

**Oral versus pulse intravenous
cyclophosphamide: a retrospective analysis of
adverse events in a high infectious diseases
burdened setting**

by
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Oral versus pulse intravenous cyclophosphamide: a retrospective analysis of adverse events in a high infectious diseases burdened setting

Abstract

Background

Cyclophosphamide (CPM) is still considered to be the first line treatment of many life-threatening autoimmune conditions. It does however carry significant risk for severe adverse events especially infections. At present CPM is either administered as a daily oral dose (DOC) or as an intravenous pulse (PIVC). There is uncertainty regarding the safety profiles of either regimen in high infectious diseases burdened settings.

Objective

To compare the frequency and nature of adverse events related to the use of DOC and PIVC in a high infectious diseases burdened setting.

Methods

A retrospective cohort of all patients treated from 1 January 2008 to 31 May 2013 with CPM for autoimmune diseases at Tygerberg Academic Hospital was studied comparing DOC and PIVC. Disease characteristics and occurrence of major adverse events of participants in each group was compared.

Results

A total of 134 (92 DOC and 42 PIVC) participants were included. Participants in the DOC group were treated for longer (174 vs. 101 days, $p < 0.01$) and with higher cumulative doses (17 276 mg vs. 3 327 mg $p < 0.01$). Risk for infection was similar in both groups although 6 vs. 0 ($p = 0.18$) participants in the DOC group died due to leukopaenic sepsis. Nadir leukocyte counts were also lower in the DOC group (median $3.8 \times 10^9/l$ vs. $5.3 \times 10^9/l$, $p = 0.02$).

Conclusion

Infection rates in both groups were similar. DOC was, however, associated with longer treatment duration, greater cumulative CPM doses and more severe leukopaenia. If resources allow and available literature provides support for efficacy, consideration should be given to greater use of PIVC.

Oral versus pulse intravenous cyclophosphamide: a retrospective analysis of adverse events in a high infectious diseases burdened setting

Autoimmune diseases affecting major organs carry significant morbidity and mortality. Immunosuppressive therapy with agents such as cyclophosphamide (CPM) significantly improves quality of life and survival in many patients suffering from such diseases.^[1,2]

Cyclophosphamide is still considered to be the first line treatment of many life-threatening autoimmune conditions due to its well-established therapeutic benefits. It does however carry significant risk for severe adverse events including cytopenias, infections, infertility and bladder toxicity. At present cyclophosphamide is either administered as a daily oral dose (DOC) or as an intravenous pulse at various intervals (PIVC). The optimal dosing route and regimen remains controversial, especially in the treatment of lupus nephritis.

Large head-to-head trials comparing DOC versus PIVC are lacking. Many opinions exist on the optimal dosing regimen based on small studies or indirect conclusions from larger groups. Overall it seems that DOC has the advantages of lower cost, simpler administration and better safety regarding the avoidance of high dose exposure should the drug be inappropriately administered.^[3,4] PIVC has the advantage of reduced incidence of short- and long-term adverse events and avoids the need for daily compliance with treatment. Data regarding the comparative efficacy of the two regimens are conflicting and briefly discussed below.

Total drug cost for treatment regimens are lower for DOC compared to PIVC. PIVC also requires allocated space, consumables and personnel to administer the infusion. Patients need to take time off work and have additional travel expenses, which all contribute to the overall cost of this regimen.^[3,4]

Although DOC is associated with an increase in long-term side-effects, adverse events due to inappropriate dosing are more easily managed. Examples include administration when a contraindication exists, mistaking sepsis for a flare of disease, or not adjusting doses for renal function. Reducing or omitting further oral doses under these circumstances reduces the toxicity, which cannot be done with PIVC.^[4]

Austin et al^[5] initially published data in 1986 supporting superior treatment outcomes and reduced side-effect profiles with the use of PIVC compared to DOC in patients with lupus nephritis. This led to PIVC becoming the standard treatment in lupus nephritis with fewer subsequent trials and recommendations that include DOC.^[3,6] This practice is now contested as subsequent trials^[4,7,8] and a recent Cochrane review^[9] showed no difference in outcomes or adverse events. An increased tendency to relapse has also been shown in patients with lupus nephritis treated with PIVC^[10]. DOC was associated with a higher frequency of adverse events in the same study. Another small trial showed a slightly bigger increase in serum albumin in patients with membranous nephropathy treated with PIVC in comparison to DOC.^[11]

Trials in ANCA-associated vasculitides have also suggested equal to increased ability of PIVC compared to DOC to induce remission, but with a greater tendency toward relapse.^[12-14] Episodes of leukopenia and infection were less frequent in ANCA-associated vasculitides treated with PIVC.^[14-17] Increased gonadal toxicity with oral cyclophosphamide has also been shown in patients

treated for ANCA-associated vasculitides.^[18] Decreased toxicity with PIVC is thought to be due to the lower cumulative cyclophosphamide doses used.

