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Vasculitis

Is there a place for cyclophosphamide in the treatment of giant-cell arteritis? A case series and systematic review

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ABSTRACT

Objective: To report on the effectiveness of cyclophosphamide (CYC) to treat glucocorticoid (GC)-dependent giant-cell arteritis (GCA) and/or severe GC-related side effects.
Methods: Fifteen patients with GCA and treated with CYC were retrieved from the computerized patient-record system. Glucocorticoid dependence was defined as a prednisone dose of >20 mg/day for 6 months or >10 mg/day for 1 year in order not to relapse. Response to CYC was defined as improved clinical and biological findings. Remission was defined as a sustained absence (>12 months) of active signs of vasculitis at a daily GC dose of <7.5 mg. A literature review searched PubMed for all patients diagnosed with GCA and who received CYC.
Results: Our 15 patients responded to monthly pulses of CYC, and all experienced a GC-sparing effect, including five patients who discontinued GC long term. At a median follow-up of 43 (range: 14–75) months after CYC, nine (53%) patients were still in remission and six (40%) had relapsed at 6 (3–36) months after the last CYC infusion. Twelve (80%) patients experienced side effects, leading to discontinuation of CYC in two (13%). A literature review retrieved 88 patients who received CYC: 66 for GC-dependent disease, 53 for GC toxicity, and 14 for severe organ involvement. Their median follow-up time was 24 (4–60) months. Among the 88 patients, 74 (84%) were responsive to CYC and 17 (19%) relapsed, although all were receiving a maintenance therapy with immunosuppressive agents (such as methotrexate). Twenty-nine (33%) patients experienced side effects and 11 (12.5%) discontinued treatment.
Conclusion: Cyclophosphamide is an interesting option for GCA patients with GC-dependent disease or with severe GC-related side effects, especially when conventional immunosuppressive agents have failed.

Introduction

Giant-cell arteritis (GCA) is the most common type of primary vasculitis. It mainly affects large- and medium-sized vessels, including the cephalic arteries (especially the superficial temporal, the vertebral, the ophthalmic, and the posterior ciliary arteries) as well as the aorta with its first-division branches [1]. Glucocorticoids (GC) have been found to be quite effective and remain a mainstay treatment for GCA. The natural course of the disease includes frequent relapses, which occur in ~50% of patients, especially when daily doses of GC are tapered to <10 mg [2]. Relapses require GC dose to be raised and some patients need long-term GC therapy at a moderate- to high-dose, which increases the iatrogenic risks for elderly populations [3]. Some authors define these patients as GC dependent as they have to continue GC in order not to suffer a relapse [4]. It has been suggested that a daily dose of GC of >10 mg/day for >6 months is negatively correlated with long-term survival [5,6].

Glucocorticoid-sparing agents have been tried, such as methotrexate (MTX), azathioprine (AZT), dapsone, hydroxychloroquine, or TNF-α blockers, with inconstant results [4,7–11]. To date, MTX, when initiated at disease onset, is the most studied sparing agent and can reduce relapse rate and decrease the cumulative doses of GC [9,11]. However, even though it is considered a potential GC-sparing agent, there are only anecdotal data on its use in GC-dependent GCA [4]. A few reports, including two recent studies, suggest that cyclophosphamide (CYC) could be a good

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GC-sparing agent for those patients [12–15]. In necrotizing vasculitides, such as granulomatosis with polyangiitis or microscopic polyangiitis, CYC is a cornerstone of treatment, allowing faster tapering of GC and improved immunosuppressive action [16].

Thus, in order to discuss and challenge these findings, we report on the treatment of 15 patients with GCA using intravenous pulses of CYC. In addition, a comprehensive systematic literature review of CYC in GCA was conducted.

Methods

Patients

Patients' data were retrieved through a search of the computerized patient-record system in our hospital, using the keywords "giant-cell arteritis" and "cyclophosphamide". Each patient's characteristics were then analyzed to ensure they satisfied the four following criteria: (1) GCA was diagnosed according to the 1990 American College of Rheumatology (ACR) criteria [17]; (2) all patients responded initially to GC (i.e., improved clinical symptoms and inflammatory laboratory features) but then needed to continue GCs for long term at a moderate- to high-dose, or they experienced serious side effects, which led to the use of CYC as a steroid-sparing agent; (3) absence of another condition potentially associated with GCA, such as malignancy, infection, or other inflammatory disease; and (4) a follow-up of at least 1 year after the last pulse of CYC (with available data on outcomes and repeated clinical examinations and laboratory tests).

