Cyclophosphamide for large-vessel vasculitis: assessment of response by PET/CT

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ABSTRACT

Introduction. *Glucocorticosteroids (GC) are the standard treatment for large-vessel vasculitis, but some patients are refractory. Cyclophosphamide (CYC) has been shown to be effective in autoimmune diseases.*

Methods. *The study consisted of a retrospective analysis of 10 patients with active large-vessel arteritis who received pulse CYC after failure of GC or because of organ threatening stenosis. CYC pulse therapy was started with a dose of 750mg/m² body surface every 3 weeks and increased if necessary. Clinical response was assessed by the Birmingham Vasculitis Activity Score (BVAS), the C-reactive protein and the erythrocyte sedimentation rate (ESR). PET/CT was performed at baseline and during treatment to determine disease activity.*

Results. *The median BVAS at the time of the initial PET/CT was 6.5 (5–13). The median ESR was 42mm/h (6–94mm/h), and the medium CRP was 4.6mg/dl (0.18–11.8mg/dl). All but one patient experienced a complete clinical remission during CYC treatment after a median of 10 cycles. PET/CT confirmed the efficacy of the treatment by normalisation of FDG uptake during therapy. One patient with persisting inflammation was lost to follow-up. One patient experienced a relapse after 21 months. The remaining 8 patients are still in remission with low-dose GC and a maintenance therapy (azathioprine, methotrexate or mycophenolate) after a median follow-up of 45 months.*

Conclusion. *Pulse cyclophosphamide is effective in patients with large-vessel vasculitis resistant to glucocorticosteroids. The high rate of sustained response in our patients suggests that treatment decisions based on clinical parameters combined with PET/CT may have a beneficial effect on the clinical outcome.*

Introduction

Vasculitides of large vessels include Takayasu arteritis (TA) and giant cell arteritis (GCA), two related inflammatory diseases affecting primarily the aorta and its branches. Large-vessel vasculitis may lead to luminal changes such as stenosis, aneurysm formation, and subsequently to ischaemia of organs or limbs (1-5).

Standard therapy consists of glucocorticosteroids (GC) usually at a dosage of 1mg/kg bodyweight (6, 7). Steroid sparing medication with methotrexate MTX and azathioprine (AZA) proved only moderately effective in GCA (8, 9). Since relapse rates are high after initial GC treatment (6-9), a more intensive immunosuppression may be required. Cyclophosphamide (CYC) is a commonly used agent, especially for the treatment of antineutrophile cytoplasmic antibody (ANCA) associated vasculitis. No controlled trials on CYC are available for TA or GCA, only-case series (10).

18-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is a hybrid imaging modality which uses the glucose analogon 18-FDG to evaluate glucose metabolism. Several authors have described the beneficial use of FDG-PET to diagnose the extent and activity of inflammation in arterial walls in large-vessel vasculitis (11-15). Morphologic information at the same localisation may be assessed by CT in one session.

Materials and methods

A retrospective analysis was conducted on all patients treated with CYC for large-vessel vasculitis, and at least two PET/CT examinations were done between 10/2004 and 04/2008. The indication for CYC therapy was severe, and active vasculitis not responsive to GC and/or immunosuppressives or with organ/limb threatening stenosis.

The dosage of GC and the tapering intervals were determined by the treating physician. CYC (750mg/m body surface) was given every 3 weeks in all patients and increased to 900mg/m body surface or a daily oral treatment of 100mg/day in case of no improvement. 2-mercaptoethanesulfonic acid was given with every cycle. Patients received trimethoprim/sulfamethoxazole for pneumocystis jirovecii pneumonia (PJP) prophylaxis. In all patients AZA served as maintenance therapy after the CYC pulses, and 3 patients switched to MTX (n=2) or MMF (n=1) due to liver toxicity.

PET/CT scan

PET/CT examinations were performed using a whole-body PET/CT scanner (Biograph 16, Siemens Medical Solutions, USA) with a 3D lutetium oxyorthosilicate (LSO) PET detector and a 16-row multi-slice-CT (MSCT). After patient agreement and overnight fasting, FDG was administered intravenously, and image acquisition was started one hour later. CT was performed prior to the FDG-PET scan. CT data were used for attenuation correction, anatomical localisation and evaluation of luminal changes.

