A phase 0 analysis of ixazomib in patients with glioblastoma

Joseph Quillin MD; Jeffrey J. Olson MD
Emory University

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Introduction

Improving overall survival in recurrent glioblastoma remains a challenge, and drugs working by unique mechanisms are urgently needed. Ixazomib is an orally-administered proteasome inhibitor used to treat multiple myeloma. Activity against glioblastoma has been investigated with intravenous agents of this drug class, with their efficacy limited by penetration of the blood-brain barrier. Ixazomib's ability to reach brain tumors was not studied during its development. We report a phase 0 analysis of ixazomib's pharmacodynamics and pharmacokinetics in recurrent glioblastoma patients.

Learning Objectives

By the conclusion of this session, participants should be able to:

1) Describe the importance of proteasomes inhibitors as emerging glioblastoma therapies

2) Discuss the basic mechanism of action of ixazomib

3) Identify future directions for application of ixazomib as an investigational therapy for glioblastoma

Methods

We studied 3 patients with recurrent glioblastoma after administration of oral ixazomib citrate (MLN 9708) at a fixed 4.0mg dose within a 3-hour preoperative window. Blood samples were taken from each patient at time of incision, tumor sampling, and closure. Brain tumor samples were collected during tumor resection. These samples were then used to measure plasma and brain tumor tissue concentration of MLN 2238, the biologically-active boronic form of ixazomib. The samples were analyzed with a new and unique assay via liquid chromatography tandem mass spectrometry using a qualified curve range of 0.500ng/mL to 500ng/mL for plasma and 0.500ng/g to 500ng/g for brain homogenate.

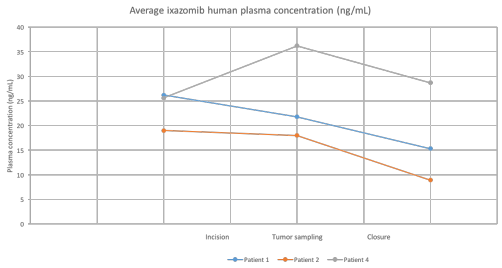
Results

- Patient 1 had plasma concentrations of ixazomib averaging 26.2ng/mL, 21.8ng/mL, and 15.3ng/mL at incision, tumor sampling, and closure respectively. Brain tissue concentration was 7.88ng/g.

- Patient 2 had the same interval and brain tissue measurements of 19.0ng/mL, 18.0ng/mL, and 8.93ng/mL and 2.03ng/g.

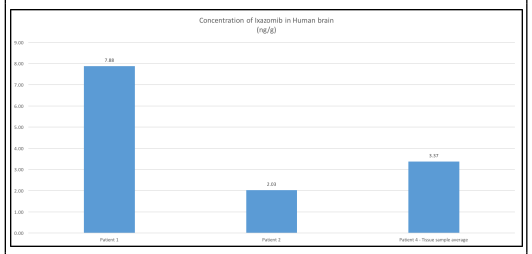
- Patient 3 had the same interval measurements of 25.6ng/mL, 36.2ng/mL, and 28.7ng/mL, and

Average ixazomib human plasma concentrations



Patient concentrations of ixazomib in plasma at incision, tumor sampling, and closure.

Concentrations of ixazomib in human brain



The documented concentrations of ixazomib in human brain samples taken during tumor resection.

Conclusions

MLN 2238 was found at plasma concentrations commensurate with its previously established time and dose-dependent pharmacokinetic profiles in both mice and humans with multiple myeloma without significant adverse events. Ixazomib reaches glioblastoma tissue at measurable concentrations at time of tumor resection, confirming target tissue delivery. This justifies the phase I study of ixazomib in recurrent glioblastoma currently in development.

References

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