No difference in outcomes has been shown between the two regimens in treating pulmonary involvement in scleroderma.^[19]

The use of cyclophosphamide in a resource-constrained and infectious diseases burdened environment as encountered in our setting at Tygerberg Academic Hospital, has unique challenges and considerations regarding cost, efficacy and safety. Cost of treatment to hospitals, lack of allocated space and trained personnel to administer intravenous medication, patients' ability to travel to a tertiary setting to receive treatment, compliance with treatment and follow-up, access to health care in the event of drug toxicity and the overall increased infectious diseases burden associated with a low socio-economic environment are all factors to consider in choosing an appropriate treatment plan.

Of special concern in our setting is the matter of safety. The high frequency of infections such as tuberculosis and exposure to overpopulated and unhygienic environments can significantly endanger patients should they become severely immunosuppressed. To our knowledge no studies comparing DOC and PIVC are available addressing these safety issues when cyclophosphamide is used in such settings.

Clinicians at Tygerberg Academic Hospital make use of both intravenous pulse and oral regimens of cyclophosphamide for the treatment of autoimmune diseases. Treatment choice is largely based on the condition treated and the preference of the discipline involved in initiating treatment (e.g. lupus nephritis is generally treated with DOC by nephrologists whilst vasculitis and other severe systemic complications of connective tissue diseases are treated with PIVC by rheumatologists). As a general guideline DOC is initiated at a dose of 1.5 mg/kg and PIVC at 750 mg/m² and then titrated according to disease severity and leukocyte count. Serious adverse events related to therapy have been encountered with both regimens. The overall prevalence, differences in frequency and spectrum of adverse events between the two treatment regimens are however not known.

Methods

Our primary objective was to compare the frequency and nature of adverse events related to the use of oral and intravenous cyclophosphamide in patients with autoimmune diseases.

A retrospective cohort study was conducted at Tygerberg Academic Hospital to compare patients treated with DOC to those who were treated with PIVC. Data were extracted from hospital records of adult patients (>18 years) suffering from autoimmune diseases treated with cyclophosphamide. Pharmacy records were used to identify all patients starting treatment with cyclophosphamide from 1 January 2008 to 31 May 2013. Participants were included if they had been on treatment with cyclophosphamide for at least 1 month, unless adverse events due to cyclophosphamide occurred earlier, in which case the participant was also included. Patients who had received cyclophosphamide for indications other than autoimmune disease (e.g. chemotherapy, transplant recipient patients) were excluded. Patients on treatment for purely neurological diseases were also excluded due to the different dosing regimens and treatment duration used in these patients.

Data collected included demographics, co-morbid disease, mass, diagnosis and disease involvement, duration of disease prior to cyclophosphamide initiation, treatment prior to cyclophosphamide initiation, baseline leukocyte and neutrophil counts, indication for

cyclophosphamide therapy, initial dosage, subsequent adjustment to dosing and indication for changes, cumulative total drug dose, concurrent immunosuppressive drug use, the use of preventative therapy (isoniazide, co-trimoxazole, contraception and gonadal protection), documentation of counselling regarding contraception, occurrence of major side-effects and discontinuation due to drug toxicity. Data collected on side effects included cytopaenias, infections, bladder toxicity and infertility. Adverse events were reported and graded according to the Common Terminology Criteria for Adverse Events guidelines.^[20]

Data was captured in a Microsoft Excel spread sheet and analysed using Statistica® version 11. The two groups were compared with regards to patient characteristics, disease profiles and risk factors for developing major side-effects. Continuous variables were analysed using the Mann-Whitney U test, while categorical data were analysed using the Chi-squared and Fisher's exact tests. A significance level of 5% was used throughout.

The study was approved by the Health Research Ethics Committee of the University of Stellenbosch (protocol no. S13/07/121). Due to the retrospective nature of this study, the difficulty in tracing individual participants and the absence of risk to the participants, a waiver of informed consent was granted. Data were collected on standardised capture sheets using study codes assigned to each participant. Codes linking confidential data to the identity of the participants were kept separately and securely.

Results

Pharmacy records of patients receiving oral and intravenous cyclophosphamide from 1 January 2008 to 31 May 2013 were accessed. A total of 134 participants were included in the study, 92 in the DOC group and 42 in the PIVC group (Figure 1). A summary of excluded subjects is provided in Table 1.