Assessment of disease activity

Clinical and serological assessment was performed at every CYC cycle. After discontinuation of CYC, the patients were seen on a regular basis every 3–4 months. PET/CT was performed before and during the cyclophosphamide therapy, usually after the 6th cycle and during the further course in order to identify a relapse depending on the clinical and laboratory assessment. According to Meller *et al*. (12) FDG uptake in arterial walls was evaluated through application of a visual vessel-to-liver score, which was defined as follows: Wall uptake is not visible (grade 0); visible but lower (grade 1); similar (grade 2) or higher than liver uptake (grade 3). Grades 2 and 3 were considered pathological. This score was evaluated at 7 regions: ascending aorta with aortic arch, descending thoracic aorta, abdominal aorta, common carotid artery, subclavian with axillary artery, common iliac artery, and superficial femoral artery. At each PET/CT examination, a summarising response-score was assessed as follows:

grade 3: Increase of FDG uptake in at least one region

grade 2: Decrease of FDG uptake in some regions, similar uptake in the other regions

grade 1: Decrease of uptake in all pathologic regions

grade 0: No more pathologic FDG uptake in all regions (Meller score <2)

ESR (normal range: 0–15mm/h) and C-reactive protein (CRP, normal range 0–0.5mg/dl) served as serological markers. The Birmingham Vasculitis Activity Index (BVAS) was used for clinical response assessment. All patients gave written informed consent for the PET/CT examination and for the CYC therapy.

Results

Demographic data are presented in Table I. Ten patients (2 men, 8 women) were included. The median age was 61.5 years (range 41–65), and the median disease duration was 7 months (range 0–36 months). Arterial stenoses were present in 8 patients. One patient (no. 10) showed ectasia of the abdominal aorta. The predominant clinical manifestations were arm/leg claudication (50%), abdominal pain (40%), weight loss (40%), pulselessness (20%), and polymyalgia (20%). Additional immunosuppressive treatment was given in 6 patients before relapse occurred. The median initial $BVAS_{new/worse}$ was 6.5 (range: 5–13). ESR was 42mm (6–94mm), and the CRP was 4.6mg/dl (0.18–11.8mg/dl), respectively. All patients had pathological FDG uptake at baseline PET/CT examination with a maximum score grade 3 in 8 and grade 2 in 2 patients.

The first control PET/CT was performed after the 3rd/4th cycle in 3 patients, after the 6th cycle in 6 patients, and after the 7th cycle in 1 patient. A decrease in FDG uptake with a response-score ≤2 was found in all patients, and 1 patient no longer showed a pathological FDG uptake.

Table II summarises the follow-up examinations and the therapeutic decisions after acquisition of all diagnostic parameters, with 9 out of 10 patients achieving complete remission according to the BVAS and serological markers, as well as documented in the PET/CT by normalised FDG uptake. The cumulative dosage of CYC required for induction of remission varied between 6 and 20.5gr. Prednisolone therapy in parallel to the CYC treatment was very heterogeneous. Two patients received a GC pulse with 1000mg for 3 days followed by a reduction to 1mg/kg bodyweight, 5 patients were treated with 1mg/kg bodyweight, and 3 with low dose prednisolone (<10mg), but therapy could be tapered in all patients to a dose ≤7.5mg. The effect of CYC based on clinical and serological parameters was sustained in 8 patients with a median follow-up of 45 months (21–52 months).

Patient no. 3 had persistent disease activity. Unfortunately she was lost to follow-up. Patient no. 10 experienced a relapse after 21 months with back pain, weight loss, elevated serological markers and a localised pathological FDG uptake of her abdominal aorta (Fig. 2). She was successfully treated with an elevation of the prednisolone and MTX dosage. Patient no. 4 had severe stenosis of her abdominal arteries with ongoing weight loss and abdominal pain, although the vasculitis was effectively controlled according to measurable parameters. She benefited from an aorto-mesenterial bypass after 11 cycles of CYC.

Adverse events

Six serious adverse events occurred. One patient experienced sepsis with streptococcus mitis after the 2nd cycle and varizella zoster infection. Patient no. 5 had a reactivation of PJP several months after her last CYC cycle despite prophylaxis. She had had a PJP before initiation of CYC. Both manifestations were successfully treated by high dose trimethoprim/sulfamethoxazole. Because of recurrent urinary tract infections, she had to be hospitalised several times for i.v. antibiotics, and CYC was reduced to 500mg/m.

Table I. Patients demographics, pretreatment and affected vessels.

