Clinical trial of proton craniospinal irradiation for leptomeningeal metastases

T. Jonathan Yang, Neil A. Wijetunga, Josh Yamada, Suzanne Wolden, Michelle Mehallow, Debra A. Goldman, Zhigang Zhang, Robert J. Young, Mark G. Kris, Helena A. Yu, Andrew D. Seidman, Igor T. Gavrilovic, Andrew Lin, Bianca Santomasso, Christian Grommes, Anna F. Piotrowski, Lauren Schaff, Jacqueline B. Stone, Lisa M. DeAngelis, Adrienne Boire,[†◉] and Elena Pentsova[†]

Department of Radiation Oncology (T.J.Y., N.A.W., J.Y., S.W., M.M.), PROMISE (Precision Radiation for OligoMetastatIc and MetaStatic DiseasE) Program (T.J.Y., J.Y.), Department of Epidemiology and Biostatistics (D.A.G., Z.Z.), Department of Radiology (R.J.Y.), Division of Solid Tumor Oncology, Thoracic Oncology Service (M.G.K., H.A.Y.), Division of Solid Tumor Oncology, Breast Medicine Service (A.D.S.), Department of Neurology (I.T.G., A.L., B.S., C.G., A.F.P., L.S., J.B.S., L.M.D., A.B., E.P.), Brain Tumor Center (T.J.Y., I.T.G., A.L., B.S., C.G., A.F.P., L.S., J.B.S., L.M.D., A.B., E.P.), and Human Oncology and Pathogenesis Program (A.B.), Memorial Sloan Kettering Cancer Center, New York, New York

Corresponding Author: T. Jonathan Yang, MD, PhD, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065 (yangt@mskcc.org).

[†]Contributed equally to this work.

Abstract

Background. Leptomeningeal metastases (LM) are associated with limited survival and treatment options. While involved-field radiotherapy is effective for local palliation, it lacks durability. We evaluated the toxicities of proton craniospinal irradiation (CSI), a treatment encompassing the entire central nervous system (CNS) compartment, for patients with LM from solid tumors.

Methods. We enrolled patients with LM to receive hypofractionated proton CSI in this phase I prospective trial. The primary endpoint was to describe treatment-related toxicity, with dose-limiting toxicity (DLT) defined as any radiation-related grade 3 non-hematologic toxicity or grade 4 hematologic toxicity according to the Common Terminology Criteria for Adverse Events that occurred during or within 4 weeks of completion of proton CSI. Secondary endpoints included CNS progression-free survival (PFS) and overall survival (OS).

Results. We enrolled 24 patients between June 2018 and April 2019. Their median follow-up was 11 months. Twenty patients were evaluable for protocol treatment–related toxicities and 21 for CNS PFS and OS. Two patients in the dose expansion cohort experienced DLTs consisted of grade 4 lymphopenia, grade 4 thrombocytopenia, and/or grade 3 fatigue. All DLTs resolved without medical intervention. The median CNS PFS was 7 months (95% CI: 5–13) and the median OS was 8 months (95% CI: 6 to not reached). Four patients (19%) were progression-free in the CNS for more than 12 months.

Conclusion. Hypofractionated proton CSI using proton therapy is a safe treatment for patients with LM from solid tumors. We saw durable disease control in some patients.

Key Points

1. Proton CSI is safe for patients with LM.

2. Proton CSI is potentially effective for LM.

Importance of the Study

This is the first prospective trial evaluating hypofractionated proton CSI for patients with LM from solid tumors. We found that hypofractionated proton CSI is well tolerated with limited bone marrow effects, which is critical in this often heavily pretreated population. We also found promising durable CNS control and survival in a subset of patients.

Leptomeningeal metastasis (LM), the spread of a malignancy into the cerebrospinal fluid (CSF), is a dreaded complication of solid tumors. Although approximately 20% of patients with cancer with neurologic symptoms harbor LM at autopsy,[1,2] it is clinically detected in only 5–8% of patients with solid tumors.[3] The incidence of LM is rising, likely due to improved MRI[4] and better systemic treatments.[5–7] The current incidence of LM varies widely depending on primary site, with lung cancer and breast cancers most commonly associated with LM (5–25%), followed by melanoma (6–18%) and gastrointestinal malignancies (4–14%).[2,4,8,9]

Within the subarachnoid space, tumor cells disseminate throughout the central nervous system (CNS). As a result, patients with LM develop headache, pain, and multifocal neurologic deficits, including cranial neuropathies, cerebellar dysfunction, radiculopathy, and cauda equina syndrome. Treatments for LM are palliative, with the goals of stabilizing or improving neurologic symptoms. The prognosis for patients with LM is poor. Untreated, LM can lead to death within 4–6 weeks.[10] Therapy prolongs overall survival (OS) to 3–11 months.[9,11–14] Responses to therapies and outcomes vary widely, impacted by performance status, tumor histology, and disease outside the CNS.

Radiation therapy (RT) effectively relieves local symptoms due to LM and, in the form of involved-field RT, is commonly used to treat symptomatic or bulky disease sites.[15–17] Because LM disseminates throughout the entire CSF compartment, involved-field RT cannot halt the progression of LM along the entire neuroaxis. Given RT's effectiveness in treating symptomatic LM, craniospinal irradiation (CSI), treatment of the entire leptomeningeal compartment, may be advantageous for symptom and disease control.

