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Treatment of cerebral radiation necrosis with nerve growth factor: A prospective, randomized, controlled phase II study

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ABSTRACT

Purpose: A prospective, placebo controlled phase II trial was conducted to test the efficacy of Nerve Growth Factor (NGF) for the treatment of symptomatic temporal lobe necrosis (TLN).

Materials and methods: Patients with progressive TLN were randomly assigned to either the control or the study group in a 1:1 ratio. The control group received corticosteroids with gradually reduced dosage. The study group received NGF with corticosteroids. NGF was dissolved in 2 mL normal saline and injected intramuscularly at 18 μg/time, once a day for 2 months. The efficacy was evaluated by both the objective and subjective methods every 3–4 months after treatment. The objective method compared volumes of the necrotic masses on MRI before and after treatment. The subjective method compared the neurocognitive score as evaluated by the mini–mental status examination (MMSE).

Results: Twenty-eight cases were enrolled into this study. The objective evaluation showed that the response rate (RR) in the study group was higher than the control group. The ratio was 10 versus 2 ($p = 0.006$), and 12 versus 3 ($p = 0.002$) at 3–4 months and 6–8 months after intervention, respectively. The subjective evaluation demonstrated both groups were effective in controlling the necrosis related symptoms in the first 6 months after treatment. But NGF was more effective than corticosteroids at 9 months (13 versus 4, $p = 0.001$). The only observed side effect was mild pain at the injection site in 3 patients in the study group.

Conclusions: Our results demonstrated that the process of TLN is not irreversible. NGF is more effective in recovering TLN than corticosteroids with little side effect. NGF has a longer duration in controlling the necrosis related symptoms than corticosteroids.

Radiotherapy (RT) has become the mainstay of treatment for nasopharyngeal carcinoma (NPC). Due to the proximity of the nasopharynx to the skull base, the medial temporal lobes were inevitably included in the radiation field. Therefore, temporal lobe necrosis (TLN) might occur years after RT. The development of TLN is a function of dose per fraction, total dose, irradiated volume and time after completion of radiation. The risk of necrosis increases with higher total RT doses, and with larger daily RT fractions. In addition, the higher the dose per fraction or total dose, the sooner CRN would appear [1]. The reported rates of TLN range from 3% to 40% [2–5].

TLN is one of the most feared late complications after radical RT, because some patients with TLN may have obvious symptoms such as headache, mental confusion, mild dizziness, memory loss, personality change, or general seizures. These symptoms severely affect the patient's quality of life (QOL). Treatment of TLN has typically been symptomatic management. A common practice is the use of corticosteroids to control edema-related symptoms. However, long-term usage of corticosteroids is problematic because of the debilitating chronic side effects. Antiplatelet agents, hyperbaric oxygen, high-dose vitamins, and surgery have also been tried as treatments for this condition [6–9]. However, up to date, none of these approaches have been proved effective in reversing cerebral necrosis. Therefore, cerebral necrosis is generally regarded as a progressive and irreversible complication of RT [10].

In the past decades, advances in histopathology and neuroradiology have helped shedding light on the mechanism of cerebral radiation necrosis (CRN). Vascular injury, glial and neuron damage have been demonstrated to be associated with the development of CRN [11–13]. Correspondingly, some new drugs that related to angiogenesis and neuron regeneration have been tried to treat CRN.

The efficacy of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has recently been suggested in two retrospective studies. Radiologic response and

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clinical stabilization or improvement was observed in all cases [14,15]. Another placebo- controlled double-blind study randomized 14 patients to receive either intravenous saline or bevacizumab at 3-week intervals [16]. The study demonstrated that all bevacizumab-treated patients showed a decrease in the necrosis volumes, improvement in neurologic symptoms or signs was also noted. However, bevacizumab therapy associated toxicities occurred in most patients. In addition, the control group only received saline, not the commonly used corticosteroids.

Nerve growth factor (NGF) plays a significant protective effect on both peripheral and central nervous systems, prevents the apoptosis and degeneration of neurons, and promotes the functional recovery and regeneration of injured neurons [17]. Our previous case study showed that NGF could successfully reverse TLN [18], this prompted us to carry out a prospective, randomized, controlled study comparing the efficacy of NGF with corticosteroids in treating TLN.

