A multicenter phase II trial of intrathecal topotecan in patients with meningeal malignancies

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To determine the therapeutic efficacy (13-week and 26-week CNS progression-free survival [PFS], response rate, and overall survival) and safety of intraventricular (IVent) topotecan in patients with neoplastic meningitis (NM), we conducted a phase II, open-label, nonrandomized, single-arm trial of IVent topotecan in patients with NM using 400 μg of topotecan IVent twice weekly for 6 weeks, followed by evaluation with imaging, cerebrospinal fluid (CSF), and physical examinations. In the absence of disease progression, patients were then treated with IVent topotecan weekly for 6 weeks, twice monthly for 4 months, and monthly thereafter. Sixty-two patients (23 males and 39 females) were enrolled from April 2001 through March 2006. Median age and KPS at enrollment were 56 (range 5–83) and 80 (range 60–100), respectively. Primary cancers included breast (19), lung (13), CNS (14), and others (16). Forty patients (65%) completed the 6-week induction period, among whom 13 (21%) had CSF clearance of malignant cells. Kaplan-Meier estimates of PFS at 13 and 26 weeks were 30% (95% confidence interval [CI], 20%–45%) and 19% (95% CI, 11%–34%). Overall median survival (50 deaths) was 15 weeks (95% CI, 13–24 weeks). The most common side effect was chemical meningitis in 32% of patients (5% grade 3); 32% experienced no drug side effects. IVent topotecan is well tolerated, but provides no added benefit over other IVent therapies. Because of its modest side effect profile, combining IVent topotecan with other IVent or systemic interventions should be considered. *Neuro-Oncology 10, 208–215, 2008 (Posted to Neuro-Oncology [serial online], Doc. D07-00056, March 3, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2007-059)*

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Neoplastic meningitis (NM) is a devastating complication of both hematologic and solid tumors, and is estimated to occur in 5%–8% of cancer patients.[1] Typical survivals of patients with NM range from 8 to 16 weeks, even with treatment.[1] In adults, the most common cancers that metastasize to the leptomeninges are carcinomas of the breast and lung, melanoma, lymphomas, and leukemias.[1] The impact of NM is likely to increase in the future as advances in systemic treatments have improved survival but leave the leptomeninges and cerebrospinal fluid (CSF) as a sanctuary site.

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Although optimal treatment for NM is debated, in the United States intraventricular (IVent) chemotherapy is frequently administered, attempting to circumvent the issues of drug delivery imposed by the blood-brain, blood-spine, and blood-CSF barriers. However, only a small number of anticancer agents are available for administration by the intra-CSF route. Currently, only four agents are regularly used: methotrexate, cytarabine, liposomal cytarabine, and thiotepa. None of these have resulted in significantly prolonged patient survivals,[2–5,7,8] and combinations of intra-CSF drugs have not improved outcomes over single agents.[3,9] Because of the limited efficacy of the available intra-CSF agents, new and effective agents are needed.

Topotecan is a water-soluble semisynthetic topoisomerase I inhibitor approved for systemic use in small-cell lung cancer and ovarian cancer. It has a broad spectrum of anticancer activity against many cancer cell lines, including hematological malignancies, colorectal, breast, non–small-cell lung, and ovarian cancer, and childhood solid tumors.[10–12]

Pharmacokinetic studies performed following an IVent dose of 0.1 mg demonstrated that a 450-fold greater CSF exposure to topotecan could be achieved with only 1/100 the systemic dose.[13] This prompted a phase I study of intrathecal topotecan in patients with NM demonstrating that intra-CSF topotecan was well tolerated and was associated with objective responses.[13] Based upon its broad spectrum of activity and evidence of efficacy, we chose to test IVent topotecan in patients with NM, looking for improved outcomes.

