs. other donors [27]. Increased risk of bacterial and fungal infections by degree of neutropenia was evaluated using a test for trend across the neutropenia categories 1500-1000, 1000-500, and <500. Unadjusted and adjusted hazard ratios were estimated using proportional hazards regression models. Given the increased prevalence of poor risk cytogenetics among the neutropenic cohort, adjustments were made for cytogenetic status (good, intermediate, and poor risk). Additionally, the analyses were adjusted for marrow myeloblast percentages (<5, 5-9, 10-19, 20-29, and ≥30). We did not adjust for IPSS classification because the IPSS includes neutropenia within the number of blood cytopenias. There were no differences between the two

cohorts in regards to other potential confounding variables such as age, etiology, GVHD prophylaxis, stem cell source, donor type, and conditioning regimen.

RESULTS

Among the 178 patients with pre-transplant neutropenia, 7 (4%) died before day 28 without evidence of GVHD and were considered not evaluable for engraftment. An additional 5 patients (3%) died with graft failure or graft rejection at 38 to 343 days. The median time to neutrophil engraftment in the remaining 166 patients was 17 (range: 10-31) days. There were no differences observed in median engraftment by severity of neutropenia (ANC 1500-1000/μL, 1000-500/μL, and <500/μL). Among the 113 patients without pre-transplant neutropenia, 6 patients (5%) died before day 28 without evidence of GVHD and were considered not evaluable for engraftment. One patient (1%) died with graft failure at 46 days. The median time to engraftment in the remaining 106 patients was 17 (range: 10-33) days.

The cumulative incidences of grades II-IV GVHD were not different between the neutropenic (80%) and the non-neutropenic cohorts (76%) (p=0.42), nor were the cumulative incidences of grades III-IV GVHD (32% vs. 24%, p=0.15). The 3-year overall survival was 39.7% for the neutropenic cohort and 55.7% for the non-neutropenic cohort (**Figure 1**). The decreased overall survival observed in the neutropenic cohort was chiefly secondary to differences in NRM. The neutropenic cohort had higher incidences of NRM than the non-neutropenic cohort, 24.4% vs. 14.3% and 39.6% vs. 26.7% at day 100 and 1 year, respectively (**Figure 2**). Specifically, the neutropenic cohort had an increased incidence of infection-related mortality at 3 years in comparison to the non-neutropenic cohort (26% vs. 12.3%) (**Figure 3**). The 3-year cumulative incidences of relapse were similar between the two cohorts, 20.3% and 19.3%, respectively.

The neutropenic cohort had significantly higher hazards for overall mortality, NRM and infection-related mortality (**Table 2)**; however, patients in this cohort were also more likely to

have poor risk cytogenetics and an overall higher IPSS classification. Therefore, adjusted analyses were performed using cytogenetic risk and marrow myeloblast percentages as detailed in the statistical section. Following adjustment, the neutropenic cohort no longer had significantly higher hazards for overall survival or NRM; however, the hazard for infection-related mortality remained significantly higher.

We also evaluated whether the hazards of NRM, mortality, and relapse increased with increasing degrees of neutropenia. To that end, neutropenic patients were compared to non-neutropenic patients using ANC cut-offs of 1000-1500/μL (n=41), 500-1000/μL (n=51), and <500/μL (n=86). There was no increased risk of poor HCT outcomes with increasing severity of neutropenia (data not shown).

Time from diagnosis to HCT had no effect on infection-related mortality; however, the distribution was highly skewed towards a short time interval from diagnosis to HCT: 75% of the patients in both neutropenic and non-neutropenic cohorts were transplanted within 500 days of diagnosis.

