Response of radiochemotherapy-associated cerebral edema to a phytotherapeutic agent, H15

Article abstract—Twelve patients with brain tumors and progressive edema caused by tumor progression or radiochemotherapy-related leukoencephalopathy were treated with H15, a phytotherapeutic anti-inflammatory agent. Edema was reduced in two of seven patients with glioblastoma with tumor progression and in three of five patients with treatment-related leukoencephalopathy. All patients with leukoencephalopathy improved clinically for several months.

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Tumor-associated edema contributes significantly to neurologic deficits and disability in patients with brain tumors. Corticosteroids such as dexamethasone are highly effective in controlling brain tumor–associated edema but their prolonged administration has multiple serious side effects, including redistribution of body fat, osteoporosis, myopathy, immunosuppression, and depression and other mental changes.[1] In addition, corticosteroids stabilize blood–brain and blood–tumoral barriers, reduce tumor perfusion, and inhibit drug-induced apoptosis in glioma cells.[2-4]

Boswellic acids are thought to be the active ingredients of H15, a phytotherapeutic agent obtained from the gum resin of *Boswellia serrata* that has been attributed anti-inflammatory properties and therapeutic effects in inflammatory bowel disease and rheumatoid arthritis.[5,6] These actions may be mediated by the inhibition of 5-lipoxygenase and leukocyte elastase. Preliminary observations indicated that boswellic acids have beneficial effects on cerebral edema in patients with glioma.[7] In vitro, boswellic acids induced apoptosis of glioma cells at higher concentrations but, more importantly, did not interfere with the cytotoxic effects of cancer chemotherapy at lower concentrations, in contrast to dexamethasone.[8] More recently, boswellic acid preparations were shown to inhibit the growth of experimental C6 gliomas in the rat.[9] Based on these data, we studied the effects of H15 on tumor growth and tumor-associated versus treatment-related edema and leukoencephalopathy in a small series of patients with brain tumors.

Patients and methods. Clinical data of 12 patients treated with H15 are summarized in the table. Seven patients had glioblastoma, two had anaplastic astrocytoma, two had low-grade astrocytoma, and one had cerebral metastases from malignant melanoma. To be eligible for the study, patients needed to have progressive cerebral edema with or without overt tumor progression. The Karnofsky index had to be 50% or more. The patients needed to be off steroids or on stable steroids for at least 4 weeks. Written informed consent was obtained from all patients. H15 was given orally, 1,200 mg three times per day. Clinical examinations and cranial MRI scans were performed prior to H15 treatment and at 1 week and 4 weeks after treatment was started. Axial T1-weighted MR scans were performed before and after contrast medium application (0.1 mmol gadolinium–diethylenetriamine pentaacetic acid per kg). The size of brain edema was analyzed in axial T2-weighted images.

The following laboratory parameters were obtained prior to study entry and at 1, 4, and 12 weeks after initiation of H15 therapy: erythrocyte and differential leukocyte count, and glucose, sodium, potassium, chloride, liver enzymes, creatinine, urea, and total protein levels. Responses were assessed by clinical evaluation and by MRI. Tumor progression was defined by Macdonald criteria.[10] Steroid medication was not changed during H15 treatment; requirement for an increase in steroid doses was considered an H15 failure. The treatment strategy was approved by the Ethical Committee of the Medical Faculty of the University of Tübingen (no. 91/1997).

Results. All patients tolerated H15 well. There were no side effects and no worsening of clinical signs attributable to H15. Patients 1 through 7 had progressive tumor and tumor-associated edema documented by MRI prior to the initiation of H15 therapy. There was no tumor response to H15 in any patient. MRI showed a significant reduction of edema in two of the seven patients with glioblastoma, after 1 week in Patient 1 and after 4 weeks in Patient 5 (figure, A through D). The reduction in edema was associated with clinical improvement that included reduction in drowsiness and headaches in Patient 1, with aphasia unchanged, and reduction in drowsiness in Patient 5, who had no focal neurologic deficit. Patient 1 did not tolerate steroid tapering, and Patient 5 was steroid-free when H15 was initiated. Patient 1 received H15 for 4 months until death from tumor progression. Patient 5 received H15 with symptom improvement for 6 months, at which time he was started on dexamethasone again to prepare for a second tumor resection because of major tumor progression. Patient 6 reported clinical improvement that lasted for 6 weeks, until tumor progression, even though no radiologic response was observed. The other four patients with glioblastoma deteriorated clinically and radiographically within 4 weeks after the start of H15 therapy.

