Treatment of refractory giant cell arteritis with cyclophosphamide: A retrospective analysis of 35 patients from three centres

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ABSTRACT

Patients with giant cell arteritis (GCA) refractory to standard immunosuppressive therapy may constitute a significant clinical problem with a high risk of glucocorticoid-related adverse effects.

Objective. *To evaluate efficacy and safety of cyclophosphamide for remission induction in GCA patients with persistent disease activity despite standard immunosuppressive treatment.*

Methods. *Thirty-five individuals from 3 tertiary rheumatological centres treated for persistently active GCA unresponsive to treatment with glucocorticoids plus at least either methotrexate or azathioprine for a minimum of 3 months and unable to reduce daily glucocorticoid dose to <10 mg prednisolone equivalent. We recorded signs of disease activity (clinical, laboratory, imaging); course of glucocorticoid doses during cyclophosphamide treatment and follow-up; relapse rate; treatment-related adverse events; and survival. Since all patients had been refractory to standard therapy, a matched control group could not be defined.*

Results. *Data from 31 patients completing cyclophosphamide treatment were available for analysis. Twenty-eight patients (90.3%) responded with improved disease activity and sustained reduction of daily prednisolone intake to <10 mg (mean reduction -13.1 mg or -51.6%, p<0.001). Twelve months later, doses <7.5 or <5 mg were achieved in 89.3% and 67.7% of these patients on maintenance immunosuppressive treatment, respectively. Relapses occurred in 12 patients after a median of 20.5 months. Survival over 5 years was similar to expected rates of the general population. Adverse events comprised transient leucopenia, infections and 1 case of haemorrhagic cystitis.*

Conclusion. *Cyclophosphamide can be considered a therapeutic option with an acceptable safety profile for remission induction in GCA refractory to standard immunosuppressive treatment.*

Introduction

Glucocorticoids are the currently recommended first-line therapy for the treatment of giant cell arteritis (GCA, 1-2). However, long-term or even indefinite treatment may be necessary (3-7), and a sustained reduction of glucocorticoid doses to an acceptable range may be hampered by frequent recurrence of disease activity. As a consequence, up to 86% of GCA patients have been affected by glucocorticoid-related side effects (8-10). Long-term glucocorticoid use has been correlated with an increased risk of severe and opportunistic infections (11), and increased death rates have been associated with initial high dose treatment of GCA within the first months as well as with daily maintenance doses of >10 mg prednisolone equivalent (3, 8, 12, 13). On the other hand, the incidence of large-artery stenoses and aortic aneurysms / dissections during follow-up is high (about 25%), and active aortitis was demonstrated on autopsy in the majority of cases of fatal thoracic aortic dissection (14-17). To enable tapering of the glucocorticoid dose as quickly as possible while maintaining adequate disease control, the early consideration of adjunctive immunosuppressive treatment has been recommended (1, 2). A meta-analysis of three clinical studies indicates significant glucocorticoid-sparing effects of methotrexate, and a small study suggests similar effects for azathioprine (18-20). However, there are refractory cases in whom an acceptable glucocorticoid dose reduction cannot be achieved in spite of concurrent use of these agents. There are currently no recommendations or guidelines for this setting, and treatment has to rely largely on clinical judgement and personal experience of the responsi-

ble physicians. The role of biological therapies in GCA treatment is yet to be established (1). In an attempt to control the disease in critical situations, successful treatment with cyclophosphamide has been reported in single cases and small case-series (21-24). The aim of this study from 3 tertiary care rheumatological centres was to evaluate the use of cyclophosphamide for induction of remission in GCA refractory to standard treatment in a larger patient cohort.

Patients and methods

Inclusion and exclusion criteria

All patients satisfying American College of Rheumatology (ACR) and/or Chapel Hill criteria for GCA (25, 26) were considered eligible, if the criteria for *refractory disease* defined as follows were fulfilled, *i.e.* if the patient showed evidence of a persistently active or progressive disease requiring systemic glucocorticoid doses of ≥10 mg daily prednisolone equivalent in spite of adjunctive steroid-sparing treatment by at least either methotrexate or azathioprine for at least 3 months. As an exception, less than 3 months of treatment with either one of these agents were permitted if side effects or contraindications precluded its continuation.

In addition, patients *not* satisfying ACR or Chapel Hill criteria (lack of clinical involvement of cranial arteries, unavailable or inconclusive histology) were included if both refractory disease as defined above was present and <u>*all*</u> of the following criteria were fulfilled:

I the clinical features were very suggestive of the disease, defined as either:
   a. concomitant polymyalgia rheumatica and/or constitutional symptoms (fever, weight loss, night sweats) in the acute phase; *or*
   b. evidence of cranial and / or limb ischaemia

   together with an elevated erythrocyte sedimentation rate (ESR) ≥50 mm/h *and* a favourable clinical response to glucocorticoid treatment (at least 20 mg/day prednisolone equivalent),

II the patient was over 50 years of age at disease manifestation,

III imaging showed typical inflammatory changes of the thoracic aorta and / or proximal large (subclavian, axillar, carotid, iliac) arteries, and

IV no other disease was found accountable (specifically, no evidence of systemic infection, ongoing malignancy or other rheumatic diseases such as systemic lupus erythematodes, rheumatoid arthritis, other vasculitides).

