Immunochemotherapy with Rituximab and Temozolomide for Central Nervous System Lymphomas

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BACKGROUND. Methotrexate-based and alkylator-based chemotherapy regimens are associated with renal and bone marrow toxicities, which limit their use in patients with central nervous system (CNS) lymphomas. The authors report their experience with an immunochemotherapy regimen consisting of rituximab and temozolomide in patients with primary or metastatic CNS lymphoma.

METHODS. Seven patients who had received rituximab and temozolomide were identified from the database of the brain tumor clinic at the authors' institution: three patients had developed recurrent primary CNS lymphoma (PCNSL), one patient had newly diagnosed PCNSL but had poor renal function, and three other patients with systemic non-Hodgkin lymphoma developed recurrent lymphoma in the brain only. Patients were scheduled to receive 4 cycles of induction rituximab on Day 1 and temozolomide on Days 1–5 of a 28-day cycle. Thereafter, their treatment included a total of up to 8 maintenance cycles of temozolomide alone on Days 1–5 of a 28-day cycle. A gadolinium-enhanced magnetic resonance image of the head was obtained after every two cycles of treatment.

RESULTS. All patients received rituximab without toxicity. Of the 4 patients who received induction temozolomide at doses $>$ 150 mg/m^2 daily on Days 1–5, 2 experienced Grade 2 leukopenia and thrombocytopenia. Five patients achieved a radiographic complete response, and two patients had partial responses after induction treatment. The median response duration was 6 months (range 3–12+ months), and the median survival was 8 months (range 3+–12+ months).

CONCLUSIONS. Although median survival was short, immunochemotherapy with rituximab and temozolomide was well tolerated and exhibited efficacy in this elderly and heavily pretreated cohort. The data obtained in the current study suggest that the optimal induction dose combination consists of rituximab 375 mg/m^2 on Day 1 and temozolomide 150 mg/m^2 daily on Days 1–5. ***Cancer* 2004; 101:139–45.** © *2004 American Cancer Society.*

KEYWORDS: rituximab, temozolomide, brain, lymphoma.

Primary and metastatic central nervous system (CNS) lymphomas are chemosensitive malignancies. Although combined-modality methotrexate-based chemotherapy yields the best survival results,[1] patients with poor renal function and patients who have received whole-brain irradiation cannot tolerate this regimen. Recurrent primary CNS lymphoma (PCNSL) following methotrexate therapy may respond to procarbazine, lomustine, and vincristine (PCV)[2]; topotecan[3]; or high-dose cytarabine,[4] but myelosuppression is a serious dose-limiting toxicity for patients with this malignancy. For patients with non-Hodgkin lymphoma (NHL) metastatic to the CNS, major treatment limitations include chemoresistant disease, poor bone marrow reserve, and inadequate CNS penetration of chemotherapy

TABLE 1
Pretreatment Patient Characteristics and Corticosteroid Use

Patient no.	Age (yrs)	Disease	Significant concurrent medical conditions	Initial daily dexamethasone dose (mg)	Daily dexamethasone dose at best response (mg)	Prior chemotherapy
1	41	CD20+ recurrent PCNSL	None	2	None	HD methotrexate, HD cytarabine, topotecan
2	73	CD20+ newly diagnosed PCNSL	Cervical spondylosis, celiac sprue	24	2	None
3	64	CD20+ recurrent PCNSL	Waldenstrom macroglobulinemia, DVT, Stage I seminoma (no active disease)	8	3	HD methotrexate
4	71	CD20+ recurrent PCNSL	Atrial fibrillation	4	2	HD methotrexate
5	76	CD20+ recurrent NHL in the brain only	Renal insufficiency, chronic urinary tract infection, radical cystectomy with ileal conduit	8	Prednisone, 5 mg	CHOP
6	55	CD20+ recurrent NHL in the brain only	Gastric ulcer	2	None	CHOP
7	47	CD20+ recurrent NHL in the brain only	None	None	None	CHOP, RIME with stem cell rescue

PCNSL: primary central nervous system lymphoma; HD: high-dose; DVT: deep vein thrombosis; NHL: non-Hodgkin lymphoma; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; RIME: rituximab, ifosfamide, mitoxantrone, and etoposide.

agents. High-dose methotrexate, topotecan, high-dose cytarabine, and PCV in combination with whole-brain or craniospinal irradiation are potentially efficacious regimens. However, these treatments can cause significant renal failure or myelosuppression. It is clear that an efficacious regimen with less associated toxicity is required for patients with primary or metastatic CNS lymphoma.