Patients and Methods

Eligibility Criteria and Treatment Plan

Eligibility criteria are listed in Table 1, and patient characteristics in Table 2. Prior to enrollment, all patients underwent a complete history and physical examination, neurological examination, CSF evaluation (ventricular and lumbar), complete blood count, bone marrow aspiration (leukemia/lymphoma patients only), standard chemistry evaluations, MRI scans of brain and spine (lymphoma/leukemia patients underwent spine MRIs only if clinically indicated), CSF flow study (solid tumor patients), and quality of life (QOL) questionnaire (Functional Assessment of Cancer Therapy-CNS Module [FACT-CNS]). Patients treated at the University of Texas M. D. Anderson Cancer Center (UTMDACC) were registered in the UTMDACC patient data management system. Data from other centers were collected and retained by the coinvestigators and compiled with the UTMDACC data at the completion of patient enrollment.

During induction, patients received 0.4 mg of IVent topotecan twice weekly for a total of 6 weeks. If patients had no evidence of progressive NM, they received con-

Table 1. Eligibility criteria

IRB-approved informed consent signed by all patients (or legal guardian)
⩾3 years of age[a]
Diagnosis of NM
Meningeal leukemia/lymphoma patients
• required to be refractory to conventional therapy
• have CSF cell count at least 5/mm^3 and evidence of blast cells on cytospin preparation
Solid tumor patients
• could be enrolled without prior CSF-directed therapy
• tumor cells on cytology, or radiographic evidence of NM on MRI scans and histologic diagnosis of systemic malignancy needed
KPS ⩾60%
Without significant systemic illness
Recovered from the acute toxic effects of all prior therapies
• at least 3 weeks from last systemic leptomeningeal-directed therapy
• 1 week from last intra-CSF chemotherapy
• 1 week from any prior CNS-directed irradiation
Adequate bone marrow and organ function
Ventricular access device in place
No other chemotherapy designed specifically to treat NM allowed
Patients receiving concomitant chemotherapy to control systemic disease or bulk CNS disease were eligible, but
• agent not in phase I evaluation and
• agent not known to significantly penetrate the CSF
No evidence of obstructive hydrocephalus or compartmentalization of the CSF flow as documented by radioisotope indium^{111} or technetium^{99}–DTPA flow study
• patients with blocks that were reversed with focal radiation were eligible

Abbreviations: IRB, institutional review board; NM, neoplastic meningitis; CSF, cerebrospinal fluid; DTPA, diethylene triamine pentaacetic acid..

[a]Included based on eligibility criteria established in the phase I study.[13]

Table 2. Patient characteristics

Total no. of patients	62
Median age (range), years	56 (5–83)
Gender	
Male	23 (37%)
Female	39 (63%)
KPS score	
100	3 (5%)
90	17 (27%)
80	14 (23%)
70	19 (31%)
60	9 (14%)
Tumor type	
Breast cancer	19 (31%)
Brain	14 (23%)
Lung (11 NSCLC, 1 SCLC, 1 BA)	13 (21%)
Sinus (2 esthesio, 2 sinonasal)	4 (6%)
Melanoma	3 (5%)
Other[a]	9 (15%)
Enrollment CSF and imaging information	
CSF +/suspicious, imaging +	37 (60%)
CSF +, imaging –	12 (19%)
CSF –, imaging +	13 (21%)
Prior therapy for NM	
None	42 (68%)
Intrathecal chemotherapy	13 (21%)
Intrathecal I^{131}	1 (2%)
WBRT	8 (13%)
XRT to lumbar spine	1 (2%)
Other (gefitinib)	1 (2%)
Additional therapy while on study	
None	28 (45%)
Chemotherapy[b]	27 (44%)
Radiotherapy[c]	2 (3%)
Chemo and radiotherapy[d]	4 (6%)
Unknown	1 (2%)
Enrollment by center	
UTMDACC	31 (50%)
University of Massachusetts	16 (26%)
Moffitt Cancer Center	15 (24%)

Abbreviations: NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; BA, broncheoalveolar cancer; CSF, cerebrospinal fluid; NM, neoplastic meningitis; WBRT, whole brain radiation therapy; XRT, external radiation therapy; UTMDACC, University of Texas M. D. Anderson Cancer Center.

[a]Includes one each, granulocytic sarcoma, esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma, diffuse large cell lymphoma, ocular lymphoma, neurogenic sarcoma, ovarian cancer, parotid gland squamous cell carcinoma, primary peritoneal carcinoma with mesothelioma features.