Although the diagnosis cannot be regarded as definitive in these individual patients due to the lack of histological evidence and incompliance with evaluated classification criteria for GCA, we decided to include these cases, since they comprise a significant and clinically important fraction of patients, and from the available evidence GCA can be considered the most likely disease entity underlying a large-vessel vasculitis in the vast majority of patients above the age of 50 years. In support of this view, granulomatous changes compatible with GCA have been shown previously by others in 77–85% of resected thoracic aortic segments with aneurysms or dissections due to noninfectious aortitis (27-28).

Patients with ongoing or recent (distance <2 years) malignant disease, and patients incompliant with recommended therapeutic measures were excluded.

Table I. Patient characteristics and previous immunosuppressive treatment. The first column contains data for all included patients. The right columns display data for subgroups: patients with evident inflammatory involvement of the aorta and/or proximal large arteries ("large-artery involvement"), and patients satisfying the American College of Rheumatology criteria for giant cell arteritis ("ACR+"). GC: glucocorticoid; CYC: cyclophosphamide.

	All patients	Large artery involvement	ACR+
Patient number (n)	35	24	29
Histology positive (Chapel Hill)	13	7	13
Gender			
male (% of total)	8 (23%)	5 (21%)	7 (24%)
female (% of total)	27 (77%)	19 (79%)	22 (76%)
Age at GCA diagnosis (years)			
mean ± standard deviation	65.3 ± 7.7	65 ± 7	65.7 ± 7.4
Prior GC treatment (months)			
mean ± standard deviation	30.9 ± 35.3	32.4 ± 36.4	28.3 ± 31.9
median	16	18	16
Clinical manifestations and involvement of aorta / large arteries			
new onset headache	28 (80%)	17 (71%)	28 (97%)
polymyalgia rheumatica	29 (83%)	20 (83%)	24 (83%)
B-symptoms	25 (71%)	19 (79%)	23 (79%)
large artery involvement	24 (69%)		18 (62%)
signs of aortitis on imaging	19 (54%)	19 (79%)	14 (48%)
proximal artery stenoses / occlusions	16 (46%)	16 (67%)	12 (41%)
aortic ectasia / aneurysm	3 (9%)	3 (12%)	2 (7%)
amaurosis fugax, ischaemic stroke	8 (23%)	4 (17%)	7 (24%)
Prior GC-sparing treatment			
methotrexate	30 (86%)*	19 (79%)	24 (83%)
azathioprine	14 (40%)**	8 (33%)	14 (48%)
leflunomide	8 (23%)***	5 (21%)	6 (21%)
Number of different previous GC-sparing agents (single or combined)			
1	22 (63%)	19 (79%)	18 (62%)
2	9 (26%)	2 (8%)	8 (28%)
3	4 (11%)	3 (12%)	3 (10%)
Indications for CYC treatment			
- persistent, intolerable symptoms requiring high GC intake	35 (100%)	24 (100%)	29 (100%)
- stenoses of large proximal arteries	13 (37%)	13 (54%)	9 (31%)
- aortitis ± aortic aneurysm	11 (31%)	11 (46%)	9 (31%)
- recurrent visual impairment / stroke	8 (23%)	4 (17%)	7 (24%)

*median methotrexate dose 0.28 mg/ kg body weight weekly (all parenteral)
**median azathioprine dose 1.94 mg/kg body weight daily
***median leflunomide dose 20 mg daily (7/8 cases combined with methotrexate)

Table II. Performance of cyclophosphamide treatment. Data are provided on application route, dosing, inter-infusion intervals and treatment duration, including cumulative cyclophosphamide doses. All patients received prophylactic treatment with mesna and forced hydration for bladder protection during cyclophosphamide treatment. In addition, all patients received pneumocystis jiroveci prophylaxis with cotrimoxazole three times weekly unless contraindicated while on glucocorticoid doses of ≥15 mg prednisolone daily. The right columns display data for subgroups: patients with evident inflammatory involvement of the aorta and/or proximal large arteries ("large-artery involvement"), and patients satisfying the American College of Rheumatology criteria for giant cell arteritis ("ACR+").