The combination of rituximab and temozolomide may be synergistic in the treatment of CNS lymphomas. Such synergism was observed for the combination of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in elderly patients with systemic, CD20-positive (CD20+) diffuse large B-cell NHL.[5] Unfortunately, CHOP does not penetrate the CNS.[6] Rituximab[7,8] and temozolomide,[9] however, can penetrate the CNS, and these drugs have mild and nonoverlapping toxicities. In the current report, we describe our experience with rituximab and temozolomide in seven patients with primary or metastatic CNS lymphoma.

MATERIALS AND METHODS

Cases of CNS lymphoma diagnosed between 1997 and 2003 were extracted from the database of the brain tumor clinic at our institution. Seven patients were retrospectively identified who underwent treatment with rituximab and temozolomide after providing informed consent. Although these seven patients were not enrolled in a protocol, all were treated in a uniform fashion using the same schedule of rituximab and temozolomide. All of these patients also underwent magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) disease staging at diagnosis and during follow-up. They were treated with 375 mg/m^2 rituximab on Day 1 after premedication with 650 mg acetaminophen and 25 mg diphenhydramine. The infusion was initiated at a rate of 50 mg per hour and was gradually titrated to a maximum rate of 400 mg per hour. Temozolomide, which was initiated at a dose of 150–200 mg/m^2 daily, was administered after rituximab infusion, on Days 1–5, and 100 mg dolasetron was administered 1 hour before temozolomide administration. This treatment was repeated every 28 days. Before the start of each cycle, patients' general clinical status, neurologic function, blood counts, electrolytes, and liver function were assessed. Blood counts also were obtained weekly after treatment, and patients who experienced Grade $\geq$ 2 myelotoxicity had their temozolomide doses reduced in subsequent cycles. Patients would receive a total of 4 cycles of induction rituximab and temozolomide followed by 8 cycles of maintenance temozolomide alone every 28 days. Gadolinium-enhanced MRI scans of the head also were obtained after every two cycles of treatment.

RESULTS

Pretreatment patient characteristics and corticosteroid use are summarized in Table 1. The median pretreatment dexamethasone dose was 4 mg (range, 0–24 mg), and the median dose at the time of best response was 2 mg (range, 0–3 mg). All patients tolerated dose

TABLE 2
Treatment Results after Administration of Rituximab and Temozolomide

Patient no.	Age (yrs)	Disease	Cycles of R + T[a]	Dose of T (mg/m^2 per day)	Cycles of T	Response	Duration of response (mos)	Survival (mos)	Initial CSF cytology	Intrathecal chemotherapy	Final CSF cytology
1	41	CD20+ recurrent PCNSL	4	175–200	2	CR	6	6	Negative	Cytarabine	Negative
2	73	CD20+ newly diagnosed PCNSL	3	150–200	0	PR	3	6	Negative	Methotrexate	Negative
3	64	CD20+ recurrent PCNSL	4	150	5	CR	9+	9+	Negative	None	Negative
4	71	CD20+ recurrent PCNSL	1	200	0	CR	3+	3+	Negative	None	Negative
5	76	CD20+ recurrent NHL in the brain only	4	75–150	8	CR	12+	12+	Negative	None	Negative
6	55	CD20+ recurrent NHL in the brain only	4	150	2	PR	6	8+	Negative	None	Negative
7	47	CD20+ recurrent NHL in the brain only	4	150–200	1	CR	5	6	Positive	Liposomal cytarabine	Negative

R: rituximab; T: temozolomide; CSF: cerebrospinal fluid; CR: complete response; PR: partial response; PCNSL: primary central nervous system lymphoma; NHL: non-Hodgkin lymphoma.
[a] All patients received 375 mg/m^2 rituximab.