CSI is standard of care treatment in pediatric patients with leptomeningeal spread of some CNS primary tumors such as medulloblastoma[18,19] and germinomas,[20,21] and for select patients with leukemia and lymphoma.[22,23] In solid tumors, the role of CSI is less clearly defined. Small studies have demonstrated its effectiveness in alleviating neurologic symptoms caused by LM but have also revealed significant side effects associated with photon CSI.[24–27] These are the result of the gradual dose fall-off of the exit dose of photon radiation.[28–30] When delivering photon radiation to the entire neuroaxis, photons exit the body anteriorly, exposing the entire spinal column and anterior organs to radiation. In contrast, protons deposit the bulk of their energy at the last few millimeters of their range. This results in diminished delivery of RT beyond the neuroaxis with proton CSI. The vertebral column and the anterior structures are largely spared. This unique property of proton radiation plans translates into dosimetric superiority compared with photon radiation for CSI, resulting in significantly less gastrointestinal and hematologic toxicity.[31]

In this phase Ib study, we evaluated the safety of proton CSI for patients with LM due to solid tumors. In addition, we explored efficacy, survival, and patient-reported symptoms of this approach.

Materials and Methods

Patient Eligibility

Patients aged 10 or above with pathologically proven solid tumor malignancies with LM established radiographically and/or through CSF cytology were eligible for this study. Additional eligibility criteria included a Karnofsky or Lansky performance score of 60; no serious major neurologic deficits including encephalopathy; no previous RT that precluded developing a treatment plan respective of normal tissue tolerance (Supplement 1); available systemic treatment options; and adequate bone marrow function (hemoglobin 9 g/dL, absolute neutrophil count 1500/mm^3, and platelet count 100 000/mm^3). Systemic therapy was held 7 days prior to initiation and during proton CSI treatment, with the exception of endocrine therapy and trastuzumab for breast cancer patients. Patients resumed their previous systemic therapy after the completion of proton CSI. Patients were not allowed to initiate a new systemic therapy until the end of the dose-limiting toxicity (DLT) evaluation period, 4 weeks after completion of proton CSI. Patients with parenchymal brain metastases and with radiographically/CSF established LM were eligible. No restriction on steroid use was required for the study.

The protocol was reviewed and approved by the institutional review board and registered with ClinicalTrials.gov (NCT03520504). The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki. Informed consent was obtained from all participants.

Study Design and Protocol Therapy

This was a phase Ib study with a dose expansion cohort evaluating hypofractionated proton CSI for patients with LM from solid tumors. The primary endpoint was to determine the frequency of treatment-related toxicity. Secondary endpoints included duration of CNS disease control, CNS progression-free survival (PFS), OS, and patient-reported symptoms.

DLT was defined as any radiation-related grade 3 non-hematologic toxicity or grade 4 hematologic

toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4 that occurred during or within 4 weeks of completion of proton CSI. We employed a 3 + 3 design with de-escalation. The first 3 patients received a dose of 30 Gy (relative biological effectiveness [RBE]) in 3 Gy_{RBE} fractions. If 1 or no patients experienced a DLT, 3 additional patients would be enrolled at this dose of proton CSI. If 1 or none of the 6 patients experienced a DLT, the trial would proceed to the dose expansion cohort at 30 Gy_{RBE} in 3 Gy_{RBE} fractions. In contrast, if 2 or more patients experienced a DLT, 3 patients would then be enrolled at a dose level of 25 Gy_{RBE} in 2.5 Gy_{RBE} fractions. If 1 or no patients experienced a DLT, an additional 3 patients would be enrolled at 25 Gy_{RBE}. If 2 or more patients experienced a DLT at 25 Gy_{RBE}, the study would stop and treatment would be declared too toxic. If 1 or no patients developed a DLT among the 6 patients who received 25 Gy_{RBE}, the trial would proceed to the dose expansion cohort at 25 Gy_{RBE} in 2.5 Gy_{RBE} fractions.

Patients were simulated supine using standard CSI immobilization including a customized rigid mask. The clinical target volume (CTV) of the proton CSI treatment fields consisted of the entire brain, thecal sac, and proximal sacral nerve roots. The planning target volume (PTV) was the CTV plus margin to ensure that the prescribed dose was delivered to the CTV, accounting for variation in treatment delivery and range uncertainties in the proton beam direction. The PTV was a 4 mm margin from the brain CTV and 5 mm margin from the spine CTV. The radiation planning time for all patients was 2 weeks or less as mandated by the protocol. Dose volume constraint guidelines for organs at risk (Supplement 1) were used in the optimization process during treatment planning. Patients were treated with pencil beam scanning proton therapy.[32]

Pretreatment evaluations included a history and physical exam, including standardized neurological examination per Response Assessment in Neuro-Oncology Leptomeningeal Metastases (RANO-LM) neurological assessment[33]; complete blood count (CBC), electrolytes, renal and liver function tests; lumbar puncture for CSF assessment; MRI of brain and MRI of total spine with and without contrast; patient-reported symptoms using MD Anderson Symptom Inventory–Brain (MDASI-BT) and MDASI–Spine (MDASI-SP); and baseline adverse event evaluation using CTCAE. During proton CSI, patients underwent history and physical examination including standardized neurological examination, weekly CBC, and adverse event evaluation. At 1 month, 3 months, 6 months, and/or at time of disease progression after the completion of protocol treatment, patients underwent history and physical examination including standardized neurological examination, CBC, lumbar puncture for CSF assessment, MRI brain and MRI total spine, MDASI-BT, MDASI-SP, and adverse event evaluation. CNS disease progression was defined by a combination of clinical, radiographic, and cytologic examinations. Patients with new neurologic deficit(s) and/or progressive radiographic change not related to therapeutic intervention, and/or new positive cytology, were considered to have progressive LM.

