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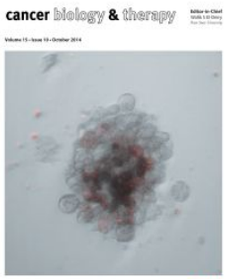

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Potential novel role of bevacizumab in glioblastoma and cervical cancer

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Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014; 370:734-43; PMID:24552320; http://dx.doi.org/10.1056/NEJMoa1309748

The VEGF-A binding monoclonal antibody bevacizumab is a widely prescribed angiogenesis inhibitor and indicated for many types of cancer. As shown by three randomized phase 3 trials recently published in the *New England Journal of Medicine*, novel indications for this drug are still being explored. In the RTOG 0825 and AVAglio trials the effect of bevacizumab addition to standard therapy in newly diagnosed glioblastoma (radiotherapy plus temozolomide) was investigated, while in GOG 240 the combination of platinum-based chemotherapy plus bevacizumab was explored in advanced cervical cancer.

In RTOG 0825, addition of bevacizumab to standard therapy did not result in survival benefit, and moreover, quality of life was more deteriorated in the bevacizumab arm. In AVAglio, however, progression-free survival (PFS) was significantly increased in the bevacizumab group and these patients also experienced a longer deterioration-free survival. These conflicting results do not fully support the incorporation of bevacizumab in the first-line treatment of glioblastoma. In contrast, in GOG 240 the bevacizumab group (including paclitaxel plus topotecan or paclitaxel) experienced a significant longer PFS and overall survival, and quality of life was not negatively affected in these patients. Thus, these results favor the use of bevacizumab in the treatment of advanced cervical cancer.

Targeted therapy against vascular endothelial growth factor A (VEGF-A) is a widely used strategy to inhibit angiogenesis of many tumors. To this purpose, the application of VEGF-A binding agents (bevacizumab, aflibercept), antibodies blocking the VEGF receptor 2 (ramucirumab) and antiangiogenic tyrosine kinase inhibitors (e.g., sunitinib, sorafenib, pazopanib, axitinib) is expanding.

Since its introduction in 2004 as the first angiogenesis inhibitor in the USA, bevacizumab has been approved for a wide range of cancer types including metastatic colorectal cancer, non-squamous non-small cell lung cancer, metastatic renal cell carcinoma, and recurrent glioblastoma. Two randomized, placebo-controlled, double-blinded, phase 3 trials recently published in the *New England Journal of Medicine* (*NEJM*)[1,2] investigated the potential role of bevacizumab in newly diagnosed glioblastoma. Glioblastoma is the most lethal primary brain tumor in humans with a five-year survival rate of only 3 percent. Targeting VEGF-A in glioblastoma is appealing because VEGF-A-overexpression and angiogenesis are prominent features of this type of cancer.[3] Current standard therapy in newly diagnosed glioblastoma consists of temozolomide in combination with radiotherapy followed by maintenance temozolomide that results in a median overall survival of only approximately 15 mo.[4] Thus, there is a high demand for novel, more effective treatment options.

RTOG 0825 and AVAglio

In the Radiation Therapy Oncology Group (RTOG) 0825 trial by Gilbert et al.,[1] patients with newly diagnosed glioblastoma underwent radiotherapy for 6 wk (5 d/week × 2 Gy), while receiving daily temozolomide (75 mg/m^2, oral) until completion of radiotherapy. At week

4 of radiotherapy, patients were randomized for treatment with bevacizumab (10 mg/kg every 2 wk, IV, n = 320) or placebo (n = 317). Administration of bevacizumab or placebo continued until disease progression, severe treatment-related toxicities, or completion of adjuvant therapy. Four weeks after completion of radiotherapy, patients underwent maintenance therapy with temozolomide (150 mg/m^2 for 5 consecutive days of a 28-d cycle, 6–12 cycles). Overall survival (OS) and progression-free survival (PFS) were the primary endpoints.

In this trial, addition of bevacizumab did not significantly improve OS, which was 15.7 mo in the bevacizumab and 16.1 mo in the placebo group (hazard ratio for death in bevacizumab group: 1.13, P = 0.21). Also PFS did not differ significantly between the bevacizumab and placebo group, which was 10.7 and 7.3 mo, respectively. Hazard ratio for PFS was 0.79, P = 0.007 (α = 0.004).

The lack of survival benefit was accompanied with a higher incidence of grade 3 or higher serious adverse events (e.g., hypertension, fatigue, neutropenia) in the bevacizumab group compared with placebo. Quality of life of patients in the bevacizumab arm was also more deteriorated due to worsening of neurocognitive and motoric function, and activity- and mood-related symptoms.

In the Avastin in Glioblastoma (AVAglio) study, Chinot et al. also studied the effect of bevacizumab addition to radiotherapy and temozolomide in newly diagnosed glioblastoma.[2] During the initial 6-wk phase of this study, treatment consisted of radiotherapy (5 d/week × 2 Gy, maximum 60 Gy), temozolomide (75 mg/m^2, oral) and bevacizumab (10 mg/kg every 2 wk, IV) or placebo. After a 28-d break, maintenance therapy (four 6-wk cycles) started with temozolomide (150 mg/m^2/day for 5 d in cycle 1, 200 mg/m^2/d in subsequent cycles) plus bevacizumab (10 mg/kg) or placebo every 2 wk, for six 4-wk cycles. In the subsequent monotherapy phase, bevacizumab (15 mg/kg) or placebo was administered every 3 wk until disease progression or development of unacceptable toxicities. Four hundred and fifty-eight patients were randomized to the bevacizumab group, while 463 patients received placebo. Similar to the RTOG 0825 study, OS and PFS were the primary endpoints in this trial.

