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Role of Intrathecal Rituximab and Trastuzumab in the Management of Leptomeningeal Carcinomatosis

Anthony J Perissinotti

David J Reeves

Abstract

OBJECTIVE: To review evidence for the use of intrathecal rituximab and trastuzumab in the management of leptomeningeal carcinomatosis.

DATA SOURCES: A search of MEDLINE (1966-July 2010) and *International Pharmaceutical Abstracts* (1970-July 2010) was performed using search terms intrathecal, trastuzumab, rituximab, and monoclonal antibody. Additionally, American Society of Clinical Oncology, San Antonio Breast Conference, American Association for Cancer Research, and American Society of Hematology meeting abstracts were searched.

STUDY SELECTION AND DATA EXTRACTION: Publications were reviewed for inclusion. Those reporting use of rituximab and trastuzumab intrathecally are reviewed and include 1 Phase 1 trial, 2 small prospective studies, 1 case series, and 15 case reports.

DATA SYNTHESIS: The treatment of leptomeningeal carcinomatosis is challenging due to the presence of the blood-brain barrier. Numerous systemically administered therapies do not readily penetrate into the site of leptomeningeal disease and have been ineffective. Intrathecal administration of 2 monoclonal antibodies (trastuzumab and rituximab) has been investigated in case reports and case series. Additionally, intrathecal rituximab has been investigated in a Phase 1 study. Survival after intrathecal trastuzumab ranged from 39 days to greater than 72 months and the drug was well tolerated, with no adverse events attributed to it. Doses used in these reports ranged from 5 to 100 mg. Survival after intrathecal rituximab ranged from 1.1 weeks to greater than 3.5 years. In the Phase 1 trial, the maximum tolerated rituximab dose was 25 mg and 60% of patients responded. Four of the 6 responding patients experienced a complete response. Intrathecal rituximab exhibited minor toxicities that resolved quickly without long-term effects.

CONCLUSIONS: Reports suggest that both trastuzumab and rituximab may be utilized intrathecally. Patients with refractory leptomeningeal carcinomatosis may benefit from a trial of intrathecal trastuzumab or rituximab; however, their use remains investigational, as more data and experience are necessary before intrathecal administration can be considered standard.

Request

Is there a role for intrathecally administered rituximab and trastuzumab in the treatment of leptomeningeal carcinomatosis?

Response

BACKGROUND

Leptomeningeal carcinomatosis, also known as neoplastic meningitis, occurs when malignant cells enter the leptomeningeal space via hematogenous dissemination or direct extension.¹ The malignant cells are spread throughout the neuraxis by the flow of the cerebrospinal fluid (CSF), leading to disease throughout the central nervous system (CNS). Leptomeningeal carcinomatosis leads to substantial morbidity and mortality, and there are few, if any, effective treatments.

Fortunately, the incidence of leptomeningeal carcinomatosis remains low, at approximately 5% of patients with cancer.^{1,2} However, the frequency with which this complication is diagnosed is believed to be increasing due to greater control of systemic disease, longer survival, and improvements in neuroimaging.^{1,2} This incidence varies among the solid tumors and is most common with breast cancer, smallcell lung cancer, and melanoma.² Lymphoma may also cause neoplastic meningitis, termed lymphomatous carcinomatosis. Typically, survival is measured in weeks without treatment and approaches 3–6 months with traditional treatments.² Treatments commonly utilized for the management of leptomeningeal carcinomatosis include radiation, systemic chemotherapy, and intrathecal chemotherapy. Drugs currently utilized intrathecally include cytarabine, liposomal cytarabine, methotrexate, and thiotepa. According to the National Comprehensive Cancer Network, patients with leptomeningeal carcinomatosis may be considered for either supportive care, fractionated external beam radiation to symptomatic sites, or intrathecal chemotherapy.¹ Patients with lymphomatous carcinomatosis have additional options, including steroid administration and systemic chemotherapy with high-dose methotrexate.¹ Despite these conventional therapies, response still remains low.

Due to the presence of the blood—brain and blood—cerebrospinal barriers, it is difficult for systemically administered chemotherapy to penetrate into the site of leptomeningeal disease. Further hindering penetration of chemotherapy into the CSF are the adverse effects associated with the high doses of systemically administered drugs required to achieve adequate CNS concentrations. Many agents, including monoclonal antibodies, tend to be large molecules and those weighing above 200 kDa have minimal penetration into the CSF. Due to low CNS penetration of most chemotherapy, the CNS often acts as a sanctuary site for tumor cells. For these reasons the desired route of administration is intrathecal; however, response is generally short lived and patients may develop adverse effects such as arachnoiditis from the chemotherapy.

