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Low incidence of opportunistic Infections in Lupus Patients treated with Cyclophosphamide and Steroids in a Tertiary care setting

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Abstract

Background—Infection is common cause of morbidity and mortality in systemic lupus erythematosus (SLE). Our objective was to determine incidence and types of infections, particularly opportunistic infections, in SLE patients receiving cyclophosphamide, and to identify contribution of variables like demographics, steroid, other immunosuppressives, white blood cell and absolute neutrophil count to infection risk.

Patients and Methods—We did retrospective chart review of SLE patients in our institute over last 10 years, who received minimum six cyclophosphamide infusions. Types of infection, cumulative steroid dose, and maintenance medications were recorded. Statistical analyses were done using SAS software.

Results—87.1% of the 31 patients were female. Mean age was 37.9 years, 48.4% Hispanic, 25.8% African American, 6.4% Asian and 19.4% were Caucasian. No one was on pneumocystis jirovecii pneumonia (PJP) prophylaxis. There were 42 episodes of infection in 31 patients. Different infections were urinary tract infections (UTI), upper respiratory infections (URI), line sepsis, bacterial pneumonia, PJP, mucocutaneous infections and viral gastroenteritis. Infection frequency was significantly higher among Asians compared to Caucasians (p =0.0152). Infection rate was significantly higher during cyclophosphosphamide induction phase (65.9%) compared to maintenance phase (34.1%) (p value=0.0041). Infection rate was higher with higher cumulative steroid dose and in patients on quarterly cyclophosphamide infusion compared to those on oral azathioprine or mycophenolate mofetil. No association found among baseline white blood cell (WBC) or absolute neutrophil count (ANC) and infection rate.

Conclusion—We found higher infection rates among Asians and in patients with higher cumulative steroid dose. Single incidence of PJP noted despite absence of prophylaxis. Quarterly

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Conflict of Interest

None of the authors have any financial interests or conflict of interest with regard to this work.

cyclophosphamide was associated with higher infection rates. Larger prospective studies are needed to confirm our results.

Keywords

Lupus; infection; cyclophosphamide; Pneumocystis jirovecii pneumonia

Introduction

Infections remain a major cause of morbidity and mortality in Systemic Lupus Erythematosus (SLE) (1–8). Immune dysregulation associated with lupus is purported to increase the risk of infection (1,5, 9). Previous studies have also suggested that patients with older age, longer disease duration, and lupus nephritis have a higher risk of infection (1, 4). Furthermore, intense immunosuppressive regimens using cyclophosphamide and steroids for the treatment of lupus nephritis or lupus cerebritis adds to the risk of infections (1, 2, 5–7, 9).

Cyclophosphamide is an alkylating agent, which has been shown to improve outcomes in lupus nephritis (10). The relative roles of the disease itself and the consequences of immunosuppressive therapy in the development of infections are debatable (3, 4). In addition to common bacteria and viruses, SLE patients are prone to opportunistic infections like candida, herpes zoster, pneumocystis jirovecii (formerly *P. carinii*) and cryptococcus neoformans (1, 4, 6, 9).

Pneumocystis jirovecii pneumonia (PJP) is associated with significant morbidity and mortality and is particularly concerning in patients treated with cyclophosphamide (1, 9). Diagnosis of PJP is also challenging in these patients because symptoms often mimic pulmonary complications of lupus (9).

Presently, there are no clear guidelines regarding prophylaxis of opportunistic infections such as PJP in lupus patients on intense immunosuppressive regimens such as cyclophosphamide and steroid combination (9).

Our objectives were to determine systematically the incidence and types of infections in SLE patients treated with cyclophosphamide, and to identify the relative contribution of additional variables such as patient demographics, other immunosuppressive agents, baseline white blood cell (WBC), absolute neutrophil count (ANC) and steroid to the risk of infection. We were particularly interested in the incidence of opportunistic infections including PJP in this patient population.

