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A placebo-controlled, randomized phase II study of maintenance enzastaurin following whole brain radiation therapy in the treatment of brain metastases from lung cancer☆

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ABSTRACT

Introduction: Enzastaurin is a protein kinase C inhibitor with anti-tumor activity. This study was designed to determine if maintenance enzastaurin improved the outcome of whole brain radiotherapy (WBRT) in lung cancer (LC) patients with brain metastases (BMs).
Methods: Patients with LC (any histology) who had received WBRT for BMs were randomized to receive oral maintenance enzastaurin (1125 mg on Day 1 followed by 500 mg daily) or placebo. The primary endpoint was time to progression (TTP) of BMs.
Results: Fifty-four patients received enzastaurin and 53 patients received placebo. The median TTP of BMs was (months) enzastaurin: 6.9 (95% confidence interval [CI]: 3.4–11.9); placebo: 4.9 (95% CI: 3.6–not assessable); $p = 0.82$. Median overall survival (OS) was (months) enzastaurin: 3.8 (95% CI: 2.6–5.6); placebo: 5.1 (95% CI: 3.7–5.7); $p = 0.47$. Median progression-free survival (PFS) was (months) enzastaurin: 2.2 (95% CI: 1.1–2.3); placebo: 2.0 (95% CI: 1.3–2.3); $p = 0.75$. The overall response rate (ORR) for extracranial disease was enzastaurin: 0%; placebo: 4.5% ($p = 0.49$) and for intracranial disease was enzastaurin: 9.3%; placebo 6.8% ($p = 0.71$). Grade 4 hematologic treatment-emergent adverse events were (enzastaurin vs. placebo) thrombocytopenia (5.6% vs. 1.9%) and neutropenia (5.6% vs. 0%). There was 1 treatment-related death in each arm (enzastaurin: unknown cause; placebo: pulmonary embolism). No significant differences in health-related quality of life (HRQoL) were observed.
Conclusions: Enzastaurin was well tolerated but did not improve TTP of BMs, ORR, OS, PFS, or HRQoL after WBRT in LC patients with BMs.

1. Introduction

Approximately 40–50% of patients with lung cancer (LC) develop brain metastases (BMs); the majority have multiple lesions [1,2]. Responses to chemotherapy reflect chemosensitivity of the primary tumor, with best responses seen in small cell lung cancer (SCLC) and intermediate responses seen in non-small cell lung cancer (NSCLC); these responses may be less durable than with whole brain radiotherapy (WBRT) [3]. Thus, corticosteroids and WBRT remain the standard of care for patients with multiple BMs [1,2]. Approximately 60% of patients clinically respond to such therapy, but it is unclear if responses are due to WBRT and/or corticosteroids [2] With median overall survival (OS) under 4 months [4], improvements are needed.

Enzastaurin (LY317615) is an orally active protein kinase C and PI3K/AKT inhibitor with apoptotic, anti-proliferative, and

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anti-angiogenic activities [5,6]. It has anti-cancer and anti-proliferative activity in cells and xenografts derived from solid tumors, including NSCLC and SCLC [6–9]. In phase I trials, enzastaurin was active and well tolerated in solid tumors including LC [10]. In a phase II trial involving second- or third-line NSCLC patients treated with enzastaurin monotherapy, 13% of patients experienced progression-free survival (PFS) ≥6 months [11]. A phase I–II trial showed anti-tumor activity in recurrent malignant gliomas, suggesting that enzastaurin crosses the blood–brain barrier [12]. Enzastaurin's tolerability made it attractive to use after radiotherapy. When the study was designed, no data were available regarding tolerability of concurrent enzastaurin and WBRT. Thus, we conducted a randomized phase II trial comparing maintenance therapy with enzastaurin to placebo following WBRT in patients with BMs from LC.

2. Materials and methods

2.1. Patient eligibility

Patients (≥18 years old) with histologically or cytologically proven SCLC or NSCLC; radiologically proven BMs prior to the initiation of WBRT; Eastern Cooperative Oncology Group performance status (PS) of 0–2; and not in immediate need for systemic cancer therapy were eligible. Patients with single brain lesions were eligible if they were ineligible for surgery or radiosurgery. Prior to randomization, patients received WBRT of 20 Gy (4 Gy × 5 or 5 Gy × 4) or 30 Gy (3 Gy × 10); the schedule was decided by the study sites.