[b]Includes biological therapies gefitinib, erlotinib, 13-*cis*-retinoic acid, bisphosphonates, and aromatase inhibitors

[c]Two patients received whole brain radiotherapy while on the study without additional chemotherapy.

[d]While on the study, two patients received radiation to the lumbar spine along with cytotoxic chemotherapy including fludarabine and mitozantrone or cisplatin plus gemcitabine. One patient received gamma knife along with carboplatin plus temozolomide. One patient received whole brain radiation along with paclitaxel plus carboplatin.

solidation therapy with topotecan weekly for six doses. In patients who still showed no evidence of progression, maintenance therapy was administered (twice monthly for 4 months and then monthly thereafter). Treatment was continued until patients developed progression of disease, refused treatment, or developed unacceptable toxicity.

Efficacy evaluations included physical examinations weekly during induction and at the time of each treatment administration during consolidation and maintenance therapy. CSF evaluations were performed weekly during induction, every 2 weeks during consolidation, every 2 months during maintenance therapy, and 6 weeks after the first negative CSF evaluation (confirmation CSF cytology). Evaluation for response required both lumbar and ventricular CSF assessments. At one participating center (UTMDACC), FACT-CNS QOL evaluations[14] were planned at the completion of induction, consolidation, and completion of maintenance or study termination. Contrast MRI scans of the brain and spine were carried out prior to the start of consolidation therapy and maintenance therapy and every 2 months during maintenance therapy.

Progression was defined cytologically, radiographically, and clinically. Cytological progression was defined as persistently positive cytology at the end of induction, or, for patients who attained a complete cytologic remission, development of positive cytology after two serial negative cytologies. Radiographic progression was defined as the development of any new lesion or 50% increase in the size of any previously noted nodule or area of meningeal thickening. For lesions less than 1 cm, 100% increase in size was considered progressive disease.

Patients who we believed had progressed clinically due to their leptomeningeal malignancy were removed from the study, regardless of the status of their cytological or radiographical measures. Determination of clinical progression due to leptomeningeal disease was based upon the examination and interpretation of the treating clinician.

Statistical Design

The primary objective of this study was to determine the proportion of patients with progression-free survival (PFS) at 13 weeks. Secondary objectives included determination of the proportion with PFS at 26 weeks, median overall survival, percentage of responding patients, QOL, and toxicity. For the 13-week PFS analysis, historical values for comparison were obtained from two published randomized trials that enrolled patients with a variety of primary tumor histologies.[4,5] The percentage of patients free from neurologic progression at 12 weeks in these two studies was approximately 12% for methotrexate and 45% for liposomal cytarabine in solid tumor patients. In lymphomatous meningitis patients, the percentage free from neurologic progression at 12 weeks was 45% for free cytarabine and 75% for liposomal cytarabine.[4,5]

In the present study, a response was defined as a patient

being alive and progression-free at 13 weeks. A modified Gehan two-stage design with a type II error rate (beta) of 10% and a "therapeutic effectiveness" threshold of 20% was used.[6] A stopping rule required study termination if none of the first 11 patients enrolled were responders. If at least 1 of the first 11 patients was a responder, then the study would continue to enroll a total of 43 evaluable patients, enabling us to estimate the response proportion with a 95% confidence interval width of 30% (equivalent to a standard error of about 8%). Our pretrial estimate of the response rate was 45%.

Time to progression (TTP) was measured from the time of enrollment to the time patients had cytologic or radiographic evaluations that clearly documented progressive CNS disease. If a patient was removed from the study for clinical progression only, then TTP was computed using the date of exam at which progression was documented.

Cox proportional hazards regression modeling was used to evaluate possible prognostic factors.

Results

The study was opened for enrollment in April 2001 at UTMDACC only. To increase enrollment, two centers (authors M.C.C. and M.J.G.) were added in November 2002. Full enrollment to 43 patients was completed in March 2004. The two additional centers continued to enroll an additional 19 patients through April 2006, and those patients are included in this report.

