Glioma

Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase III study.

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BACKGROUND

The CATNON trial investigated the addition of concurrent, adjuvant, and both current and adjuvant temozolomide to radiotherapy in adults with newly diagnosed 1p/19q non-co-deleted anaplastic gliomas. The benefit of concurrent temozolomide chemotherapy and relevance of mutations in the IDH1 and IDH2 genes remain unclear.

METHODS

This randomised, open-label, phase III study done in 137 institutions across Australia, Europe, and North America included patients aged 18 years or older with newly diagnosed 1p/19q non-co-deleted anaplastic gliomas and a WHO performance status of 0.0-2.0. Patients were randomly assigned (1:1:1:1) centrally using a minimisation technique to radiotherapy alone (59·4 Gy in 33 fractions; three-dimensional conformal radiotherapy or intensity-modulated radiotherapy), radiotherapy with concurrent oral temozolomide (75 mg/m2 per day), radiotherapy with adjuvant oral temozolomide (12 4-week cycles of 150-200 mg/m2 temozolomide given on days 1.0-5.0), or radiotherapy with both concurrent and adjuvant temozolomide. Patients were stratified by institution, WHO performance status score, age, 1p loss of heterozygosity, the presence of oligodendroglial elements on microscopy, and MGMT promoter methylation status. The primary endpoint was overall survival adjusted by stratification factors at randomisation in the intention-to-treat population. A second interim analysis requested by the independent data monitoring committee was planned when two-thirds of total required events were observed to test superiority or futility of concurrent temozolomide. This study is registered with ClinicalTrials.gov, NCT00626990.

FINDINGS

Between 4 Dec 2007, and 11 Sept, 2015, 751 patients were randomly assigned (189 to radiotherapy alone, 188 to radiotherapy with concurrent temozolomide, 186 to radiotherapy and adjuvant temozolomide, and 188 to radiotherapy with concurrent and adjuvant temozolomide). Median follow-up was 55·7 months (IQR 41·0-77·3). The second interim analysis declared futility of concurrent temozolomide (median overall survival was 66·9 months [95% CI 45·7-82·3] with concurrent temozolomide vs 60·4 months [45·7-71·5] without concurrent temozolomide; hazard ratio [HR] 0·97 [99·1% CI 0·73-1·28], p=0·76). By contrast, adjuvant temozolomide improved overall survival compared with no adjuvant temozolomide (median overall survival 82·3 months [95% CI 67·2-116·6] vs 46·9 months [37·9-56·9]; HR 0·64 [95% CI 0·52-0·79], p<0·0001). The most frequent grade 3.0 and 4.0 toxicities were haematological, occurring in no patients in the radiotherapy only group, 16 (9%) of 185 patients in the concurrent temozolomide group, and 55 (15%) of 368 patients in both groups with adjuvant temozolomide. No treatment-related deaths were reported.

INTERPRETATION

Adjuvant temozolomide chemotherapy, but not concurrent temozolomide chemotherapy, was associated with a survival benefit in patients with 1p/19q non-co-deleted anaplastic glioma. Clinical benefit was dependent on IDH1 and IDH2 mutational status.