Statistical Considerations

Treatment-related toxicities were evaluated during and after proton CSI by CTCAE value and grade. CNS responses at 1 month, 3 months, and 6 months were estimated along with 95% confidence intervals. Patients with improved or stable disease were considered as having a response. Patients who progressed earlier were counted in the denominator; patients who died without progression were excluded from the denominator. CNS PFS was evaluated from the first day of proton CSI until CNS progression or death. Patients who were alive and progression-free at the end of study were censored. OS was evaluated from the first day of proton CSI until death. Patients alive at the end of study were censored. Survival outcomes were estimated with Kaplan–Meier methods and plots. Median follow-up time was calculated using the reverse Kaplan–Meier method.

Overall MDASI-BT and MDASI-SP symptom scores were described with medians and ranges and visualized with box plots. One-month, 3-month, and 6-month scores were compared with baseline scores with the Wilcoxon signed rank test. Changes from baseline for individual symptoms were visualized with bar charts of median and interquartile range. In these bar charts, a score difference of 0 corresponded to symptom stability, a negative score difference corresponded to symptom improvement, and a positive score difference corresponded to symptom worsening. Due to the exploratory nature of this study, no adjustment for multiple comparisons was performed.

Two-sided *P*-values less than 0.05 were considered statistically significant. All analyses were performed with SAS 9.4TS1 M6.

Results

Dose Determination

Between June 2018 and April 2019, twenty-four patients enrolled. The majority of patients had non-small-cell lung cancer, and patients with molecularly driven disease all had CNS progression on small-molecule tyrosine kinase inhibitors at the time of enrollment. The median age was 52 and the median KPS was 70. Patient characteristics are presented in Table 1. Four patients were inevaluable for protocol-related toxicity assessment: 1 patient did not start protocol treatment due to systemic progression, 2 patients did not complete protocol treatment due to systemic progression, and 1 patient completed protocol treatment outside of the allowed treatment window (this patient was included exclusively in efficacy and survival analyses). Of the 3 evaluable patients enrolled at 30 Gy_{RBE} in 3 Gy_{RBE} fractions, no patient experienced DLT and therefore 3 additional evaluable patients were enrolled at the 30 Gy_{RBE} dose again with no further DLTs observed. The study went on to enroll 14 additional evaluable patients to the expansion cohort at the same dose of 30 Gy_{RBE} in 3 Gy_{RBE} fractions, for a total of 20 patients evaluable for all analyses, including toxicity, and 21 patients evaluable for efficacy and survival analyses.

Table 1 Characteristics of all evaluable patients (*N* = 21)

Characteristics	Median (range)	Number (%)
Age, y	52 (30–67)	
Sex		
Female		15 (71)
Male		6 (29)
KPS	70 (60–90)	
Histology		
Non-small-cell lung cancer		11 (52)
ALK+		1 (5)
EGFR+		7 (33)
ROS1+		1 (5)
Breast carcinoma		7 (33)
ER + HER2−		3 (14)
ER + HER2+		1 (5)
ER−HER2+		1 (5)
TN		2 (10)
Esophageal adenocarcinoma		1 (5)
Rectal adenocarcinoma		1 (5)
Adenoid cystic carcinoma of parotid		1 (5)
LM Diagnosis at Enrollment		
Newly diagnosed LM		9 (43)
LM progression on prior therapies		12 (57)
Number of Prior Metastatic Disease Therapies at Enrollment		
Systemic Therapies		2 (0*-5)
Afatinib		1 (5)
Alectinib		1 (5)
Brigatinib		1 (5)
Enctrectinib		1 (5)
Erlotinib		4 (19)
Lorlatinib		1 (5)
Osimertinib		7 (33)
Local Therapies (surgery, radiation therapy)		1 (0-6)
Baseline Evaluation		
Positive MRI		21 (100)
Positive cytology		16 (76)
With Parenchymal Brain Metastases at Enrollment		
Yes		11 (52)
No		10 (48)

Abbreviations: EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; KPS = Karnofsky performance status; LM = leptomeningeal metastasis; MRI = magnetic resonance imaging; ROS1 = ROS proto-oncogene 1; TN = triple nega-tive breast cancer
*One patient with metastatic adenoid cystic carcinoma of parotid did not receive prior systemic therapy prior to enrollment

Proton CSI Toxicities

Of the 20 patients evaluable for protocol treatment–re-lated toxicities, 2 patients in the dose expansion co-hort experienced DLTs: 1 patient (5%) experienced grade 4 lymphopenia; another patient experienced grade 4 lymphopenia, grade 4 thrombocytopenia, and grade 3 fatigue. All DLTs resolved without medical intervention. Protocol treatment–related toxicities that occurred within the DLT period in the majority of patients include:

- fatigue (19 patients [95%]: 10 [50%] grade 1, 8 [40%] grade 2, 1 [5%] grade 3),
- lymphopenia (18 patients [90%]: 1 [5%] grade 2, 15 [75%] grade 3, 2 [10%] grade 4), and
- thrombocytopenia (10 patients [50%]: 7 [35%] grade 1, 2 [10%] grade 2, 1 [5%] grade 4).