More recently, intrathecal administration of 2 monoclonal antibodies has been investigated, representing a novel and targeted treatment for leptomeningeal carcinomatosis. Intrathecal trastuzumab, an anti-human epidermal growth factor receptor (HER2) monoclonal antibody, has been utilized and reported in HER2-positive breast cancer. Additionally, intrathecal rituximab, an anti-CD20 monoclonal antibody, has been investigated in B-cell lymphoma and leukemia. Though

much of the data are preliminary, there has been interest in utilizing such novel agents in the management of leptomeningeal carcinomatosis.

Another emerging option for the treatment of HER2-positive breast cancer with leptomeningeal carcinomatosis is the oral tyrosine kinase inhibitor lapatinib. It shows promise for leptomeningeal carcinomatosis, as it is a small molecule (<1 kDa) able to penetrate the blood-brain barrier. However, 2 Phase 2 trials (EGF105084 and NCI-6969) that studied lapatinib monotherapy for leptomeningeal carcinomatosis were both terminated prematurely, as they failed to meet their primary endpoints.³⁴ The modest effects observed in clinical trials may be attributed to efflux transporters that pump the drug out of the CNS. Lapatinib is not discussed in this review.

LITERATURE REVIEW

A search of MEDLINE (1966-July 2010) and *International Pharmaceutical Abstracts* (1970-July 2010) was performed using the search terms intrathecal, trastuzumab, rituximab, and monoclonal antibody. Relevant articles were identified and references of these articles were reviewed for additional reports. Meeting abstracts of the American Society of Clinical Oncology, the San Antonio Breast Conference, the American Association for Cancer Research, and the American Society of Hematology were also searched. Reports most pertinent to the use of intrathecal trastuzumab and rituximab are reviewed here.

HER2-Positive Breast Cancer and Intrathecal Trastuzumab

Trastuzumab plays a central role in the treatment of HER2-positive breast cancer and has been shown to increase survival. Whether due to this increase in survival, the lack of trastuzumab penetration into the CNS, or the aggressive natural history of HER2-positive breast cancer, patients receiving trastuzumab may have a higher incidence of CNS metastases.⁵ It has been shown that CSF concentrations of trastuzumab are 300- to 400-fold lower than serum concentrations.^{6,7} These concentrations may be increased by inflammation or whole-brain radiation therapy; however, concentrations still remain between 1/76 and 1/49 of those in plasma and may not be consistently high enough to have a therapeutic effect.⁷ With the known activity of trastuzumab and difficulty in achieving adequate CNS concentrations, intrathecal administration has been considered.

In a rat model, trastuzumab was administered via direct intracerebral microinfusion or intraperitoneally after transplantation of HER2 breast cancer cells into the cerebrum.⁸ Among rats receiving systemic (intraperitoneal) trastuzumab, survival was 26.5 days, while the median survival of those receiving intracerebral trastuzumab was 52 days. No toxicity was evident in those receiving intracerebral trastuzumab. Another animal model utilizing cynomolgus monkeys evaluated the toxicity and pharmacokinetics of intrathecal trastuzumab.⁹ Doses equated to approximately 3.4- to 67-fold higher than doses used in human clinical case reports. Notably, upon neurologic, clinical, and anatomic pathology examinations, no trastuzumab-related adverse effects occurred. CSF concentrations attained were much higher than in clinical models, as doses in this animal model were much higher. However, there was large variation in CSF concentrations. The authors attributed this variation to uneven distribution of drug throughout the CNS and rapid transfer of trastuzumab from the CSF into the serum after intrathecal administration. In addition

to these animal studies, there are a limited number of reports in which intrathecal trastuzumab was utilized in humans (Table 1^{10–18}).

