Phase II study of neoadjuvant imatinib in glioblastoma: evaluation of clinical and molecular effects of the treatment.

Razis E, Selviaridis P, Labropoulos S, Norris JL, Zhu MJ, Song DD, Kalebic T, Torrens M, Kalogera-Fountzila A, Karkavelas G, Karanastasi S, Fletcher JA, Fountzilas G.

Source

1st Department of Medical Oncology, Hygeia Hospital, Athens, Greece. e.razis@hygeia.gr

Abstract

PURPOSE:

Phase I-II studies indicate that imatinib is active in glioblastoma multiforme. To better understand the molecular and clinical effects of imatinib in glioblastoma multiforme, we conducted a neoadjuvant study of imatinib with pretreatment and posttreatment biopsies.

EXPERIMENTAL DESIGN:

Patients underwent a computerized tomography-guided biopsy of their brain tumors. If diagnosed with glioblastoma multiforme, they were immediately treated with 7 days of imatinib 400 mg orally twice daily followed by either definitive surgery or re-biopsy. Pretreatment and posttreatment tissue specimens were tested by immunohistochemistry for Ki67 and microvessel destiny, and posttreatment specimens were analyzed for the presence of intact imatinib in tissue. Furthermore, pretreatment and posttreatment pairs were analyzed by Western blotting for activation of platelet-derived growth factor receptor, epidermal growth factor receptor (EGFR), phosphoinositide 3-kinase/AKT, and mitogen-activated protein kinase signaling pathways. Pharmacokinetic studies were also done.

RESULTS:

Twenty patients were enrolled. Median survival was 6.2 months. Intact imatinib was detected in the posttreatment tissue specimens using mass spectrometry. There was no evidence of a drug effect on proliferation, as evidenced by a change in Ki67 expression. Biochemical evidence of response, as shown by decreased activation of AKT and mitogen-activated protein kinase or increased p27 level, was detected in 4 of 11 patients with evaluable, matched pre- and post-imatinib biopsies. Two patients showed high-level EGFR activation and homozygous EGFR mutations, whereas one patient had high-level platelet-derived growth factor receptor-B activation.

CONCLUSIONS:

Intact imatinib was detected in glioblastoma multiforme tissue. However, the histologic and immunoblotting evaluations suggest that glioblastoma multiforme proliferation and survival mechanisms are not substantially reduced by imatinib therapy in most patients.