Other protocol treatment–related grade 3 toxicities in-cluded grade 3 leukopenia within 1 month of protocol therapy in 3 patients (15%), grade 3 anemia within 1 month of protocol therapy in 1 (5%), grade 3 anorexia at 6 months after protocol therapy in 1 (5%), and grade 3 back pain at 6 months after protocol therapy in 1 patient (5%). All pro-tocol treatment–related toxicities during the DLT period and at 3 months and 6 months after protocol therapy are listed in Table 2.

CNS Progression-Free Survival and Overall Survival

The median follow-up was 11 months (95% CI: 8–15 mo). The median OS of the study cohort was 8 months (95% CI: 6–not reached), with estimated OS of 71% (95% CI: 47–86%) at 6 months and 47% (95% CI: 23–68%) at 12 months (Figure 1A). The median CNS PFS was 7 months (95% CI: 5–13), with estimated CNS PFS of 62% (95% CI: 38–79%) at 6 months and 33% (95% CI: 13–55%) at 12 months (Figure 1B). Of the 21 patients evaluable for treatment outcomes, 9 patients had progressed in the CNS and 10 patients had died: 5 from concurrent sys-temic progression and CNS progression, 2 from pneu-monia, 1 from CNS progression, 1 from liver failure, and 1 from a pulmonary embolism. CNS response rate to protocol therapy was 100% (95% CI: 84–100%, *N* = 21/21) at 1 month, 86% (95% CI: 64–97%, *N* = 18/21) at 3 months, and 63% (95% CI: 35–85%, *N* = 10/16) at 6 months. At the time of this analysis, 4 patients (19%) achieved CNS disease control for more than 12 months after protocol therapy (Figure 2).

Patient-Reported Symptoms

Patients completed MDASI-BT and MDASI-SP as as-sessments for patient reported symptoms: 21 patients completed assessments at baseline, 18 at 1 month, 16 at 3 months and 11 at 6 months. Compared with base-line graphically, a trend toward worsening of patient reported symptoms was found at 3 months with sta-bilization or improvement of symptoms at 6 months (Figure 3). Specifically, patients reported gradually worsening spine-specific symptoms—such as weakness and change in bowel pattern—that are statistically sig-nificant at 1 month (median 0.9, *P* = 0.041) and 3 months (median 2.4, *P* = 0.002), but such symptoms improved by 6 months (median = 0.4, *P* = 0.43) compared with base-line (Table 3). While no significant difference was ob-served at 1 month (median = 1.0, *P* = 0.25) or 3 months (median = 1.0, *P* = 0.058), patients also reported worse brain-interference symptoms, such as mood or ability to work, at 6 months (median = 2.2, *P* = 0.009). Changes in individual specific symptoms compared with baseline

Table 2 Proton CSI-related toxicities ($N = 20$)

# Patients (%)		≤1 Month	3 Months	6 Months
General Disorders				
Dry Skin	Grade 1	1 (5)	1 (5)	0 (0)
Fatigue	Grade 1	10 (50)	2 (10)	1 (5)
	Grade 2	8 (40)	2 (10)	1 (5)
	Grade 3	1* (5)	0 (0)	0 (0)
Pain	Grade 2	1 (5)	0 (0)	0 (0)
Radiation Dermatitis	Grade 1	6 (30)	0 (0)	0 (0)
	Grade 2	1 (5)	0 (0)	0 (0)
Gastrointestinal Disorders				
Anorexia	Grade 2	1 (5)	1 (5)	0 (0)
	Grade 3	0 (0)	0 (0)	1 (5)
Dysgeusia	Grade 1	0 (0)	1 (5)	0 (0)
Dyspepsia	Grade 1	1 (5)	0 (0)	0 (0)
Vomiting	Grade 1	2 (10)	0 (0)	0 (0)
Neurologic Disorders				
Back Pain	Grade 3	0 (0)	0 (0)	1 (5)
Gait Disturbance	Grade 2	1 (5)	0 (0)	0 (0)
Headache	Grade 1	1 (5)	1 (5)	1 (5)
	Grade 2	0 (0)	1 (5)	0 (0)
Memory Impairment	Grade 1	0 (0)	1 (5)	0 (0)
Nausea	Grade 1	8 (40)	0 (0)	1 (5)
	Grade 2	0 (0)	1 (5)	0 (0)
Sensory Impairment	Grade 1	0 (0)	1 (5)	0 (0)
Hematologic Disorders				
Anemia	Grade 1	2 (10)	0 (0)	0 (0)
	Grade 2	1 (5)	0 (0)	0 (0)
	Grade 3	1 (5)	0 (0)	0 (0)
Leukopenia	Grade 1	3 (15)	0 (0)	0 (0)
	Grade 2	2 (10)	0 (0)	0 (0)
	Grade 3	3 (15)	0 (0)	0 (0)
Lymphopenia	Grade 2	1 (5)	0 (0)	0 (0)
	Grade 3	15 (75)	0 (0)	0 (0)
	Grade 4	2* (10)	0 (0)	0 (0)
Neutropenia	Grade 2	5 (25)	0 (0)	0 (0)
Thrombocytopenia	Grade 1	7 (35)	0 (0)	0 (0)
	Grade 2	2 (10)	0 (0)	0 (0)
	Grade 4	1* (5)	0 (0)	0 (0)

* = Dose limiting toxicity.

are depicted through a bidirectional bar graph and can be found in Supplement 2–3.