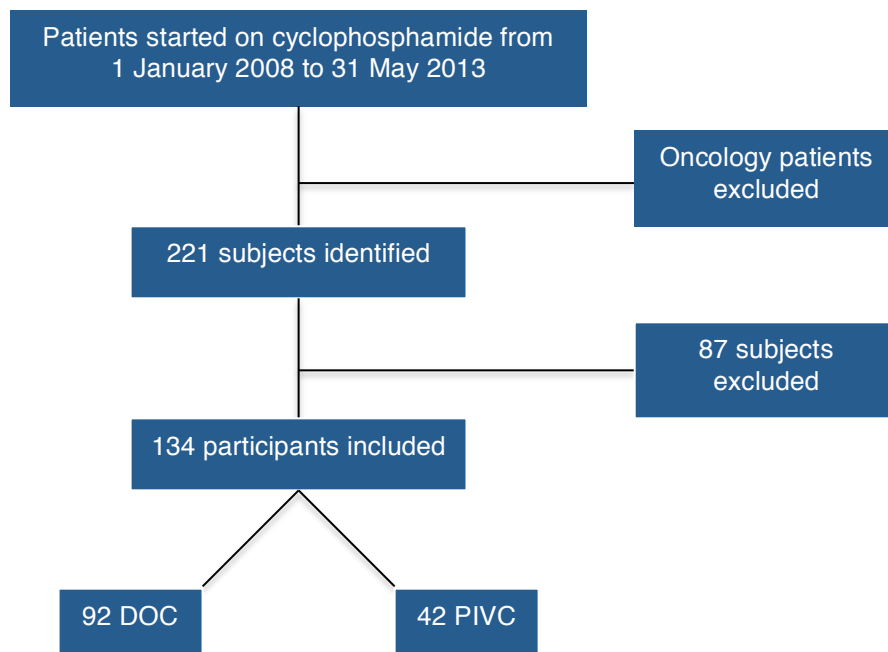


Figure 1. Selection of participants

Non-rheumatological disease	19	Lost to follow up	22
Neurological	8	Crescentic nephritis	8
Haematological	6	Lupus nephritis	7
Organ transplant recipient	3	SLE myocarditis	2
Sarcoidosis	1	Neurolyupus	2
Ophthalmological	1	FSGS	1
Pharmacy record error	1	SLE/Dermatomyositis overlap	1
Early death*	9	Membranous GN	1
Crescentic nephritis	5	Subject received both PIVC and DOC†	5
Lupus nephritis	2	Early withdrawal of treatment ‡	11
Polyangiitis with granulomatosis	1	Missing records	17
SLE/polymyositis overlap	1	Concomitant participation in drug trials	3

*Death within 1 month of treatment with cyclophosphamide unrelated to drug side-effects

†Changes for logistical reasons only

‡Less than 1 month of treatment

Participant characteristics are summarised in Tables 2a and 2b. There were no significant differences between the groups in terms of age, mass, co-morbid disease (HIV and diabetes mellitus) and leukocyte count at baseline. Overall our participants were young (mean 34 years) with a female predominance (74.6%), which was greater in the PIVC group (85.7 vs. 69.6%, $p=0.03$).

As expected, there was a marked difference in disease spectrum, both in terms of primary diagnosis and organ involvement, between the two groups (Figure 2).