Types of Post-transplant Infections

Overall, the neutropenic cohort had significantly increased rates of bacterial and fungal infections in comparison to non-neutropenic patients within the first 100 days after HCT (RR=1.59, p=0.001 and RR=2.89, p=0.01, respectively) (**Table 2**). Most fungal infections were caused by Aspergillus species (27/32), and the remaining fungal infections were due to Candida glabrata (2/32) and mucor (3/32). The propensity for neutropenic patients to develop bacterial infections varied by type of organism. There was an increase in the rate of infections with gram positive organisms (RR=1.77, p=0.02), but not with gram negative rods. The increased rate of fungal and gram positive bacterial infections among the neutropenic patients was most prominent more than 60 days after HCT (**Figure 4**). The rate ratio for fungal infections remained unchanged after adjustment for acute GVHD grades II-IV (RR=2.76, 95% CI 1.1-6.7, p=0.01),

indicating there was no evidence of confounding by acute GVHD. There was no association between pre-transplant colonization with bacteria or fungal organisms and the subsequent development of bacterial or invasive fungal infections; however, these data are limited by the fact that no routine surveillance for colonization was employed. The increasing levels of neutropenia (ANC 1500-1000/μL, 1000-500/μL, and <500/μL) had no further significant impact on an increased risk of fungal and bacterial infections using a test for trend (data not shown).

Effects of Single Lineage Pre-Transplant Cytopenias

Among the patients evaluated in these analyses, there were 16 (4.6%) with isolated neutropenia (ANC<1500/μL), 22 (6.3%) with isolated thrombocytopenia (platelet count <100,000/μL), and 25 (7.1%) with isolated anemia (Hgb <10g/dL). Given the inferior HCT outcomes observed with neutropenia, we were interested in determining whether isolated neutropenia was associated with worse HCT outcomes than observed in patients with other single lineage cytopenias. Patients with each of the isolated cytopenias were compared to patients without cytopenias (n=32) using proportional hazards regression and adjusted for cytogenetic risk and marrow myeloblast percentages (**Table 3**). Although the numbers of patients within the subgroups were small, there was a strong trend for an increased risk of worse outcomes among patients with isolated neutropenia and thrombocytopenia.

DISCUSSION

For the study interval January, 1994 to December, 2006, 61% of patients with MDS and tAML met the definition of neutropenia (ANC <1500/μL). The neutropenia present in this patient population was secondary to the underlying disease rather than the receipt of chemotherapy or alternative treatments. Neutropenia was associated with pre-transplant poor risk cytogenetics and a high IPSS classification, but not a higher marrow myeloblast percentage. However, a limitation of the present analysis was that only HCT patients were included and, therefore, the

correlation of neutropenia and poor risk cytogenetics may be due to a referral bias. Biologically, an association of poor risk cytogenetics with an overall decrease in marrow function in MDS patients appears plausible, but this possibility has not been examined systematically.

Pre-transplant neutropenia was associated with significantly increased hazards of NRM, overall mortality and infection-related mortality. Of note, the hazard did not increase significantly with the severity of neutropenia. There may be a critical level of neutropenia combined with intrinsic abnormalities in the neutrophils that confers the increased risk of infectious complications; therefore, increasing levels of neutropenia did not results in increased risk of infectious complications. However, there were few patients in this subgroup analysis and it is possible that we were not able to detect a difference due to lack of power. Neutropenic patients were not found to be at an increased risk of relapse-related mortality despite adverse factors such as poor risk cytogenetics and increased IPSS scores. The increased rate of earlier NRM may have removed the neutropenic patients from a later risk of relapse. Following adjustment for IPSS cytogenetic classification and marrow myeloblast percentage, the neutropenic cohort no longer showed a significantly increased hazard for overall mortality and NRM, but the increased hazard for infection-related mortality remained significant.

Overall, neutropenic patients were at an increased risk of developing bacterial and invasive fungal infections in comparison to non-neutropenic patients. The median time to engraftment was similar between the neutropenic and non-neutropenic patients. Furthermore, there was no difference in median engraftment with increasing severity of neutropenia. Therefore, it is unlikely that the difference in infection rates were secondary to differences in engraftment. The types of bacterial infections that developed in neutropenic patients tended to be different from those in non-neutropenic patients. Neutropenic patients more frequently developed infections with gram positive organisms rather than gram negative organisms. Indicative of a possible increased risk of catheter associated infections in neutropenic patients in comparison to non-neutropenic patients. The increased rate of fungal and bacterial infections

among patients with pre-transplant neutropenia was most prominent after day 60 post-transplant, thereby indicating a possible multiplicative association between pre-transplant neutropenia and therapy for GVHD (generally with steroids) with invasive fungal infections.