reductions of dexamethasone during treatment. There were four patients with PCNSL, including three patients who were treated for recurrent PCNSL and one patient who had newly diagnosed PCNSL. All patients with PCNSL had histologically documented CD20+ disease. The most common preimmunochemotherapy treatment received was high-dose combined-modality methotrexate ($n = 3$). One patient also received high-dose cytarabine at the time of her first recurrence and topotecan at the time of her second recurrence. Three additional patients were treated for systemic NHL recurrences in the brain only, including two patients with biopsy-confirmed CD20+ lymphoma cells in the brain and one patient with known systemic CD20+ NHL. All three patients were treated initially with CHOP for systemic NHL, whereas one patient received high-dose systemic chemotherapy consisting of rituximab, ifosfamide, mitoxantrone, and etoposide (RIME) followed by stem cell rescue for consolidation after CHOP.

All patients received rituximab at 375 mg/m^2 without experiencing toxicity. Of the 4 patients who received temozolomide at doses > 150 mg/m^2 daily on Days 1–5 during induction, 2 experienced Grade 2 leukopenia and thrombocytopenia. When the temozolomide dose was reduced to ≤ 150 mg/m^2 in subsequent cycles received by those patients, there were no further episodes of leukopenia or thrombocytopenia. One patient (Patient 4) developed persistent myelosuppression for 3 months after 1 cycle of induction rituximab and temozolomide; after phenytoin was replaced by levetiracetam for this patient, the myelosuppression resolved.

Treatment results are summarized in Table 2. The median survival was 8 months (range, 3+–12+ months), and the median duration of response was 6 months (range 3–12+ months). There were five complete responses (CRs) and two partial responses (PRs) after administration of induction rituximab and temozolomide (Figs. 1, 2). Three of four patients developed recurrent disease while receiving maintenance temozolomide alone, but only one patient developed a recurrence during rituximab and temozolomide induction therapy. Furthermore, although only one of seven patients had positive CSF cytologic findings for lymphoma, three patients were treated with concomitant intrathecal chemotherapy. CSF cytologic findings remained negative for the six patients who initially had negative findings, whereas the one patient who initially had positive CSF cytologic findings was found to have negative findings after four cycles of induction immunochemotherapy and intrathecal liposomal cytarabine. It is noteworthy that two patients in the current cohort had chronic renal insufficiency. One patient had a calculated creatinine clearance rate of 28 mg.L per minute that was caused by chronic urinary tract infection following radical cystectomy with ileal conduit and thus was not a candidate for high-dose systemic methotrexate therapy. This patient experienced a CR and was alive and healthy after 12+ months. Although the other patient had a 24-hour urine creatinine clearance of 64 mg.L per minute, he was not treated with high-dose methotrexate because of his advanced age, uncertain cardiac status, and suboptimal renal function. This patient had a PR after two cycles of induction rituximab and temozolomide but developed recurrent disease after the third induction cycle. Despite receiving whole-brain cranial irra-

