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Effectiveness of antiangiogenic drugs in glioblastoma patients: A systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Background: glioblastomas are highly vascularized tumors and various antiangiogenic drugs have been investigated in clinical trials showing unclear results. We performed a systematic review and a meta-analysis to clarify and evaluate their effectiveness in glioblastoma patients.
Patients and methods: we searched relevant published and unpublished randomized clinical trials analyzing antiangiogenic drugs versus chemotherapy in glioblastoma patients from January 2006 to January 2016 in MEDLINE, WEB of SCIENCE, ASCO, ESMO and SNO databases.
Results: fourteen randomized clinical trials were identified (7 with bevacizumab, 2 cilengitide, 1 enzastaurin, 1 dasatinib, 1 vandetanib, 1 temsirolimus, 1 cediranib) including 4330 patients. Antiangiogenic drugs showed no improvement in overall survival with a pooled HR of 1.00, a trend for an inferior outcome, in terms of overall survival, was observed in the group of patients receiving antiangiogenic drug alone compared to cytotoxic drug alone (HR = 1.24, p = 0.056). Bevacizumab did not improve overall survival. Twelve trials (4113 patients) were analyzed for progression-free survival. Among antiangiogenic drugs, only bevacizumab demonstrated an improvement of progression-free survival (HR = 0.63, p < 0.001), both alone (HR = 0.60, p = 0.003) or in combination to chemotherapy (HR = 0.63; p < 0.001), both as first-line treatment (HR = 0.70, p < 0.001) or in recurrent disease (HR = 0.52, p < 0.001).

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Conclusions: antiangiogenic drugs did not improve overall survival in glioblastoma patients, either as first or second-line treatment, and either as single agent or in combination with chemotherapy. Among antiangiogenic drugs, only bevacizumab improved progression-free survival regardless of treatment line, both as single agent or in combination with chemotherapy

1. Introduction

Glioblastoma is the most common and malignant form of primary brain tumor and has a poor prognosis with a 2-year survival rate of 30% and a 5-year survival rate of 10% (Stupp et al., 2009). To date, the standard treatment for newly diagnosed glioblastoma is surgical debulking followed by radiation therapy and temozolomide followed by 6 to 12 cycles of maintenance temozolomide (Stupp et al., 2005). Despite this treatment, relapse is inevitable and the median overall survival is about 15 months (Wen and Kesari, 2008).

Given the poor results of cytotoxic therapy over the last few years, new approaches such as antiangiogenic drugs have been analyzed in various studies including newly diagnosed glioblastoma or relapsed patients (Lu-Emerson et al., 2015). Indeed, glioblastomas are highly vascular tumors, with high expression of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) with the ensuing attachment to its VEGF receptor 2 (VEGFR2) localized to endothelial cells (Wong et al., 2009). Increased levels of VEGF lead to abnormal vasculature and increased tumor vessel permeability; consequently, glioblastomas develop hypoxia which leads to further increase of VEGF expression (Fischer et al., 2005). Moreover, angiogenesis has been demonstrated in preclinical studies to be vital for the proliferation and survival of glioblastoma. Moreover, neoangiogenesis is one of the diagnostic hallmarks of glioblastoma and, according to the WHO classification, it is pivotal for the diagnosis (Norden et al., 2009). Therefore, there is a strong biologic rationale for using antiangiogenic drugs against glioblastoma. Antiangiogenic agents may be classified as direct, indirect or miscellaneous angiogenesis inhibitors depending on their mechanism of action and target (Gasparini et al., 2005a); in fact, antiangiogenic treatments include several mechanisms of action such as targeting VEGF and VEGFR with antibodies or small-molecule tyrosine kinase inhibitors (TKIs) or inhibition of tumor growth and endothelial cell adhesion by integrin inhibitors (Lu-Emerson et al., 2015). Direct angiogenesis inhibitors target the tumor endothelial cells by inhibiting their ability to proliferate, migrate or form new vessels; indirect agents block the production of angiogenic factors and/or downstream angiogenic signalling pathways; mixed angiogenic inhibitors such as multitargeted kinase inhibitors or protein kinase C inhibitors or integrin receptor inhibitors, primarily have a direct cytotoxic function but as a secondary mechanism they also inhibit angiogenesis (Gasparini et al., 2005a).

