Imatinib for glioblastoma

Imatinib mesylate, a tyrosine kinase inhibitor of platelet-derived growth factor receptor-alpha and -beta, c-fms, c-kit, abl and arg kinase (imatinib targets), has been shown to prevent tumor progression in early studies of recurrent glioblastomas, but has shown weak activity in randomized controlled trials.

Preclinical studies indicated that imatinib may have single-agent activity in glioblastoma through inhibition of tyrosine kinase activity and also that it might enhance the efficacy of radiotherapy. We therefore sought to investigate clinical efficacy in patients with newly diagnosed and recurrent glioblastoma in combination with radiotherapy.

METHODS: We conducted a nonrandomized, 2-arm, open-label phase II trial including patients aged 18 years or older with an ECOG performance status of 0-2 that were either newly diagnosed (arm A) with a measurable tumor (i.e., after incomplete resection or biopsy) or that were diagnosed with progression of a glioblastoma after initial therapy (arm B). Patients in arm A received 600 mg/day imatinib in combination with hypofractionated radiotherapy (2.5 Gy per fraction, 22 fractions). Patients in arm B received 600 mg/day imatinib alone or in combination with re-irradiation at various doses. In case tumor progression occurred, CCNU was added (2 cycles, 100 mg/m2) to imatinib. The primary end point was progression-free survival (PFS). The secondary end point was safety, defined as per Common Terminology Criteria for Adverse Events (version 2.0). Overall survival (OS) was analyzed as an exploratory end point.

Fifty-one patients were enrolled, of which 19 were included in arm A and 32 in arm B. The median follow-up was 4 (0.5-30) months in arm A and 6.5 (0.3-51.5) months in arm B. The median PFS was 2.8 months (95% CI 0-8.7) in arm A and 2.1 months (95% CI 0-11.8) in arm B. The median OS was 5.0 (0.8-30) months (95% CI 0-24.1) in arm A and 6.5 (0.3-51.5) months (95% CI 0-32.5) in arm B. The major grade 3 events were seizure (present in 17 patients), pneumonia (11 patients), and vigilance decrease (7 patients).

Imatinib showed no measurable activity in patients with newly diagnosed or recurrent glioblastoma [1].

Responses to imatinib observed in patients where imatinib inhibitable tyrosine kinases were documented on the original biopsy are marginally better than that previously reported in imatinib treatment of unselected recurrent glioblastoma patients. Hassler et al. present a suggestion for defining a patient sub-population who might potentially benefit from imatinib [2].

1)
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2)
Hassler MR, Vedadinejad M, Flechl B, Haberler C, Preusser M, Hainfellner JA, Wöhrer A, Dieckmann KU, Rössler K, Kast R, Marosi C. Response to imatinib as a function of target kinase expression in recurrent glioblastoma. Springerplus. 2014 Feb 25;3:111. doi: 10.1186/2193-1801-3-111. eCollection

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