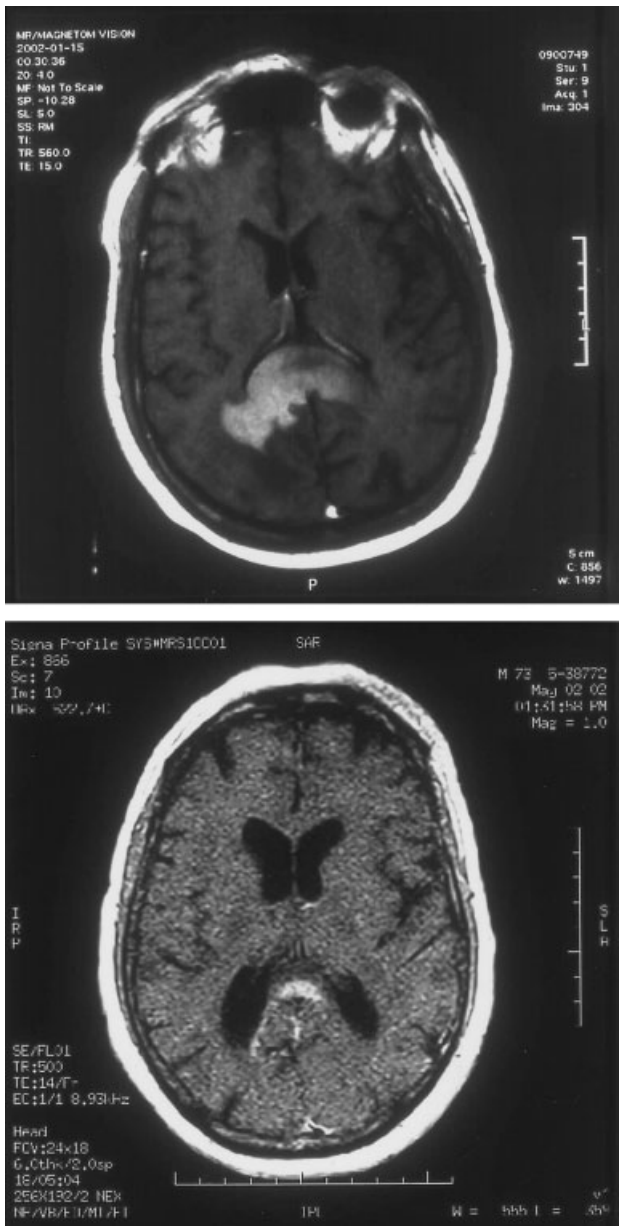

FIGURE 1. (A) Axial view of a gadolinium-enhanced magnetic resonance image of Patient 2 at the time of initial diagnosis of primary central nervous system lymphoma. Because of old age, uncertain cardiac status, and suboptimal 24-hour urine creatinine clearance (64 mg.L per minute), this patient was not a candidate for high-dose systemic methotrexate therapy. (B) The patient subsequently had a partial response after two cycles of immunochemotherapy with rituximab and temozolomide.

diation, he developed significant side effects due to dexamethasone treatment and lived for an additional 3 months.

DISCUSSION

Rituximab is a chimeric monoclonal antibody against the CD20 antigen commonly found in B-cell NHL. Its mechanisms of action include complement-mediated cytotoxicity, antibody-mediated phagocytosis, and antibody-dependent growth inhibition and apoptosis.[10] Delayed hematologic toxicity is observed in $< 10\%$ of patients. Infectious complications are rare, despite the fact that reversible B cell depletion persists for 6 months after rituximab administration. Raizer et al.[7] reported two PRs and one case of stable disease after rituximab treatment in three patients who had recurrent PCNSL. The limited efficacy of single-agent rituximab in those patients may have been caused by resistant disease or incomplete penetration of the blood-brain barrier (BBB). It is interesting to note that despite its high molecular weight, rituximab antibody was detectable in the CSF.[7,8] Rituximab transport to the CSF may occur via leakage across areas of BBB breakdown in the lymphoma and/or macromolecular vesicular transport of the antibody across an intact BBB.[11] Although Rubenstein et al.[8] reported that the CSF concentration of rituximab was 0.1% of that in the serum after systemic administration in 2 patients, their findings remain in the preliminary stages and await further pharmacokinetic analysis.

Temozolomide does not possess the cumulative myelotoxicity that is associated with similar alkylators, such as lomustine and procarbazine in the PCV regimen, which is effective in treating recurrent PCNSL.[2] In addition, temozolomide is an alkylator that is bioavailable to the CNS, as one-third of temozolomide received orally can be detected in the CSF.[9] In addition, it has been shown that temozolomide effects response rates, including CRs and PRs, in patients with PCNSL.[12–16] However, a recent Phase II trial involving patients with PCNSL suggested that temozolomide possesses limited efficacy as a single agent, with 4 of 9 patients (44%) experiencing responses, 3 of 9 patients (33%) experiencing disease progression, and 2 of 9 patients (22%) dying unexpectedly during treatment.[16] Our data also suggest the limited efficacy of temozolomide as a single agent for the treatment of CNS lymphoma, as three of four recurrences in the study cohort occurred while patients were receiving maintenance temozolomide.