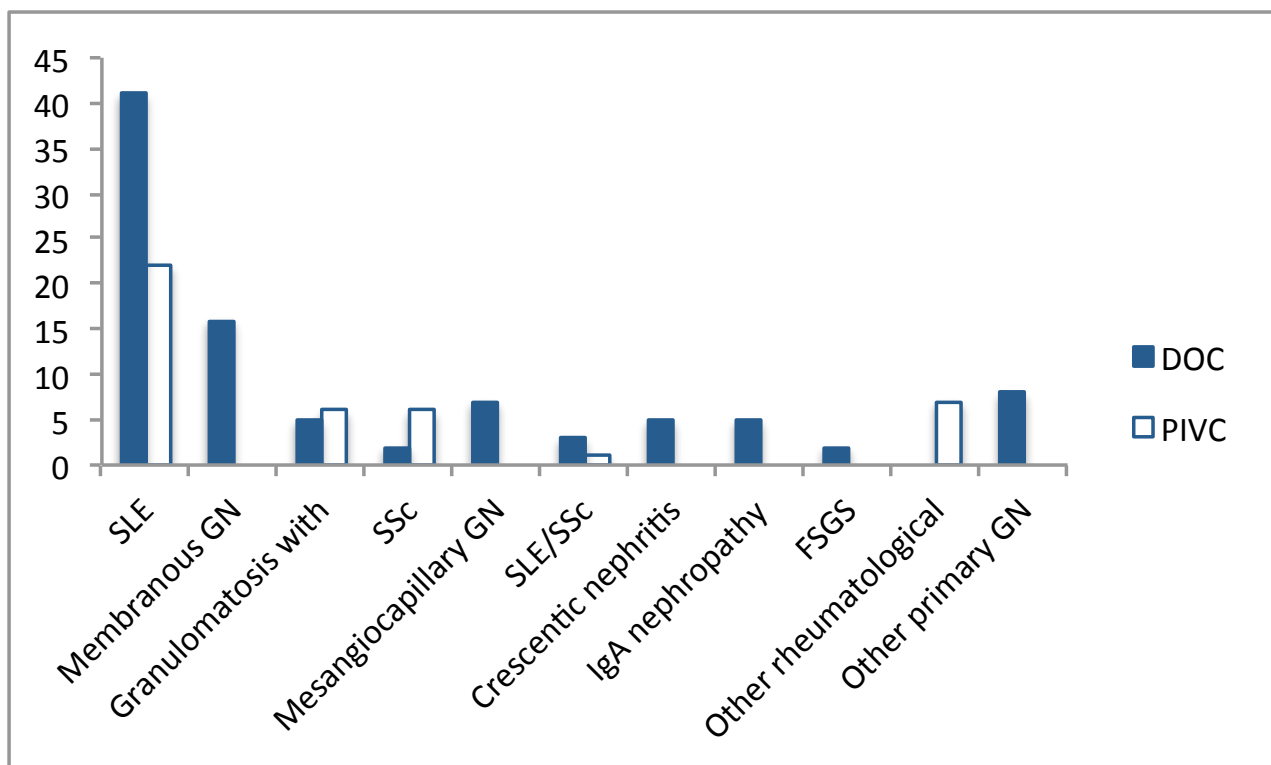


Figure 2. Primary disease (SLE – Systemic lupus erythematosus, GN – Glomerulonephritis, SSC – Systemic sclerosis, FSGS – Focal segmental glomerular sclerosis)

The indications for starting cyclophosphamide varied significantly (Figure 3). More patients were started on cyclophosphamide in the DOC group for nephrotic syndrome and class IV lupus nephritis, whilst in the PIVC group more frequent indications were neuropsychiatric lupus, cardiac involvement, interstitial lung disease and vasculitis. Overall the most frequent indication to initiate cyclophosphamide in the DOC group was class IV lupus nephritis (32.6%), followed by nephrotic syndrome (27.1%) and renal failure other than lupus nephritis (22.7%). The most frequent indication in the PIVC group was neuropsychiatric lupus (45.2%), followed by interstitial lung disease (28.6%) and cardiac involvement (28.6%).

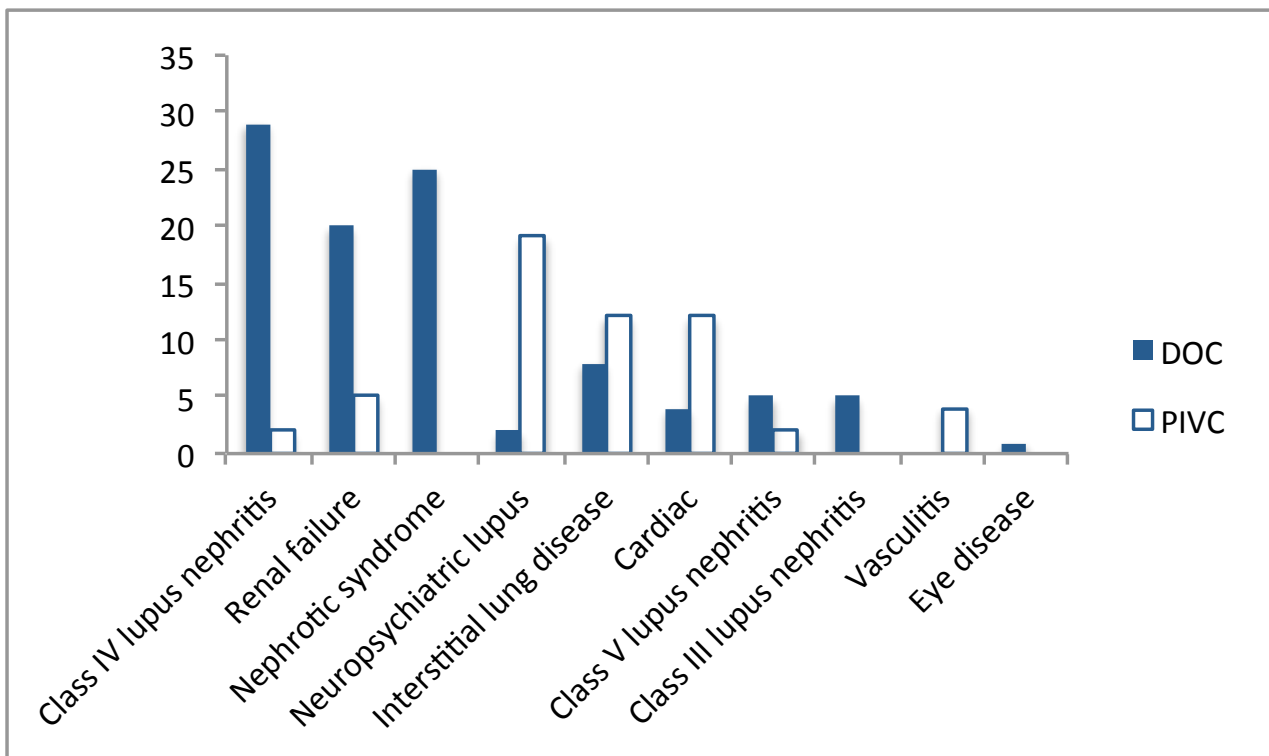


Figure 3. Indication to initiate cyclophosphamide

A total of 676 patient-months of treatment were observed. Treatment details are summarised in table 3. Participants in the PIVC group were treated for significantly shorter periods (mean 101 vs. 174 days, $p < 0.01$) and much lower mean cumulative doses (3 327 mg vs. 17 276 mg, $p < 0.01$).