Patient Characteristics

Twenty-three males and 39 females were enrolled, ranging in age from 5 to 83 years (median, 56 years), with a median enrollment KPS of 80 (range, 60–100). Breast cancer, primary brain tumors, and lung cancer made up 74% of the enrolled patients, with 11 other tumor types comprising the remainder. Thirteen patients had evidence of slow CFS flow but no frank CSF block; one patient had a CSF block at the base of the brain and was treated with whole brain radiotherapy prior to enrollment.

Six-Week Induction Period

Forty patients (65%) completed the 6-week induction period, 21 (34%) did not, and data from 1 patient are not available. Of the 21 patients who did not complete the 6-week induction, 13 stopped due to clinical NM progression, 2 stopped due to systemic disease progression, 3 died (1 from suicide, 1 from gastrointestinal bleeding, 1 of unknown causes), 1 refused to complete induction, 1 stopped due to drug toxicity, and 1 stopped due to the development of *Staphylococcus epidermitis* meningitis.

CSF Responses after 6-Week Induction Period

For the 21 patients who did not complete the 6-week induction period, CSF results were not available. CSF was cleared of malignant cells in 13 of 62 patients (21%) at 6 weeks. CSF was originally negative at the beginning of treatment (diagnosis made on the basis of MRI findings) and remained clear of malignant cells in two patients (3%). CSF remained positive in 25 patients completing induction therapy (40%). Eleven of the 14 patients previously treated with intrathecal chemotherapy completed the 6-week induction period; 2 of the 11 patients had CSF cleared of malignant cells (1 patient with breast cancer and 1 with primary CNS lymphoma).

Imaging Responses after 6-Week Induction Period

MR imaging improved (partial response) in 6 patients (10% of 62 patients), remained unchanged in 27 patients (44%), and revealed progression in 7 patients (11%).

Clinical Responses after 6-Week Induction Period

Clinically, 10 patients improved (16% of 62 patients; all clinical improvements were related to mental status, fatigue level, and ambulation ability). Eighteen patients remained clinically stable (29%), 1 was stable from the NM standpoint but progressed systemically (2%), 11 had progressive NM symptoms (18%), and 2 progressed simultaneously systemically (3%). See Table 3 for correlation of CSF, imaging, and clinical results.

Thirteen-Week Progression-Free Survival

At 13 weeks after enrollment, 30% (95% CI, 20%–45%) were free from neurological progression by Kaplan-Meier estimate. Five of these patients (8% of 62 patients) received IVent topotecan alone, and nine (15%) received additional systemic therapies concurrently.

Time to Progression

Sixty of 62 patients were included in the TTP determination. Two patients were excluded due to early removal from the study. One patient stopped therapy after two IVent treatments associated with fever and confusion, and the other was removed from the study after one IVent injection of topotecan due to the need for emergency radiotherapy. For the 60 remaining patients, 47 progressed with a median TTP of 7 weeks (95% CI, 6–11 weeks) with a median of 70 weeks follow-up. Freedom from progression was 83% (95% CI, 74%–93%) at 3 weeks, 55% (95% CI, 43%–69%) at 6 weeks, 42% (95% CI, 31%–57%) at 9 weeks, 30% (95% CI, 20%–45%) at 13 weeks, 19% (95% CI, 11%–34%) at 26 weeks, and 14% (95% CI, 7%–29%) at 52 weeks. TTP and median overall survival based upon underlying histology are depicted in Table 4.

Prognostic Factors for TTP

Univariate and multivariate Cox analyses of the impact of enrollment prognostic factors were carried out. Factors included in the analysis included gender, age, primary histology, prior therapies versus not, anatomic