We defined the disease as GC dependent when prednisone dose has to remain >20 mg/day for 6 months or >10 mg/day for 1 year in order not to relapse. However, CYC was proposed earlier if serious side effects secondary to GC occurred (e.g., unstable type-2 diabetes mellitus, severe psychiatric disorders, Cushing's syndrome, or severe osteoporosis with fractures).

All eligible patients had a complete workup, i.e., a temporal artery biopsy (TAB), a whole-body tomodensitometry, or an ^{18}FDG PET (positron emission tomography) scan. Exhaustive laboratory investigations included a hemogram, ionogram, serum-creatinine level, coagulation tests (activated partial thromboplastin time), erythrocyte-sedimentation rate (ESR), C-reactive protein (CRP) level, liver-function tests, serum-protein electrophoresis, immunological screening [anti-nuclear antibodies (ANA) and anti-DNA antibodies when ANA were positive, antineutrophil cytoplasmic antibodies (ANCA), complement exploration (C3, C4, CH50), and rheumatoid factor], and infectious serologies (including HIV, HBV, HCV, Lyme disease, and syphilis).

All patients gave their informed consent to receive treatment.

Studied parameters and definitions

Demographics and clinical manifestations at onset of GCA and during the follow-up were extracted directly from the original patients' medical charts plus the results from biological tests, TABs, radiological investigations, treatment regimens (actual and anterior), and the patients' outcomes. Doses of GC at initiation and later, as well as dose, frequency, and tolerance to CYC infusions, were recorded.

Response to CYC was defined as improved clinical and biological findings following the introduction of CYC. Remission was defined as a sustained (>12 months) absence of active signs of vasculitis from receiving a daily dose of <7.5 mg GC. Relapse consisted of reoccurrence of symptoms and/or inflammatory parameters on laboratory findings, attributable to GCA, which required a sustained increase of therapeutics. Each patient was seen monthly during CYC pulses and continued follow-ups at our department.

Literature review

We focused our literature review on patients who were given CYC for GC-dependent GCA or for serious GC side effects. To identify relevant articles, we searched PubMed. The search strategy combined the following terms: giant-cell arteritis, temporal arteritis, or Horton's disease and cyclophosphamide. All relevant articles were retrieved and additional references quoted in these articles were checked. We excluded articles when a doubtful diagnosis persisted or when data were lacking.

All eligible articles were analyzed regarding the course of GCA, the therapeutic regimen, the indications for CYC initiation, and the responses based on clinical and laboratory findings.

Statistical analyses

Categorical variables are expressed as numbers (percentages); quantitative variables are expressed as means $\pm$ SDs [or medians (range)]. Wilcoxon signed rank test was used to compare the doses of GC before and after CYC. Differences were considered significant when $P < 0.05$. All tests were performed using GraphPad Prism 5.0c.

Results

Patients' characteristics at diagnosis

From our computerized patient-record system, we extracted the data of $\sim$300 patients whose history included a diagnosis of GCA: of these, 15 patients (male:female = 2:13) had also received CYC, and all 15 fulfilled the entry criteria. The demographic and clinical characteristics of these 15 patients are summarized in Table 1. Median age at diagnosis was 67 (55–83) years. Five patients had a long-term history of high blood pressure that had been stabilized with adequate treatment, two had diabetes mellitus, and two had coronary disease. All patients had a GCA diagnosis that included at least three ACR criteria. Recent headaches were present at onset in all patients concomitant with visual disturbance in five (33%). Laboratory tests showed increased levels of inflammatory parameters at diagnosis in all patients with elevated ESR and CRP levels [median ESR: 95 (31–113) mm; median CRP: 127 (42–268) mg/L].

A temporal artery biopsy was performed in all patients and showed typical features of GCA in eight (53%), whereas the seven others were considered normal. We ensured that a complete workup ruled out all other mimics, such as infectious diseases or malignancies, especially in patients with negative TAB. All patients had a whole-body tomodensitometry and seven had an ^{18}FDG PET scan, which showed involvement of the aorta and other large vessels in four patients (nos. 6, 13, 14, 15). One patient (no. 11) also had aortitis as assessed by CT angiography. Although patients 6 and 14 had negative TAB, other conditions causing aortitis, such as Behçet's disease, syphilis, tuberculosis, connective tissue disorders, or sarcoidosis, were excluded after exhaustive investigations.

Treatment regimen

Treatment modalities are listed in Table 2. All patients received GC [median initial dose of prednisone: 50 (30–70) mg] and experienced dramatic improvement a few hours or days after starting therapy. However, all but one patient (no. 15) relapsed