	DOC (n=92)		PIVC (n=42)		All (n=134)		p-value
	No	%	No	%	No	%	
Sex:							
Male	28	30.4	6	14.3	34	25.4	0.03
Female	64	69.6	36	85.7	100	74.6	0.03
Co-morbid disease:							
Diabetes mellitus	9	9.8	6	14.3	15	11.2	0.44
HIV	5	5.4	0	0.0	5	3.7	0.12
Primary diagnosis:							
Systemic lupus erythematosus	41	44.6	22	52.4	63	47.0	0.45
Membranous GN	16	17.4	0	0.0	16	11.9	*
Granulomatosis with polyangiitis	5	5.4	6	14.3	11	8.2	*
Systemic sclerosis	2	2.2	6	14.3	8	6.0	*
Mesangiocapillary GN	7	7.6	0	0.0	7	5.2	*
SLE/Systemic sclerosis overlap	3	3.3	2	4.8	5	3.7	*
Crescentic nephritis	5	5.4	0	0.0	5	3.7	*
IgA nephropathy	5	5.4	0	0.0	5	3.7	*
Mesangioproliferative GN	3	3.3	0	0.0	3	2.2	*
Focal segmental glomerular sclerosis	2	2.2	0	0.0	2	1.5	*
Minimal change nephropathy	2	2.2	0	0.0	2	1.5	*
Rheumatoid arthritis	0	0.0	2	4.8	2	1.5	*
Good Pasture's	1	1.1	0	0.0	1	0.8	*
Eosinophilic granulomatosis with polyangiitis	0	0.0	1	2.4	1	0.8	*
SLE/Rheumatoid arthritis overlap	0	0.0	1	2.4	1	0.8	*
SLE/Dermatomyositis overlap	0	0.0	1	2.4	1	0.8	*
SLE/Polymyositis overlap	0	0.0	1	2.4	1	0.8	*
Vasculitis of unknown cause	0	0.0	1	2.4	1	0.8	*
Indication for CPM:							
Class IV lupus nephritis	29	31.5	2	4.8	31	23.1	<0.01
Renal failure other than lupus nephritis	20	21.7	5	11.9	25	18.7	0.18
Nephrotic syndrome	25	27.2	0	0.0	25	18.7	<0.01
Neuropsychiatric lupus	2	2.2	19	45.2	21	15.7	<0.01
Interstitial lung disease	8	8.7	12	28.6	20	14.9	<0.01
Cardiac	4	4.4	12	28.6	16	11.9	<0.01
Class V lupus nephritis	5	5.4	2	4.8	7	5.2	0.87
Class III lupus nephritis	5	5.4	0	0.0	5	3.7	0.12
Vasculitis	0	0.0	4	9.5	4	3.0	0.01
Eye disease (granulomatosis)	1	1.1	0	0.0	1	0.8	0.50
Duration of disease prior to CPM initiation:							
0 to 3 months	51	55.4	19	45.2	70	52.2	0.04
3 months to 12 months	16	17.4	3	7.1	19	14.2	0.04
>12 months	25	27.2	20	47.6	45	33.6	0.04

* Due to low observation frequency, p-values were not determined

	DOC (n=92)		PIVC (n=42)		All (n=134)		
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	34.2	13.3	33.4	11.4	34.0	12.7	0.95
Mass (kg)	70.5	18.0	67.0	19.5	69.5	18.4	0.37
Diagnosis to initiation of CPM (days)	17.4	42.2	36.2	48.1	23.3	44.8	0.04
Leukocyte count at baseline (x10 ⁹ /l)	9.2	4.3	11.4	11.9	9.9	7.7	0.72
Initiation dose (mg/kg)	1.6	0.4	10.3	4.4			

	DOC (n=92)		PIVC (n=42)		All (n=134)		
	Mean	SD	Mean	SD	Mean	SD	
Treatment duration (days)	174.0	127.9	100.9	61.1	151.4	116.3	<0.01
Cumulative dose (mg)	17275.5	12210.7	3327.4	2489.3	12903.7	12087.5	<0.01
Cumulative dose (mg/kg)	262.6	205.5	46.7	32.5	193.9	198.0	<0.01

The most frequent indication to stop therapy was the successful completion of induction therapy. This was significantly more frequent in the PIVC group, whilst cessation of treatment due to treatment failure was more frequent in the DOC group (Table 4). Loss to follow up, infection and leukopaenia were also frequent reasons for discontinuation of treatment in both groups. There were 9 patients remaining on cyclophosphamide at the time that the study concluded whilst one patient had requested to be transferred to a private physician for further management.