Patients and Methods

We identified SLE patients from our computerized research database who have received cyclophosphamide over the last 10 years (October 2004 – September 2014). We excluded patients who received oral cyclophosphamide to minimize heterogeneity in the study. Previous literature suggests that continuous oral cyclophosphamide is associated with higher risk of infections compared to pulse cyclophosphamide treatment (11). We also excluded

subjects who received less than 6 infusions of intravenous cyclophosphamide. We do not have sufficient medical records on some of these subjects as they were either transferred back to the referring rheumatologist or lost to follow up. Few subjects were stem cell transplant recipients and thereby not included in our study.

We reviewed electronic medical records of the remaining SLE patients who received at least six cycles of intravenous cyclophosphamide in the induction phase of treatment and followed up for a minimum period of 6 months post-induction.

The data were recorded for patient demographics, indication for cyclophosphamide therapy, laboratory data and incidence of infections by causative agents (viral/bacterial/fungal) and site during the induction phase and for six months following treatment. We recorded the timing of infections with respect to cyclophosphamide dosing. We also calculated the cumulative steroid dose for the induction phase and type of immunosuppressive regimen used during the maintenance phase.

Total cumulative steroid exposure was calculated by review of inpatient orders, outpatient prescriptions, and provider notes in the NIH Clinical Center electronic medical record. Steroids included in the calculation were methylprednisolone, prednisone, and dexamethasone. Oral steroid doses were included in the cumulative exposure if they were ordered and filled starting from the date of the first dose of cyclophosphamide and extending for 30 days following the last dose of the induction phase of cyclophosphamide.

Methylprednisolone intravenous bolus doses were included starting seven days prior to the first dose of cyclophosphamide and extending for 30 days following the last dose of the induction phase. All cumulative doses are expressed in “mg prednisone equivalents” by using standard steroid equivalency ratios (12). Patients with a lack of documentation regarding steroid doses throughout the treatment course in provider notes and prescriptions were excluded from the analysis.

All episodes of infections as documented in progress notes were included. In addition, the laboratory and imaging data were reviewed to gather any additional reports of infections.

For statistical analysis, descriptive statistics were used to characterize patients. Characteristics of the SLE patients treated with cyclophosphamide were presented using mean, with standard deviation. Statistical analysis for the study group patients who developed one or more infections were compared to the patients who did not develop an infection in the observed time period and who acted as No-infection. Some patients received multiple courses of cyclophosphamide and in those cases each cycle of cyclophosphamide was treated as a separate entity. Comparisons of means between infected and non-infected groups were performed with independent samples t-tests when variables were normally distributed; otherwise, nonparametric Wilcoxon-Mann-Whitney test was applied for continuous variables. Frequencies were compared by using the 2-sided Fisher exact test ($2P$), for all 2×2 comparisons, and the Chi-square (χ^2) test for all other frequency comparisons. Multivariable Cox proportional-hazard test was used for the time-dependent multivariate analysis adjusted by risk factors as a covariate simultaneously explore the effects of cumulative steroids on incidence of infection.

We used Poisson regression models in SAS using PROC GENMOD (a procedure for fitting generalized linear models) adjusted by age and ANC as a covariate to calculate the incidence rates per 100 patient-years and their 95% confidence intervals (95% Cls). We also did the calculations by adjusting the total white blood cell count and the results were unchanged. The time variable indicates the time, measured in months, from the time the patient begin treatment with cyclophosphamide till the patient developed infection or till the end of the study period. Results were considered as statistically significant if the *P*-value was less than 0.05. All statistical analyses were carried out using the SAS program version 9.3 (SAS Institute Inc., Cary, NC, USA) and JMP version 11 (SAS Institute Inc., Cary, NC).

Results

We identified 57 lupus patients from our computerized database who received cyclophosphamide over the ten-year time window. All of these patients fulfilled the 1997 revised classification criteria of American College of Rheumatology (ACR) for SLE (13, 14). We excluded six patients who received oral cyclophosphamide, ten patients due to insufficient clinical data or follow-up, and ten patients who received cyclophosphamide as conditioning for stem cell transplant.

Data from the remaining 31 patients who were administered at least six infusions of intravenous cyclophosphamide at the NIH in the induction phase and who were followed for at least six months post-induction were included in this study.

