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RITUXIMAB MONOTHERAPY FOR PATIENTS WITH RECURRENT PRIMARY CNS LYMPHOMA

Rituximab, a chimeric monoclonal antibody against the CD20 antigen, increased survival when it was added to chemotherapy for patients with systemic, CD20+ diffuse large B-cell (DLBCL) non-Hodgkin lymphoma (NHL). Consequently, it is now a standard component of the treatment for these patients. Approximately 90% of primary CNS lymphomas (PCNSL), a rare extranodal variant of NHL, are CD20+ DLBCL. Rituximab has been incorporated into some treatment regimens for newly diagnosed and relapsed PCNSL, although it is not known whether this agent will improve outcomes to the extent that it has for patients with systemic DLBCL.[1,2] Rituximab may not traverse the normal blood–brain barrier (BBB) and this could limit the effectiveness of this agent in PCNSL. Rituximab concentrations in CSF are 0.1% of plasma levels when it is administered at a standard IV dose of 375 mg/m^2, suggesting poor BBB penetration.[3] Moreover, in a report of 4 patients with PCNSL administered I^{123}-labeled rituximab, there was weak tumor uptake in only one out of 4 patients.[4] However, in another study of the ^{90}Y-labeled anti-CD20 antibody ibritumomab tiuxetan target accumulation of the antibody was observed in 4 out of 6 patients with PCNSL assessed by SPECT imaging with ^{111}In-labeled ibritumomab tiuxetan.[5] The latter report is consistent with the hypothesis that rituximab may achieve therapeutic concentrations in regions of a brain tumor manifesting contrast enhancement secondary to BBB disruption.

Level of evidence. This is a Class III case series of 12 patients with PCNS lymphoma treated with rituximab, with MRI responses achieved in 36% of patients and extension of median progression-free survival to 57 days (95% CI 29–175 days), overall survival to 20.9 months (95% CI 2.9–47 months).

Methods. This pilot study was conducted by the National Cancer Institute–sponsored New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium to determine the response rate to rituximab monotherapy in patients with recurrent or refractory PCNSL (NCT00072449). Rituximab was administered at a dose of 375 mg/m^2 as a single IV infusion every week for up to 8 weeks. MRI scans were performed every 2 months and radiographic responses were determined using standard criteria.[6] Responses were confirmed with a follow-up MRI 1 month after first declaration of complete response (CR) or partial response (PR).

Table Patient characteristics

Characteristics	Values
Median age, y (range)	64 (31–81)
Male:female	7:5
Median KPS score (range)	85 (60–100)
Median MMSE score (range)	29 (18–30)

Abbreviations: KPS = Karnofsky Performance Scale; MMSE = Mini-Mental State Examination.

Results. Twelve patients were enrolled at 4 NABTT institutions. Patient characteristics are enumerated in the table. The median time from initial diagnosis of PCNSL to relapse was 19 months (3.1–64.3 months). All patients had failed prior methotrexate-based treatment. The median number of rituximab infusions for patients treated on this study was 6 (range 3–8). Confirmed responses were achieved in 4/11 (36%) patients (3 CR, 1 PR). One additional patient achieved a CR but died of infection 63 days after starting rituximab and before the response could be confirmed on follow-up MRI. Including the latter patient resulted in an unconfirmed response proportion of 5/12 (42%). One patient was on dexamethasone at the time of radiographic PR but steroids were subsequently discontinued. No other responding patients were on corticosteroids at the time of rituximab treatment. The median progression-free survival was 57 days (95% confidence interval [CI] 29–175 days) and the median overall survival was 20.9 months (95% CI 2.9–47 months). Ten patients have developed progressive disease and 8 patients have died. The median progression-free survival and overall survival for the 4 patients achieving a confirmed radiographic response were 7.6 (5.7 to 36.2) months and 47 (9.1 to 47)

months. One of these patients remains in remission. Toxicity was modest with 4 episodes of grade 3–4 toxicities possibly related to rituximab (allergic reaction, fatigue, anxiety, back pain).

Discussion. This report is the largest series of patients with PCNSL treated with IV rituximab monotherapy. Radiographic responses were observed in approximately one-third of enrolled patients and these responses were durable in some. These data provide evidence of activity of IV rituximab monotherapy in patients with PCNSL and support the incorporation of this agent into chemotherapy regimens for this rare form of NHL. Further studies are required to determine the optimal dose and schedule of rituximab in this clinical setting.

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