A new strategy of CyberKnife treatment system based radiosurgery followed by early use of adjuvant bevacizumab treatment for brain metastasis with extensive cerebral edema

Abstract

Bevacizumab blocks the effects of vascular endothelial growth factor in leakage-prone capillaries and has been suggested as a new treatment for cerebral radiation edema and necrosis. CyberKnife is a new, frameless stereotactic radiosurgery system. This work investigated the safety and efficacy of CyberKnife followed by early bevacizumab treatment for brain metastasis with extensive cerebral edema. The eligibility criteria of the patients selected for radiosurgery followed by early use of adjuvant bevacizumab treatment were: (1) brain tumors from metastasis with one solitary brain lesion and symptomatic extensive cerebral edema; (2) >18 years of age; (3) the patient refused surgery due to the physical conditions and the risk of surgery; (4) no contraindications for bevacizumab. (5) bevacizumab was applied for a minimum of 2 injections and a maximum of 6 injections with a 2-week interval between treatments, beginning within 2 weeks of the CyberKnife therapy; (6) Karnofsky performance status (KPS) ≥30. Tumor size and edema were monitored by magnetic resonance imaging (MRI). Dexamethasone dosage, KPS, adverse event occurrence and associated clinical outcomes were also recorded. Eight patients were accrued for this new treatment. Radiation dose ranged from 20 to 33 Gy in one to five sessions, prescribed to the 61–71 % isodose line. Bevacizumab therapy was administered 3–10 days after completion of CyberKnife treatment for a minimum of two cycles (5 mg/kg, at 2-week intervals). MRI revealed average reductions of 55.8 % (post-gadolinium) and 63.4 % (T2/FLAIR). Seven patients showed significant clinical neurological improvements. Dexamethasone was reduced in all patients, with five successfully discontinuing dexamethasone treatment 4 weeks after bevacizumab initiation. Hypertension, a bevacizumab-related adverse event, occurred in one patient. After 3–8 months, all patients studied were alive and primary brain metastases were under control, 2 developed new brain metastases and underwent salvage CyberKnife treatment. Recurrent edema and emerging radiation necrosis were not observed. CyberKnife radiosurgery followed by early use of bevacizumab is promising and appears safe for treatment of brain metastases with extensive cerebral edema.
A new strategy of CyberKnife treatment system based radiosurgery followed by early use of adjuvant bevacizumab treatment for brain metastasis with extensive cerebral edema

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Keywords CyberKnife · Bevacizumab · Brain metastasis · Edema · Vascular endothelial growth factor

Introduction

Brain metastases occur in 20–40 % of cancer patients, account for a considerable percentage of morbidity in cancer patients, and still represent a significant cause of death [1]. The treatment regimens for brain metastasis include corticosteroids, surgery, whole brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS). The survival of patients with a single metastasis can be prolonged by a combination of surgery and WBRT. For surgically unresectable brain metastases, SRS has tended to be used, especially for tumors in eloquent areas [2].

Cerebral edema which is mainly vasogenic is a prominent feature of metastatic brain tumors and often contributes to neurologic dysfunction and impaired quality of life.
Cerebral edema in brain metastasis is the result of leakage of plasma into the parenchyma through dysfunctional cerebral capillaries. Vascular endothelial growth factor (VEGF)-induced dysfunction of tight junction proteins probably plays an important role in the formation of edema [3].