Seven subjects received multiple cycles of IV cyclophosphamide, one patient received four cycles, two patients received three cycles and four patients received two cycles of cyclophosphamide. Overall 31 patients received 42 cycles of cyclophosphamide. Each cycle of cyclophosphamide has been considered as separate entity for analysis.

The majority (87.1%) of the 31 patients were female. Mean age of the subjects in this cohort was 37.9years (22–57 years), 48.4% were Hispanic, 25.8% African American, 6.4% Asian and 19.4% were Caucasian (Table 1).

Most of the patients received cyclophosphamide for lupus nephritis, four patients received cyclophosphamide for neuropsychiatric lupus, and one patient received cyclophosphamide for treatment of retinal vasculitis. During the induction phase with cyclophosphamide all the patients were on variable doses of steroid. Seven subjects out of 31 received concomitant rituximab of at least two 1000 mg doses during cyclophosphamide induction therapy.

None of our patients were on routine prophylaxis for infections including PJP.

There were 42 episodes of infection in 31 patients. Different types of infections were UTI, URI, line sepsis, bacterial pneumonia, PJP, muco-cutaneous infections (fungal/viral/bacterial) and viral gastroenteritis.

Seven episodes of bacterial UTI were reported in six patients, two incidences of line sepsis (indwelling venous catheter) from acinetobacter in two different patients, two occurrences of pneumonia, two cases of superficial fungal infection (oral thrush/candidiasis), 13 reports of

viral URI in 11 patients, single incidence of gardnerella vaginalis, five cases of herpes zoster, three cases of HSV infection and three reported incidences of viral gastroenteritis were noted. Only one case of PJP was observed. Incidence rate of all infections was 67.42 per 100 person years (Table 2).

Incidence of infection was significantly higher among Asians compared to Caucasian patients (p =0.0152). Hispanics were also found to have a higher rate of infections, but it was not statistically significant (p = 0.0768). We did not find any difference in the incidence of infections in the different age groups (p =0.095).

Predictably, the rate of infection was significantly higher during the induction phase of monthly cyclophosphamide infusions (65.9%) compared to the maintenance phase (34.1%) (p value=0.0041).

Higher cumulative steroid doses during the induction phase were associated with significantly higher rates of infection (Table 3).

No difference in the infection rates was observed between the subjects who received concomitant rituximab versus those who did not (p = 0.7306)

Incidence of infection during maintenance phase tended to be higher in patients on quarterly cyclophosphamide infusion compared to those on daily oral azathioprine or mycophenolate mofetil.

We did not find any association between baseline WBC count or ANC and risk of infection (Table 5).

Discussion

A higher rate of infections have been reported in literature in lupus patients compared to other autoimmune conditions such as rheumatoid arthritis (4).

There are various physiologic contributory factors predisposing SLE patients to infection including intrinsic defects in the innate and adaptive immune responses such as compromised chemotaxis and phagocytosis, possible deficiency of mannose-binding lectin, hypocomplementemia, impaired immune complex clearing, and defective T cell production (15–17).

In addition, use of immunosuppressive drugs, including mycophenolate mofetil, azathioprine, cyclophosphamide, and glucocorticoids further increase the risk of infection (4, 6). In a national population based study, Ward et al reported a high rate of hospitalization in SLE patients for pneumonia, sepsis, skin infections, UTI and opportunistic infections. The rates were significantly higher in lupus patients compared to those without lupus (13).

Similar to previous reports, we found a positive correlation between the cumulative dose of glucocorticoids and the incidence of infections in our cohort (1, 4). We also found maintenance treatment with quarterly cyclophosphamide was associated with higher rates of infection as compared to azathioprine or mycophenolate (not statistically significant).

One interesting finding noted in previous literature is a negative correlation between hydroxychloroquine use and the occurrence of major infections. We were unable to study this beneficial effect in the current study as all except one of our patients were on hydroxychloroquine (4, 17).

Previous reports have suggested that prevalence of SLE and its life threatening manifestations like lupus nephritis are more common and have a more aggressive course in racial and ethnic minorities including Hispanics and African Americans as compared to Caucasians (18, 19). Feldman et al reported higher infection rates among black and Native American patients as compared to white patients (4).