Table 3. Six-week induction CSF, imaging, and clinical results

Patient Number	Induction CSF Results	Induction Imaging Results	Induction Clinical Results
2	+	NC	SD
5	–	NC	Improved
11	–	MR	PD (NM)
15	–	PD	PD (NM)
16	+	NC	SD
17	–	MR	Improved
18	+	PD	SD
20	+	NC	SD
22	+	PD	PD (NM)
23	+	NC	SD
24	+	NC	SD
25	+	NC	Improved
26	+	NC	SD
27	+	NC	SD
28	+	NC	SD
29	+	CR	SD
30	+	PD	PD (NM)
31	+	NC	PD (NM)
32	+	NC	PD (NM)
33	+	NC	PD (NM + systemic)
34	+	NC	PD (NM + systemic)
35	– (CSF clear at enrollment)	NC	Improved
36	– (CSF clear at enrollment)	NC	PD (NM)
37	+	NC	SD
38	+	PD	SD
39	–	NC	SD
40	+	NC	Improved
41	+	NC	PD (NM)
44	–	MR	Improved
45	–	NC	SD
47	–	MR	Improved
49	–	NC	SD (NM); PD systemic disease symptoms
50	–	NC	Improved
51	+	NC	SD
53	–	MR	Improved
55	–	NC	Improved
56	+	NC	PD (NM)
57	–	NC	SD
61	+	PD	SD
62	+	PD	SD

Abbreviations: CSF, cerebrospinal fluid; NC, no change; SD, stable disease; MR, minor response; PD, progressive disease; NM, neoplastic meningitis; CR, complete response; + , –, CSF cytology positive (or negative) for malignant cells.

location of symptoms and imaging evidence of disease, CSF protein, glucose, cell count, cytology, CSF flow study results, and KPS at enrollment. Results of the multivariate analysis are presented in Table 5. On univariate analysis, brain primary, presentation with cerebral symptoms, and negative CSF cytology had a positive impact on survival, while slow CSF flow had no impact. On multivariate analysis, cerebral symptoms, lack of lumbar nerve root involvement on imaging, negative CSF cytology, and high CSF glucose were all associated with an improved TTP. Seventeen patients received systemic chemotherapy while also receiving intrathecal topotecan, the systemic chemotherapy possibly having CSF penetration. Seven patients received capecitabine, four patients received temozolomide, three patients received lomustine, two patients received cyclophosamide, and one patient received topotecan. Using the log rank test, there was no difference in TTP ($p = 0.63$) and no difference in the overall survival from the study enrollment ($p = 0.72$) between those patients who received potentially CSF-penetrating drugs versus those who did not.

Overall Survival

The median overall survival for all 62 patients (50 deaths) was 15 weeks (95% CI; 13–24 weeks). For patients completing the 6-week induction period, median overall survival was 22.3 weeks. Median survival for those who had received prior intrathecal chemotherapy ($n = 14$) was 13 weeks (range, 2–78 weeks), and for those who had not received prior intrathecal chemotherapy ($n = 48$), 13.5 weeks (range, 2–128 weeks).

Quality of Life

Because only six patients had adequate follow-up, the longitudinal QOL is inadequate to draw any conclusions.

Safety/Toxicity

All 62 patients were assessable for toxicity. A total of 38 (61%) patients suffered some toxicity (common toxicity criteria [CTC] grade 1–4) from IVent topotecan, while 20 (32%) reported no toxicity. The most common adverse event was chemical meningitis (defined as one or more of the following: fever, nausea, vomiting, meningismus, CSF pleocytosis, all or fragments occurring within 1 day of topotecan administration and resolving by day 5 after topotecan), which occurred in 20 (32%) patients. In most patients, this was easily relieved with oral steroids or analgesics. Details of adverse events are presented in Table 6.

MRI scans from the patients treated at UTMDACC were assessed for the development of topotecan-related leukoencephalopathy. Of the 31 UTMDACC patients, 8 had no follow-up scans; 1 patient had only two IVent doses of topotecan and was felt not to be evaluable for topotecan-related leukoencephalopathy. Of the 22 remaining patients, the median number of follow-up scans was 2 (range 1–17), and the last available scan

Table 4. Median time to progression and overall survival (in weeks) by histology

	All Histologies, $n = 62$	Breast Cancer, $n = 19$	Lung Cancer, $n = 13$	Brain Tumors, $n = 14$	Other Cancers, $n = 16$
MTP (95% CI)	7 (6,11)	6 (5,NR)	6 (5,NR)	17 (7,NR)	6 (4,NR)
OS (95% CI)	15 (13,24)	13 (11,32)	22 (12,NR)	21 (14,NR)	13 (7,NR)

Abbreviations: MTP, median time to progression; CI, confidence interval; NR, not reached; OS, overall survival.