Reference	Pts. (n)	Intrathecal Dose (mg)	Doses (n)	Other Intrathecal Drugs Coadministered	Concurrent Systemic Therapy	Outcome	Survival ^a
Stemmler (2008) ¹⁰	1; CR	20	4	Methotrexate	Yes	Condition improved; remission of leptomeningeal carcinomatosis	39 days
Laufman (2001) ¹¹	1; CR	5–20	4	Methotrexate, thiotepea	Yes	Neurologically stable for 30 days	66 days
Colozza (2009) ¹²	1; CR	12.5	23		Yes	Neurological condition improved; responded for 19 mo	>72 mo
Stemmler (2006) ¹³	1; CR	5–20	4		Yes	Condition improved; disappearance of tumor cells in cerebrospinal fluid	>5 mo
Ferrario (2009) ¹⁴	1; CR	20–50	~29	Thiotepea, methotrexate	Yes	Neurological condition improved; significant improvement on MRI; clearance of malignant cells, responded for >2 y	>2 y
Mir (2008) ¹⁵	1; CR	20–100	6		NR	Neurological condition improved; stable disease on MRI at 6 wk	5 mo
Platini (2006) ¹⁶	1; CR	20–25	46	Prednisone, thiotepea	Yes	Higher functions and balance improved; general state maintained	>21 mo
Shojima (2008) ¹⁷	1; CR	25	6		NR	Disappearance of malignant cells in cerebrospinal fluid; shrinkage of brain tumors	>6 wk
Allison (2009) ¹⁸	16 ^b ; PS	20–60	4		NR	Breast cancer: 2/4 pts. responding; glioblastoma: 7/11 pts. responding; medulloblastoma: 1/1 pt. responding	4 wk to >14 wk

CR = case report; MRI = magnetic resonance imaging; NR = not reported; PS = prospective study.
^aApproximate time from first dose of intrathecal trastuzumab.
^bIncluded patients with glioblastoma, breast cancer, and medulloblastoma.

The use of intrathecal trastuzumab has been described in 8 case reports involving patients with leptomeningeal carcinomatosis following HER2-overexpressing metastatic breast cancer.^{10–17} Patients were administered intrathecal trastuzumab as salvage therapy after failing extensive treatment with either neurosurgery, systemic chemotherapy, intrathecal chemotherapy, or whole-brain radiation; in many, a combination of the 4 was utilized. Intrathecal trastuzumab was used as monotherapy in 4 cases and given concurrently with intrathecal methotrexate or intrathecal thiotepea in the other 4. Doses of trastuzumab ranged from 5 to 100 mg and were repeated after as little as 3 days in 1 report to as long as 3 weeks in others.^{10,12–14} The most common schedule was 20–30 mg weekly. All doses, including doses up to 100 mg, and schedules were well tolerated. In fact, an autopsy failed to reveal any toxicity, including arachnoiditis, in 1 case report.¹¹

Intrathecal therapy with trastuzumab resulted in noticeable relief of clinical symptoms (overflow incontinence, paraparesis of the legs, mental status changes, headaches, ataxia, and visual impairment) for 7 of the 8 patients. Two patients showed a decrease or disappearance of brain lesions on magnetic resonance imaging.^{14,17} The duration of disease control from the initiation of intrathecal trastuzumab ranged from 39 days to greater than 72 months, with 6 patients surviving greater than 5 months.^{12–17} Interestingly, the patient who died at day 39 of intrathecal trastuzumab treatment died due to progression of visceral metastases and was considered to be in remission with regard to the leptomeningeal carcinomatosis.¹⁰ Tumor cell counts were also found to be eliminated or substantially decreased in 4 of 5 patients.^{10,13,14,17}

In 2 reports, response appeared to be related to dose.^{14,15} In 1 of these, the patient was started on 20 mg weekly and benefits from intrathecal trastuzumab were not appreciated until doses were increased past 30 mg.¹⁴ Intrathecal trastuzumab was coadministered with intrathecal thiopeta and the greatest response occurred when both trastuzumab and thiopeta doses were increased to 50 and 12 mg, respectively. A second report also suggests that trastuzumab at doses higher than 20–30 mg may result in increased efficacy.¹⁵ These cases, as well as other preclinical data, hint at a dose-response relationship and the possibility of a synergistic relationship with trastuzumab and thiopeta.¹⁹

Two patients had CSF concentrations of trastuzumab measured prior to dose administration. Intrathecal therapy showed a substantial increase in CSF concentrations of trastuzumab compared with systemic therapy alone. Measured CSF concentrations after intrathecal trastuzumab peaked at 3460 and 6425 ng/mL during therapy.^{10,13} Although CSF concentrations were higher than those seen with systemically administered trastuzumab, concentrations were still lower than serum concentrations (34,274 and 82,303 ng/mL, respectively). Both reports utilized a maximum dose of 20 mg and, given the lack of toxicity (even at 100 mg) and relatively low CSF concentrations, higher doses may be reasonable. It is also important to remember that the 2 CSF concentrations described above were obtained 4 and 3 days after the dose, respectively, prior to the next dose.