In this study cohort with a disproportionate representation of Hispanic patients we found a higher incidence of infections among Asians (statistically significant) and Hispanic subjects although that was not statistically significant.

Unlike previous literature, our study did not show any significant difference in infection rates in older patients versus younger patients. This is probably because our cohort was younger (maximum age 57 years) compared to others (38.8 ±12.48, maximum age 64 years) (4). Similar to our findings, no significant difference in the age range of infected and uninfected lupus patients was reported by Gladman et al and Bosch et al (6, 8).

Different types of infections found in our cohort of patients are summarized in table 2. We found much higher overall incidence of infections (67.42 per 100 person years) in our previous reports (6). We found a high incidence of upper respiratory tract infections (URI) (33.33%), mostly viral (except 1 case of bacterial otitis media), in our cohort. Previous studies have not commented on the incidence viral URI in their cohort (5, 6). However Zonana-Nacach et al included bacterial URI (6%) in their study (5). High rate of infections in our cohort compared to previous literature could be partially secondary to high rate of URI in our patients.

In addition, all of our patients had severe lupus characterized by lupus nephritis and/ or neuropsychiatric lupus and all were receiving cyclophosphamide. High disease activity in lupus patients has been correlated to increased risk of infections in previous literature (5, 6). Glomerulonephritis in SLE specifically has been reported to be an independent risk factor for infections (3). Treatment with cyclophosphamide has also been implicated as a contributing factor for infections in previous literature (1, 20).

The incidence rate (11.9%) of serious infections is similar to previous reports (Table 4) (4). There was no mortality associated with cyclophosphamide infusion in our cohort.

Opportunistic infections have been commonly reported in lupus and are a well-known cause of morbidity and mortality in SLE patients. Various risk factors associated with opportunistic infections are presence of multiple organ disease, lower WBC nadir, and a higher maximum steroid dose (1, 21). Different opportunistic infections in our study are summarized in Table 4. Overall 28.5% of all infections that occurred during the review period of our study were classified as opportunistic. We found Herpes Zoster (HZ) to be the most common opportunistic infection in our cohort (41.6%). Feldman et al also reported

Herpes Zoster as the most common viral infection in their lupus nephritis cohort (77 cases in 1825 patients which is 4.22%) in addition to 160 cases of HZ in lupus cohort of 5068 patients, without nephritis (3.2%) (4). Hellman et al reported disseminated Herpes Zoster infection in 1 patient in their cohort of 44 patients, who died from the infection (21).

Pryor et al reported a high rate (24% of all infections and half of infection related deaths) of opportunistic infections in their cohort (1). A high rate of fatal opportunistic infections have also been reported in literature (21). In our cohort there was only a single incidence of serious opportunistic infection with Pneumocystis jirovecii. This particular patient had recalcitrant lupus with renal and CNS involvement and had been on multiple immunosuppressive regimens in the past. All other opportunistic infections as listed in Table 4 were mucocutaneous infections.

Pneumocystis jirovecii has been reported to be associated with significant morbidity and mortality, but the exact incidence of PJP infection in SLE patients is not known (1, 9, 21). No specific guidelines exist regarding use of prophylactic antibiotic for PJP in lupus patients, especially when they are being treated with cyclophosphamide.

Similar to Gupta et al (9), we too found a very low incidence of PJP in cyclophosphamide treated lupus patients, which would not support routine antibiotic prophylaxis for PJP. In addition, lupus patients have been reported to have higher incidence of side effects, such as skin rash, lupus flares and aseptic meningitis from sulfonamides, which are commonly prescribed agents for PJP prophylaxis (9, 22–24). Unlike some previous reports (1, 9), our study did not show any significant association between incidence of infection and WBC count or absolute neutrophil count. However, similar to our findings, Yuhura et al also reported no correlation between WBC count or ANC and the incidence of infections (7). In their report the baseline WBC count and ANC were 4.1 K/ul and 2.5 K/ul in patients who subsequently developed infections and 3.6 K/ul and 2.1 K/ul respectively in patients who remained infection free throughout the course of therapy with steroid +/− other immunosuppressive agents. In our study the baseline WBC and ANC were 7.7± 4.2 K/μl and 6.0 ± 4 K/μl in patients who developed infections as compared to 8.1±3.2 K/μl and 6.3±3 K/μl in patients with no infections. The younger population and higher baseline WBC count and ANC of our cohort could be the probable reasons that no correlation was found between baseline white cell count and the rate of infection.

