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CLINICAL INVESTIGATION **Brain**

MOTEXAFIN GADOLINIUM COMBINED WITH PROMPT WHOLE BRAIN RADIOTHERAPY PROLONGS TIME TO NEUROLOGIC PROGRESSION IN NON–SMALL-CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES: RESULTS OF A PHASE III TRIAL

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Purpose: To determine the efficacy of motexafin gadolinium (MGd) in combination with whole brain radiotherapy (WBRT) for the treatment of brain metastases from non–small-cell lung cancer.

Methods and Materials: In an international, randomized, Phase III study, patients with brain metastases from non–small-cell lung cancer were randomized to WBRT with or without MGd. The primary endpoint was the interval to neurologic progression, determined by a centralized Events Review Committee who was unaware of the treatment the patients had received.

Results: Of 554 patients, 275 were randomized to WBRT and 279 to WBRT+MGd. Treatment with MGd was well tolerated, and 92% of the intended doses were administered. The most common MGd-related Grade 3+ adverse events included liver function abnormalities (5.5%), asthenia (4.0%), and hypertension (4%). MGd improved the interval to neurologic progression compared with WBRT alone (15 vs. 10 months; $p = 0.12$, hazard ratio [HR] = 0.78) and the interval to neurocognitive progression ($p = 0.057$, HR = 0.78). The WBRT patients required more salvage brain surgery or radiosurgery than did the WBRT+MGd patients (54 vs. 25 salvage procedures, $p < 0.001$). A statistically significant interaction between the geographic region and MGd treatment effect (which was in the prespecified analysis plan) and between treatment delay and MGd treatment effect was found. In North American patients, where treatment was more prompt, a statistically significant prolongation of the interval to neurologic progression, from 8.8 months for WBRT to 24.2 months for WBRT+MGd ($p = 0.004$, HR = 0.53), and the interval to neurocognitive progression ($p = 0.06$, HR = 0.73) were observed.

Conclusion: In the intent-to-treat analysis, MGd exhibited a favorable trend in neurologic outcomes. MGd significantly prolonged the interval to neurologic progression in non–small-cell lung cancer patients with brain metastases receiving prompt WBRT. The toxicity was acceptable. © 2009 Elsevier Inc.

Brain metastases, Non–small-cell lung cancer, Whole brain radiotherapy, Motexafin gadolinium, Neurologic progression, Neurocognitive function.

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INTRODUCTION

Brain metastases from non–small-cell lung cancer (NSCLC) are a major cause of morbidity (1). Up to 50% of NSCLC patients may develop brain metastases (2). Whole brain radiotherapy (WBRT) is the standard of care for patients with multiple lesions. No approved drugs are available for the treatment of brain metastases. Nearly one-half of patients develop progressive neurologic problems, and only 10–15% survive 1 year.

The prevention and palliation of neurologic problems due to progression are important goals of treatment. Improvement in survival might not be an ideal measure of the benefit of a local therapy, because overall survival is commonly determined by extracranial disease. Tumor size, number, location, extracranial disease, comorbidities, steroid use, and previous therapies complicate the evaluation of clinical benefit. In a previous Phase III trial (PCI-P120-9801, termed 9801) of WBRT with or without motexafin gadolinium (MGd) for patients with brain metastases, the interval to neurologic progression was determined by an Events Review Committee (ERC), unaware of the treatment received, that reviewed the standardized neurologic examination data, neurologic symptoms, and neurocognitive test results (3–5). The trial demonstrated that standardized neurologic and neurocognitive assessments and the ERC-determined neurologic progression endpoint could be used effectively in an international trial. The ERC-determined neurologic progression endpoint is sensitive to change, objective, clinically relevant, and validated against conventional endpoints such as survival and radiologic progression (6). This endpoint captures data indicating severe neurologic decline that is related to brain metastasis progression.