Recently, results of a small pilot study utilizing intrathecal trastuzumab have been reported in abstract form.¹⁸ Sixteen patients (11 with glioblastoma multiforme, 4 with breast cancer, and 1 with medulloblastoma) were treated with 4 treatments of intrathecal trastuzumab 20–60 mg either weekly or every other week. Responders and those with stable disease continued therapy every other week indefinitely or until neurologic progression. Ten patients responded (7 with glioblastoma multiforme, 2 with breast cancer, 1 with medulloblastoma), with response durations lasting from 4 to more than 14 weeks. Despite the relatively small sample size and heterogeneous patient population, over 60% of the patients receiving intrathecal trastuzumab responded, with 2 of the 4 patients with breast cancer responding. At the time this abstract was presented, patients continued to respond, making response duration difficult to determine from this analysis. Final results are necessary in order to determine trastuzumab's full effect in this study.

Based on this pilot study and the reviewed case reports, intrathecal trastuzumab appears to be a promising therapy. Its use led to survivals ranging from 4 weeks to more than 72 months, and most patients had resolution of leptomeningeal carcinomatosis symptoms. None of the reported patients experienced clinical toxic effects. These observed results must be interpreted with caution given the heterogeneity in the doses, schedules, and concomitant therapies used in the patients. Although it is difficult to distinguish between the effects of systemic therapies and other intrathecal therapies in these reports, intrathecal trastuzumab deserves further investigation in the setting of leptomeningeal carcinomatosis due to HER2-positive breast cancer in order to determine the biologically optimal dose, schedule, and place in therapy.

Lymphoma and Intrathecal Rituximab

Similar to the interest in intrathecal trastuzumab, the use of intrathecal rituximab for the treatment of CNS lymphoma and leukemia has garnered attention. The majority of B-cell non-Hodgkin's

lymphomas and B-cell leukemias express the CD20 antigen, and systemic rituximab (anti-CD20 monoclonal antibody) has been shown to be effective in their treatment. Rituximab has been shown to increase survival; however, it has not been associated with a decrease in the risk of secondary CNS occurrence.^{20,21} The lack of an effect in decreasing the risk of CNS dissemination may be due to the relatively low penetration of rituximab into the CNS. In fact, CSF concentrations of rituximab after systemic administration have shown to be only 0.1% of the serum concentrations.²² Like trastuzumab, the activity of rituximab coupled with relatively poor CNS penetration led to the current interest in the intrathecal use of this agent. An animal model utilizing intrathecal rituximab in cynomolgus monkeys showed this intervention to be well tolerated, with no clinical evidence of toxicity.²² In addition to this animal model, the use of intrathecal rituximab has been reported in case reports, case series, and a Phase 1 trial (Table 2^{23–32}).

Reference	Pts. (n)	Intrathecal Dose (mg)	Doses (n)	Tumor Type	Other Intrathecal Drugs Coadministered	Concurrent Systemic Therapy	Outcome	Survival ^a
Villela (2008) ²³	1; CR	25	5	MCL		Yes	Complete remission	>25 mo
Antonini (2007) ²⁴	1; CR	10–40	8	Primary large B-cell NHL		Yes	Decrease in neurological symptoms after 2 wk; clearance of lymphoma cells by 7 days; full regression of lymphoma infiltration on MRI	>7 mo
van de Glind (2008) ²⁵	1; CR	40	12	PTLD	Methotrexate, cytarabine, prednisone	Yes	Seizures/headaches disappeared; tumor reduction and less edema visualized on MRI	>16 mo
Pels (2002) ²⁶	1; CR	10–40	4	PCNSL		No	Clearance of lymphoma cells in cerebrospinal fluid; slight improvement in clinical symptoms	4 mo
Liu (2008) ²⁷	1; CR	20–30	6	DLBCL		No	Gradual improvement in neurological condition; pt. fully recovered	>3.5 y
Akyuz (2007) ²⁸	1; CR	10–35	4	PCNSL		No	Regression of tumor; increased cognitive functions	>15 mo
Hong (2009) ²⁹	1; CR	20	4	PCNSL		Yes	Partial remission of parenchymal tumor	>28 mo
Schulz (2004) ³⁰	6; CS	10–40	4–10	PCNSL, DLBCL, or Burkitt's lymphoma		Yes	3 pts. with clearance of malignant cells in cerebrospinal fluid; 1 pt. with disappearance of leptomeningeal tumors; 1 pt. with minor response; 2 pts. with disease progression	2–14 mo
Jaime-Perez (2008) ³¹	7; PS	10	4	B-cell ALL		Yes	5/7 pts. had complete response	7 mo to >24 mo
Rubenstein (2007) ³²	10; P1	10–50	1–9	PCNSL or SCNSL		No	4 pts. had complete responses; 6 pts. had cytologic responses	1.1 wk to >134 wk