Compared with patients suffering from edema associated with tumor progression, H15 appeared to be more effective in controlling edema attributed to prior radiotherapy or radiochemotherapy (see table, Patients 8 through

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Table *Clinical characteristics of H15-treated patients*

Patient no./ sex	Age, y	Dx	Prior therapy (date)	Cause of edema and start of H15 (date)	Steroid status*	Response
1/M	65	GB	RT (9/96), 2 × ACNU (4–7/97)	Tumor progression (7/97)	6 mg; no change	R, C
2/F	61	GB	RT (6/97), 2 × ACNU/AraC (6–7/97), 1 × PCV (8/97)	Tumor progression (11/97)	—; 16 mg on PD	—
3/F	60	GB	RT (8/96), 5 × ACNU/AraC (8/96–3/97), 1 × PCV (6/97)	Tumor progression (10/97)	—; no change	—
4/M	59	GB	RT (12/97), 2 × ACNU/AraC (12/97–1/98)	Tumor progression (2/98)	—; 16 mg at PD	—
5/M	52	GB	RT (12/97), 2 × ACNU/AraC (12/97–1/98), 2 × PCV (2–5/98)	Tumor progression (3/98)	—/—	R, C
6/F	53	GB	RT (6/96), 5 × ACNU/VM26 (6/96–3/97), 3 × PCV (6/97–11/97)	Tumor progression (1/98)	—/—	C
7/M	59	GB	RT (3/98) 3 × ACNU/Ara-C (3–7/98)	Tumor progression (8/98)	—; 16 mg (9/98)	—
8/M	36	AA	RT (7/96) 2 × ACNU/VM26 (7–9/96), 7 × PCV (9/96–11/97)	Leukoencephalopathy (12/97)	6 mg; withdrawn over 6 months	C
9/F	35	LGA	RT (7/95), 5 × ACNU/VM26 (12/95–8/96)	Leukoencephalopathy (10/96)	10 mg; withdrawn in 4 months	R, C
10/M	52	LGA	RT (seed implantation) (1993), conventional RT (11/99–1/00)	Focal necrosis and leukoencephalopathy (3/00)	16 mg; reduced to 8 mg in 2 months	C
11/F	36	AA	RT (3/97), 1120 mg CCNU (4/97)†	Focal necrosis and leukoencephalopathy (6/98)	—/—	R, C
12/F	49	MM	RT (12/94 whole brain RT), multiple chemotherapies,‡ stereotactic RT (6/96)	Focal necrosis and leukoencephalopathy (4/97) (10/98 death)	6 mg; withdrawn in 3 months	R, C

* Dexamethasone dose in mg at time of first H15 treatment; whether steroid doses were changed on H15.
† Received an overdose of CCNU (dosing error, 160 mg × 7 d).
‡ Received multiple chemotherapies for metastatic malignant melanoma: BCG/DTIC (dacarbaziene) (7/80); 6 × DTIC (1/92); 5 × BCNU (carmustine) (4/95).

Dx = diagnosis; GB = glioblastoma; AA = anaplastic astrocytoma; ACNU = nimustine; LGA = low-grade astrocytoma (World Health Organization grade II); MM = malignant melanoma; PD = progressive disease; RT = radiotherapy; R = radiological; C = clinical; Ara-C = cytosine arabinoside; CCNU = lomustine; VM26 = teniposide.

12). All of these patients had diffuse leukoencephalopathy, and three had focal necrotic lesions in addition (Patients 10, 11, and 12). Focal necrosis was confirmed by biopsy in Patient 10. Patients 9, 11 and 12 showed a clear radiologic response to H15. The response to H15 of the focal lesion and of the associated white matter changes in Patient 11 are depicted in the figure, E through H. All patients benefited clinically from H15: Patients 8 through 11 had relief of clinical symptoms and signs, and Patient 12 (who reported no clinical symptoms) could be withdrawn from long-term steroid administration. Major clinical benefits included reduction in drowsiness and headaches in Patient 8, remission of Cushing syndrome after steroid withdrawal and reduction in focal seizures in Patient 9, and partial remission of hemiparesis in both Patients 10 and 11. Patients 8, 9, and 12 were withdrawn from steroids and remained clinically stable. Patient 10 was still being slowly withdrawn at the time of writing, and Patient 11 was not using steroids when H15 was started. Three of these patients are on continuous treatment, and the durations of the clinical responses were 31 months in Patient 8, 7 months in Patient 10, and 24 months in Patient 11 at the time of writing. Patient 9 had a low-grade (World Health Organization grade II) glioma diagnosed by biopsy in June 1994. She had received radiotherapy for progressive disease without contrast enhancement in July 1995. New contrast-enhancing lesions suggestive of progression to high-grade glioma were noted in November 1995. There was no leukoencephalopathy at that time. The contrast-enhancing lesions were interpreted to signify tumor progression, and the patient received five cycles of ACNU (nimustine) and VM26 (teniposide) chemotherapy from December 1995 to August 1996. There was no progression of the contrast-enhancing lesions during chemotherapy. In October 1996, in the apparent absence of tumor progression defined by contrast enhancement, there was progressive edema and H15 treatment was initiated. The patient showed minor clinical improvement for 5 months until April 1997 when a large, preexisting cystic lesion with rim enhancement progressed. The patient underwent biopsy again and received a Selker reservoir to drain the cyst. Histologically, the lesion was consistent with glioblastoma,