Motexafin gadolinium is a novel drug that disrupts redox-dependent pathways by targeting oxidative stress-related proteins such as thioredoxin reductase and metallothioneins (7–9). Thioredoxin reductase is overexpressed in lung cancer and is associated with a poor prognosis (10). Clinical trials have shown that MGd concentrates in tumor cells and is visible on magnetic resonance imaging (11–13). In preclinical studies, MGd enhanced the effects of ionizing radiation (14). The purpose of the present trial, PCYC-0211, was to confirm the results from the 9801 study that demonstrated a benefit of MGd in patients with brain metastases from NSCLC (4).

METHODS AND MATERIALS

Patients

The institutional review board at each center approved the study, and all patients provided informed consent in accordance with the Helsinki Declaration (15). Adults with brain metastases from NSCLC and a Karnofsky performance status (KPS) of ≥70 were eligible. Patients were excluded if they had liver metastases, two or more sites of extracranial metastases, leptomeningeal metastases, or had undergone previous resection of a single brain metastasis, previous WBRT, previous stereotactic radiosurgery (SRS) if more than one treatment had been given or more than lesions had been treated, or had an absence of new lesions after SRS. The laboratory requirements included an absolute granulocyte count of ≥1,500/mm^3; platelet count of ≥50,000/mm^3; total bilirubin, alanine aminotransferase, and aspartate aminotransferase less than two times the upper limit of normal; serum creatinine of ≤2.0 mg/dL; and lactate dehydrogenase of ≤1.3 times the upper limit of normal.

Treatment

Patients underwent WBRT (30 Gy in 10 fractions) or WBRT with MGd (5 mg/kg/d, 2–5 hours before each fraction; MGd group).

Efficacy

The primary endpoint was the ERC-determined interval to neurologic progression or death with evidence of neurologic progression. Secondary endpoints included the interval to investigator-determined neurologic progression, the interval to neurocognitive progression, survival, and safety.

The patients were evaluated at study entry, monthly for 8 months, and then every 2 months until death. If neurologic deterioration was noted, the patients had a confirmatory visit 2 weeks later. Follow-up concluded 6 months after the last randomization.

Each study visit included a neurologic examination that used standardized and commonly used scales for alertness, orientation, language, speech, cranial nerves, and motor, sensory, and cerebellar function, and focused on eliciting clinically significant neurologic findings specific for brain metastases, standardized neurocognitive tests (Hopkins Verbal Learning Test, Controlled Oral Word Association, and Trailmaking Test Parts A and B) (5), and grading of neurologic symptoms. All investigators had undergone training and certification in neurologic examination and neurocognitive test administration. The raw neurocognitive data were scored by a blinded central reviewer (C.A.M.) and converted to z-scores. Adverse events were graded using the National Cancer Institute Common Toxicity Criteria, version 2.0.

The ERC, a panel of neuro-oncologists (W.R.S., R.A.P., M.G., L.R.), who were unaware of the treatment assignment, reviewed the neurologic and clinical data according to a prospective charter (3, 4). Neurologic events were categorized as major or minor. The major criteria were most specific for an acute deterioration caused by a brain tumor and had a profound effect on a patient's neurologic status, consisting of a severe decline in consciousness (stupor or coma), aphasia/dysphasia, severe decline in motor strength (three-grade decline), new-onset visual field deficit, ataxia (two or more decline in grade), or a decline in executive function (Controlled Oral Word Association and Trail Making Test B). The minor criteria comprised a set of findings consistent with the worsening of a brain tumor, but each finding by itself was insufficient for progression. Neurologic progression required a combination of three or more minor criteria followed by confirmation. Minor criteria included a change in orientation, papilledema, a change in motor strength (two grades), oculomotor palsy, loss of limb sensation, cerebellar dysfunction, facial weakness, ataxia, facial numbness, new-onset seizures, unequal or nonreactive pupils, a decline in neurocognitive test scores, or dysarthria. Radiologic progression alone was insufficient for neurologic progression.

Neurologic progression was also determined by the investigators using predefined criteria, but this information was not included in the primary endpoint analysis.

Statistical analysis and sample size calculation

Treatment was randomly assigned according to an urn randomization scheme (16) that balanced allocation by center, KPS (70–80 vs. 90–100), and age (≤65 vs. >65 years). The sample size was calculated using a two-sided Type I error rate of 0.001 and a power of 80% to detect an approximate 2.2-month increase