The time from diagnosis to HCT in neutropenic patients was thought to be an important predictor of NRM and specifically infection-related mortality. With increased time, it was suspected that increased colonization would result in increased rates of death from infection in the neutropenic cohort as compared to the non-neutropenic cohort. However, as specified in the results section the time from diagnosis to HCT was highly skewed towards a short time interval for both cohorts (<500 days), and we were not able to adequately address this issue because of a lack of discordance between the neutropenic and non-neutropenic cohorts. Since we studied only patients who underwent HCT, we cannot comment on outcome for neutropenic patients treated with other modalities. Neutropenic patients who had a long delay between diagnosis and consideration of HCT may have developed serious infectious complications that precluded the option of and referral for HCT.

In summary, neutropenia in patients with MDS was associated with poor risk cytogenetic features and with an increased hazard of overall mortality, NRM, and infection-related mortality following HCT. After adjusting for cytogenetics and marrow myeloblast percentage, neutropenia remained significantly associated with an increased hazard of infection-related mortality. The numbers of patients were too small to evaluate the impact of isolated cytopenias in this analysis, although there was a suggestion that patients with isolated neutropenia or thrombocytopenia fared less well than patients with isolated anemia. We observed increased rates of fungal and gram positive bacterial infections in the neutropenic cohort. The primary disadvantage among neutropenic patients was infection-related mortality. Therefore, increased surveillance and more intensive infection prophylaxis may be warranted in neutropenic MDS patients who undergo HCT.

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Table 1. Patient, Disease and Transplant Characteristics

Characteristic	No. of Patients (%) ANC <1500/μL	No. of Patients (%) ANC ≥1500/μL
No. of patients	178	113
Age yrs, median (range)	49 (3-66)	45 (1-66)
Gender, M/F, no. of patients	103/75	63/50
Follow-up yrs, median (range)	5 (0.1-12)	6.3 (1.2-12)
Time from diagnosis to transplant days, median (range)	223 (51-4867)	244 (22-3150)
WHO stage, no. of patients (%)		
<5% marrow myeloblasts; no peripheral blasts	66 (37)	48 (42)
RA	21	15
RARS/RCMD-RS	4	4
RCMD	28	14
MDS-U	5	5
5q-	8	10
RAEB-1	23 (13)	15 (13)
RAEB-2	27 (15)	12 (11)
tAML	62 (35)	38 (34)
IPSS risk group, no. of patients (%)		
Low	11 (6)	22 (19)
Intermediate-1	46 (26)	41 (36)
Intermediate-2	56 (31)	30 (27)
High	65 (37)	20 (18)
Cytogenetic Risk Group, no. of patients (%)		
Good	87 (49)	71 (63)
Intermediate	31 (17)	28 (25)
Poor	60 (34)	14 (12)
Related donor	93 (52)	57 (50)
HLA-identical sibling	79 (44)	46 (40)
HLA-mismatched family member	10 (6)	7 (6)
HLA-matched family member	4 (2)	2 (2)
Syngeneic	0	2 (2)
Unrelated donor	85 (48)	56 (50)
HLA-matched	55 (31)	42 (37)

Table 1. Patient, Disease and Transplant Characteristics

Characteristic	No. of Patients (%)	
	ANC <1500/μL	ANC ≥1500/μL
HLA-mismatched	30 (17)	14 (13)
Source of stem cells		
Peripheral blood	92 (52)	51 (45)
Marrow	86 (48)	61 (54)
Cord blood	0	1 (1)
Conditioning regimen		
tBuCy	99 (56)	74 (65)
BuFlu	13 (7)	4 (4)
BuTBI	35 (20)	10 (9)
CyTBI	28 (15)	22 (19)
I-131	3 (2)	2 (2)
MelBu	0	1 (1)

*Syngeneic donor.

Abbreviations: Bu, busulfan; CSP, cyclosporine; Cy, cyclophosphamide; FK506, tacrolimus; Flu, fludarabine; I-131, radio-iodine labeled monoclonal antibody; IPSS, International Prognostic Scoring System; MMF, mycophenolate mofetil; MTX, methotrexate; TBI, total body irradiation; WHO, World Health Organization.