Discussion

Patients with LM who receive CSI traditionally receive X-ray–based photon RT. While photon CSI alleviates neurologic symptoms, it is associated with significant side effects.[25,26] Here, we have demonstrated that proton CSI of 30 Gy in 10 fractions can be safely delivered to patients with LM due to solid tumors with limited toxicity. It is important to note that 30 Gy in 10 treatments or 3 Gy per fraction of RT is a hypofractionated approach. Traditionally CSI is given in 1.8 Gy or 2 Gy per fraction requiring 20 or more treatments. For patients with LM, hypofractionated RT would be preferable to long-course RT. It is more
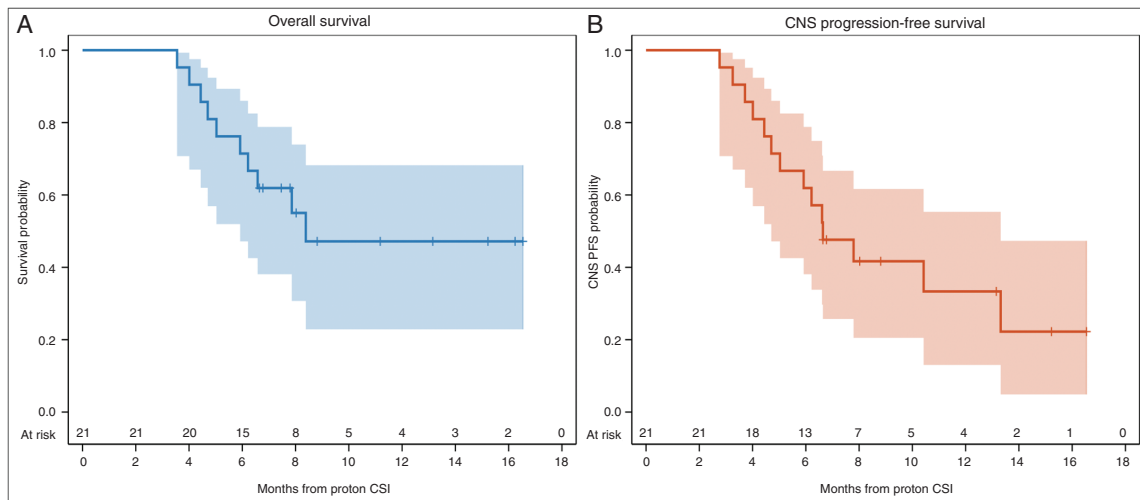
Fig. 1 Kaplan–Meier plot of (A) overall survival of the study cohort (B) central nervous system progression-free survival of the study cohort.
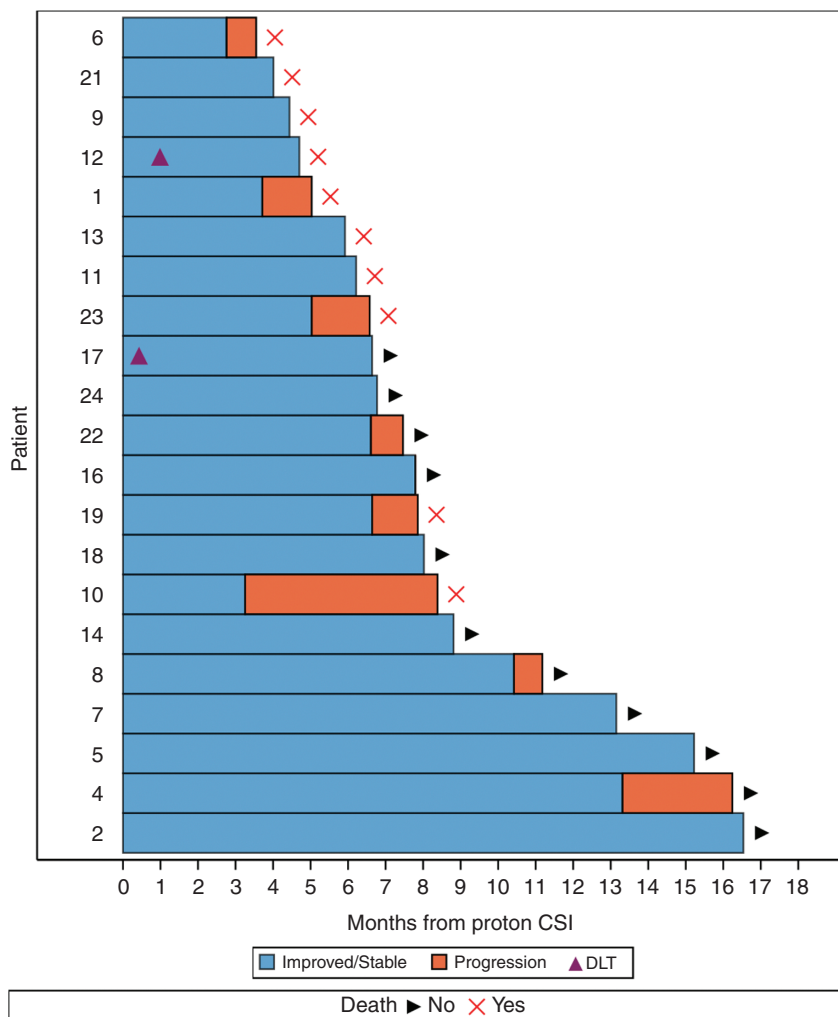