Various antiangiogenic drugs have been analyzed over the last few years; noteworthy, bevacizumab, a monoclonal antibody against VEGF-A, alone or in combination with cytotoxic agents showed interesting results in terms of radiographic response rates and progression-free survival in initial phase 2 studies (Friedman et al., 2009; Kreisl et al., 2009; Vredenburgh et al., 2007); however, these studies lacked a non-bevacizumab-containing comparator arm and overall survival was not prolonged compared to historical data. More recently, a randomized three-arm phase 2 study (BELOB) examined bevacizumab alone versus lomustine alone versus bevacizumab plus lomustine in recurrent glioblastoma (Taal et al., 2014) showing the best results for the combination arm; indeed, the 9-month overall survival rate was 38% in patients treated with bevacizumab alone, 43% in lomustine alone, 88% in lomustine with bevacizumab. GLARIUS trial evaluated the combination of bevacizumab and irinotecan versus standard temozolomide in newly diagnosed, MGMT unmethylated glioblastoma patients; this study demonstrated a longer progression-free survival with bevacizumab and irinotecan (Herrlinger et al., 2014). Notwithstanding, two subsequent randomized, placebo-controlled phase 3 trials of bevacizumab with chemoradiotherapy in patients with newly diagnosed glioblastoma showed a longer progression-free survival with bevacizumab but failed to demonstrate an improvement in overall survival (Gilbert et al., 2014; Chinot et al., 2014).

Cediranib, a VEGFR TKI, and enzastaurin, an inhibitor of protein kinase C beta, also failed to demonstrate any benefit in overall survival in recurrent glioblastoma in two phase III trials. Cilengitide, an integrin receptor inhibitor, has an important and complex influence on tumor cell survival enhancing neoplastic apoptosis and blocking integrin-mediated angiogenesis and tumor migration, since integrins are widely expressed by both glioblastoma cells and endothelial cells in tumor-associated vasculature (Gasparini et al., 2005a). Cilengitide demonstrated a modest improvement in overall survival and progression-free survival in a phase II study (CORE) (Nabors et al., 2015) enrolling patients with newly diagnosed glioblastoma with an unmethylated MGMT gene promoter, while in a phase III trial (CENTRIC) (Stupp et al., 2014) evaluating patients with newly diagnosed glioblastoma and methylated MGMT, it showed a trend for benefit in terms of overall survival.

Various other drugs such as, dasatinib, vandetanib and temsirolimus were analyzed in randomized studies (Laack et al., 2015; Lee et al., 2015; Wick et al., 2010).

2. Objectives

To contribute to clarifying this issue, we carried out a systematic review and meta-analysis of randomized trials evaluating the efficacy of antiangiogenic treatment in patients with glioblastoma. We analyzed its efficacy in terms of overall survival (OS) and progression-free survival (PFS), as first or second-line therapy, and as antiangiogenic drug used alone or in association with cytotoxic treatment, bevacizumab or other antiangiogenic drugs.

3. Methods

The review and meta-analysis were conducted according to a predefined written protocol developed by G.L (Giuseppe Lombardi).

3.1. Outcome definition

The analysis was conducted to determine the impact of antiangiogenic treatment in glioblastoma patients. We defined an antiangiogenic treatment arm when an antiangiogenic agent was used both alone or in association with chemotherapy/radiotherapy. The arm with cytotoxic drugs was considered as a comparator arm. Analysis was conducted in order to identify eventual significant differences in survival outcomes: overall survival and progression-free survival.