Table 5. Multivariate analysis of significant prognostic factors

Variable	Contrast	Hazard Ratio (95% CI)	*p*-Value
Cerebral symptoms	Yes vs. no	0.4 (0.2,0.8)	0.011
LS imaging	Positive vs. negative	2.4 (1.1,5.5)	0.031
Cytology	Positive vs. negative	3.5 (1.3,9.8)	0.017
CSF glucose	>65 vs. ≤65 mg/dl	3.1 (1.3,7.7)	0.012

Abbreviations: CI, confidence interval; LS, lumbosacral; CSF, cerebrospinal fluid.

Because of a large number of comparisons (18) compared to the number of events (43), we could not fit all the covariates into a single stable model. Because several of the covariates had some missing values, we performed manual backward stepping starting with all the covariates in the model and omitting all covariates with $p > 0.5$.

was obtained at a median of 12.5 weeks (range, 3–108 weeks) after the pretreatment scan. Ten of 22 patients (45%) did not develop leukoencephalopathy, 4 (18%) had preexisting leukoencephalopathy that did not worsen after IVent topotecan treatment, and 8 (36%) had new onset or worsening of leukoencephalopathy. Seven of these 8 patients had received whole brain radiotherapy, and the other had received orbital radiotherapy prior to IVent topotecan.

Table 6. Adverse events associated with intraventricular topotecan, $n = 62$

Adverse Event	Grades 1–2 No. of Patients	Grades ⩾3 No. of Patients	All Grades % of All Patients
Chemical meningitis	17	3	32%
None = 20			32%
CNS symptoms[a]		11	18%
Leukopenia		4 (2 with grade 4)	6%
Anorexia, N or *V*	1	3	6%
Constipation		4	6%
Fatigue	2	2	6%
Dyspnea	1	3	6%
Infection		3	5%
Pain		3	5%
Anemia		2	3%
Hyponatremia		2	3%
Thrombocytopenia		1	2%
Chest pain		1	2%
Diarrhea		1	2%
Fever		1	2%
Pruritus		1	2%
Seizure		1	2%
Upper GI bleed		1 (grade 4)	2%
Thrombosis		1 (grade 4)	2%

Abbreviations: N, nausea; V, vomiting; GI, gastrointestinal.

[a]Includes confusion grade 3, $n = 2$; "cortical" grade 3, $n = 2$; mood grade 3; $n = 1$; motor grade 3, $n = 3$; sensory grade 3, $n = 2$; speech changes grade 3, $n = 1$.

Discussion

Based upon preliminary data suggesting safety and activity, and the need for improved therapies for patients with NM, we evaluated IVent topotecan in patients with NM. Even though it was well tolerated, the outcomes for patients treated with IVent topotecan were no better than those reported in three recent randomized controlled trials that employed other IVent chemotherapies.[2–5] Furthermore, the 21% CSF malignant cell clearance rate is similar to that in prior reports.[2–4,8]

The lack of improvement of outcomes using IVent topotecan over other therapies is disappointing, although IVent topotecan's similar efficacy and low toxicity offer another IVent chemotherapy alternative in those patients intolerant of other therapies or in whom the other IVent therapies have become ineffective. Whether the level of efficacy attained here is due to a pharmacodynamic issue (terminal half-life of IVent topotecan, 157 ± 54 min[13]) may require a concentration × time, multidose methodology, or continuous infusion system of administration to determine.

Prognostic Factors

Factors in the present study that were found to be predictive of longer PFS on multivariate analysis were of interest, but were not always consistent with the literature. Cerebral symptoms (including dysphasia, seizures, gait difficulties, nausea, vomiting, memory loss, fatigue, headaches, and visual field impairments) were associated with a longer PFS (hazard ratio, 0.4; 95% CI, 0.2–0.8). This finding differs from those of other studies.[15–17] One report found a worse survival (10 weeks) in patients presenting with encephalopathy versus not

(24 weeks).[15] If we look only at patients with memory complaints ($n = 6$) or confusion ($n = 1$), median survival was 13 weeks (range, 3–78 weeks), nearly the same as the overall study population. The reason for the slightly improved outcomes in our patients with cerebral symptoms at enrollment could be due to earlier disease detection stimulated by the presence of difficult-to-ignore cerebral symptoms.