Specific therapies such as surgery, osmotherapy, and corticosteroids contribute to the treatment of brain edema. Surgery, for the purpose of edema treatment, should be considered only when life is in immediate danger and should be considered with increased morbidity. Evidence from randomized studies for the role of osmotherapy in brain tumor edema is lacking. Osmotherapy may also have negative effects on brain cancer; as a result of a disrupted blood-brain barrier, the osmotic agent may leak into the brain parenchyma, with further disturbance of the osmotic gradient [4]. Corticosteroids have been in use since the 1960s, and play a decisive role in the management of brain edema; however, they are associated with substantial side effects such as behavioral changes, altered sleep patterns and changes in appetite [3]. Moreover, the effect of edema-reduction through corticosteroids seems to be less rapid, especially for extensive cerebral edema [5]. Treatment with corticosteroids over a long period of time can also delay the use of SRS. A lower radiation dose is usually used to decrease the risk of acute and late side effects that can develop, the most common and serious of which is radiation necrosis for tumors with preexisting extensive cerebral edema [6]. Reports have also shown that local control with SRS was favorably influenced by the lack of extensive tumor edema, although detection of less edema might just reflect a situation with smaller and/or slower growing tumors [7]. Recent data suggest that therapeutic anticoagulation and hyperbaric oxygen therapy may provide some relief for these symptoms, but the efficacy of these treatments is still controversial [8]. So, brain metastasis with extensive edema, especially those located in an eloquent area, was considered to be a difficult problem. None of the treatments noted above were thought to be useful with confidence.

Brain metastases induced peritumoral edema at the time of presentation may be due to many factors, including secretion of endothelial growth factors, inflammatory cytokines, destruction of part of the blood brain barrier, or even secertories subtypes of certain tumors [9]. Bevacizumab (Avastin, Genentech, San Francisco, CA, USA) is a humanized murine monoclonal antibody that is used directly against VEGF. Previously, VEGF was referred to as a “vascular permeability factor” with the potential to cause capillary endothelial leakage in cerebral tissues [10]. When it is released in the presence of hypoxia and necrosis, increased permeability of the blood-brain barrier and subsequently increased edema result [11]. The breakdown of the blood brain barrier leads to significant edema formation that is readily apparent through T2-weighted magnetic resonance imaging (MRI), fluid attenuated inversion recovery (FLAIR) images, and T1-weighted gadolinium-enhanced MRI. Given its association with radiation necrosis and blood-brain barrier dysfunction, VEGF may become a logical putative therapeutic target for the reversal of edema achieved by preventing VEGF from reaching its capillary targets. A growing number of researchers have published positive findings using bevacizumab as a treatment strategy for cerebral radiation edema and necrosis due to its ability to block the effects of VEGF in leakage prone capillaries [12, 13]. A retrospective review of 14 lesions in 11 patients was recently published, that suggests bevacizumab as an effective and safe treatment for radiation necrosis [14]. A randomized controlled clinical trial further demonstrated class I evidence of the efficacy of bevacizumab treatment for progressive radiation necrosis [15].

Our approach has been to use multimodality therapy of SRS followed by early adjuvant use of bevacizumab treatment for brain metastasis with extensive cerebral edema. The rationale for this was to maintain the intensity of local therapy with SRS without treatment delay and radiation dose compromise through the early use of bevacizumab as an assistant.

Methods

In this prospective study the eligibility criteria were: (1) brain tumors from metastasis with one solitary brain lesion and symptomatic extensive cerebral edema; (2) >18 years of age; (3) the patient refused surgery due to the physical conditions and the risk of surgery; (4) no contraindications for bevacizumab; (5) bevacizumab was applied for a minimum of 2 injections and a maximum of 6 injections with a 2-week interval between treatments, beginning within 2 weeks of the CyberKnife therapy; (6) Karnofsky performance status (KPS) ≥30. Hematology analysis, biochemistry tests and patient history were analyzed in each case, resulting in exclusion based on the occurrence of major surgical procedures or traumatic injuries within the past 28 days, uncontrolled hypertension, cardiovascular or cerebrovascular disease within the last 6 months, coagulopathy with an increased risk of bleeding, proteinuria or renal dysfunction, and non-healing wounds or ulcers. MRI imaging was applied prior to the combined treatment in order to exclude cerebral hemorrhaging. All data were prospectively recorded and analyzed. Approval was obtained from the Ethics Committee of Shanghai Gamma-knife Hospital. Each patient provided written informed consent prior to treatment and inclusion in the present study. The cost of the bevacizumab was met by the patients themselves.
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