No	Age (years)	Diagnosis	Disease duration (months)	Follow-up (months)	Symptoms	Pre-treatment	CYC cycles	Maintenance therapy	Affected arteries in PET	Stenosis /Ectasia seen in CT scan
1.	45	TA	0	45	pulselessness, arm claudication, bruits sc artery	–	12	AZA	AA, DA, SA, CA	SA
2.	50	TA	36	37	abdominal pain, weight loss, bruit aorta	GC, AZA	8	MMF	AA, AB, IA	–
3.	41	TA	0	10; lost to follow-up	abdominal pain, diarrhea, bruit aorta, weight loss, malaise	–	9	AZA, lost	AA, DA, AB, IA	COT
4.	54	TA	10	39	abdominal pain, weight loss	GC, MTX	11	AZA	AB	COT, RA, MA
5.	65	GCA	16	44	headache, jaw claudication, positive histology of temporal artery	GC, MTX	12	AZA	AA, DA, AB, SA, IA,FA	SC
6.	64	GCA	4	46	abdominal pain, leg claudication, cutaneous ulcers	GC, MTX	7	AZA	AA, DA, AB, SA	COT, MA, RA, FA
7.	61	GCA	36	38	polymyalgia, arm/leg claudication, pulselessness	GC, AZA	13	MTX	AA, DA, AB, CA, IA; FA	AX
8.	65	GCA	4	40	arm claudication, malaise, pos. histology of temporal artery	GC	12	AZA	AA, DA, AB, SA, CA, IA, FA	SC, AX
9.	62	GCA	2	27	cutaneous ulcers, fever, weight loss	GC	6	AZA	AA, DA,BA, SA	–
10	62	GCA	12	16	severe back pain, polymyalgia	GC, MTX	9	AZA, MTX	AA, DA, AB, IA	Ectasia AB

TA: Takayasu arteritis; GCA: giant cell arteritis; GC: glucocorticosteroids; MTX: methotrexate; AZA: azathioprine; MMF: mycophenolate mofetil; CYC: cyclophosphamide; AA: ascending aorta, DA: descending aorta, AB: abdominal aorta, SA: subclavian + axillary artery; SC: subclavian artery; IA: iliac artery; FA: femoral artery, RA: renal artery; AX: axillary artery; CA: carotid artery; MA: mesenterial artery; COT: coeliac trunk.

Discussion

This is the first study to show the efficacy of CYC for large-vessel vasculitis documented and guided by clinical routine diagnostics and repeated FDG-PET/CT. With this rather aggressive approach a long lasting response could be achieved in 8 patients. After a median follow-up of 45 months only one minor relapse occurred, one patient was lost to follow-up.

Only a few studies included FDG PET/CT in order to assess disease activity during therapy. Arnaud *et al*. (14) found a lack of correlation between FDG uptake and biologic or radiological disease activity and a trend towards association between uptake and clinical activity in 28 patients with TA. Meller *et al*. (12) suggest that FDG-PET may be more reliable than magnetic resonance imaging (MRI) in monitoring disease activity during immunosuppressive therapy. Blockmans *et al*. (15) found a decrease of FDG uptake in GCA only during the first 3 months of therapy, suggesting that vascular remodelling may also convey metabolic activity. The definite role for PET in assessing disease activity – especially during treatment – remains to be defined. All but one of our patients showed normalisation of vascular uptake during the treatment period. In our patients no discrepancy between FDG uptake and clinical and serological response was observed, which demonstrates the need to clarify the benefits of imaging methods and clinical parameters. Since ESR or CRP alone is not considered to be a reliable parameter to assess disease activity in large-vessel vasculitis, especially during immunosuppressive therapy, we decided to include FDG-PET/CT as an imaging modality. Our experience in clinical practice suggests that a whole body scan with PET/CT in addition to

Table II. PET/CT follow-up examinations with corresponding therapy decisions, BVAS and laboratory findings.