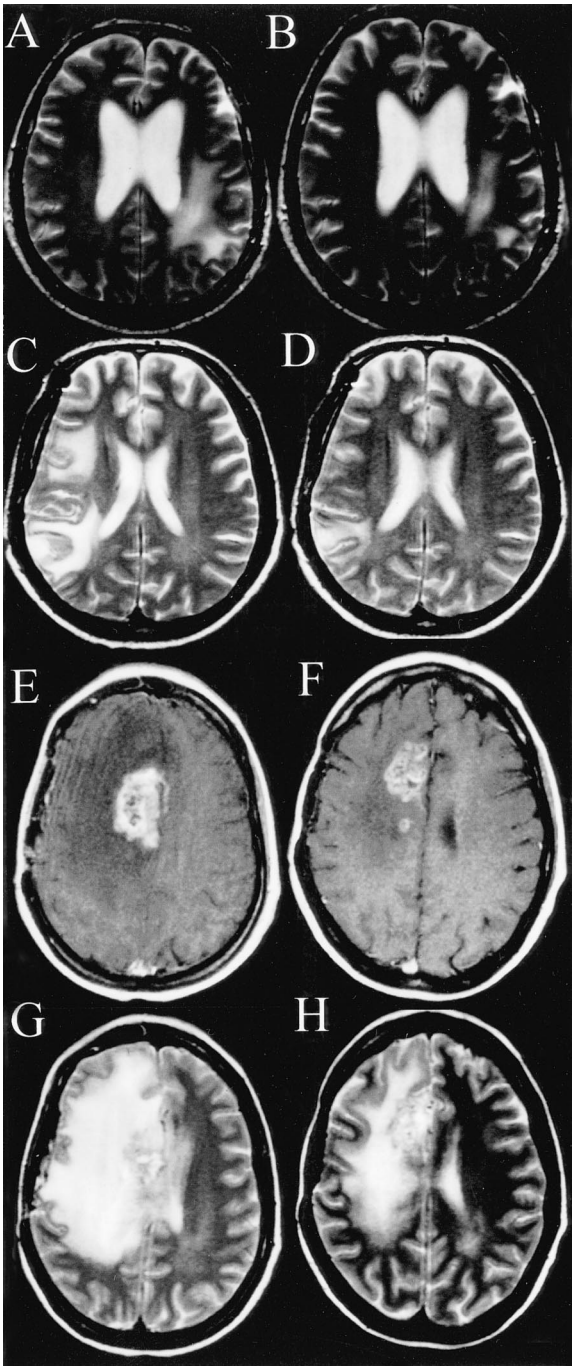

Figure. Radiologic responses to H15 in patients with brain tumors with progressive edema. (A and B) Patient 1 before and 1 week after initiation of H15 treatment (axial T2-weighted images). (C and D) Patient 5 before and 4 weeks after initiation of H15 treatment (axial T2-weighted images). (E through H) Patient 11 before and 4 weeks after initiation of H15 treatment; E and F are postcontrast axial T1-weighted images, and G and H show axial T2-weighted images.

progressing from a low-grade glioma. After surgery, the patient was able to discontinue both steroids and H15 without clinical deterioration until December 2000 when tumor progression defined by contrast-enhancement became apparent. Patient 9 thus showed an unusual course for glioblastoma in that the tumor appeared to grow rather slowly, and a cytostatic effect of H15 cannot be excluded in this patient. Patient 12 received H15 with a prolonged response for 18 months until she died from progressive leptomeningeal metastasis.

After the first 4 weeks on H15, all patients were seen at 3-month intervals for at least 1 year, with longer intervals thereafter. Most patients received MRI monitoring at these 3-month intervals, although some patients had cranial CT instead. The maximum response was observed within 4 weeks after initiation of H15 in all patients, and no further reduction of edema was observed thereafter, even in the long-term responders. In general, the diffuse white matter changes responded to H15 whereas the focal necrotic lesions in Patients 10, 11, and 12 did not change, except for a minor response in Patient 11 (see figure, E through F).

Discussion. The present study indicates that H15 may exert distinct biologic effects on cerebral edema in patients with brain tumors. Although this is a small series, our preliminary observations indicate that H15 is more effective in controlling edema attributed to prior cytotoxic therapy than edema associated with tumor progression (see table). This may signify differing pathogenic mechanisms underlying these types of edema formation. In the absence of a control group, there is as yet no proof of definite activity of H15. It cannot be excluded that clinical improvement occurred spontaneously rather than as a consequence of H15 treatment. At the doses used, H15 was well tolerated. Toxicity in previous clinical studies was limited to gastrointestinal symptoms.[6] Future studies need to clarify whether higher doses of H15 result in better edema control especially in patients with tumor progression and whether boswellic acids are truly the active ingredients of H15.

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