Our study has some limitations. It is a single center retrospective study with a modest sample size and relatively short follow up. We did not have the exact SLE disease activity indices calculated on our subjects, however, all of our patients had significantly high baseline disease activity, as almost of them had active lupus nephritis.

Our study does address a few important clinical concerns. As reported previously, we also found that the risk of infection increases proportionately to the cumulative dose of glucocorticoids. Hence, patients on high doses of glucocorticoids such as pulsed doses of intravenous methylprednisolone should be monitored closely for infection. Infection rates during the maintenance phase of cyclophosphamide therapy were higher compared to other immunosuppressive agents like azathioprine and mycophenolate mofetil, although

statistically not significant. Therefore attempts should be made to transition patients to immunosuppressive regimens other than cyclophosphamide during the maintenance phase to minimize infection risk. Our findings do not support prophylactic use of antibiotics for PJP in SLE patients on cyclophosphamide treatment. On the other hand, the most common opportunistic infection in our cohort was herpes zoster. We therefore suggest vaccinating with herpes zoster vaccine prior to starting intense immunosuppressive regimens when possible. Although we did not have information about previous vaccination in our subjects, based on their average age, we assume that none of them received zoster vaccine prior to initiating therapy with cyclophosphamide. Larger prospective studies with long-term follow-up are needed to confirm our results.

From this study, we can conclude that minimum possible dose of steroid should be used to reduce the risk of infection during induction phase of cyclophosphamide therapy. Maintenance phase treatment with azathioprine or mycophenolate mofetil is preferable to quarterly cyclophosphamide due to lower risk of infection. Before starting patients on monthly cyclophosphamide administration of Herpes Zoster vaccine may help reduce the incidence of this common opportunistic infection. Our data does not support routine use of PJP prophylaxis in SLE patients on cyclophosphamide therapy.

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References

1. Pryor BD, Bologna SG, Kahl LE. Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. Arthritis Rheum. 1996 Sep; 39(9):1475–82. [PubMed: 8814058]
2. Zandman-Goddard G, Shoenfeld Y. Infections and SLE. Autoimmunity. 2005 Nov; 38(7):473–85. [PubMed: 16373252]
3. Noel V, Lortholary O, Casassus P, Cohen P, Genereau T, Andre MH, et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. Ann Rheum Dis. 2001 Dec; 60(12):1141–4. [PubMed: 11709457]
4. Feldman CH, Hiraki LT, Winkelmayer WC, Marty FM, Franklin JM, Kim SC, et al. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheumatol. 2015 Jun; 67(6):1577–85. [PubMed: 25772621]
5. Zonana-Nacach A, Camargo-Coronel A, Yanez P, Sanchez L, Jimenez-Balderas FJ, Fraga A. Infections in outpatients with systemic lupus erythematosus: a prospective study. Lupus. 2001; 10(7):505–10. [PubMed: 11480850]
6. Gladman DD, Hussain F, Ibanez D, Urowitz MB. The nature and outcome of infection in systemic lupus erythematosus. Lupus. 2002; 11(4):234–9. [PubMed: 12043887]
7. Yuhara T, Takemura H, Akama T, Suzuki H, Yamane K, Kashiwagi H. Predicting infection in hospitalized patients with systemic lupus erythematosus. Intern Med. 1996 Aug; 35(8):629–36. [PubMed: 8894737]
8. Bosch X, Guilabert A, Pallares L, Cerveral R, Ramos-Casals M, Bove A, et al. Infections in systemic lupus erythematosus: a prospective and controlled study of 110 patients. Lupus. 2006; 15(9):584–9. [PubMed: 17080913]
9. Gupta D, Zachariah A, Roppelt H, Patel AM, Gruber BL. Prophylactic antibiotic usage for Pneumocystis jirovecii pneumonia in patients with systemic lupus erythematosus on

cyclophosphamide: a survey of US rheumatologists and the review of literature. J Clin Rheumatol. 2008 Oct; 14(5):267–72. [PubMed: 18679133]