	DOC		PIVC		All		p-value
	No	%	No	%	No	%	
Completion of induction	36	39.1	25	59.5	61	45.5	0.02
Treatment failure	15	16.3	1	2.4	16	11.9	0.02
Leukopaenia	13	14.1	3	7.1	16	11.9	0.25
Infection	10	10.9	5	11.9	15	11.1	0.86
Lost to follow-up	9	9.8	5	11.9	14	10.5	0.71
Not stopped	8	9.0	1	2.4	9	6.7	0.18
Transferred	0	0.0	1	2.4	1	0.8	0.14

Prescription of prophylactic antimicrobials was consistently done with 91.8% and 94.8% of all participants receiving isoniazide and co-trimoxazole respectively. There was no difference between the groups. Contraception was poorly documented. Only 43.3% of the participants who required contraception were documented to have been prescribed contraception. All patients received concomitant prednisone.

A total of 64 episodes of infection were documented, of which 37 were considered serious and required hospitalisation. The profile of infections is illustrated in Figure 4. There were no statistically significant differences in the number of infections between the DOC and PIVC groups (42 vs. 22, p=0.53) or hospitalisations (25 vs. 12, p=0.12). The most frequent infection was urinary tract infection followed by pneumonia. The most common opportunistic infection was herpes zoster in the PIVC group and CMV pneumonitis in the DOC group. There were no new cases of tuberculosis diagnosed in either group. Infections occurred early during therapy (mean 73.2 days) in both groups with no significant difference between the groups (74.2 vs. 71.9 days, p=0.72), but

occurred at a higher cumulative dose at the time of infection in the DOC group (7 964 mg vs. 2 126 mg, $p < 0.01$).

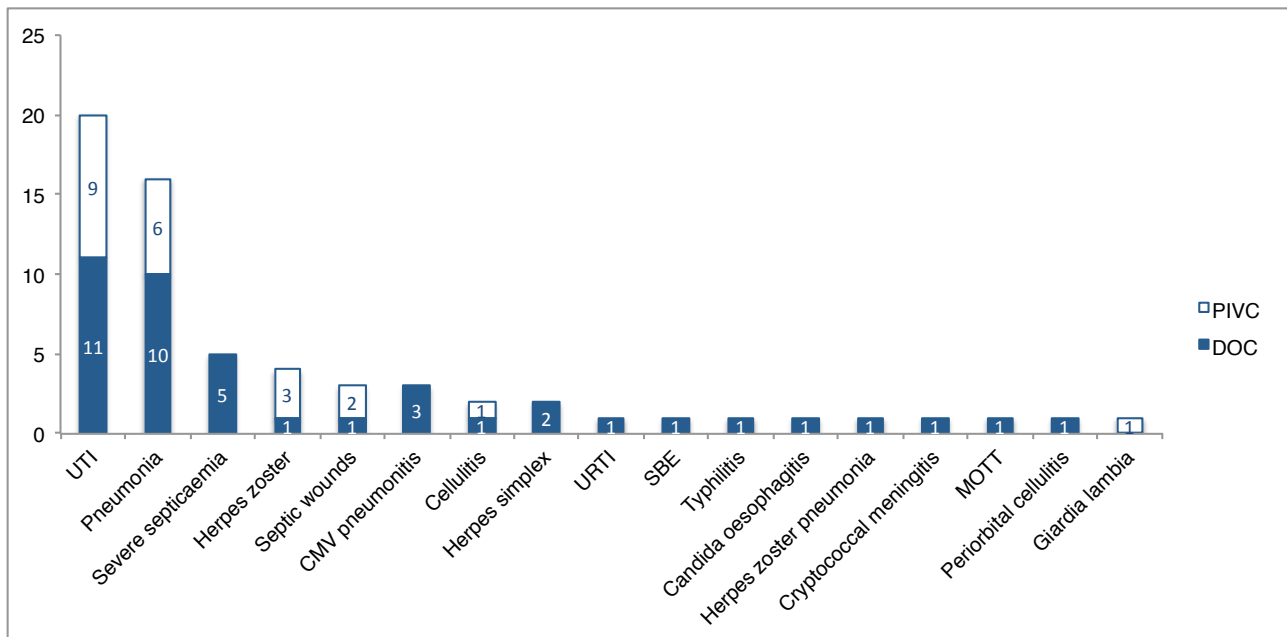


Figure 4. Infections during cyclophosphamide treatment (UTI – Urinary tract infection, URTI – Upper respiratory tract infection, SBE – Subacute bacterial endocarditis, MOTT – Mycobacterium other than tuberculosis)

Overall, 61.2% of all participants had one or more treatment related adverse events (infection or leukopaenia), 59.8% of the DOC group and 64.3% of the PIVC group ($p = 0.70$). The relative risk for developing an adverse event in the DOC group versus the PIVC group was 0.93 (0.70-1.23 95% CI).

