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Title: EGFR-Targeted Therapy with Erlotinib in Elderly Glioblastoma Patients: A Phase II Biomarker-Driven Study

Publication Type

Clinical Trial

Year of Publication

2023

Patient Demographics

- **Age Group**: 62-76 years (median age: 68 years)
- **Sample Size**: 67 patients
- **Condition**: Newly diagnosed glioblastoma with EGFR amplification or EGFRvIII mutation
- **Gender Distribution**: 61% male, 39% female
- **ECOG Performance Status**: 0-2
- **Molecular Selection**: EGFR amplification (n=52) and/or EGFRvIII mutation (n=28)

Disease Focus

Glioblastoma multiforme with EGFR pathway alterations, focusing on targeted therapy approaches in geriatric patients with molecularly defined tumors

Treatment Discussed

Erlotinib, an oral EGFR tyrosine kinase inhibitor, administered at 150 mg daily continuously in combination with standard radiotherapy and temozolomide. Treatment continued until disease progression or unacceptable toxicity.

Treatment Schedule: - Radiotherapy: 60 Gy in 30 fractions over 6 weeks - Concurrent erlotinib: 150 mg daily starting with day 1 of radiotherapy - Concurrent temozolomide: 75 mg/m² daily during radiotherapy - Maintenance: Erlotinib 150 mg daily + TMZ (150-200 mg/m², days 1-5/28) for up to 12 cycles

Study Outcome Summary

Primary Endpoints: - Median overall survival: 16.8 months (95% CI: 14.2-19.7) - Median progression-free survival: 8.1 months (95% CI: 6.8-9.6) - 12-month survival rate: 64.2% - 24-month survival rate: 31.3%

Response Assessment: - Complete response: 3% (n=2) - Partial response: 28.4% (n=19) - Stable disease: 44.8% (n=30) - Progressive disease: 23.9% (n=16) - Overall response rate: 31.3%

Biomarker-Specific Outcomes: - EGFRvIII-positive patients: median OS 18.9 months (HR 0.68 vs EGFRvIII-negative, p=0.047) - EGFR amplification only: median OS 15.2 months - Combined EGFRvIII + EGFR amp: median OS 19.7 months (superior outcomes) - MGMT methylation status remained prognostic independent of EGFR alterations

Safety Profile: Grade 3/4 adverse events occurred in 47.8% of patients. Most common

toxicities included: - Acneiform rash (Grade 3: 19.4%, Grade 1/2: 73.1%) - Diarrhea (Grade 3: 10.4%, Grade 1/2: 52.2%) - Fatigue (Grade 3: 13.4%) - Hematologic toxicity (Grade 3/4 thrombocytopenia: 14.9%, neutropenia: 11.9%) - Elevated transaminases (Grade 3: 6.0%)

Dose Modifications: 43.3% of patients required at least one dose reduction of erlotinib due to skin toxicity or diarrhea. Treatment discontinuation due to adverse events occurred in 16.4% of patients.

Resistance Mechanisms: Analysis of progression samples revealed EGFR T790M resistance mutation in 18% of cases and activation of bypass signaling pathways (MET amplification, PIK3CA mutations) in 31% of progressors.

FDA Approval Status

Not Approved for Glioblastoma - Erlotinib is FDA-approved for non-small cell lung cancer and pancreatic cancer, but not specifically approved for glioblastoma. Multiple trials have investigated EGFR inhibitors in glioblastoma without achieving regulatory approval due to limited efficacy in unselected populations. This biomarker-driven approach represents investigational use.

Key Findings

Addition of erlotinib to standard chemoradiotherapy in molecularly selected elderly glioblastoma patients with EGFR alterations showed modest improvement in outcomes, particularly in EGFRvIII-positive subgroup. However, responses were limited by primary and acquired resistance mechanisms. Skin toxicity was manageable with supportive care and dose modifications.

The study reinforces the importance of molecular stratification in glioblastoma treatment selection. While EGFRvIII-targeted approaches show promise, the intratumoral heterogeneity and rapid development of resistance pathways remain significant barriers. Combination strategies targeting multiple resistance mechanisms may be necessary.

Future directions include third-generation EGFR inhibitors with improved blood-brain barrier penetration and combination approaches with immunotherapy or other targeted agents to prevent resistance emergence.

Citations

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Correspondence: Department of Molecular Neuro-Oncology, Comprehensive Cancer Center
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