ALL = acute lymphoblastic leukemia; CR = case report; CS = case series; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; P1 = Phase 1 trial; PCNSL = primary central nervous system lymphoma; PS = prospective study; PTLD = posttransplant lymphoproliferative disease; SCNSL = secondary central nervous system lymphoma.

^aApproximate time from first dose of intrathecal rituximab to death.

Seven individual case reports have been published studying the use of intrathecal rituximab for CNS lymphoma.^{23–29} Doses ranged from 10 to 40 mg and were most commonly initiated at 10 mg and increased to the highest tolerated dose or until acceptable clinical response occurred. All 7 patients showed response in tumor cell clearance. Cytologic responses were also accompanied with symptomatic improvements in 4 cases and included neurologic improvements, disappearance of seizures and headaches, and cognitive improvement.^{24,25,27,28} Only 1 report described progression of CNS lymphoma.²⁶ Survival in these 7 case reports ranged from 4 months to greater

than 3.5 years. Three of 7 patients received high-dose chemotherapy with autologous stem cell rescue after receiving intrathecal rituximab.^{23,24,29} Adverse effects reported include neuropathic pain, headache, cramps, back pain, and leg weakness. Infusion reactions characterized by tingling sensations in the extremities, transient upward gaze of eyes, nausea, chills, hypotension, and disorientation were reported. These reactions occurred with the 40-mg doses and did not produce any long-lasting sequelae.

The results of a case series and a prospective study investigating the safety and efficacy of intrathecal rituximab have also been reported. In the case series (n = 6), doses were intensified (10–40 mg) during the course of treatment and were given as frequently as 3 times weekly.³⁰ Final outcomes were described as total clearing of malignant cells in 1 patient, disease progression in 2 patients, and minor response in 1 patient. The prospective study included 7 pediatric patients with B-cell acute lymphoblastic leukemia refractory to triple intrathecal therapy (methotrexate, cytarabine, hydrocortisone) with or without radiation.³¹ Patients received intrathecal rituximab 10 mg twice weekly for 4 weeks. After 24 months, 5 patients remained in complete remission. Patients receiving rituximab showed no signs of neurotoxicity. Of the 13 patients studied in both reports, only 1 had neurologic complications.³⁰ This patient suffered from Burkitt's lymphoma and experienced a severe pain attack and paraparesis. This was thought to be related to a high tumor burden and rapid tumor cell lysis. Another patient experienced nausea/chills with a 40-mg dose immediately after administration. Survival in both reports ranged from 2 months to more than 24 months. Similar to the small study with trastuzumab, it is difficult to determine the drug's true potential from these studies. Given the studies' small size, along with the differing doses and administration schedules, more data are necessary. However, as seen in both the case reports and the case series, it appears that doses of 40 mg may increase the likelihood of adverse effects.

Intrathecal rituximab has been investigated in a Phase 1 study that sought to define its safety, pharmacokinetics, and efficacy.³² Doses of 10–50 mg were administered to 10 patients. Rituximab was administered over 1–5 minutes either diluted with NaCl 0.9% or as undiluted stock solution. Prior to administration, patients received acetaminophen, diphenhydramine, and famotidine or cimetidine and had 5 mL of CSF removed. None of the 8 patients receiving 10 and 25 mg exhibited signs of major toxicity. Both patients receiving 50 mg suffered from toxicities (hypertension, diplopia, nausea/vomiting, chest pain, and tachypnea). Symptoms resolved within 20 minutes with medical management. Overall, 6 patients had cytologic responses, 4 of whom had complete responses. The longest cytologic response was 9 months, while survival ranged from 1.1 week to more than 134 weeks. Mean 1-hour postdose CSF concentrations were 214 µg/mL with the 10-mg dose and 472 µg/mL with the maximum tolerated dose of 25 mg. These concentrations are similar to peak concentrations in the serum after intravenous injection of rituximab. Concentrations rapidly declined after the dose, with a half life of 34.9 hours at the 25-mg dose. This rapid decline in concentrations was also observed in 1 of the case reports.²⁶ As demonstrated previously with systemic rituximab for lymphoma, response may correlate with sustained rituximab concentrations.²⁶ This Phase 1 study, along with the aforementioned small studies and 7 case reports, has revealed the potential of intrathecal rituximab. Although toxicities have been described, the majority have been with doses of 40 mg or greater and have been manageable. Similar to trastuzumab, additional data are necessary to determine the biologically optimal dose

and schedule. Administration of doses more frequently may help mitigate the rapid removal of drug from the CSF; however, this schedule requires validation in a clinical trial.