	All patients	Large artery involvement	ACR+
Application route [patient number (%)]			
intravenous (*i.v.*) only	21 (60%)	16 (67%)	16 (55%)
oral only	8 (23%)	5 (21%)	8 (28%)
both i.v. and oral (subsequently)*	6 (17%)	3 (12%)	5 (17%)
*indications for switching:			
leucopenia during oral application	2		2
inadequate response to i.v. doses	4	3	3
Application details			
i.v. [mean ± standard deviation]			
number of infusions	7.5 ± 2.7	7.8 ± 3	7.8 ± 3
dose per infusion (mg/kg body weight)	15.8 ± 6.4	14.5 ± 3.1	16.8 ± 6.9
inter-infusion interval (days)	23.1 ± 4	22.8 ± 3.9	23.9 ± 4.1
cumulative dose (g)	9.2 ± 5.7	9 ± 6.4	9.6 ± 6.4
oral [mean ± standard deviation]			
daily dose (mg/kg body weight)	1.6 ± 0.4	1.6 ± 0.4	1.5 ± 0.4
treatment duration (weeks)	23.9 ± 15.4	26.8 ± 16.6	25.5 ± 15.1
cumulative dose (g)	14.4 ± 7.4	16.3 ± 6.7	15 ± 7.5
total [mean ± standard deviation]			
cumulative dose (g)	12.4 ± 7.6	12.9 ± 8.3	13.5 ± 7.7

Chart review and data collection

According to the above stated criteria, eligible patients were retrieved from the chart archives of the participating rheumatology centres in Germany (centre 1: University of Lübeck, Department of Rheumatology, Klinikum Bad Bramstedt, January 1990 – December 2009; centre 2: University Hospital of Tübingen, Department of Internal Medicine, Haematology, Oncology, Immunology, Rheumatology and Pulmology, January 2004 – December 2009; centre 3: Hannover Medical School, Clinic for Immunology and Rheumatology, April 2007 – December 2009). A comprehensive data collection was performed including detailed history of prior disease course, clinical presentation, imaging results, previous and cyclophosphamide treatment, incidence of adverse events. Follow-up data included the clinical course, further immunosuppressive treatment, steroid dose, relapse, potential treatment-related sequelae, malignancy and survival. If not available from the hospital charts, follow-up data were collected from the patient's general practicioner, rheumatologist or family members.

Definition of disease states and outcome parameters

– Refractory disease

See above.

– Response

Substantial improvement of evident active vasculitis (clinical and/or imaging) as estimated by radiologist and treating physician, *and* ability to reduce glucocorticoid intake to <10 mg prednisolone daily (alternatively by >50% of the dose before cyclophosphamide initiation).

– Remission

Absence of signs of active vasculitis (clinical, imaging if available, ESR ≤20mm/h) *and* glucocorticoid dose <7.5 mg prednisolone daily.

– Relapse

Reoccurrence of significant signs of active vasculitis (clinical and/or imaging and/or ESR>40 mm/h attributable to active disease) requiring a sustained increase of the glucocorticoid dose to >10 mg prednisolone daily for more than 4 weeks and/or escalation of glucocorticoid-sparing treatment.

– Primary outcome parameter:

Response (as defined above) at the time of cyclophosphamide discontinuation.

Statistical analysis

The Wilcoxon test was used for comparison of glucocorticoid requirement at different time-points.

Results

Thirty-five patients satisfying the above stated inclusion criteria qualified for analysis (26, 6 and 3 from centres 1–3, respectively). Baseline characteristics of the patients at the time of initiation of cyclophosphamide treatment are displayed in Table I. All patients were older than 50 years at disease manifestation. While the majority of patients (82.9%) fulfilled ACR criteria (ACR+), six patients not satisfying ACR or Chapel Hill criteria (no new localised headache, no tender / pulsless temporal arteries, no jaw claudication, histology unavailable) but showing signs of large-vessel arteritis on imaging together with other symptoms suggestive of GCA as defined above were also included. Differences between these groups regarding age and gender were not significant. Polymyalgia was a frequent accompanying symptom present in more than 82% of all patients independent of the presence or absence of clinical involvement of cranial arteries. Twenty-four patients (68.6%) showed evidence of large artery involvement on imaging. All tables include separate analyses for all patients as well as for the subgroups of ACR-positive patients and individuals with large-artery involvement. The overall median time from introduction of glucocorticoid treatment until cyclophosphamide initiation was 16 months. Thirteen patients (37.1%) had received previous trials with more than one glucocorticoid-sparing agent. All subjects had persistent symptoms of active disease preventing reduction of glucocorticoid intake to <10 mg prednisolone equivalent daily, either since

