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Rituximab for remission induction in elderly patients with ANCA-associated vasculitis

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Abstract

Objectives—Advancing age is a risk factor for treatment-related side effects and mortality in AAV patients treated with cyclophosphamide (CYC) and glucocorticoids (GC) for remission induction. The efficacy and safety of rituximab (RTX) in elderly AAV patients has not been well described.

Methods—We performed a single center retrospective review of 31 consecutive AAV patients aged 60 or more at the time of RTX use for remission induction. All patients received RTX with GC for remission induction. Four patients received concomitant CYC for a mean duration of 52 days. We evaluated clinical and laboratory variables at diagnosis, rates of complete remission defined as Birmingham Vasculitis Activity Score/Wegener's Granulomatosis (BVAS/WG) = 0 and patient survival, renal survival, infections requiring hospitalization, and vasculitis relapse 24 months following RTX use.

Results—Of the 31 patients, 77% were Caucasian, 68% female, mean age was 71 ± 6 years, 58% were MPO ANCA positive, and 42% had relapsing disease. The mean BVAS/WG score entry was 4.4 ± 1.5 , 71% had glomerulonephritis (GN) and 10% had alveolar hemorrhage. The mean baseline e-GFR was 40 ± 28 ml/min/1.73 m². Thirty patients achieved remission with a mean time to remission of 57 ± 27 days. The single patient with refractory vasculitis responded to CYC. The mean prednisone dose at 6 months was 5.6 ± 4 mg. Remission maintenance therapy was started within 12 months of RTX induction in 6 patients (4 with RTX, 1 with azathioprine, and 1 with mycophenolate mofetil). One patient suffered a limited relapse 10 months post RTX use. Among the 22 patients with GN at baseline, 1 developed ESRD. One-year patient survival among 25 patients with at least 1 year of follow-up was 100%. There were no episodes of infusion reaction or leukopenia. There were 3 episodes of bacterial pneumonia, 1 episode of candida pneumonia, and 1 episode of disseminated cutaneous zoster.

Conclusions—This study demonstrates that rituximab is effective for remission induction in elderly patients with AAV. Furthermore, we observed a high incidence of infectious complications. Our experience was limited by its retrospective design, and further studies are needed to evaluate the efficacy and safety of RTX in elderly AAV patients.

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Keywords

RTX (rituximab); CYC (cyclophosphamide); Granulomatosis with polyangiitis (Wegener's); Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); Microscopic polyangiitis (MPA); Renal-limited vasculitis; mAb (monoclonal antibody); Elderly; AAV (ANCA-associated vasculitis)

Introduction

Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) are systemic small vessel vasculitis and categorized as granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), and renal-limited vasculitis. The routine use of cyclophosphamide dramatically changed the prognosis associated with AAV, transforming many of these previously fatal diseases into chronic illnesses [1]. However, the cost of remission induction with cyclophosphamide is substantial with 42% of patients experiencing treatment-related side effects [2] with older age and renal dysfunction being important predictors of treatment-related adverse effects [3,4]. Strategies minimizing or eliminating use of cyclophosphamide for remission induction have been the subject of randomized vasculitis trials in the last decade. Rituximab, a chimeric mAb that binds to the CD20, was approved for remission induction in AAV in 2011 based on RAVE and RITUXVAS trials [5,6]. The mean age of patients in the rituximab arm of RAVE trial was 54 years and the median age of patients in the RITUXVAS study was 68 years with a range of 56–75 years. The efficacy and safety of rituximab for remission induction for AAV in elderly patients has not been well studied. We report our experience with using remission induction for AAV in elderly patients defined as age greater than or equal to 60 years at a single university medical center.

Methods

Study population

Potential patients for this retrospective study were identified from a vasculitis clinic database for the study period 2005–2014. To be included in the study, individuals had to be 60 years or older at the time of rituximab infusion, have a clinical diagnosis of GPA or MPA and received rituximab for remission induction. This study protocol was approved by the Office of Human Subjects Research and Institutional Review Board.

Acquisition of clinical and laboratory data

Patient demographics, clinical features at the time of diagnosis or relapse treated with rituximab, details of immunosuppressive therapy including dosing of rituximab, adverse events including rituximab infusion reaction, episodes of leukopenia (WBC less than 4.0), and infections requiring hospitalization were abstracted retrospectively from the electronic clinical source documents. Peak serum creatinine, erythrocyte sedimentation rate, and C-reactive protein at the time of diagnosis were recorded. Available data on urine protein quantification data based on a spot urine sample or a 24 h urine collection at the time of diagnosis was recorded. ANCA testing was done by standard indirect immunofluorescence

assay on ethanol fixed neutrophils for cytoplasmic ANCA (c-ANCA) and perinuclear ANCA (p-ANCA). PR3 and myeloperoxidase (MPO) testing was done by direct enzyme linked immunosorbent assay (ELISA) with commercially available kits at the local lab. If the testing for c-ANCA, p-ANCA, PR3 ELISA, and MPO ELISA was negative, patients were labeled as having ANCA negative vasculitis. Available data on B-cell counts and the presence of hypogammaglobulinemia were recorded.