Table 2. Hazard Ratios and Rate Ratios Comparing Neutropenic and Non-neutropenic Cohorts

	ANC <1500/μL		ANC <1500/μL Adjusted	
Outcomes	**HR (95% CI)**	**P-value**	**HR (95% CI)***	**P-value***
Overall Mortality	1.55 (1.1-2.1)	0.007	1.19 (0.8-1.7)	0.34
Non-relapse mortality (NRM)	1.62 (1.1-2.4)	0.01	1.31 (0.9-2.0)	0.2
Relapse	1.31 (0.8-2.3)	0.33	0.96 (0.5-1.8)	0.9
Infection-related mortality	2.22 (1.2-4.2)	0.01	1.94 (1.0-3.8)	0.05
	RR (95% CI)	**P-value**	**RR (95% CI)†**	**P-value†**
Bacterial infection‡ (223 in 60 pts)	1.59 (1.2-2.1)	0.001	1.42 (1.1-1.9)	0.01
Gram-negative rods (21 in 11 pts)	1.33 (0.5-3.3)	0.53	1.27 (0.5-3.2)	0.6
Gram-positive organisms§ (84 in 37 pts)	1.77 (1.1-2.9)	0.02	1.51 (0.9-2.1)	0.09
Coagulase-negative staph (102 in 40 pts)	1.46 (1.0-2.2)	0.07	1.35 (0.9-2.1)	0.16
Bacillus and Corynebacterium (8 in 6 pts)	////¶	0.004	N/A	N/A
Fungal infection‡ (32 in 31 pts)	2.89 (1.2-7.0)	0.01	2.89 (1.2-7.0)	0.01

* Adjusted for cytogenetic risk group and bone marrow myeloblast percentage.

† Adjusted for TBI conditioning and CMV recipient + vs. – for bacterial infections or HLA-matched related donor vs. other and age ≤ or > 40 years for fungal infections.

‡ All infection rates estimated using Poisson regression, truncated at death or day 100.

§ Excluding Coagulase-negative staph, Bacillus and Corynebacterium.

¶ All Bacillus and Corynebacterium infections occurred in neutropenic patients.

Abbreviations: HR, hazard rate ratio; RR, rate ratio.

Table 3. Hazard Rate Ratios* Comparing Isolated Cytopenic Patients to Patients without Any Cytopenias (n=32)

Outcomes	**ANC <1500/μL n=16**		**Platelets <100,000/μL n=22**		**Hgb <10 g/dL n=25**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Overall mortality	2.39 (0.9-6.1)	0.07	2.25 (0.9-5.6)	0.08	1.25 (0.5-2.9)	0.6
NRM	2.96 (1-8.6)	0.05	3.49 (1.1-11)	0.03	1.52 (0.5-4.6)	0.45
Relapse	/////†	0.08	0.46 (0.1-3.1)	0.43	1.09 (0.3-4.3)	0.9
Infection-related	8.19 (0.8-86)	0.08	6.22 (0.6-66)	0.13	5.67 (0.6-54)	0.13

* Adjusted for cytogenetic risk group and bone marrow myeloblast percentage.

† No events occurred in the isolated neutropenic cohort.