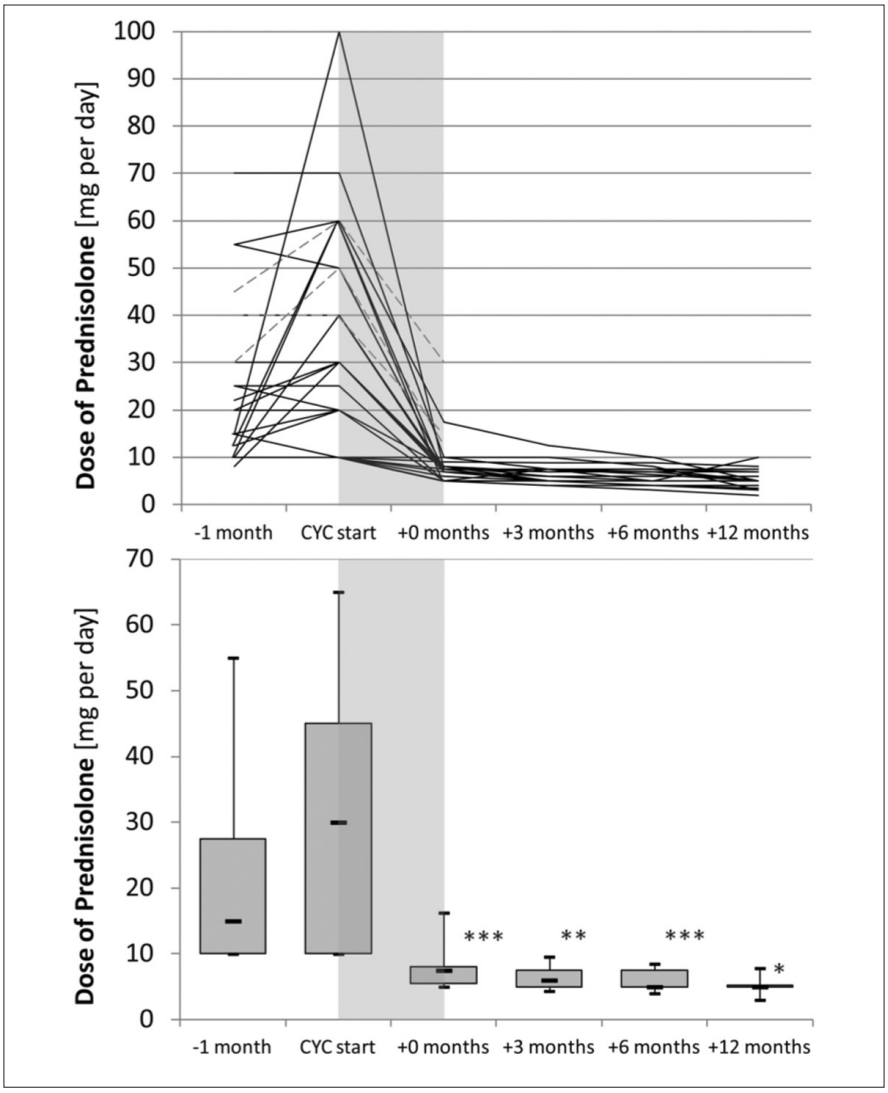

Fig. 1. Course of glucocorticoid dose from before initiation of cyclophosphamide (CYC) until 12 months after completion. Shaded area corresponds to the time of cyclophosphamide treatment. The *upper panel* shows dose curves for all 31 individual patients with available follow-up who completed cyclophosphamide treatment including the 3 patients with inadequate response to cyclophosphamide (dashed lines, confined to time until cyclophosphamide termination). Box plots in the *lower panel* show median (thick horizontal bars), 1st and 3rd quartile (box) as well as 5th and 95th percentile (whiskers) from the 28 patients who fulfilled the response criteria after cyclophosphamide treatment, illustrating the ability to continuous further glucocorticoid tapering after cyclophosphamide completion. In 13 patients (41.9%), the prednisolone dose had been increased simultaneously to cyclophosphamide initiation, while in the majority (18 cases, 58.1%) it had not (overlapping graphs in upper panel). Stars indicate significant dose reductions between the values *before* cyclophosphamide initiation (-1 month) and termination (CYC end) as well as between succeeding time-points during follow-up (***$p<0.001$, **$p<0.01$, *$p<0.05$).

disease onset (primarily refractory, n=30) or due to disease recurrence. Thirteen patients had developed severe large-artery stenoses despite treatment, eleven showed evidence of active aortitis on imaging, in part combined with aortic ectasia or aneurysm formation. Eight patients presented with a history of recurrent visual impairment or ischaemic stroke attributed to active vasculitis. Significant glucocorticoid-related side effects (diabetes mellitus, glaucoma, zoster, candida esophagitis, osteoporosis with fractures, avascular osteonecrosis, Cushing's syndrome, severe skin atrophy) were present in 25 patients (71.4%).

Cyclophosphamide treatment was initiated by intermittent intravenous (i.v.) bolus infusions in 25 patients (71.4%) and orally in 10 patients (28.6%). Despite persisting signs of active disease, the glucocorticoid dose was not escalated further in the majority of patients (increase by >5 mg per day in only 10 of 35 cases). Details regarding cyclophosphamide application are displayed in Table II. For i.v. cyclophosphamide, a standard infusion series consisted of 6 applications, but infusion number, doses and intervals were adapted on clinical grounds depending on the achieved effect and patient tolerance. Intravenous glucocorticoid (100 mg prednisolone equivalent) and 5-HT_3 receptor blockade were used for antiemetic purposes prior to each cyclophosphamide infusion. In four cases, cyclophosphamide application was switched from *i.v.* to oral because of insufficient treatment efficacy, leading to disease remission in all 3 cases available to follow-up. Two patients were switched from oral to *i.v.* application due to leucopenia during oral intake. The overall mean cumulative cyclophosphamide dose for all patients was 12.4 g (*i.v.* 9.2 g, oral 14.4 g; seven patients >20 g, maximum 30 g).