Imaging evidence of lumbar root involvement was associated with a poorer outcome. At least one other study showed better outcomes in patients with spinal involvement by their disease.[16] The reasons for our findings are not clear, but contrary to cerebral symptoms leading to earlier detection of disease, symptoms related to the lumbar roots might be disregarded for longer periods, resulting in an apparent "shortening" of PFS.

CSF cytology that was positive for malignant cells was associated with a poorer PFS outcome. This could be due to a higher overall burden of disease with a resulting higher number of cells shed into the CSF, or possibly to a more aggressive biology unrelated to disease burden, but related to other factors associated with cells being present in the CSF (e.g., higher apoptotic fraction and cell shedding, reflective of higher cell turnover rate, or alternatively, a less adhesive cell phenotype associated with a more aggressive behavior in CSF pathways).

Finally, an elevated CSF glucose level was associated with a poorer PFS, contrary to at least one other report.[17] Changes in CSF glucose levels in the setting of NM could be related to changes in glucose transport or to glucose consumption by malignant cells. Furthermore, plasma levels of glucose may affect CSF glucose levels (data not available). Because of these issues, the meaning of the association of higher CSF glucose levels and poorer PFS is not clear.

Histological Subtypes

A few patients from each histological category had CSF cleared of malignant cells, improvement of their imaging studies, or improvement of their clinical status while on therapy. Likewise, similar proportions of patients rapidly progressed in each histology. Therefore, it is difficult to draw conclusions about subtypes of patients who might derive any special benefit from IVent topotecan. Patients with primary CNS lymphoma and ocular lymphoma did well, with TTPs of 70, 78, and 68 weeks for the two primary CNS lymphomas and ocular lymphoma, respectively. These favorable outcomes may be related to the underlying biology of these tumors.

Trial Design Issues

One issue raised by the study is the difference in PFS between patients with primary brain tumors and the other histological groups. The longest PFS times were seen in patients with primary brain tumors: one patient with anaplastic oligodendroglioma (1p/19q deleted) (PFS = 99 weeks), one with anaplastic astrocytoma (PFS = 70 weeks), and two with primary CNS lymphomas (PFS = 78 and 70 weeks). Future studies may need to treat brain tumor patients as a separate category to make studies more informative. Large, multi-institutional studies will be needed to complete studies restricted to single histologies once preliminary studies identify agents with activity.

Time from prior therapy is an issue in all cancer clinical trials, including trials treating patients with meningeal cancer. Here we chose to include patients who had prior leptomeningeal-directed therapy, but were at least 3 weeks after their last systemic leptomeningeal-directed therapy, 1 week after their last intra-CSF chemotherapy, and 1 week after any prior CNS-directed irradiation. This was done to minimize the possibility of significant toxicity overlap. The results of the study appear to validate this time frame since no significant added efficacy benefit was seen, although a possible increase in chemical meningitis was seen in those patients previously treated with liposomal cytarabine (7/8 [88%] of those previously treated vs. 9/54 [17%] of those not previously treated). Due to the prolonged half-life of liposomal cytarabine, in future studies it may be prudent to extend the time to treatment from prior liposomal cytarabine from 1 week to 2 weeks.

Trials with treatment continuation decisions based primarily on clinical and secondarily on CSF and craniospinal imaging data, may be the most logical designs for future studies. The "decision to change therapy" may be more useful than the "objective," yet variable-laden, end points of CSF cytology and imaging. This method of decision-making might allow for longer use of agents that may be helping patients, and that might otherwise be discontinued prematurely.

Conclusion

IVent topotecan is well tolerated, and its use results in CSF clearance rates, progression, and survival outcomes similar to those of other IVent agents. Because of its ease of use and mild side effect profile, it may be a useful agent for testing in combination with other IVent agents or with systemic agents with high CSF penetration.

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