Overall, 38.1% of participants developed one or more infections during cyclophosphamide therapy. In the DOC group 35.9% of participants developed infections as compared to 42.9% in the PIVC group ($p = 0.45$). The overall risk for a participant to have one or more hospitalisations due to serious infection was 24.6%. This was slightly higher in the DOC group (26.1 vs. 21.4% $p = 0.67$) (Table 5).

	DOC		PIVC		All		p-value
	Number	%	Number	%	Number	%	
Any adverse event	55	59.8	27	64.3	82	61.2	0.70
Leukopaenia	47	51.1	14	33.3	61	45.5	0.06
Infection	33	35.9	18	42.9	51	38.1	0.45
Hospitalisation	24	26.1	9	21.4	33	24.6	0.67

In the DOC group 6 participants (6.5%) died due to leukopaenia related sepsis. There were no treatment related deaths recorded in the PIVC group; this difference was not statistically significant ($p = 0.18$). Treatment related deaths are summarised in Table 6.

Table 6. Leukopaenia related deaths

Age & Sex	Diagnosis	Duration of treatment	Lowest leukocyte count ($\times 10^9/l$)	Cause of death
41 yr F	Mesangiocapillary GN with crescents	59 days	0.79	Varicella zoster pneumonia
21 yr F	SLE with class IV nephritis and myocarditis	21 days	3.31	Severe pneumonia and renal failure*
23 yr F	SLE with class IV nephritis	69 days	0.54	CMV pneumonitis
51 yr F	Crescentic nephritis	25 days	0.65	Neutropaenic sepsis (unknown source)
37 yr F	SLE with class IV nephritis and myocarditis	31 days	1.58	CMV pneumonitis
30 yr F	SLE with class IV nephritis	49 days	0.34	Overwhelming acinetobacter baumannii sepsis‡

*Subject had renal failure which significantly contributed to

‡ Leukocyte count at baseline 2.66

The frequency of monitoring leukocyte counts was very variable and we therefore determined the proportion of participants who became leukopaenic at any time during therapy, rather than the leukopaenic event rate. Neutrophil counts were infrequently done. The lowest recorded leukocyte counts were significantly lower in the DOC group with a median of $3.8 \times 10^9/l$ vs. $5.3 \times 10^9/l$ ($p=0.02$). See Figure 5. Leukopaenia also occurred later in the DOC versus PIVC groups (99 vs. 76 days, $p=0.04$) and at higher cumulative doses (mean 3 542 vs. 1 929 mg, $p<0.01$).

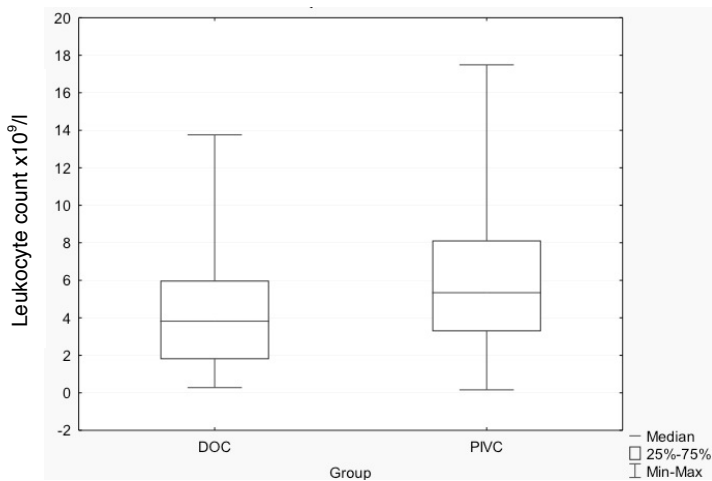


Figure 5. Distribution of lowest leukocyte count during the course of treatment

Comparing the DOC and PIVC groups, 51.1 vs. 33.3% ($p=0.06$) of participants developed leukopaenia during treatment. More participants developed severe leukopaenia in the DOC group ($p=0.26$) (Table 7). The mean duration of leukopaenia before the cyclophosphamide dose was adjusted or stopped, was 5 days, with a maximum delay of up to 28 days. A delay in stopping cyclophosphamide was however not contributory to any of the leukopaenic related deaths.

Severity class (x10 ⁹ /l)	DOC (n=47)		PIVC (n=14)		All (n=61)	
	No	%	No	%	No	%
1 (3.01-4.00)	14	29.8	6	42.9	20	32.8
2 (2.01-3.00)	8	17	5	35.7	13	21.3
3 (1.01-2.00)	11	23.4	2	14.3	13	21.3
4 (<1.00)	8	17	1	7.1	9	14.8
5 Death	6	12.8	0	0	6	9.8

*No statistical significance

Discussion

Adverse events due to the use of cyclophosphamide were frequent in both groups. This emphasises that cyclophosphamide is a potent cytotoxic drug that should be prescribed with caution and with careful follow-up and monitoring. To our knowledge this is the first study from a developing country comparing DOC and PIVC. Other studies have reported leukopaenic episodes in 17-26% of PIVC and 19-45% of DOC participants^[7,14,16] and infection in 10-39% of PIVC and 14-57% of DOC participants.^[5,7,10,14] Similar infection rates were observed in our study (DOC 36% vs. PIVC 43%), while leukopaenia was more frequent (DOC 51% vs. PIVC 33%). Due to the heterogeneous nature of our participants, any direct comparison is difficult.