Methods and materials

Patient selection

Patients must have undergone only one course of definitive RT for histologically confirmed NPC years before, using conventional fractionation (2.0 Gy per fraction with five daily fractions per week for about 7 weeks). They were required to have at least two consecutive magnetic resonance imaging (MRI) study supporting the diagnosis of CRN with an interval of 3–4 months, with the second MRI showing progressive disease compared with the first MRI (Figs. 1 and 2). The necrotic mass shown on MRI must be measured in two dimensions in order to define the response to treatment. Other radiologic studies were also required to exclude local or regional recurrence, or distant metastasis. Patients must have progressive neurologic symptoms or signs, mini–mental status examination (MMSE) [19] score must be $\leqslant$27. In addition, they were required to have a Karnofsky performance status of at least 70 and were supposed to live more than 6 months. This trial was approved by the institutional review boards, and was registered online (National Clinical Trial [NCT] 02032147). All participating patients were given written informed consent.

Exclusion criteria

CRN cases with the following conditions were excluded from this study: (1) CRN after the second course of radiotherapy for recurrent NPC. (2) CRN combined with local or regional relapse, or with distant metastasis. (3) CRN combined with other cerebrovascular disease. (1) CRN combined with the second primary malignancy. (5) CRN without neurologic symptoms or signs. (6) CRN combined with diabetes. (7) CRN patients that were supposed to live less than 6 months.

MRI studies

The MRI studies for CRN included pre- and post-gadolinium administration sequences. The images obtained before administration of the contrast agent were axial T1- and T2-weighted images (6-mm sections, 1-mm gap); sagittal T1-weighted images (4-mm sections, contiguous). The images obtained after the administration of the contrast agent were as follows: axial and coronal thin-section images (4-mm, contiguous) T1-weighted images (fast spoiled gradient recalled echo acquisition, FSPGR, TR 120-215, TE 2.2-2.8). All MRI studies were carried out by the same team of medical imaging technologists and neuro-radiologists, and were to be performed on the same 1.5 Tesla MRI machine (GE Healthcare, Waukesha, WI).

Drug administration

Patients were randomly assigned to the control group or the study group in a 1:1 ratio. The control group received corticosteroids with gradually reduced dosage. The study group received nerve growth factor (NGF) [Produced in Xiamen Beida Road Bioengineering Co., Ltd, Fujian Province, China. Trade name: Enjingfu, Permission No. S20060052] and the same corticosteroids with the control arm. NGF was dissolved in 2 mL normal saline and then injected intramuscularly at 18 μg/time, once a day for 2 months. Dose modification was not allowed for NGF.

Evaluation of efficacy

The efficacy of NGF for CRN was evaluated by objective and subjective methods. The objective method compared volumes of the necrotic masses on MRI before and after treatment. The subjective method compared the neurocognitive score as evaluated by the mini–mental status examination (MMSE) [19].

Objective evaluation of efficacy

The necrotic masses on MRI before treatment were defined as baseline. MRI scans were performed every 3–4 months, using the same parameters as mentioned above. Axial and coronal T1weighted images with contrast enhancement were selected to compare the volumes of necrotic masses. Response Evaluation Criteria in Solid Tumors (RECIST) were used to test the prognosis of CRN [20].

Subjective evaluation of efficacy

The patients' neurocognitive function was scored using Mini-Mental State Examination (MMSE) before and every 3–4 months after treatment, respectively. The MMSE score before treatment was used as baseline. The difference value was calculated by the MMSE score during follow-up minus the baseline MMSE score. The *d*-value was used to evaluate subjective efficacy. Complete recovery (CR) was defined as the *d*-value $\geqslant$3 and the total MMSE score between 29 and 30. Partial recovery (PR) was defined as the d-value $\geqslant$2 and the total MMSE score between 26 and 28. Stable symptom (SS) was defined as the *d*-value between ±1 regardless of the total MMSE score. And progressive symptom (PS) was defined as the *d*-value $\leqslant -2$.

Statistical analysis

The primary endpoint of this study was the objective response rate, and the secondary endpoint was the subjective response rate. We assume that the efficacy rate in the control group was 10%, and there will be a 60% improvement in the study group. Twenty-eight patients were required for a Type I error rate of .05 (1-sided) with 80% statistical power.

Results

From January 2008 to December 2013, a total of 56 patients were diagnosed with temporal lobe necrosis after treatment of NPC. During routine follow-up, 19 patients did not show any progression in either the necrotic mass or the necrosis-related symptoms. 37 patients showed progression in both the necrotic mass and the necrosis-related symptoms. But 35 cases met the eligibility criteria, and 7 patients refused to enter the study. In the end, only 28 cases were enrolled into this study. All necrotic masses were located at the unilateral or bilateral temporal lobes. Characteristics of these 28 patients are shown in Table 1. The mean minimum

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