Study definitions

Disease phenotype was defined according to the Chapel Hill Consensus nomenclature. Renal function was measured using the 4 variable modification of diet in renal disease (MDRD) formula for estimated GFR (e-GFR). Remission was defined as Birmingham Vasculitis Activity score (BVAS/WG) of zero. In contrast to the RAVE trial which required prednisone dose to be tapered to zero, patients in our cohort were allowed to be on prednisone at the time of remission. B-cell reconstitution was defined as the presence of more than 20 CD19 positive B cells per microliter. Renal involvement was defined by a diagnostic renal biopsy or with the presence of active urine sediment with or without renal insufficiency.

Outcomes

The principal outcomes of interest in this cohort were complete remission at 6 months. Other outcomes included patient survival, number of patients reaching end-stage renal disease, infections requiring hospitalization, and vasculitis relapse 24 months following rituximab use. ESRD was defined as need for continued renal replacement therapy or renal transplant after 3 months. We summarize data as mean with standard deviation.

Results

The baseline characteristics of the 31 patients who met the inclusion criteria for this study are presented in Table 1. The mean (SD) age at the time of rituximab infusion among the entire cohort was 71 (6) years (range: 60–83 years). Majority of patients (77%) were Caucasian and female gender (68%). Eighteen patients had a new diagnosis of AAV and the remainder had relapsing disease. Nineteen patients in the cohort had a diagnosis of GPA and 12 patients had a diagnosis of MPA. The mean (SD) BVAS/WG score at the time of rituximab infusion was 4.4 (1.5). Overall, 71% of patients had renal involvement. The mean (SD) e-GFR was 40 (28) ml/min/1.73 m² and 1 patient was dialysis dependent on presentation. Twenty two patients underwent a renal biopsy. The median follow-up was 655 days (range: 97–3220).

All patients received rituximab for remission induction. Rituximab was chosen for remission induction by physician choice in 27 patients, for vasculitis refractory to cyclophosphamide in 3 patients and 1 patient received rituximab in the setting of diagnosis of myelodysplasia. Thirty patients were dosed with 375 mg/m² and 1 patient received 1000 mg every 2 weeks for 2 doses. Four patients (2 had vasculitis refractory to cyclophosphamide and were given rituximab for remission induction and 2 had severe renal disease) received concomitant oral

cyclophosphamide for a mean duration of 52 days. Glucocorticoids were used in 29 of 31 patients. All patients were given PCP prophylaxis.

Thirty patients achieved remission with a mean (SD) time to remission of 57 (27) days. One patient with refractory vasculitis responded to oral cyclophosphamide. The mean (SD) prednisone dose at 6 months was 5.6 mg (4) (Table 2). Remission maintenance therapy was started within 12 months of rituximab use in 6 patients (4 with rituximab, 1 with azathioprine, and 1 with mycophenolate mofetil). These 6 patients who were started in remission maintenance were at high risk of relapse due to PR3 ANCA disease or relapsing disease. One patient experienced a limited disease relapse 10 months post-rituximab use. Two patients developed ESRD during the follow-up, 1 due to disease progression and another patient due to disease relapse 27 months post-rituximab infusion.

Rituximab infusion was tolerated in all patients with no infusion reactions recorded. Four patients only had 3 weekly infusions and the 4th was held due to thrombocytopenia in 2 patients, pneumonia in 1 patient, and dapsone-induced hemolytic anemia in 1 patient. B-cell depletion was present at 6 months in all 15 patients who were tested. One patient showed B-cell reconstitution and 6 remained B-cell depleted at 12 months. There were no episodes of leukopenia. There were 3 episodes of bacterial pneumonia, 1 patient had candida pneumonia and 1 patient had disseminated cutaneous herpes zoster.

A total of 25 patients were followed up for more than 1 year, and patient survival was 100% in this group (Table 2).

Discussion

This retrospective single center study demonstrates that rituximab is effective for remission induction in elderly patient with AAV. The data also demonstrates that infectious complications are common in this age group.