In our setting it appears that PIVC may be safer than DOC. Six treatment related deaths occurred in the DOC group compared to none in the PIVC group, although this difference was not statistically significant. DOC was also associated with more frequent and more severe leukopaenia, and with a non-significant increase in hospitalisations suggesting more serious infections, while PIVC was associated with a non-significant increased frequency of all infections.

The participants in the DOC group were treated for a significantly longer time and might therefore be more likely to experience adverse events. However most events in our study, as in other studies^[16], occurred early in the course of treatment.

It is important to appreciate that in our study the condition treated determined the route of cyclophosphamide administration and by default also selected for differences in management. Different teams of clinicians and differences in follow-up and monitoring may therefore have affected the results.

The high cumulative doses used in the DOC group could increase efficacy but is the likely explanation for the increased risk for leukopaenia associated with DOC. Another factor was that PIVC was only administered if an acceptable leukocyte count was present on the day of each pulse. With DOC a leukocyte count before every dose is not feasible. There was some variability in the frequency of leukocyte counts done in the DOC group. Counts were not always available at the time of follow-up and sometimes only reacted upon at the next visit. PIVC is perceived as high dose intravenous chemotherapy and instinctively enforces caution and meticulous follow-up. DOC may be perceived as less potent and not elicit the same careful follow-up by those not familiar with its serious side-effect profile.

This study has identified the need to critically evaluate the current practice of cyclophosphamide administration at our institution. Most drug-attributable deaths and infections occurred early in the course of treatment; it is therefore strongly suggested that leukocyte counts be monitored more frequently early on after initiation of cyclophosphamide and that same-day leukocyte counts be available at all follow-up visits. The paucity of neutrophil counts was disappointing. Neutrophil counts should also be requested routinely, as severe neutropaenia may be masked in mild leukopaenia if other cell lines are not affected.

An unexpected finding was that no new episodes of tuberculosis were documented in any participant. This suggests that current screening protocols for active tuberculosis prior to initiation of cyclophosphamide and the regular use of isoniazide prophylaxis are effective. CMV pneumonitis was a significant opportunistic infection in the DOC group and a cause of leukopaenia associated death. Patients on cyclophosphamide who present with leukopaenic sepsis should be screened and treated early (if not empirically) for CMV infection.

Alarming, almost 10% of participants initiated on cyclophosphamide were lost to follow up immediately after discharge from hospital. Another 10% of participants were also lost to follow-up later in the study. Considering the poor prognosis of the underlying conditions if left untreated, it can be speculated that many of these patients died due to the disease. Adverse events due to cyclophosphamide may however be a contributing factor. This emphasises the need for excellent recordkeeping and tracking of patients on cyclophosphamide. This should prompt clinic staff to contact patients should follow-up visits be missed.

If resources allow, consideration should be given to the greater use of PIVC where this is supported by current literature. This would be especially useful in patients where compliance with daily medication is in doubt. Due to the differences in conditions treated, we did not evaluate the efficacy of treatment, which might be the decisive factor in choosing between DOC and PIVC. As pointed out earlier, in many conditions compelling evidence is lacking to clearly advocate the use of either approach with regards to efficacy.

Limitations

This study relied on the completeness and accuracy of our hospital's pharmacy database to identify all patients receiving cyclophosphamide during the study period. The study was done retrospectively with data extracted from patient records. A heterogeneous group of conditions were included and allocation to PIVC and DOC was not random, but was determined by the disease process and the preference of the clinicians involved (rheumatology versus nephrology). The primary disease process as well as differences in practices by clinicians could influence treatment outcomes and risk of adverse events. Long term complications (e.g. bladder toxicity, infertility) were also not studied.

Conclusion

This study has provided new data on adverse events due to cyclophosphamide in a developing world setting with a very high burden of infectious diseases. We found that a greater proportion of participants receiving DOC developed leukopaenia, which was also more severe. Participants in the DOC group were treated with higher cumulative doses over longer periods, which may explain the increased occurrence of leukopaenia. There was however no significant difference in the proportions of participants who developed infections or required hospitalisation as a consequence

thereof. Six participants in the DOC group compared to zero in the PIVC group died due to an event related to cyclophosphamide treatment, although this was not statistically significant.

Local randomised control trials are needed to compare PIVC and DOC where follow-up is standardised and where homogenous groups of conditions are compared. Not only will this provide more data with regards to safety, but also much needed data on differences in treatment outcomes.

Acknowledgements

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