10. Austin HA 3rd, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med. 1986 Mar 6; 314(10):614–9. [PubMed: 3511372]
11. de Groot K, Adu D, Savage CO, Euvas. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2001 Oct; 16(10):2018–27.
12. Schimmer, BPPK. The Pharmacological Basis of Therapeutics. 11. 2006.
13. Tektonidou MG, Wang Z, Dasgupta A, Ward MM. Burden of Serious Infections in Adults With Systemic Lupus Erythematosus: A National Population-Based Study, 1996–2011. Arthritis care & research. 2015 Aug; 67(8):1078–85. [PubMed: 25732901]
14. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis and rheumatism. 1982 Nov; 25(11):1271–7. [PubMed: 7138600]
15. Iliopoulos AG, Tsokos GC. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. Semin Arthritis Rheum. 1996 Apr; 25(5):318–36. [PubMed: 8778988]
16. Mok MY, Ip WK, Lau CS, Lo Y, Wong WH, Lau YL. Mannose-binding lectin and susceptibility to infection in Chinese patients with systemic lupus erythematosus. J Rheumatol. 2007 Jun; 34(6): 1270–6. [PubMed: 17552055]
17. Bultink IE, Hamann D, Seelen MA, Hart MH, Dijkmans BA, Daha MR, et al. Deficiency of functional mannose-binding lectin is not associated with infections in patients with systemic lupus erythematosus. Arthritis Res Ther. 2006; 8(6):R183. [PubMed: 17166254]
18. Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcon GS, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. Arthritis Rheum. 2013 Mar; 65(3):753–63. [PubMed: 23203603]
19. Fernandez M, Alarcon GS, Calvo-Alen J, Andrade R, McGwin G Jr, Vila LM, et al. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. Arthritis Rheum. 2007 May 15; 57(4):576–84. [PubMed: 17471524]
20. Martin F, Lauwerys B, Lefebvre C, Devogelaer JP, Houssiau FA. Side-effects of intravenous cyclophosphamide pulse therapy. Lupus. 1997; 6(3):254–7. [PubMed: 9104732]
21. Hellmann DB, Petri M, Whiting-O'Keefe Q. Fatal infections in systemic lupus erythematosus: the role of opportunistic organisms. Medicine (Baltimore). 1987 Sep; 66(5):341–8. [PubMed: 3626846]
22. Petri M, Allbritton J. Antibiotic allergy in systemic lupus erythematosus: a case-control study. J Rheumatol. 1992 Feb; 19(2):265–9. [PubMed: 1629825]
23. Escalante A, Stimmler MM. Trimethoprim-sulfamethoxasole induced meningitis in systemic lupus erythematosus. J Rheumatol. 1992 May; 19(5):800–2. [PubMed: 1613713]
24. Muller MP, Richardson DC, Walmsley SL. Trimethoprim-sulfamethoxazole induced aseptic meningitis in a renal transplant patient. Clin Nephrol. 2001 Jan; 55(1):80–4. [PubMed: 11200873]

Table 1

Demographics of SLE Patients treated with Cyclophosphamide

Variables	**N (%)**
Age (Years)	
n	31
Mean	37.9
STD	8.6
Ethnicity	
African American	8 (25.8%)
Asian	2 (6.4%)
Caucasian	6 (19.4%)
Hispanic	15 (48.4%)
Sex	
Female	27 (87.1%)
Male	4 (12.9%)

** Total 42 courses of cyclophosphamide in 31 patients; denominator used is 42.

Table 2

Incidence rate using Poisson-regression model patients treated with Cyclophosphamide.