Thirty-one patients completed cyclophosphamide treatment. Follow-up data were available in each of these patients for at least 12 months, with a mean follow-up of 49 months. Twenty-eight patients (90.3%) achieved a treatment response as defined above ("responder"). The reduction of the daily glucocorticoid intake achieved in these patients was highly significant compared to the values before cyclophosphamide initiation (mean relative reduction by 51.6±23.6%, mean absolute reduction by 13.1 mg, $p<0.001$). For 8 of the 31 patients (25.8%), the criteria of remission as defined above were fulfilled at cyclophosphamide completion. During the following 12 months, glucocorticoid intake could be further reduced while on maintenance immunosuppressive treatment, and prednisolone doses of <7.5 mg daily were achieved in 60.7%, 71.4% and 89.3% of these 28 responders at 3, 6 and 12 months after cyclophosphamide completion, respectively (Fig. 1). Data on maintenance glucocorticoid-sparing treatment can be obtained from Table III. At 12 months after cyclophosphamide completion, 21 patients received glucocorticoid doses of ≤5 mg pred-

Table III. Outcome of cyclophosphamide treatment and type of maintenance immunosuppressive therapy after achieved response. The right columns display data for subgroups: patients with evident inflammatory involvement of the aorta and/or proximal large arteries ("large-artery involvement"), and patients satisfying the American College of Rheumatology criteria for giant cell arteritis ("ACR+"). GC: glucocorticoid.

	All patients	Large artery involvement	ACR+
Treatment completion			
completed with available follow-up	31 (89%)	22 (92%)	25 (86%)
terminated prematurely*	2 (5.5%)		
unavailable for follow-up	2 (5.5%)		
Outcome (compared to patient number available for follow-up)			
Response	28 (90.3%)	19 (86.4%)	22 (88%)
Remission	8 (25.8%)	7 (31.8%)	6 (24%)
Treatment failure	3 (9.7%)	3 (13.6%)	3 (12%)
Maintenance GC-sparing treatment			
methotrexate	15 (54%)	10 (53%)	10 (46%)
azathioprine	8 (29%)	6 (32%)	7 (32%)
leflunomide	2 (7%)	1 (5%)	2 (9%)
GC only	1 (4%)	1 (5%)	1 (4%)
other	2 (7%)	1 (5%)	2 (9%)

*n=1: refusal of any further treatment; n=1: haemorrhagic cystitis.

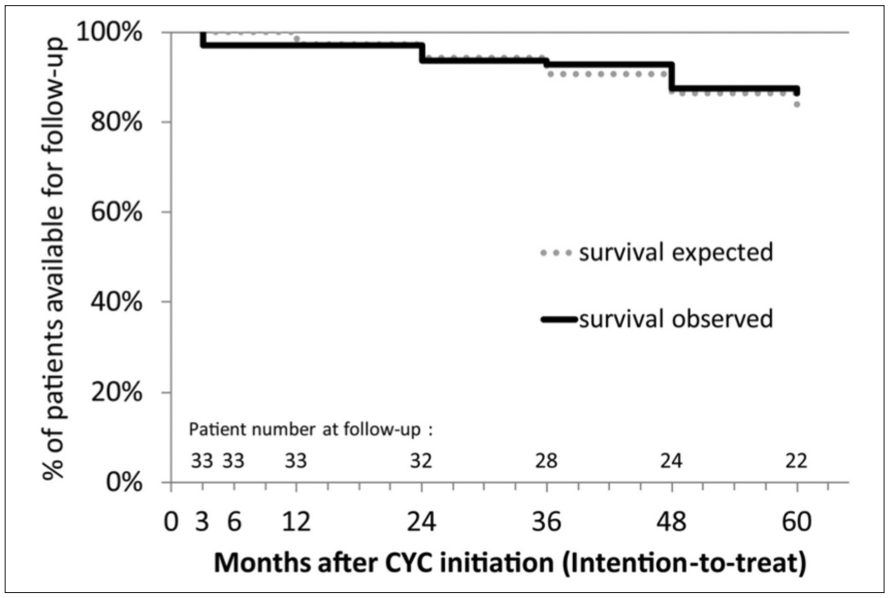

Fig. 2. Comparison of the observed survival after initiation of cyclophosphamide treatment in relation to expected survival as calculated from age- and gender-specific mortality rates of the general population obtained from the German Federal Statistical Office.

nisolone daily. Tapering of immunosuppressive therapy was attempted in the continued absence of signs of disease activity, and three patients could finally end all immunosuppressive treatment with sustained remission until the end of individual follow-up after 60 months, while two other patients could be managed on low-dose glucocorticoids alone. The remainder of the patients continued combined immunosuppressive maintenance therapy until the end of available follow-up (mean 50 months after cyclophosphamide completion). The duration of response to cyclophosphamide was mostly long-lasting. Relapses occurred in 12 cases (42.9%) after a median of 20.5 months while still on maintenance immunosuppressive treatment. All relapses could be controlled by a temporary glucocorticoid dose increase or / and intensification of glucocorticoid-sparing treatment, including 3 cases of cyclophosphamide re-treatment (additive cumulative cyclophosphamide dose ≤6 g in all cases), again leading to a good response.