Fig. 2 Event history plot of the 21 evaluable patients for treatment outcomes. Progression in the figure represents CNS progression.
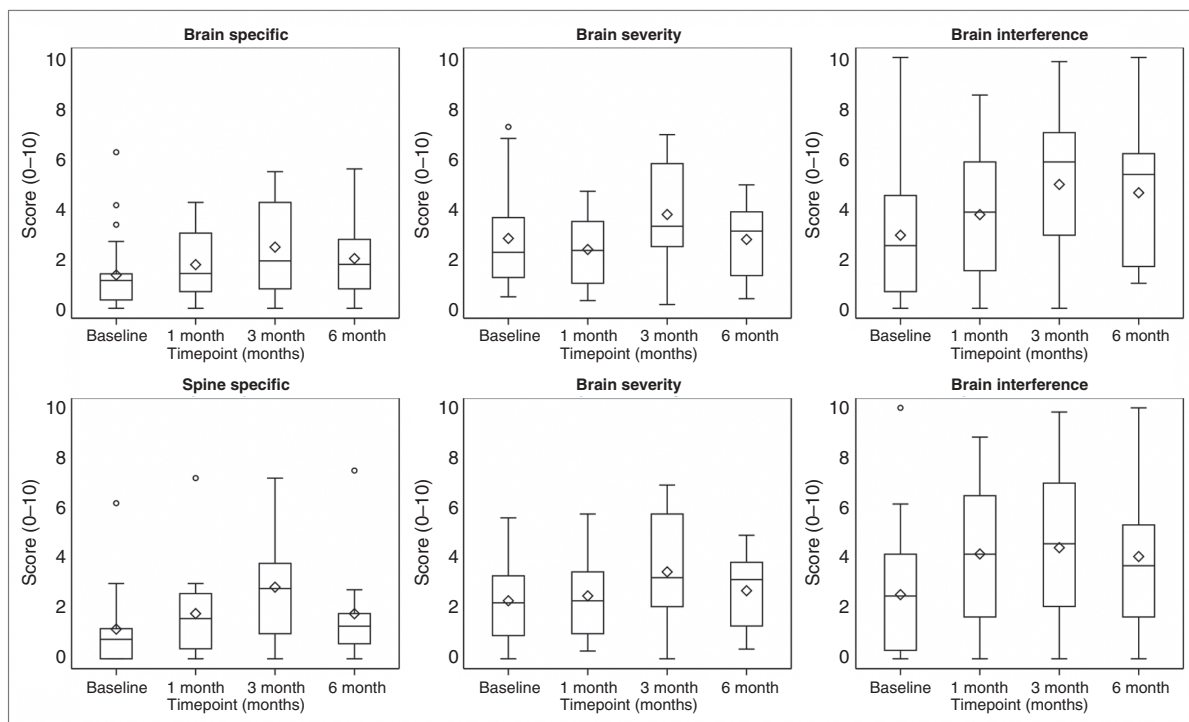
Figure 3. MDASI score distribution overtime. These plots are a schematic for the distribution of values. The ends of the box represent the 25th and 75th percentiles (or 1st and 3rd quartiles), while the center line and diamond represent the median and mean, respectively. The 75th minus the 25th percentile equals the interquartile range (IQR), and the ends of the whiskers are placed at 1.5 times the IQR. Any values lying outside these boundaries are considered outliers. Higher values indicate worsening symptoms.

Table 3. MDASI and RANO neurologic examination differences between follow-up timepoints and baseline*

Score	1 Month			3 Months			6 Months		
	N	Median (range)	P =	N	Median (range)	P =	N	Median (range)	P =
Brain Specific Score	18	0.6 (−3.2–2.9)	0.45	15	0.7 (−2.1–5.2)	0.14	11	0.7 (−1.8–4.0)	0.07
Brain Severity Score	17	−0.2 (−4.8–3.4)	0.30	16	1.0 (−2.1–5.5)	0.08	11	0.8 (−2.5–4.3)	0.13
Brain Interference Score	17	1.0 (−5.7–6.0)	0.25	16	1.0 (−4.2–6.2)	0.06	11	2.2 (−0.8–5.8)	**0.009**
Spine Specific Score	14	0.9 (−3.0–3.0)	**0.04**	13	2.4 (−0.8–4.2)	**0.002**	9	0.4 (−3.5–5.5)	0.43
Spine Severity Score	18	0.0 (−4.8–4.5)	0.85	16	1.5 (−3.0–5.5)	0.06	10	0.8 (−2.5–4.3)	0.19
Spine Interference Score	17	1.5 (−4.2–6.0)	0.08	16	1.0 (−4.2–7.0)	0.07	10	1.7 (−1.4–5.5)	0.08

Numbers represent difference from baseline, with a higher score signifying worsening of reported symptoms.

convenient for patients with functional decline, and it minimizes interruptions in systemic therapy for patients with active systemic disease. Furthermore, it is unclear whether long-course RT would result in superior outcomes in patients with significant CNS disease.[34] As 30 Gy in 10 treatments is considered the standard involved-field RT dose for patients with LM, it was used as the starting dose for this study.

In our study, only 2 patients developed DLTs (grade 3 fatigue, grade 4 lymphopenia, grade 4 thrombocytopenia), which did not interrupt therapy and resolved without medical intervention. No unexpected adverse event was observed on study. The most common protocol treatment–related toxicity was fatigue (95% of patients), a known side effect of CNS radiation, which persisted at 3 months (20%) and 6 months (10%) in some patients. Another common toxicity was lymphopenia (90% of patients), which was resolved by 3 months. No infections were observed. No patient experienced grade 3 gastrointestinal toxicities or required blood product transfusions.