No.	PET/CT Examination	GC (mg)	Therapy changes	CRP (mg/dl)	ESR (mm)	Meller score (baseline) / Response-score (follow-up)	BVAS New/worse
1.	**baseline**	**0**	**GC 1 mg/kg; CYC 750mg/m²**	**6.12**	**61**	**3**	**7**
	6 cycles	15	CYC 900mg/m²	5.47	57	2	3
	12 cycles	7.5	AZA	2.32	39	2	0
	24 month follow-up	7.5	AZA	1.23	18	0	0
2.	**baseline**	**7.5**	**CYC 750mg/m²**	**0.3**	**22**	**3**	**7**
	6 cycles	7.5	CYC 750mg/m²	0.6	21	2	0
	8 cycles	7.5	AZA	0.23	18	2	0
	20-month follow-up	5	MMF	0.48	13	2	0
	30-month follow-up	5	MMF	0.01	13	0	0
3.	**baseline**	**0**	**GC 3x1g;CYC 750mg/m²**	**8.15**	**88**	**3**	**13**
	6 cycles	30	CYC 900mg/m²	3.37	63	2	3
	lost	lost	lost	lost	lost	lost	lost
4.	**baseline**	**0**	**GC 1mg/kg; CYC 750mg/m²**	**0.43**	**11**	**2**	**5**
	6 cycles	7.5	CYC 750mg/m²	1.67	33	2	5
	11 cycles	5	AZA	1.15	32	2	5
	12-month follow-up	5	AZA	1.37	49	0	0
5.	**baseline**	**10**	**CYC 750mg/m²**	**3.08**	**8**	**3**	**6**
	4. cycles	7.5	CYC 750mg/m²	1.05	6	3	6
	9 cycles	5	CYC 500mg/m²	0.43	16	2	0
	12 cycles	5	AZA	0.54	8	2	0
	15-month follow-up	5	AZA	0.19	11	0	0
6.	**baseline**	**5**	**GC 1mg/kg; CYC 750mg/m²**	**1.46**	**6**	**2**	**7**
	7. cycle/ p.o.	40	CYC 150mg p.o.	0.14	4	2	2
	10-month follow-up	7.5	CYC p.o.	0.16	5	0	0
7.	**baseline**	**7.5**	**GC 1mg/kg; CYC 750mg/m²**	**8.55**	**94**	**3**	**6**
	3 cycles	70	CYC 900mg/m²	5.68	41	2	2
	9 cycles	7.5	CYC 900 mg/m²	1.21	29	2	0
	12 cycles	7.5	MTX	3.37	41	0	0
8.	baseline	7.5	GC 3x1g; CYC 750mg/m²	1.27	23	3	6
	6 cycles	7.5	CYC 750mg/m²	0.36	13	2	0
	12 cycles	7.5	AZA	0.27	14	0	0
9.	**baseline**	**7.5**	**GC 1mg/kg; CYC 750mg/m²**	**8.75**	**75**	**3**	**13**
	6 cycles	7.5	AZA	0.11	11	0	0
10.	**baseline**	**100**	**GC 1mg/kg; CYC 750mg/m²**	**11.8**	**75**	**3**	**6**
	3 cycles	12.5	CYC 750mg/m²	1.1	18	2	0
	8 cycles	7.5	AZA/MTX	1.4	18	0	0
	21-month follow-up	5	GC 3x100mg; MTX 25mg	4.0	35	3 (relapse)	3

The FDG uptake was assessed according to Meller *et al*. (14) at baseline and with a summarised response score to consider all 7 measured arterial regions. Patient 3 was lost to follow-up. All other patients achieved a normalisation of the FDG uptake. In 3 patients (no. 1, 3, 7) CYC was augmented to 900mg/m², in 1 patient (no. 6) therapy was escalated to daily oral CYC after 7 cycles and in 1 patient (no. 5) the dosage had to be reduced to 500mg/m² due to prolonged neutropenia. Patient no. 10 experienced a relapse after 21 months.

GC: glucocorticosteroids in mg prednisolone equivalent; CYC: cyclophosphamide; AZA: azathioprine; MTX: methotrexate; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BVAS: Birmingham Vasculitis Activity Score.

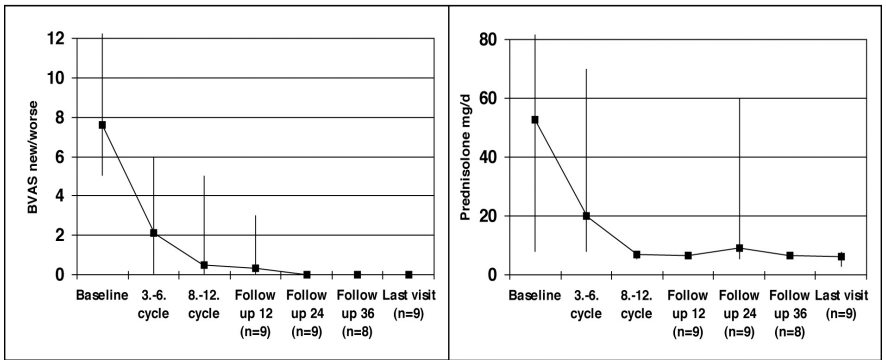

Fig. 1. BVAS new/worse (**A**) and daily prednisolone dose (**B**) during follow-up.
Maximum/minimum and median values (■) demonstrate a sustained remission in 8 patients; Patient No. 3 was lost to follow-up and no. 10 experienced a mild relapse in month 21 with a consecutive augmentation of steroid dose.