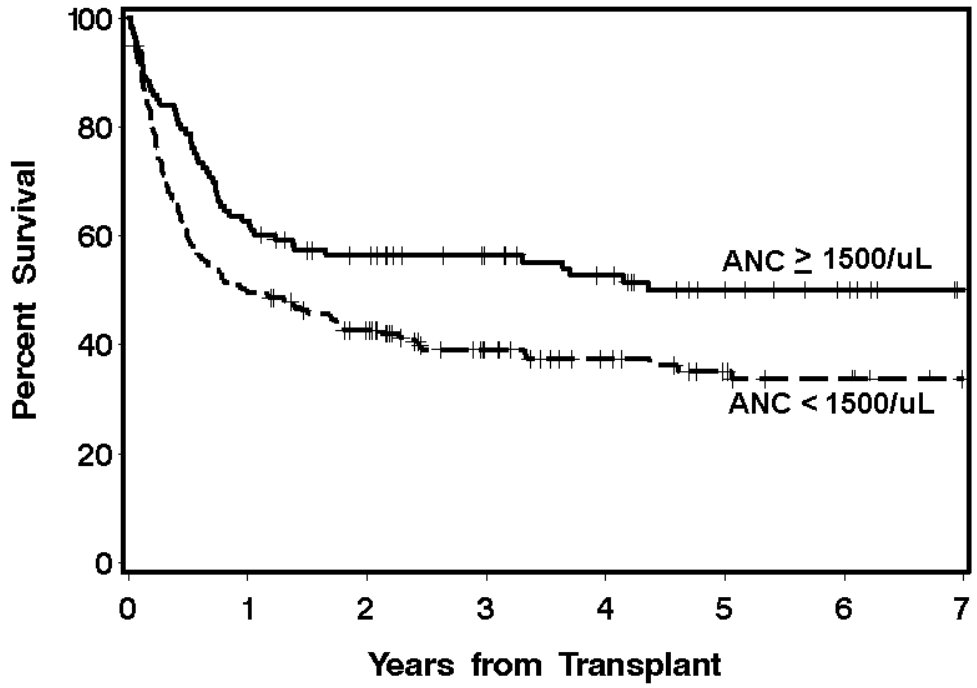

Figure 1. Overall survival among neutropenic (ANC <1500/μL) and non-neutropenic (ANC ≥1500/μL) patients. HR=1.55 (1.1-2.1), p=0.007

