Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial.


Abstract

BACKGROUND: Treatment options for recurrent glioblastoma are scarce, with second-line chemotherapy showing only modest activity against the tumour. Despite the absence of well controlled trials, bevacizumab is widely used in the treatment of recurrent glioblastoma. Nonetheless, whether the high response rates reported after treatment with this drug translate into an overall survival benefit remains unclear. We report the results of the first randomised controlled phase 2 trial of bevacizumab in recurrent glioblastoma.

METHODS: The BELOB trial was an open-label, three-group, multicentre phase 2 study undertaken in 14 hospitals in the Netherlands. Adult patients (≥18 years of age) with a first recurrence of a glioblastoma after temozolomide chemoradiotherapy were randomly allocated by a web-based program to treatment with oral lomustine 110 mg/m(2) once every 6 weeks, intravenous bevacizumab 10 mg/kg once every 2 weeks, or combination treatment with lomustine 110 mg/m(2) every 6 weeks and bevacizumab 10 mg/kg every 2 weeks. Randomisation of patients was stratified with a minimisation procedure, in which the stratification factors were centre, Eastern Cooperative Oncology Group performance status, and age. The primary outcome was overall survival at 9 months, analysed by intention to treat. A safety analysis was planned after the first ten patients completed two cycles of 6 weeks in the combination treatment group. This trial is registered with the Nederlands Trial Register (www.trialregister.nl, number NTR1929).

FINDINGS: Between Dec 11, 2009, and Nov 10, 2011, 153 patients were enrolled. The preplanned safety analysis was done after eight patients had been treated, because of haematological adverse events (three patients had grade 3 thrombocytopenia and two had grade 4 thrombocytopenia) which reduced bevacizumab dose intensity; the lomustine dose in the combination treatment group was thereafter reduced to 90 mg/m(2). Thus, in addition to the eight patients who were randomly assigned to receive bevacizumab plus lomustine 110 mg/m(2), 51 patients were assigned to receive bevacizumab alone, 47 to receive lomustine alone, and 47 to receive bevacizumab plus lomustine 90 mg/m(2). Of these patients, 50 in the bevacizumab alone group, 46 in the lomustine alone group, and 44 in the bevacizumab and lomustine 90 mg/m(2) group were eligible for analyses. 9-month overall survival was 43% (95% CI 29-57) in the lomustine group, 38% (25-51) in the bevacizumab group, 59% (43-72) in the bevacizumab and lomustine 90 mg/m(2) group, 87% (39-98) in the bevacizumab and lomustine 110 mg/m(2) group, and 63% (49-75) for the combined bevacizumab and lomustine groups. After the reduction in lomustine dose in the combination treatment group, the combined treatment was
well tolerated. The most frequent grade 3 or worse toxicities were hypertension (13 [26%] of 50 patients in the bevacizumab group, three [7%] of 46 in the lomustine group, and 11 [25%] of 44 in the bevacizumab and lomustine 90 mg/m(2) group), fatigue (two [4%], four [9%], and eight [18%]), and infections (three [6%], two [4%], and five [11%]). At the time of this analysis, 144/148 (97%) of patients had died and three (2%) were still on treatment.

**INTERPRETATION:** The combination of bevacizumab and lomustine met prespecified criteria for assessment of this treatment in further phase 3 studies. However, the results in the bevacizumab alone group do not justify further studies of this treatment.

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