We found that the toxicity profile of proton CSI was lower compared with what has been reported on X-ray–based photon CSI. Hermann et al retrospectively examined 16 patients with solid tumor LM who received 36 Gy

photon CSI in 18 fractions between 1995 and 2000 and found that the majority of patients experienced significant myelosuppression and dysphagia.[24] In another study, Harada et al evaluated 17 patients with LM from solid tumors who received X-ray–based photon CSI to a median of 41.4 Gy between 2008 and 2013 and found that the majority of patients had grade 3 or above hematologic and/or gastrointestinal side effects.[25] Involved-field photon RT can be associated with severe, persistent lymphopenia, which has been shown to negatively impact survival.[35] Given that LM is a late complication in patients with solid tumors, and patients commonly have compromised bone marrow reserve and abnormal organ function from systemic and local therapies, proton CSI may potentially be a safer approach in this patient population.

In addition, we found that CSI may be effective in achieving durable CNS disease control in patients with LM from solid tumors. The majority of evaluable patients (63%) achieved CNS disease control 6 months after proton CSI, and at the time of this analysis, 19% of patients maintained CNS disease control over 12 months. We also found favorable survival outcomes in our study cohort, with a median CNS PFS and OS of 7 months and 8 months, respectively. Although it is difficult to draw conclusions given the small number of patients in our study, our survival outcomes compared favorably with earlier reports with median survivals of 3–5 months.[26,36,37]

Our study is the first to demonstrate patient-reported neurologic symptom stability after CSI. Using MDASI-BT and MDASI-SP, we also found that patients reported worsening of spine symptoms at 1 and 3 months and worsening of brain symptoms at 6 months after protocol therapy. The change in patient-reported symptoms can be confounded by a variety of factors, including initiation of new systemic therapy after study DLT period, performance status, and systemic disease progression leading to patients coming off the study. Nevertheless, decline in neurologic function at 2–4 months after CNS RT has been reported; Saito et al reported worsening of Hopkins Verbal Learning Test–Revised scores at 4 months after whole-brain RT compared with baseline but not at 8 months,[38] and Brown et al reported decline of function at 2 months which persisted at 6 months.[39] This suggests that subacute radiation-induced toxicities can occur at 2–4 months after completion of RT and should be taken into consideration in patient evaluation and explored in a larger study.

There are several limitations to this study. Given the small number of patients enrolled in the study, the array of primary cancers included and the many systemic therapies received, we are not able to draw robust conclusions on efficacy, survival outcomes, or patient-reported symptoms. Changes in patient-reported symptoms are confounded by multiple clinical factors, including change in therapy and change in disease status, and, given the limited number of participants, should be interpreted with caution. We plan to evaluate the effects of proton CSI on patient reported symptoms in an upcoming randomized trial.

In conclusion, this is the first prospective study evaluating proton CSI with 30 Gy in 10 fractions for patients with LM from solid tumors. We have determined that hypofractionated proton CSI appears safe for patients with LM from solid tumors, a population that would benefit significantly from shorter courses of RT to minimize interruptions to systemic therapy. We have seen early evidence that hypofractionated proton CSI is an effective treatment in many patients and observed durable disease control on this study. We plan a phase II randomized trial to further determine the efficacy of hypofractionated proton CSI.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

craniospinal irradiation | leptomeningeal metastases | proton radiation

References

1. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer.* 1982;49(4):759–772.

2. Kaplan JG, DeSouza TG, Farkash A, et al. Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas and leukemias. *J Neurooncol.* 1990;9(3):225–229.

3. Beauchesne P. Intrathecal chemotherapy for treatment of leptomeningeal dissemination of metastatic tumours. *Lancet Oncol.* 2010;11(9):871–879.

4. Clarke JL, Perez HR, Jacks LM, Panageas KS, Deangelis LM. Leptomeningeal metastases in the MRI era. *Neurology.* 2010;74(18):1449–1454.

5. Lai R, Dang CT, Malkin MG, Abrey LE. The risk of central nervous system metastases after trastuzumab therapy in patients with breast carcinoma. *Cancer.* 2004;101(4):810–816.

6. Omuro AM, Kris MG, Miller VA, et al. High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. *Cancer.* 2005;103(11):2344–2348.

7. Emoto S, Ishigami H, Yamaguchi H, Yamashita H, Kaisaki S, Kitayama J. Frequent development of leptomeningeal carcinomatosis in patients with peritoneal dissemination of gastric cancer. *Gastric Cancer.* 2011;14(4):390–395.

8. Kesari S, Batchelor TT. Leptomeningeal metastases. *Neurol Clin.* 2003;21(1):25–66.

9. Mack F, Baumert BG, Schäfer N, et al. Therapy of leptomeningeal metastasis in solid tumors. *Cancer Treat Rev.* 2016;43:83–91.

10. Shapiro WR, Johanson CE, Boogerd W. Treatment modalities for leptomeningeal metastases. *Semin Oncol.* 2009;36(4 Suppl 2): S46–S54.

11. Morikawa A, Jordan L, Rozner R, et al. Characteristics and outcomes of patients with breast cancer with leptomeningeal metastasis. *Clin Breast Cancer.* 2017;17(1):23–28.

12. Remon J, Le Rhun E, Besse B. Leptomeningeal carcinomatosis in non-small cell lung cancer patients: a continuing challenge in the personalized treatment era. *Cancer Treat Rev.* 2017;53:128–137.