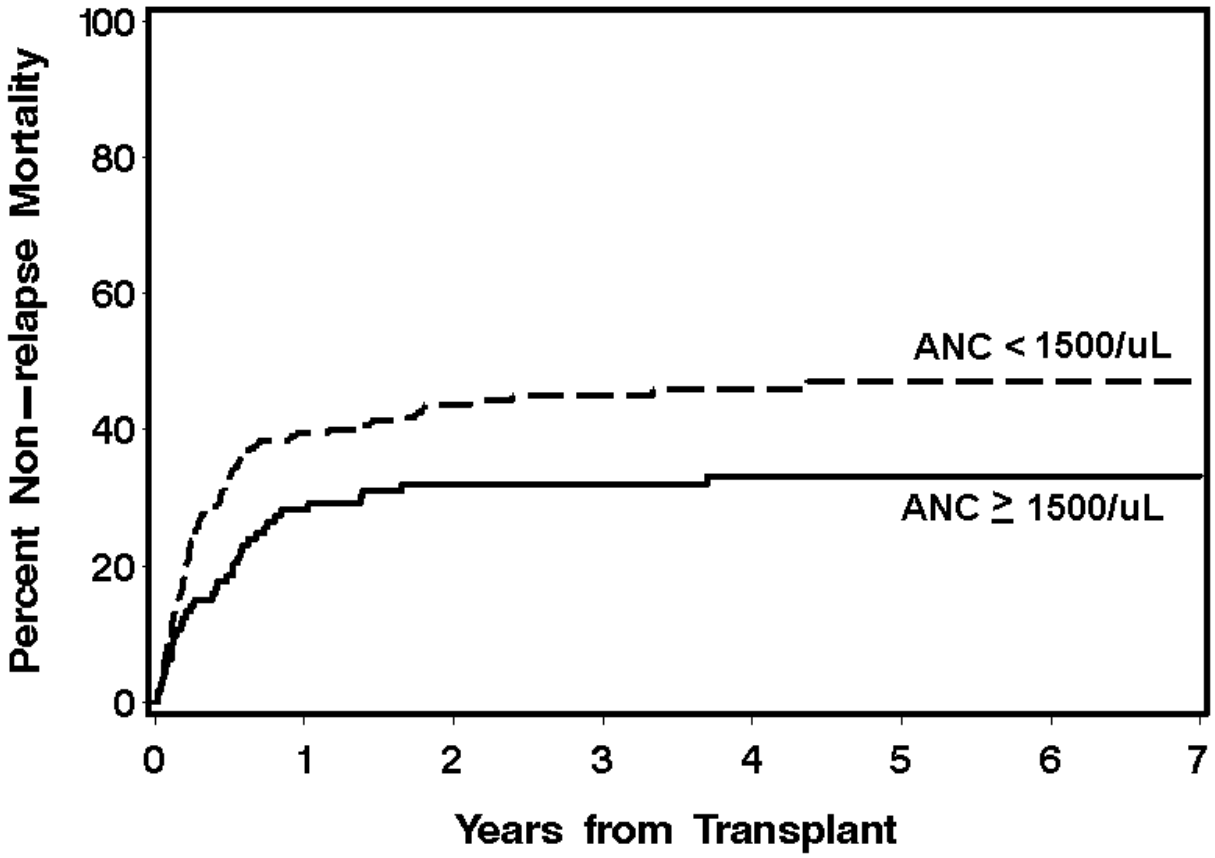

Figure 2. NRM among neutropenic and non-neutropenic patients. HR=1.62 (1.1-2.4), p=0.01

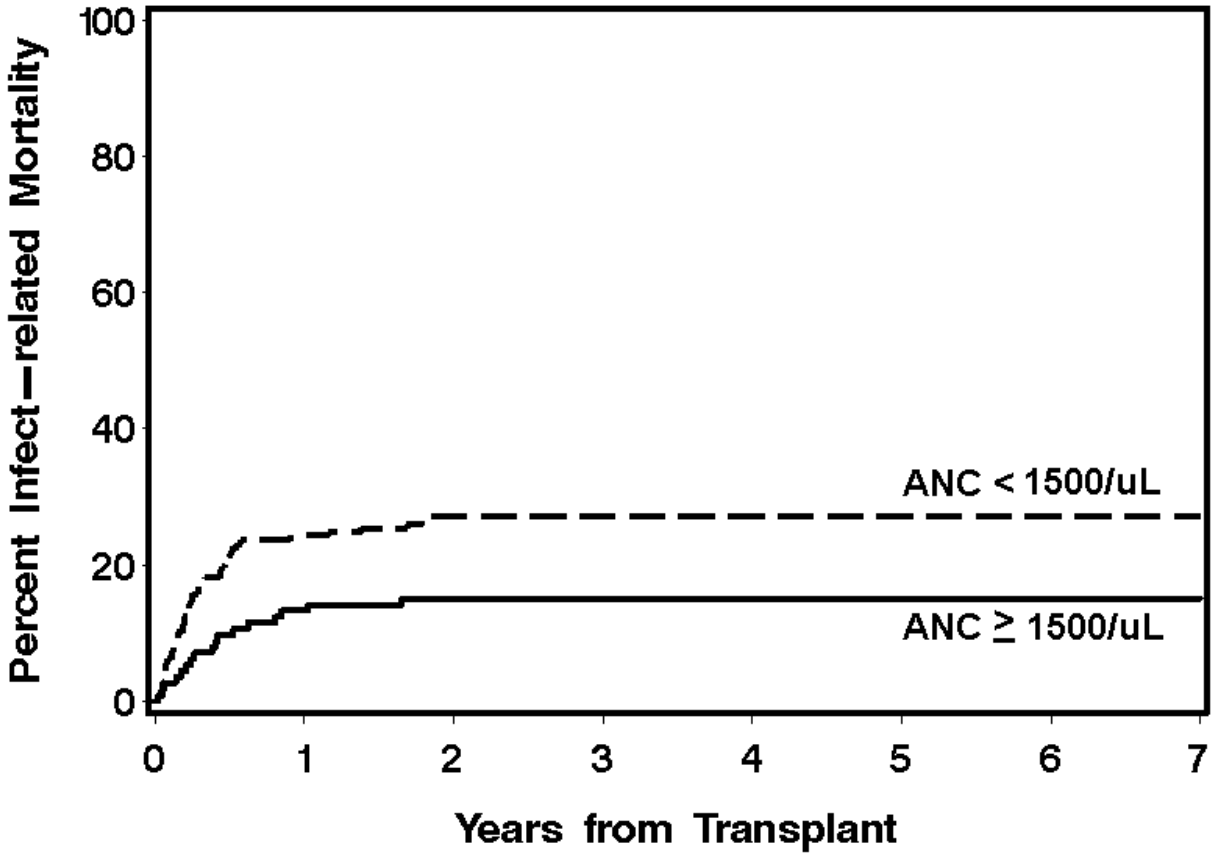

Figure 3. Infection-related mortality among neutropenic and non-neutropenic patients. HR=2.22 (1.2-4.2), p=0.01