Practical Considerations

It is important to use sterile water when preparing trastuzumab for intrathecal administration and not the provided diluent (bacteriostatic water) to prevent the intrathecal administration of preservative, which can lead to neurotoxicity or anaphylaxis.³³ Tonicity of the drug diluted in water was not an issue in the described case reports. Given the lack of the preservative and the route of administration, trastuzumab for intrathecal use should be administered immediately after preparation despite the reported physical and chemical stability of 48 hours under refrigerated conditions and 24 hours at room temperature when prepared with sterile water.³⁴ One case report gave details regarding the preparation, in which 150 mg of trastuzumab (trastuzumab is available in 150-mg vials in the UK and Australia) was diluted with 7.2 mL of sterile water.¹⁰ Rituximab was prepared in the Phase 1 trial by diluting the stock solution with preservative-free NaCl 0.9% in a 1:1 ratio for the 10- and 25-mg dosages or without dilution for the 50-mg dosage.³² All rituximab doses were administered slowly over a period of 1–5 minutes. Intrathecal trastuzumab and rituximab were delivered by either lumbar puncture or via an Ommaya reservoir in these reports. It is unknown whether the delivery method would influence outcome; however, administration of intrathecal agents via an Ommaya reservoir compared to repeated lumbar punctures may be safer.^{35,36}

Summary

The prognosis for leptomeningeal carcinomatosis is quite grim with conventional therapies. Available options are limited to supportive care, radiation, or intrathecal chemotherapy. Additional options, such as steroids and systemic chemotherapy with high-dose methotrexate, are available for lymphomatous carcinomatosis. With the poor efficacy of these therapies and the frequency of leptomeningeal carcinomatosis diagnosis increasing, oncologists have challenging decisions to make. The blood-brain and blood-cerebrospinal barriers are believed to be the prime culprits preventing the accumulation of drug at the site of leptomeningeal carcinomatosis. Consequently, while intravenous trastuzumab and rituximab are first-line agents for their respective disease states, their efficacy is poor in leptomeningeal carcinomatosis, as they are unable to penetrate these barriers. These large monoclonal antibodies require additional assistance to reach the site of leptomeningeal carcinomatosis. One way is to deliver them directly into the site of CNS disease via intrathecal administration. The available data suggest that intrathecal trastuzumab and rituximab may be safe and effective and mitigate the poor penetration associated with systemic administration. Both agents have resulted in long periods free from disease-related symptoms that may impact quality of life.

Trastuzumab was tolerated at doses ranging from 5 to 100 mg. CSF concentrations were determined with the 20-mg dose and found to be higher than with systemic therapy alone; however, CSF concentrations were lower than serum concentrations obtained with systemic therapy. Whether higher doses would yield higher CSF concentrations is unknown at this time and needs

to be addressed in the setting of a Phase 1 trial. At this time, based on the available data, no recommendations can be made regarding a standard dose.

Rituximab was tolerated at doses ranging from 10 to 30 mg. CSF concentrations in the Phase 1 trial were similar to those obtained in the serum with systemic therapy. Contrary to the available data with trastuzumab, rituximab dose escalation above 30 mg resulted in adverse effects. At this time, more data are necessary to determine intrathecal rituximab's place in therapy; however, if the drug is utilized, a dose of 25 mg would be reasonable based on the Phase 1 data. In patients with a very large CNS tumor burden, dose escalation (starting with 10 mg and increasing to 25 mg) may be considered to prevent adverse effects from tumor lysis.

Intrathecal therapy shows promise but is still in its infancy. The reports discussed above illustrate the feasibility of intrathecal administration of rituximab and trastuzumab and encourage further investigation. Larger studies are needed to determine biologically optimal doses, frequency, and duration of therapy. A patient refractory to other available treatments may benefit from intrathecal trastuzumab or rituximab; however, this approach remains investigational until more data are available.

Article Notes

Conflict of Interest: Authors reported none

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