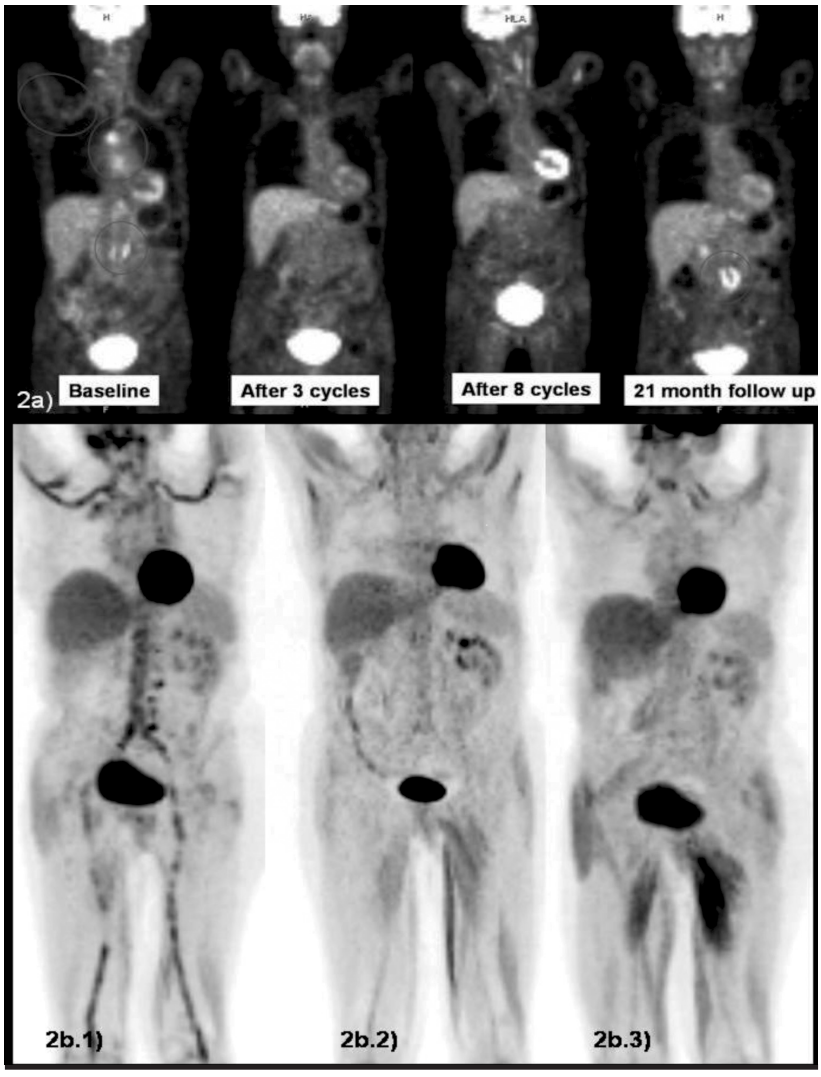

Fig. 2. Follow-up examinations of patient no. 10 (**a**) and 7 (**b**). For easier interpretation only the PET data is shown.
a) Patient 10 achieved a remission after 8 cycles CYC but experienced a relapse of the vasculitis at month 21 with focal segmental pathological FDG uptake of the abdominal aorta. No retroperitoneal fibrosis was found in the corresponding CT scan. The grey circles indicate the regions with the highest FDG uptake; **b**) Maximum intensity projection (MIP) of patient no. 7 showing a severe vasculitis affecting the aorta and all its larger branches (**b1**). After 3 cycles (**b2**) remaining elevated FDG uptake especially in the subclavian artery can be seen. After 9 cycles (**b3**) no more pathologic uptake was found.

conventional clinical and serological parameters during treatment is a helpful tool to assess active inflammation. It served as an additional basis for our decisions to further medicate, and may thus have contributed to the high rate of sustained responses.

Due to the retrospective character and the small sample size, the significance of this study is limited. Patients received different treatment schedules, especially various GC doses; hence discrimination of treatment response to CYC and/or additional immunosuppression is not definitely possible.

CYC is a cytotoxic agent with side effects, especially on bone marrow and on the reproductive system. Infectious complications are common due to leucopoenia. The risk of secondary malignancy after CYC therapy increases with the total amount of CYC. To minimise the side effects and the cumulative dose, CYC pulse therapy was preferred to daily oral treatment. Infections in our patients were diagnosed and treated quickly, but two of them were life-threatening. Since the median age of the patients was 61.5 years, effects on the reproductive system were of minor importance. With the rather aggressive cytotoxic therapy used in our patients, a long lasting (48 months) remission with a moderate immunosuppressive maintenance therapy was achieved in 8/10 patients. CYC appears to be effective in GC resistant large-vessel vasculitis in patients with severe vasculitis with organ/limb threatening stenoses.

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