Three of the 31 patients completing cyclophosphamide treatment (2 from centre 1, 1 from centre 3) did not respond adequately with persistent signs of active disease and were switched to alternative immunosuppression.

Significant adverse events during cyclophosphamide treatment were recorded in 11 of the 33 patients with available follow-up (33.3%). Transient, at least moderate leucopenia appeared in 6 patients. A case of severe leucopenia (grade 4 according to WHO definition) resulted from insufficient control of blood counts after transfer to a rehabilitation unit in a patient on oral cyclophosphamide and was complicated by bilateral pneumonia requiring intensive medical treatment. After recovery, cyclophosphamide was resumed intravenously at a reduced dose without further complications. Six other recorded cases of infection (4 moderate, 2 requiring hospital admission) likewise resolved with antibiotic or virustatic therapy. Two patients had to discontinue mesna due to allergic reactions. In one patient with unclear adherence to mesna intake, oral cyclophosphamide had to be terminated prematurely after 6 weeks for cystoscopically confirmed haemorrhagic cystitis.

The second case of premature termination of cyclophosphamide was in an 80 year-old woman treated with azathioprine and prednisolone for histologically confirmed GCA diagnosed 10 years before, who presented with persistent critical lower leg ischaemia with dry necrosis at both feet, high inflammatory markers, and angiography findings compatible with bilateral severe, occlusive atherosclerotic changes without options for revascularisation regarded as the main cause for ischaemia. Since PET showed intensive tracer uptake in the right femoral artery, a GCA recurrence contributing to the ischaemia could not be excluded and cyclophosphamide *i.v.* and high-dose prednisolone were introduced as a salvage treatment. After 2 cyclophosphamide applications, lower leg amputation was rec-

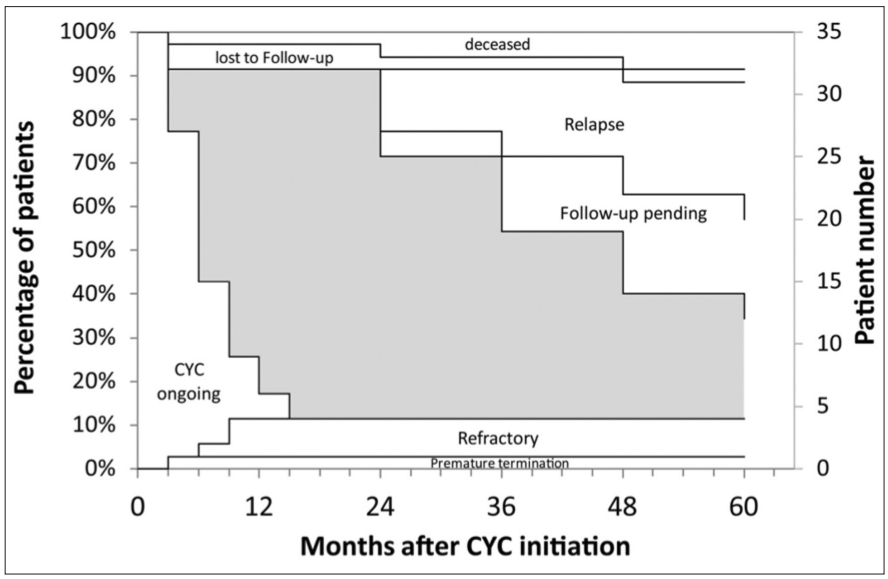

Fig. 3. Overview on duration of cyclophosphamide (CYC) treatment, outcome and available follow-up data of all 35 included patients. Shaded area corresponds to patients with a sustained response to cyclophosphamide treatment.

ommended for progressive gangrene, but the patient then refused all further medical treatment and died in a nursing home 2 weeks later. In retrospect, it appears most likely that severe arteriosclerotic disease was deciding for the lack of improvement in this patient.

For two other patients, in whom cyclophosphamide was started, follow-up on duration of treatment and response could not be retrieved. One of these patients reportedly died 23 months later from metastasised lung cancer. In one patient, an early renal cell carcinoma detected 18 months after cyclophosphamide completion (cumulative dose 5.3 g) was curatively treated by nephrectomy. In total, 3 patients died between cyclophosphamide initiation and the end of a 5-year follow-up. The observed death rate is not higher than expected from age- and gender-specific mortality rates of the general population obtained from the German Federal Statistical Office (Fig. 2). An overview on the available response and follow-up data from the 35 included patients is given in Figure 3 and Table III.

