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CLINICAL INVESTIGATION **Brain**

PHASE I TRIAL OF SIMULTANEOUS IN-FIELD BOOST WITH HELICAL TOMOTHERAPY FOR PATIENTS WITH ONE TO THREE BRAIN METASTASES

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Purpose: Stereotactic radiosurgery is an alternative to surgical resection for selected intracranial lesions. Integrated image-guided intensity-modulated-capable radiotherapy platforms such as helical tomotherapy (HT) could potentially replace traditional radiosurgery apparatus. The present study's objective was to determine the maximally tolerated dose of a simultaneous in-field boost integrated with whole brain radiotherapy for palliative treatment of patients with one to three brain metastases using HT.

Methods and Materials: The inclusion/exclusion criteria and endpoints were consistent with the Radiation Therapy Oncology Group 9508 radiosurgery trial. The cohorts were constructed with a 3 + 3 design; however, additional patients were enrolled in the lower dose tolerable cohorts during the toxicity assessment periods. Whole brain radiotherapy (30 Gy in 10 fractions) was delivered with a 5–30-Gy (total lesion dose of 35–60 Gy in 10 fractions) simultaneous in-field boost delivered to the brain metastases. The maximally tolerated dose was determined by the frequency of neurologic Grade 3-5 National Cancer Institute Common Toxicity Criteria, version 3.0, dose-limiting toxicity events within each Phase I cohort.

Results: A total of 48 patients received treatment in the 35-Gy (n = 3), 40-Gy (n = 16), 50-Gy (n = 15), 55-Gy (n = 8), and 60-Gy (n = 6) cohorts. No patients experienced dose-limiting toxicity events in any of the trial cohorts. The 3-month RECIST assessments available for 32 of the 48 patients demonstrated a complete response in 2, a partial response in 16, stable disease in 6, and progressive disease in 8 patients.

Conclusion: The delivery of 60 Gy in 10 fractions to one to three brain metastases synchronously with 30 Gy whole brain radiotherapy was achieved without dose-limiting central nervous system toxicity as assessed 3 months after treatment. This approach is being tested in a Phase II efficacy trial. © **2011 Elsevier Inc.**

Radiosurgery, Brain metastases, Helical tomotherapy, Phase I, Clinical trial.

INTRODUCTION

Brain metastases are a common cancer problem and the patient outcome with the currently available therapies remains poor. Most patients with brain metastases undergo whole brain radiotherapy (WBRT). Clinical trials have suggested that selected subgroups of patients (*i.e.,* younger age, good performance status, extracranial metastases absent or controlled, and/or a single brain metastatic site [1, 2]) might benefit from more aggressive local treatment of their intracranial disease with surgery or radiosurgery, often in combination with WBRT (3, 4).

Helical tomotherapy (HT) combines intensity-modulated fan-beam RT delivery with megavoltage computed tomography (MVCT) imaging for integrated patient positioning and treatment delivery (5, 6). Such a combination provides a potential alternative to conventional (7) stereotactic frame systems for precision RT. Dosimetric comparisons of serial tomotherapy or HT delivery for primary and metastatic brain tumors have suggested comparable normal tissue sparing and target coverage compared with other precision RT techniques (8–12). HT (and other forms of intensity-modulated RT delivery) lends itself to synchronous boost strategies, because multiple targets can be easily treated to different dose (and dose per fraction) levels in the course of intensity-

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modulated RT delivery. Therefore, HT could potentially allow for radiosurgery-type boosts to be given synchronously with the standard WBRT component; thus, the system could be used to efficiently provide a boost to multiple brain metastases without the need for separate stereotactic procedures. We have previously reported the dosimetric feasibility of using HT to deliver a boost synchronous with WBRT to achieve intralesional biologically effective doses similar to single-fraction stereotactic radiosurgery (12). Also, others have recently reported the use of volumetric arc therapy (13, 14). In the present report, we describe the results of a Phase I dose-escalation trial of HT for one to three brain metastases using WBRT with a simultaneous in-field boost technique (HT-SIB).