ANCA-associated vasculitis (AAV) are predominantly diseases of older patients with a peak age of 65–74 years [7]. Elderly patients with AAV are predominantly MPO–ANCA positive compared to PR3 ANCA. AAV in elderly [8–11] frequently involves the kidney [12]. AAV carries a substantial risk of mortality due to both the disease and treatment-related complications. Furthermore, elderly patients present more often with severe renal disease and have more infections as a consequence of immunosuppressive therapy and higher mortality [11]. The combination of older age and renal insufficiency portends a poor prognosis in AAV due to poor response to therapy and increased therapy related adverse events. Observational studies of ANCA-associated pauci-immune GN in the elderly, have demonstrated a poorer prognosis for older patients, with significantly higher rates of death, ESRD, and treatment-related complications [13]. Before the introduction of immunosuppressive treatment, mortality was as high as 85% at 1 year [7]. Bomback et al. [8] demonstrated that use of immuno-suppression resulted in lower rates of end-stage renal disease (ESRD) at 1 year and lower mortality at 2 years. Despite concerns of severe iatrogenic adverse events, studies to date have not identified a threshold where immunosuppressive therapy is considered futile since greater than 50% of patients achieve

dialysis independence even with severe disease presentation. With the anticipated doubling of Americans aged 65 or older in the next 25 years [14] and the predilection of AAV for elderly, our ability to identify safer alternatives to standard of care therapy with cyclophosphamide in this vulnerable population becomes paramount.

The mean age of our cohort was similar to those in other studies focusing on elderly AAV patients [10,11] and in agreement with other series our cohort was enriched with MPO ANCA positive patients [8,10]. Thirty patients in our cohort received rituximab 375 mg/m² once a week for 4 weeks and a single patient was dosed with 1000 mg for 2 doses 2 weeks apart. In this context it is important to note that the RAVE and RITUXVAS trials used rituximab 375 mg/m² once a week for 4 weeks. Although dose ranging studies of rituximab have not been performed to determine the optimal protocol, 1 retrospective series of 65 AAV patients with a median age of 47 years reported similar rates of remission with both the rituximab regimens (375 mg/m² once a week for 4 weeks compared to 1000 mg iv every 2 weeks for 2 doses) [15]. Similar studies are lacking in the elderly AAV patients. Thirty patients (97%) in our cohort achieved disease remission with rituximab induction therapy. Similar high rates of remission induction have been reported in cohorts using cyclophosphamide (5, 8). Prednisone dose was tapered to a mean of 5 mg within the first 6 months similar to other studies using rituximab (3). Infections requiring hospitalization were reported in 5 patients (16%). Whereas infections can occur, rituximab is associated with a lower rate of infections in elderly compared to cyclophosphamide (5, 8). The 1 year patient survival was 100% in our cohort compared to high mortality observed in cohorts using cyclophosphamide.

Our study was limited by its retrospective design, and lack of B-cell data and immunoglobulin data in all patients prior and after treatment with rituximab.

Our data confirms the efficacy of rituximab for induction of remission in AAV and extends to elderly patients with AAV. Further studies are needed to evaluate the efficacy and safety of RTX in elderly AAV patients.

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Table 1

Baseline characteristics of elderly AAV patients treated with rituximab

Age at time of infusion (yrs), mean (SD)	71 (6)
Gender, M:F	10:21
ANCA type, <i>n</i>	
PR3	12
MPO	18
Negative	1
New diagnosis, <i>n</i> (%)	18 (58)
e-GFR at entry (ml/min/1.73 m ²) mean (SD)	40 (28)
BVAS/WG score at diagnosis, mean (SD)	4.4 (1.5)
Alveolar hemorrhage, <i>n</i> (%)	3 (10%)
RTX dosing	
375 mg/m ² q week for 4 weeks, <i>n</i> (%)	30 (97)
1000 mg × 2 doses, <i>n</i> (%)	1 (3)
Cyclophosphamide use	
Oral (<i>n</i>)	4
Follow-up time, mean days (SD)	1061 (972)

Table 2

Outcomes of elderly AAV patients treated with rituximab for remission induction

Outcomes	
Remission, <i>n</i> (%) (<i>n</i> =31)	30 (97%)
Mean 6 month Prednisone dose (mg) (SD) (<i>n</i> =30)	5.6 (4)
Mean GFR rise at 6 months (SD) (<i>n</i> =28)	11 (1-32)
Infections, <i>n</i> (%) (<i>n</i> =31)	5 (16)
Leukopenia, <i>n</i> (%) (<i>n</i> =31)	0 (0%)
Death in the first 12 months (<i>n</i> =25)	0 (0)