The median PFS was 10.6 mo in the bevacizumab group and 6.2 mo in the placebo group (P < 0.001, α = 0.01). Median OS, however, did not differ significantly between these groups: 16.8 (bevacizumab) vs. 16.7 mo (placebo, P = 0.10).

Grade 3 or higher adverse events (e.g., thromboembolic events, bleeding, gastrointestinal perforation) occurred more often in the bevacizumab group than in the placebo group (66.8% vs. 51.3%).

In contrast to the RTOG 0825 study, quality of life (i.e., deterioration-free survival) and performance status were maintained significantly longer in the bevacizumab arm in AVAglio. Furthermore, the need to use glucocorticoids was lower among patients receiving bevacizumab than those who were receiving placebo.

In summary, in the RTOG 0825 and the AVAglio study addition of bevacizumab to temozolomide plus radiotherapy increased PFS with 3.4 and 4.4 mo, respectively. Compared with the statistically non-significant improvement in PFS of 3.4 mo in the RTOG 0825 study, the significant 4.4-mo-improvement of PFS in the AVAglio study was likely attributable to a higher α level in AVAglio (α = 0.01 and 0.004 in AVAglio and RTOG 0825, respectively). No significant effects on OS were observed in either trial. However, results regarding quality of life were conflicting: bevacizumab-treated patients in the RTOG 0825 experienced deteriorated quality of life, while the quality of life in the AVAglio study was not negatively affected in the bevacizumab group.

Significant PFS Improvement Often Not Accompanied by Significant Effects on OS

The results of the RTOG 0825 and the AVAglio study are consistent with previous findings that bevacizumab significantly improves PFS, but fails to have a significant impact on OS. This discordance has been reported in patients with non-small cell lung cancer,[5-8] metastatic renal cell carcinoma,[9-12] and ovarian cancer.[13] The lack of significant effects on OS may be caused by the use of additional chemotherapy (including crossover to bevacizumab) in the control group after disease progression. For example, in the RTOG 0825 study almost 50% of the patients with progressive disease in the placebo group started with bevacizumab. As such, the survival benefit of the bevacizumab arm could be mitigated. The median OS of 16.1–16.7 mo in the control group (temozolomide plus radiotherapy) in RTOG 0825 and AVAglio was approximately 1.5 mo longer than previously reported in the pre-bevacizumab era.[4] PFS, which is not affected by patient crossover or subsequent therapies,[14] rather than OS would be more accurate to estimate the efficacy of bevacizumab.

Compared with newly diagnosed glioblastoma, bevacizumab treatment appears to be more effective in other tumors. For example, in patients with metastatic colorectal cancer both OS and PFS were significantly increased in the bevacizumab-treated groups.[15] Also patients with advanced cervical cancer could benefit by adding bevacizumab to their chemotherapy regimen. While early-stage and locally advanced cervical cancer is curable, patients with recurrent or metastatic cervical cancer have limited treatment options. Tewari et al. investigated the incorporation of bevacizumab and the use of nonplatinum combination chemotherapy in the treatment of advanced cervical cancer.[16] In their phase 3, randomized trial (GOG 240), published in the *New England Journal of Medicine*, 425 patients were randomized into four groups. Group 1 (control) received cisplatin (50 mg/m^2) and paclitaxel (135 or 175 mg/m^2). In group 2 topotecan (0.75 mg/m^2 on days 1–3) and paclitaxel (175 mg/m^2, day 1) were administered. In group 3 and 4 bevacizumab (15 mg/kg on day 1) was added to the treatments in group 1 and 2, respectively.

Results show that PFS of cisplatin-treated patients (groups 1 and 3) was significantly higher compared with patients who received topotecan (7.6 vs. 5.7 mo, P = 0.008). The difference in OS was not significant.

Addition of bevacizumab (groups 3 + 4 vs. groups 1 + 2) increased OS (17.0 vs 13.3 mo, P = 0.004), PFS (8.2 vs. 5.9 mo,

P = 0.002), and response rate (48% vs. 36%, P = 0.008).

The use of bevacizumab was significantly associated with an increased incidence of grade 2 or higher hypertension (25 vs. 2%), grade 3 or higher thromboembolic events (8% vs. 1%), and grade 3 or higher gastrointestinal fistulas (3% vs. 0%). However, these increased incidences of toxicities did not significantly affect quality of life. These findings support the addition of bevacizumab to cisplatin and paclitaxel in metastatic or advanced cervical cancer.

In conclusion, based on the modest effects of bevacizumab in newly diagnosed glioblastoma in the RTOG 0825 and the AVAglio study (significant PFS prolongation, non-significant effect on OS, potential decrease of quality of life due to bevacizumab-related toxicities), bevazicumab should not be added to standard chemotherapeutic regimens for this type of cancer. In contrast, the GOG 240 study results indicate that addition of bevacizumab to platinum-based chemotherapy in patients with advanced cervical cancer is recommended.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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