METHODS AND MATERIALS

Clinical trial

The institutional review boards at the participating institution approved the Phase I trial, which was registered (Ontario Clinical Trials Registry OCT 1145 TOMO-B) according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Patient eligibility for the trial was as follows: histologically proven cancer; imaging findings and clinical presentation consistent with brain metastases; one to three brain metastases on pretreatment contrast-enhanced CT or magnetic resonance imaging; lesion size of $\geq$5 mm and $\leq$3 cm in diameter; lesion >5 mm from the brainstem optic or optic apparatus; Karnofsky performance status of $\geq$70; extracranial disease absent, controlled, or planned to be treated (in the case of synchronous presentation); anticipated survival >3 months; and no previous cranial RT. The patients were allowed to have undergone previous craniotomy provided residual tumor or additional unresected lesions were present on postoperative imaging. The trial was designed according to the typical Phase I dose escalation rules with five dose levels for the SIB boost: 35, 45, 50, 55, and 60 Gy. The original trial was designed to accrue 3 patients at each dose level, with a subsequent escalation if no dose-limiting toxicity (DLT) was seen at 3 months, with an additional 3 patients enrolled if 1 patient experienced a DLT. DLT was as defined according to the National Cancer Institute Common Toxicity Criteria, version 3.0, as Grade 3-5 central nervous system (CNS) toxicity, including necrosis (symptomatic and interfering with activities of daily living, life-threatening requiring intervention, or fatal). Once the trial began, it became evident that a considerable loss of patients had occurred to intercurrent illness and systemic disease progression (despite the eligibility criteria) before the 3-month assessment. Thus, the trial was modified to allow 6 patients to be accrued at each dose level to ensure adequate numbers of patients available for the 3-month assessment to ensure timely completion of the trial. During the 3-month waiting period for the dose level under assessment, we allowed enrollment at the previously evaluated dose level one step below the current dose level. Patients were excluded from the DLT analysis if the 3-month assessments for toxicity were unavailable, if patients had refused treatment after enrollment, or if they did not complete all RT sessions as planned. The status of the patients who were not evaluable at 3 months was confirmed by the primary care physicians to assess the reason for the lack of the 3-month assessment. This follow-up protocol was used to ensure that early treatment-related toxicity was not responsible for the nonevaluable status. The use of anticonvulsants and steroids was at the discretion of the attending oncologist.

Toxicity was monitored weekly during treatment, every month for 3 months after treatment, and then every 3 months for 1 year. The response at 3 months after treatment was assessed from the imaging findings. Patients were accrued at 3–6 patients/dose level. Escalation to the next dose level occurred if no limiting (Grade 3 or greater) toxicity was observed in >1 of 3 or >2 of 6 patients by 3 months after treatment. This endpoint was designed to be similar to the Radiation Therapy Oncology Group 9005 radiosurgery dose-finding study (15). The patients were also monitored for long-term toxicity, understanding that the treatment paradigm being explored was novel and that important CNS toxicity endpoints, such as radionecrosis, might manifest after the initial 3-month observation point. In the case of patients who were not able to attend for imaging and/or clinical assessment at the 3-month follow-up because of physical decline or death, the primary care physicians were interviewed and the medical records (hospital admission notes, death summaries, and laboratory and imaging reports) were obtained to ascertain whether the reason for the early decline could have been treatment-related toxicity. The attending radiation oncologist was consulted and reviewed the information. Also, the available information was reviewed independently by one of the study principle investigators (G.S.B.) for determination of possible treatment-related toxicity.

Selection of optimization criteria

The selection of the dose and fractionation prescription for the trial was determined by previously reported experience with single-fraction radiosurgery alone or combined with WBRT for patients with oligometastatic disease to the brain. Using the synchronous boost technique, we calculated that a total intralesion dose of 60 Gy in 10 fractions delivered with a surrounding whole brain dose of 30 Gy in 10 fractions would provide a similar biologically effective dose to a radiosurgery boost of 18 Gy in one fraction combined with WBRT to 30 Gy in 10 fractions (16, 17). Thus, we set 60 Gy in 10 fractions as the target maximal SIB dose level with an interim SIB dose level of 35, 45, 50, and 55 Gy for this Phase I trial. A maximal dose (D1) of 35 Gy in 10 fractions to the brainstem and chiasm in the SIB treatment was estimated, assuming a tolerance of 50 Gy in 25 fractions. This dose was used as a dose constraint for these critical structures during inverse planning.

Treatment planning and delivery

All patients had a custom head-and-neck thermoplastic shell (S-frame, CIVCO Medical Solutions, Kalona, IA) constructed for simulation and treatment. A planning CT scan (Phillips Healthcare, Andover, MA) through the whole head and upper neck was obtained with a 3-mm slice thickness. Patients without a recent (<3 weeks) contrast-enhanced diagnostic CT scan or magnetic resonance imaging scan underwent contrast-enhanced CT scanning at simulation; otherwise, the diagnostic CT scan was fused with the planning CT scan for treatment planning purposes. The individual contrast-enhancing lesions only were contoured as the SIB targets without a margin, and the whole cranial contents with a 3-mm three-dimensional margin was contoured as the target for the whole brain treatment.

The planning parameters (18) used for the HT plans were a fan beam thickness of 2.5 or 5.0 cm, pitch of 0.287–0.43, modulation factor of 3.0, and a normal calculation grid ($1.8 \times 1.8 \times 3$ mm^3). Plans were generated for the dose level under evaluation, as well as the next greater dose level to provide a running assessment of the feasibility of proceeding to the next level. The treatment