Discussion

From the experience with severe forms of other vasculitides, it is known that cyclophosphamide is a powerful immunosuppressive agent which can be used successfully in conjunction with glucocorticoids for the induction of disease remission. Once remission has been achieved, therapy can be safely de-escalated to a less aggressive maintenance regimen (29). In analogy, we used a limited course of cyclophosphamide for remission induction in cases of GCA refractory to standard treatment including glucocorticoids plus at least either methotrexate or azathioprine for glucocorticoid-sparing purposes. This study is the first to provide data on cyclophosphamide treatment of a larger cohort of well-characterised GCA patients. With the above mentioned regimen, an excellent response rate of 90% of previously refractory GCA patients could be achieved, which was maintained for years in most cases while on maintenance immunosuppressive treatment. Different from the majority of GCA cases from other cohorts (3, 7), the greater number of our patients required continued combined therapy with glucocorticoids plus glucocorticoid-sparing agent(s) throughout the whole follow-up period, and a significant portion of the patients experienced a relapse of disease activity during treatment de-escalation, necessitating re-escalation of therapy. Thus, it appears that patients who are refractory to the initial standard therapy may constitute a subset of GCA with an extraordinary, long-lasting tendency to relapse that may require permanent immunosuppressive therapy and close surveillance.

Although severe adverse events were recorded, overall tolerability of cyclophosphamide in this elderly patient population was acceptable, especially when weighed against the potential risks of long-term treatment with high glucocorticoid doses. Educating and advising the patient (and next of kin) and his/her general practitioner on the use and risks of toxicity and possible infections is crucial to avoid serious complications. The urgent need for frequent blood count controls during oral cyclophosphamide treatment (at least twice weekly recommended) must be emphasised, and the use of *pneumocystis jiroveci* prophylaxis during cyclophosphamide treatment is strongly advised. The cumulative cyclophosphamide doses in our patients were comparably low (overall mean 12.4 g), especially in those patients treated with *i.v.* cyclophosphamide. Higher cumulative cyclophosphamide doses have been associated with an increased risk of bladder cancer and haematologic malignancies, especially acute myeloid leukaemia (30-32), but were not reached in the majority of our patients (maximum dose 30 g). We did not observe bladder cancer or haematological malignancies in our patient cohort. The two cases of cancer recorded during follow-up (bronchial and renal cell carcinoma) did not exceed the number of malignancies expected from data of the general population.

This study is limited by its retrospective design including variations of glucocorticoid and cyclophosphamide dosing and lack of standardised follow-up. However, differences in treatment performance were minor to moderate at most, thus not preventing analysis. Screening for large-artery involvement was not performed in all patients. Since the decision for initiation of cyclophosphamide treatment had been made only in cases without other good therapeutic options and in whom a simple continuation of the pre-existing ineffective standard therapy had appeared inappropriate, we were unable to define a matched control group for comparison to cyclophosphamide treatment data.

In conclusion, cyclophosphamide induced a sustained disease remission in the vast majority of GCA patients refractory to standard therapy, enabling tapering of glucocorticoids. The safety profile of cyclophosphamide in our patient population was acceptable, but close observation, adherence to prophylactic measures and patient education are necessary to avoid potential treatment-related complications, especially in elderly patients. Use of the less toxic intravenous application appears to be effective in most cases and should be considered as the preferred application form in all cases. On the basis of the results of this study, a prospective evaluation of cyclophosphamide for remission induction in therapy-resistant cases of GCA appears warranted.