Several lines of evidence suggest that rituximab can sensitize CD20+ B lymphoma cells to cytotoxic chemotherapy by down-regulating interleukin-10 and Bcl-2 via inactivation of the signal transducer and activation of transcription 3 (STAT3) protein.[17,18] Therefore, treatment with rituximab followed by an alkylator such as temozolomide may offer synergistic lymphoma cell kill without overlapping toxicities. There is compelling clinical evidence that this synergism is operative in the combination of rituximab and CHOP for patients with systemic NHL. Compared with standard CHOP, immunochemotherapy with ritux-

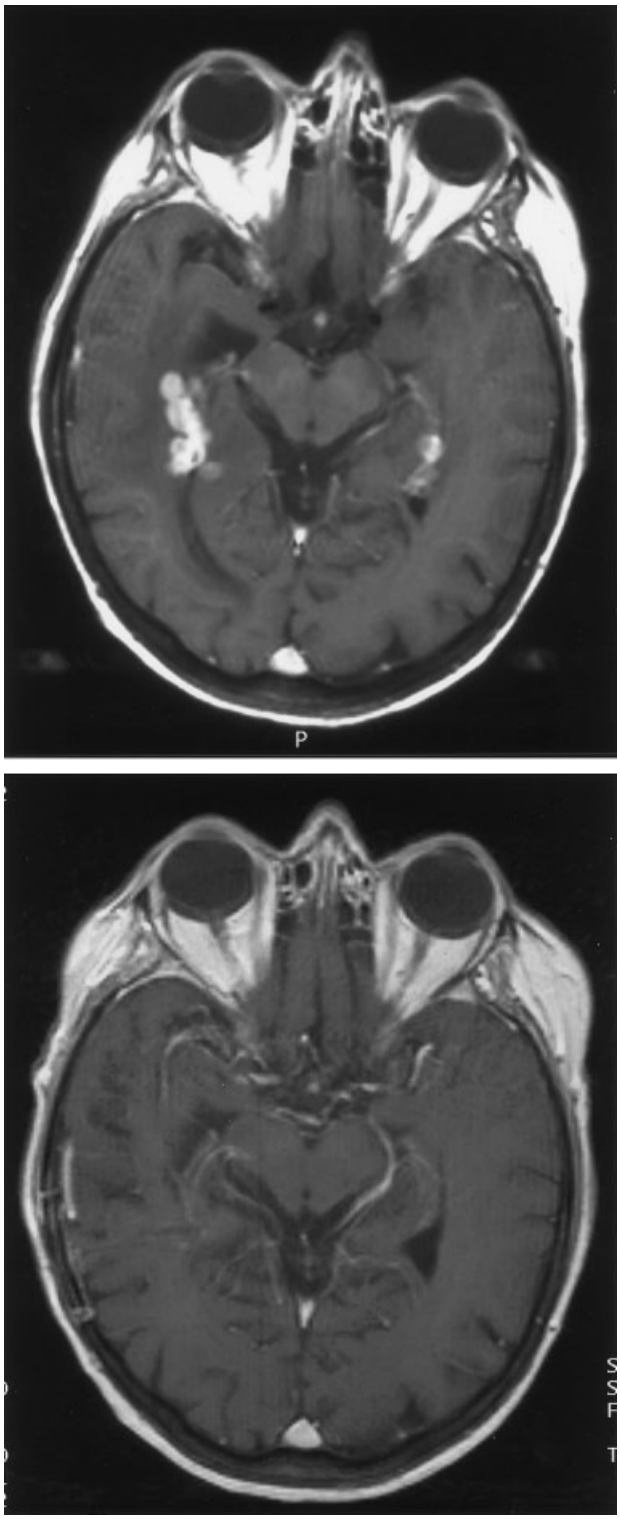

FIGURE 2. (A) Axial view of a gadolinium-enhanced magnetic resonance image of Patient 5 at the time of recurrence of systemic diffuse large B-cell non-Hodgkin lymphoma in the central nervous system only. This patient had a calculated creatinine clearance of 28 mg.L per minute as a result of renal insufficiency caused by chronic urinary tract infection following radical cystectomy with ileal conduit. (B) After 2 cycles of rituximab and temozolomide, the patient achieved a complete response, which has been maintained for $>$ 12 months.

imab and CHOP was found to increase the CR rate, progression-free survival, and overall survival in elderly patients with diffuse large cell lymphoma,[5] historically a group with poor prognosis. More notably, the toxicities (including myelosuppression) associated with rituximab and CHOP were no more severe than the toxicities associated with CHOP alone.[5]