13. Lassman AB, Abrey LE, Shah GD, et al. Systemic high-dose intravenous methotrexate for central nervous system metastases. *J Neurooncol.* 2006;78(3):255–260.

14. Morris PG, Reiner AS, Szenberg OR, et al. Leptomeningeal metastasis from non-small cell lung cancer: survival and the impact of whole brain radiotherapy. *J Thorac Oncol.* 2012;7(2):382–385.

15. Brem SS, Bierman PJ, Black P, et al; National Comprehensive Cancer Network. Central nervous system cancers: clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2005;3(5):644–690.

16. Buszek SM, Chung C. Radiotherapy in leptomeningeal disease: a systematic review of randomized and non-randomized trials. *Front Oncol.* 2019;9:1224.

17. El Shafie RA, Böhm K, Weber D, et al. palliative radiotherapy for leptomeningeal carcinomatosis-analysis of outcome, prognostic factors, and symptom response. *Front Oncol.* 2018;8:641.

18. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology, Central Nervous System Cancers Version 2.2020.* 2020. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

19. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol.* 2006;7(10):813–820.

20. Kretschmar C, Kleinberg L, Greenberg M, Burger P, Holmes E, Wharam M. Pre-radiation chemotherapy with response-based radiation therapy in children with central nervous system germ cell tumors: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2007;48(3):285–291.

21. Calaminus G, Kortmann R, Worch J, et al. SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. *Neuro Oncol.* 2013;15(6):788–796.

22. Pinnix CC, Yahalom J, Specht L, Dabaja BS. Radiation in central nervous system leukemia: guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys.* 2018;102(1):53–58.

23. Gunther JR, Rahman AR, Dong W, et al. Craniospinal irradiation prior to stem cell transplant for hematologic malignancies with CNS involvement: effectiveness and toxicity after photon or proton treatment. *Pract Radiat Oncol.* 2017;7(6):e401–e408.

24. Hermann B, Hültenschmidt B, Sautter-Bihl ML. Radiotherapy of the neuroaxis for palliative treatment of leptomeningeal carcinomatosis. *Strahlenther Onkol.* 2001;177(4):195–199.

25. Harada HM, Asakura K, Ogawa H, et al. Cranio-spinal irradiation for leptomeningeal carcinomatosis: a pilot study. *Int J Radiat Oncol Biol Phys.* 2014;90(1):S310.

26. El Shafie RA, Böhm K, Weber D, et al. Outcome and prognostic factors following palliative craniospinal irradiation for leptomeningeal carcinomatosis. *Cancer Manag Res.* 2019;11:789–801.

27. De B, Kinnaman MD, Wexler LH, Kramer K, Wolden SL. Central nervous system relapse of rhabdomyosarcoma. *Pediatr Blood Cancer.* 2017;65(1):e26710.

28. Yuh GE, Loredo LN, Yonemoto LT, et al. Reducing toxicity from craniospinal irradiation: using proton beams to treat medulloblastoma in young children. *Cancer J.* 2004;10(6):386–390.

29. Howell RM, Giebeler A, Koontz-Raisig W, et al. Comparison of therapeutic dosimetric data from passively scattered proton and photon craniospinal irradiations for medulloblastoma. *Radiat Oncol.* 2012;7:116.

30. Song S, Park HJ, Yoon JH, et al. Proton beam therapy reduces the incidence of acute haematological and gastrointestinal toxicities associated with craniospinal irradiation in pediatric brain tumors. *Acta Oncol.* 2014;53(9):1158–1164.

31. Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys.* 2013;86(2):277–284.

32. Lin H, Ding X, Kirk M, et al. Supine craniospinal irradiation using a proton pencil beam scanning technique without match line changes for field junctions. *Int J Radiat Oncol Biol Phys.* 2014;90(1):71–78.

33. Chamberlain M, Junck L, Brandsma D, et al. Leptomeningeal metastases: a RANO proposal for response criteria. *Neuro Oncol.* 2017;19(4):484–492.

34. Rades D, Bohlen G, Dunst J, et al. Comparison of short-course versus long-course whole-brain radiotherapy in the treatment of brain metastases. *Strahlenther Onkol.* 2008;184(1):30–35.

35. Grossman SA, Ellsworth S, Campian J, et al. Survival in patients with severe lymphopenia following treatment with radiation and chemotherapy for newly diagnosed solid tumors. *J Natl Compr Canc Netw.* 2015;13(10):1225–1231.

36. Le Rhun E, Taillibert S, Zairi F, et al. A retrospective case series of 103 consecutive patients with leptomeningeal metastasis and breast cancer. *J Neurooncol.* 2013;113(1):83–92.

37. Lee SJ, Lee JI, Nam DH, et al. Leptomeningeal carcinoma-
    tosis in non-small-cell lung cancer patients: impact on survival
    and correlated prognostic factors. *J Thorac Oncol.* 2013;8(2):
    185–191.
38. Saito H, Tanaka K, Kanemoto A, Nakano T, Abe E, Aoyama H. Factors
    affecting the baseline and post-treatment scores on the hopkins verbal
    learning test-revised japanese version before and after whole-brain ra-
    diation therapy. *Int J Mol Sci.* 2016;17(11):1834.
39. Brown PD, Pugh S, Laack NN, et al; Radiation Therapy Oncology Group
    (RTOG). Memantine for the prevention of cognitive dysfunction in pa-
    tients receiving whole-brain radiotherapy: a randomized, double-blind,
    placebo-controlled trial. *Neuro Oncol.* 2013;15(10):1429–1437.