Type of infection	Number of Infection onsets	Incidence rate (per100) person-Year	(95% CL) Per100 person-year
Over all Infection	42	67.42	(44.34 – 102.48)
UTI	8	24.31	(11.56 – 51.14)
Pos. Blood Cx	2	0.78	(0.01 – 74.95)
Bacterial PNA	2	1.32	(0.04 – 39.89)
Pneumocystis carinii PNA	1	1.29	(0.02 – 44.28)
Mucocutaneous Fungal Infection	3	5.62	(1.07 – 29.44)
URI	14	44.65	(24.82 – 80.35)
Mucocutaneous Bacterial Infection	1	2.41	(0.21 – 27.55)
Mucocutaneous Viral Infection	8	20.8	(8.54 – 50.65)
Viral Gastroenteritis	3	9.13	(2.67 – 31.21)

* Incidence rates are the number of events per 100 person-years.

The age and ANC adjusted Poisson-regression model were used to analyze the incidence rate and their 95% confidence intervals (95% Cls).

** Total 42 courses of cyclophosphamide in 31 patients; denominator used is 42.

Table 3

Comparing steroids on incidence of infection using time dependent multivariate analysis patients treated with Cyclophosphamide

Type of Infection	Number of Events	Cumulative Steroid (prednisone mg equivalent) Mean ± STD	*P* value
UTI			0.0240 **
Infection	*n=7*	13773.6 ± 7076.4	
No Infection	*n=35*	11432.1 ± 5433.6	
Pos. Blood Cx			0.0394 **
Infection	*n=2*	9010.8 ± 4967.4	
No Infection	*n=40*	12021.9 ± 5795.6	
Bacterial PNA			0.0247 **
Infection	*n=2*	17566.7 ± 11030.9	
No Infection		11546.7 ± 5417.2	
Pneumocystis carinii PNA			0.0150 **
Infection	*n=1*	23305.0 ± 0.0	
No Infection	*n=41*	11554.2 ± 5484.9	
Mucocutaneous Fungal Infection			0.0544
Infection	*n=3*	8418.3 ± 2392.4	
No Infection	*n=39*	12054.8 ± 5822.8	
URI			0.0168 **
Infection	*n=13*	13649.2 ± 7371.2	
No Infection	*n=29*	11039.2 ± 4749.2	
Mucocutaneous Bacterial Infection			0.0216 **
Infection	*n=1*	18360.0 ± 0.0	
No Infection	*n=41*	11678.9 ± 5710.9	
Mucocutaneous Viral Infection			0.0113 **
Infection	*n=8*	15292.3 ± 5935.1	
No Infection	*n=34*	10949.1 ± 5419.5	
Viral Gastroenteritis			0.0132 **
Infection	*n=3*	17584.4 ± 7008.6	
No Infection	*n=35*	11373.1 ± 5457.4	

** Total 42 courses of cyclophosphamide in 31 patients; denominator used is 42.

Table 4

Infection rates for opportunistic and serious infection patients treated with Cyclophosphamide

Type of infection	Number of Infection	Incidence rate (per100) person-Year	(95% CL) Per100 person-year
Opportunistic Infections	**12**	**39.648**	**(22.03 – 71.39)**
PJP	1	1.290	(0.037 – 44.280)
Mucosal candidiasis	2	4.624	(0.875 – 24.420)
Fungal skin infection	1	0.000	(0.000 – 0.000)
Shingles	5	9.107	(2.292 – 36.192)
Mucocutaneous HSV-1 infection	3	7.477	(1.945 – 28.752)
Serious Infections	**5**	**12.948**	**(4.42 – 39.94)**
Line sepsis	2	0.797	(0.009 – 73.224)
UTI	2	4.279	(0.694 – 28.388)
Serious PJP Infection	1	1.290	(0.037 – 44.280)

Incidence rates are the number of events per 100 person-years.

The age and ANC adjusted Poisson-regression model were used to analyze the incidence rate and their 95% confidence intervals (95% Cls).

** Total 42 courses of cyclophosphamide in 31 patients; denominator used is 42.

Table 5

Multivariate Analysis comparing Age, WBC and ANC associated with and without infections with Cyclophosphamide therapy

Factor	Infection (*n=24*)	No Infection (*n=18*)	*P* value	Hazard Ratio
Age (years)	34.5 ± 8.6	39.9 ±9.2	0.1158	1.050
WBC	7.7 ± 4.2	8.1 ± 3.2	0.5536	1.225
ANC	6.0 ± 4.0	6.3 ± 3.0	0.7035	0.874