References

1. DASGUPTA B, BORG FA, HASSAN N *et al*.: BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology* (Oxford). 2010; 49: 1594-7.
2. MUKHTYAR C, GUILLEVIN L, CID MC *et al*.: EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2009; 68: 318-23.
3. GRAHAM E, HOLLAND A, AVERY A, RUSSELL RWR: Prognosis in giant-cell arteritis. *Br Med J* 1981; 282: 269-71.
4. ANDERSSON R, MALMVALL BE, BENGTSSON BA: Long-term survival in giant cell arteritis including temporal arteritis and polymyalgia rheumatica. A follow-up study of 90 patients treated with corticosteroids. *Acta Med Scand* 1986; 220: 361-4.
5. GOUET D, MARÉCHAUD R, LE BERRE D *et al*.: Prognosis of treated temporal arteritis. Retrospective study of 87 cases. *Presse Med* 1986; 15: 603-6.
6. PHILLIP R, LUQMANI R: Mortality in systemic vasculitis: a systematic review [Review]. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S94-104.
7. SCHMIDT WA, MOLL A, SEIFERT A, SCHICKE B, GROMNICA-IHLE E, KRAUSE A: Prognosis of large-vessel giant cell arteritis. *Rheumatology* (Oxford). 2008; 47: 1406-8.
8. NESHER G, SONNENBLICK M, FRIEDLANDER Y: Analysis of steroid related complications and mortality in temporal arteritis: a 15-year survey of 43 patients. *J Rheumatol* 1994; 21: 1283-6.
9. PROVEN A, GABRIEL SE, ORCES C, O'FALLON WM, HUNDER GG: Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003; 49: 703-8.
10. LÓPEZ VIVES L, NARVAEZ J, ESTRADA P, GÓMEZ VAQUERO C, NOLLA JM: Adverse outcomes of glucocorticoid therapy among patients with giant cell arteritis. *Arthritis Rheum* 2010; 62 (Suppl.): S532 [Abstract].
11. NARVAEZ J, LÓPEZ VIVES L, ESTRADA P, DEL CASTILLO N, ROBUSTILLO M, NOLLA JM: Severe and opportunistic infections during giant cell arteritis course: a case-control study. *Arthritis Rheum* 2010; 62 (Suppl.): S545 [Abstract].
12. HACHULLA E, BOIVIN V, PASTUREL-MICHON U *et al*.: Prognostic factors and long-term evolution in a cohort of 133 patients with giant cell arteritis. *Clin Exp Rheumatol* 2001; 19: 171-6.
13. UDDHAMMAR A, ERIKSSON AL, NYSTRÖM L, STENLING R, RANTAPÄÄ-DAHLQVIST S: Increased mortality due to cardiovascular disease in patients with giant cell arteritis in northern Sweden. *J Rheumatol* 2002; 29: 737-42.
14. EVANS JM, O'FALLON WM, HUNDER GG: Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis: a population-based study. *Ann Intern Med* 1995; 122: 502-7.
15. NUENNINGHOFF DM, HUNDER GG, CHRISTIANSON TJ, MCCLELLAND RL, MATTESON EL: Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis Rheum* 2003; 48: 3522-31.
16. BONGARTZ T, MATTESON EL: Large-vessel involvement in giant cell arteritis [Review]. *Curr Opin Rheumatol* 2006; 18: 10-7.
17. GARCÍA-MARTÍNEZ A, ARGUIS P, PRIETO S *et al*.: Outcome of aortic structural damage after long-term follow-up of patients with giant-cell arteritis. Cross-sectional screening of 29 prospectively followed patients. *Ann Rheum Dis* 2010; 69 (Suppl. 3): 689 [Abstract].
18. MAHR AD, JOVER JA, SPIERA RF *et al*.: Adjunctive methotrexate for treatment of giant cell arteritis: An individual patient data meta-analysis. *Arthritis Rheum* 2007; 56: 2789-97.
19. DE SILVA M, HAZLEMAN BL: Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double-blind study. *Ann Rheum Dis* 1986; 45: 136-8.
20. SALVARANI C, PIPITONE N: Treatment of large-vessel vasculitis: where do we stand? *Clin Exp Rheumatol* 2011; 29 (Suppl. 64): S3-5.
21. DE LA CASA MONJE R, BARBADO HERNÁNDEZ FJ, PEÑA SÁNCHEZ DE RIVERA JM *et al*.: Giant-cell arteritis: the clinico-biological manifestations and the complications secondary to steroid treatment. *An Med Interna* 1991; 8: 161-5.
22. DE VITA S, TAVONI A, JERACITANO G, GEMIGNANI G, DOLCHER MP, BOMBARDIERI S: Treatment of giant cell arteritis with cyclophosphamide pulses. *J Intern Med* 1992; 232: 373-5.
23. RÜEGG S, ENGELTER S, JEANNERET C *et al*.: Bilateral vertebral artery occlusion resulting from giant cell arteritis: report of 3 cases and review of the literature. *Medicine* (Baltimore) 2003; 82: 1-12.
24. HENES JC, MUELLER M, PFANNENBERG C, KANZ L, KOETTER I: Cyclophosphamide for large-vessel vasculitis: assessment of response by PET/CT. *Clin Exp Rheumatol* 2011; 29 (Suppl. 64): S43-8.
25. HUNDER GG, BLOCH DA, MICHEL BA *et al*.: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990; 33: 1122-8.
26. JENNETTE JC, FALK RJ, ANDRASSY K *et al*.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
27. PACINI D, LEONE O, TURCI S *et al*.: Incidence, etiology, histologic findings, and course of thoracic inflammatory aortopathies. *Ann Thorac Surg* 2008; 86: 1518-23.
28. STONE JH, KHOSROSHAHI A, DESHPANDE V, STONE JR: IgG4-related systemic disease accounts for a significant proportion of thoracic lymphoplasmacytic aortitis cases. *Arthritis Care Res* (Hoboken) 2010; 62: 316-22.
29. MUKHTYAR C, GUILLEVIN L, CID MC *et al*.: EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009; 68: 310-7.
30. TRAVIS LB, CURTIS RE, GLIMELIUS B *et al*.: Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. *J Natl Cancer Inst* 1995; 87: 524-30.
31. VAN LEEUWEN FE: Risk of acute myelogenous leukaemia and myelodysplasia following cancer treatment. *Baillieres Clin Haematol* 1996; 9: 57-85.
32. FAURSCHOU M, SORENSEN IJ, MELLEMKJAER L *et al*.: Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. *J Rheumatol* 2008; 35: 100-5.