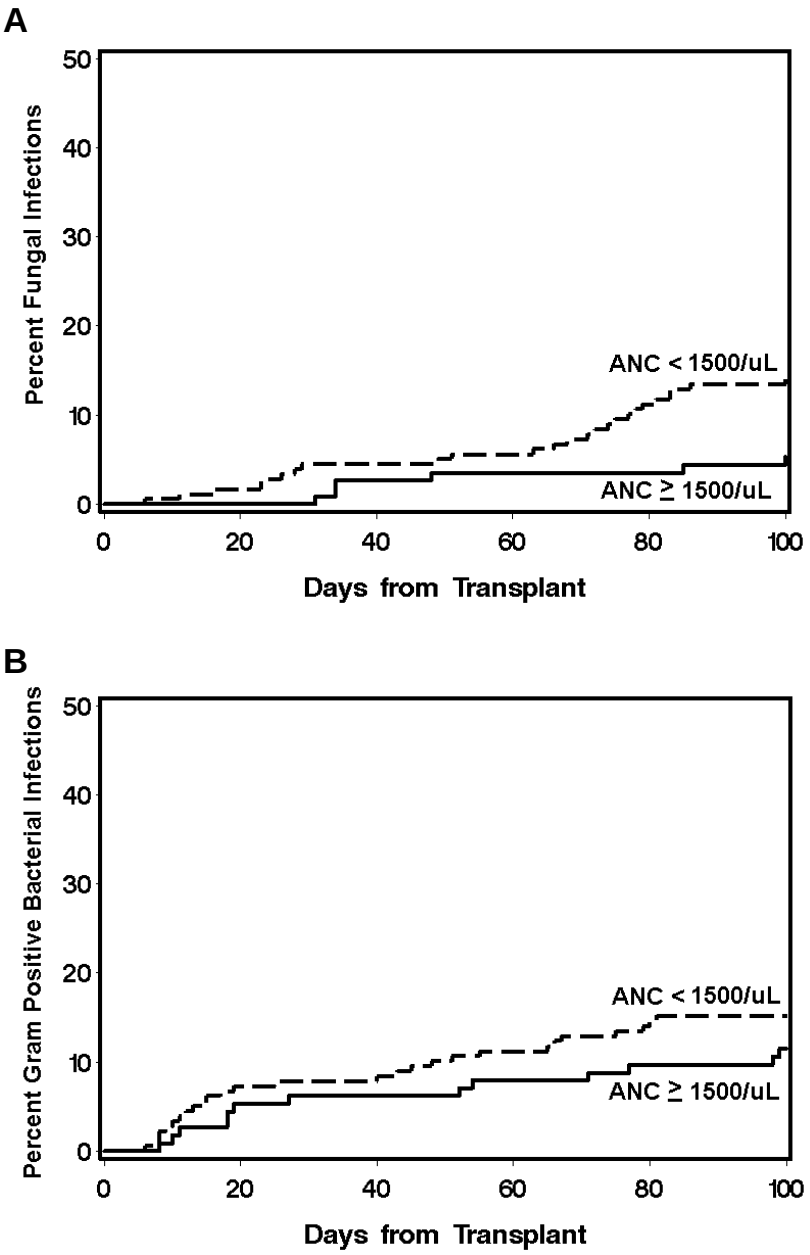

Figure 4. A) Percent of invasive fungal infections among neutropenic and non-neutropenic patients from day 0 to day 100 post-transplant. HR=2.89 (1.2-7.0), p=0.01 **B)** Percent of gram positive bacterial infections among neutropenic and non-neutropenic patients from day 0 to day 100 post-transplant. HR=1.77 (1.1-2.9), p=0.02