The inclusion of both SCLC and NSCLC patients was based on a Nordic study where there was no difference in drop-out rates between SCLC and NSCLC patients with BMs receiving WBRT [13]. The 20 Gy schedule was the standard of care at many participating centers; the 20 Gy and 30 Gy schedules have equivalent efficacy [14,15].

Key exclusion criteria were: inability to take oral medication; serious concomitant systemic disorders that could compromise patient safety; and systemic anti-cancer treatment within 2 weeks prior to enrollment. Also excluded were patients having other clinically active cancers or receiving concurrent enzyme-inducing anti-epileptic drugs (EIAEDs; phenytoin, carbamazepine, phenobarbital) because these drugs lower enzastaurin serum exposure [12]. Patients initiating EIAEDs after enrollment could remain on study.

Each center's institutional review board approved the protocol in compliance with local regulations. This study was conducted in accordance with good clinical practices, the Declaration of Helsinki, and applicable regulations. Patients provided written informed consent prior to undergoing study procedures or receiving study treatment.

2.2. Randomization

Following WBRT, patients were randomized (enrolled) 1:1 to receive either oral enzastaurin or placebo within 14 days after the last RT fraction. Treatment groups were assigned using a central computerized interactive voice response system. Randomization was stratified by PS (0/1 vs. 2), tumor type (SCLC vs. NSCLC), and WBRT (20 Gy vs. 30 Gy).

2.3. Treatment plan

Study treatment began within 14 days after the last RT fraction. Patients randomized to the experimental arm received an enzastaurin loading dose (375 mg 3 times daily) within 30 min of each meal on Day 1; beginning on Day 2, patients received enzastaurin 500 mg daily within 30 min of the largest meal. Placebo-treated patients received an equivalent number of placebo tablets appearing identical to enzastaurin. All patients received best supportive care (BSC) allowing for corticosteroids in addition to study treatment. Patients were treated until BM progression, initiation of a new systemic anti-cancer regimen, or unacceptable toxicity. Patients were followed until death or study closure.

2.4. Dose adjustments

Study treatment was suspended until resolution of Common Terminology Criteria for Adverse Events (CTCAE) grade 3/4 toxicity. If the event resolved to ≤CTCAE grade 1 or baseline, therapy was re-initiated at 250 mg daily. If the event did not recur within 21 days of restarting therapy, the dose could be re-escalated to 500 mg daily at investigator's discretion. If the event did not resolve to ≤CTCAE grade 1 or baseline within 3 weeks, or another event occurred at the reduced dose, the patient was discontinued from study therapy.

2.5. Patient evaluations

At baseline, medical history, pregnancy test, physical examination, and laboratory tests were performed; PS was assessed; health-related quality of life (HRQoL) information was collected; and magnetic resonance imaging (MRI) of intracranial lesions and computed tomography (CT) scan of extracranial lesions were performed. Within 3–4 weeks after enrollment, intracranial and extracranial lesions were assessed as before and were then repeated every 6 weeks (±7 days) during the first 6 months of treatment and every 2 months thereafter, until objective progression or start of new systemic anti-cancer therapy. Concomitant medication, PS, CTCAE grading, hematology, and HRQoL were assessed at the same intervals as imaging and 30 days post therapy. Blood chemistry was assessed every 3 weeks during the first 6 months and at the same intervals as blood counts thereafter.

2.6. Statistical considerations

This was a randomized, double-blind, parallel, placebo-controlled phase II trial. The primary objective was the between-arm comparison of TTP of BMs in enzastaurin-treated patients versus placebo-treated patients. Time to progression was determined for the full analysis population including all randomized patients. Secondary endpoints were time to objective progression (TTOP) of BMs, PFS, OS, response rates for extracranial tumor manifestation(s), HRQoL, and safety. The response rate of BMs was determined in a post hoc analysis. All secondary time-to-event efficacy endpoints were conducted on the full analysis population. Safety analyses were conducted on all patients receiving at least one dose of study drug.

Time to progression of BMs was the time from the date of study enrollment to the date of first observation of BM progression. Progression of BMs was evaluated according to both Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) [16] using MRI and clinical progression. If the PS or neurological status of a patient worsened so that radiological confirmation of progression was not feasible, the investigator could discontinue the patient based on clinical progression of BMs. In these cases, the date of increased steroid dose was considered the date of progression for TTP analysis. Deaths without evidence of intracranial progression were treated as censored events.

The planned enrollment of 108 patients was based on a 1:1 randomization and an observation of 85 events. This would allow detection of a 1.2-month improvement in TTP of BMs from 2 to 3.2 months corresponding to a TTP hazard ratio (HR) of approximately