The combination of rituximab and temozolomide may offer a synergistic benefit for patients with CNS lymphoma. Like the combination of rituximab and CHOP, rituximab may sensitize B lymphoma cells to the cytotoxic effects of temozolomide. The serum half-life of rituximab is 4.4 days,[19] suggesting that the half-life of rituximab in the CSF may be at least 4 days after systemic administration. If this is correct, then administration of temozolomide on Days 1–5 after infusion of rituximab on Day 1 would represent an ideal schedule for achieving maximum synergy. Our data do not support the use of rituximab and temozolomide to eradicate lymphomatous meningitis. However, due to rituximab's high affinity for CD20 antigen on lymphoma cells and its synergism with temozolomide, a large quantity of rituximab molecules may not be required to eradicate CD20+ lymphoma cells in CSF. Further investigation of the CSF pharmacokinetics of rituximab and temozolomide administered in combination is necessary.

Although there were 5 CRs and 2 PRs, the median response duration and the median survival were limited (6 months and 8 months, respectively). However, it is noteworthy that 4 of 7 patients were age $>$ 60 years and that 1 patient had renal dysfunction that was severe enough to preclude high-dose systemic methotrexate. Because immunochemotherapy with rituximab and temozolomide is nontoxic to the kidneys, this regimen would be favorable for patients with impaired renal function. In the current study, the patient with the best observed response, a woman age 76 years with a calculated creatinine clearance of 28 mg/L per minute, had a CR that has been maintained to date, $>$ 12 months after the initiation of treatment. For this patient, at present, treatment with rituximab and temozolomide has rendered whole-brain cranial irradiation unnecessary. Six of seven in the cohort members had been treated previously with cytotoxic chemotherapies and thus may have had chemoresistant disease. Given these unfavorable characteristics, the observed response rate was comparable to the rate reported in a series that used PCV as salvage therapy for patients with recurrent PCNSL[2]; however, the cumulative myelotoxicity associated with PCV was not observed in the current study.

The data obtained in the current study do not indicate that dexamethasone had an effect on patient responses. Although most patients had received dexa-

methasone before treatment with rituximab and temozolomide, all tolerated dexamethasone dose reduction during treatment, including three patients who eventually weaned off dexamethasone. One patient (Patient 7) did not receive dexamethasone before treatment and only began receiving this agent after he developed recurrent disease, 5 months after the start of treatment. The patient with the best response (Patient 5) experienced adrenal insufficiency and currently is receiving a maintenance prednisone regimen. However, we could not entirely exclude the possibility that dexamethasone contributed in some capacity to the responses observed in this cohort.

One patient previously had been treated with rituximab as part of the RIME regimen with stem cell rescue. Although resistance to rituximab would have been a concern, this patient had a robust response and achieved a CR after four induction cycles of rituximab and temozolomide. In the retreatment of follicular and low-grade NHL with rituximab, a 40–50% response rate has been reported, with the duration of the second response being longer than that of the first response (18 months vs. 12 months).[20,21] In patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, Hainsworth et al.[22] noted a higher response rate after retreatment with rituximab, with the overall response rate increasing from 51% (CR rate, 4%) after 1 cycle of rituximab to 58% (CR rate, 9%) in the same cohort after the completion of an additional 4 maintenance cycles of rituximab at 6-month intervals. One possible mechanism for the increase in rituximab efficacy during retreatment involves priming of the immune system for antibody-directed cellular cytotoxicity after repeat exposure. Compared with cytotoxic chemotherapy agents, rituximab may have completely different mechanisms of resistance. Therefore, previous rituximab exposure would not necessarily result in resistance to subsequent rituximab treatment.

In conclusion, the combination of rituximab and temozolomide demonstrated efficacy against recurrent PCNSL and systemic NHL metastatic to the CNS, and this immunochemotherapy combination may offer superior efficacy relative to either agent alone. The sequential administration of rituximab followed by temozolomide is important, because the observed synergy depends on the sensitization of CD20+ B lymphoma cells to temozolomide by rituximab. The optimal induction dose combination appears to consist of rituximab 375 mg/m^2 on Day 1 and temozolomide 150 mg/m^2 daily on Days 1–5. A Phase II trial will be required to estimate the efficacy of this immunochemotherapy regimen in a larger population.

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