Original Article

Boswellia serrata Acts on Cerebral Edema in Patients Irradiated for Brain Tumors

A Prospective, Randomized, Placebo-Controlled, Double-Blind Pilot Trial

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BACKGROUND: Patients irradiated for brain tumors often suffer from cerebral edema and are usually treated with dexamethasone, which has various side effects. To investigate the activity of *Boswellia serrata* (BS) in radiotherapy-related edema, we conducted a prospective, randomized, placebo-controlled, double-blind, pilot trial. **METHODS:** Forty-four patients with primary or secondary malignant cerebral tumors were randomly assigned to radiotherapy plus either BS 4200 mg/day or placebo. The volume of cerebral edema in the T2-weighted magnetic resonance imaging (MRI) sequence was analyzed as a primary endpoint. Secondary endpoints were toxicity, cognitive function, quality of life, and the need for antiedematous (dexamethasone) medication. Blood samples were taken to analyze the serum concentration of boswellic acids (AKBA and KBA). **RESULTS:** Compared with baseline and if measured immediately after the end of radiotherapy and BS/placebo treatment, a reduction of cerebral edema of >75% was found in 60% of patients receiving BS and in 26% of patients receiving placebo ($P = .023$). These findings may be based on an additional antitumor effect. There were no severe adverse events in either group. In the BS group, 6 patients reported minor gastrointestinal discomfort. BS did not have a significant impact on quality of life or cognitive function. The dexamethasone dose during radiotherapy in both groups was not statistically different. Boswellic acids could be detected in patients' serum. **CONCLUSIONS:** BS significantly reduced cerebral edema measured by MRI in the study population. BS could potentially be steroid-sparing for patients receiving brain irradiation. Our findings will need to be further validated in larger studies. ***Cancer* 2011;117:3788–95.** *© 2011 American Cancer Society.*

KEYWORDS: brain edema, brain tumor, Boswellia serrata, radiotherapy, supportive care.

Boswellia serrata (BS) is an extract of Indian frankincense. There are very few published data about the effects of BS in brain edema and brain tumors. The most promising study came from Streffer et al,[1] who investigated the use of the BS preparation H15 in 12 patients with cerebral edema and demonstrated a clinical or radiological response in 8 of 12 patients. Boeker and Winking[2] had similar results in a small prospective study. In a systematic review, Ernst[3] found 7 controlled clinical trials investigating the anti-inflammatory effects of BS. These studies were related to the treatment of asthma, rheumatoid arthritis, Crohn disease, collagenous colitis, and osteoarthritis. No serious safety issues were raised in any of the published BS trials. We conducted a randomized, placebo-controlled, double-blind study to investigate the efficacy of BS on cerebral edema in patients irradiated for brain tumors.

MATERIALS AND METHODS

Patients

A total of 44 patients were enrolled in the trial. Demographic, tumor, and radiotherapy data are depicted in Table 1. The 2 randomly assigned groups were well balanced. The CONSORT flow chart for the study is given in Figure 1. All patients received whole brain radiotherapy or partial brain radiotherapy to more than 60% of brain volume. Whole brain radiotherapy was planned by 2-dimensional x-ray simulation, whereas partial brain radiotherapy was 3-dimensional

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Table 1. Demographic, Tumor, and Therapy Data

	Boswellia	Placebo
Age, y, mean (range)	60 (32-74)	58 (39-83)
Sex, male/female	12/10	12/10
Smoker, y/n/former	8/11/3	7/12/3
Tumor, n		
Primary brain tumor (glioblastoma)	4	7
Metastases, n		
Lung cancer		
NSCLC	8	6
SCLC	3	2
Breast cancer	2	4
Melanoma	2	2
Ovarian cancer	1	1
Kidney cancer	1	0
Esophageal cancer	1	0
Therapy		
Total dose, Gy, mean	38	40
Dose/fraction, Gy, mean	2.5	2.4
Duration of radiotherapy and BS/placebo, wk, mean	3.0	3.3

NSCLC indicates non-small cell lung cancer; SCLC, small cell lung cancer; BS, *Boswellia serrata*.

computed tomography planned (Oncentra MasterPlan, Nucletron, Veenendaal, The Netherlands). Radiotherapy was delivered by a 6MeV linear accelerator (Varian Clinac 600C).

Study Design

In Germany, H15 (the *Boswellia* preparation used for the current study) is sold as a dietary supplement. Because H15 has no reported adverse effects, a classical phase 1 dose escalation study to find a maximum tolerated dose was deemed unnecessary, and we decided to conduct a pilot trial. A double-blind, randomized design was selected to obtain data reflecting the smallest bias possible. The study did not change the well-established radiotherapy for brain tumors in any way, and it did not pose an extra risk for the patients.

All patients gave written informed consent to participate in the study. The study was approved by the ethics committee of the Albert-Ludwigs-University Freiburg and was performed according to the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Inclusion criteria were (1) primary brain tumor or brain metastases; (2) radiotherapy of whole or part of the brain (>60% of brain irradiated) with a dose of 30-60 Gy in a fractionation of 5 × 1.8-3.0 Gy/week; (3) no former radiotherapy in the brain; (4) age >18 years; and (5) written informed consent. Exclusion criteria were (1) Karnofsky index <50; (2) pregnancy; (3) dexamethasone >24 mg/day before radiotherapy; and (4) lack of adequate physical/psychological condition to provide written informed consent.

BS and Placebo

After careful advice from pharmacists considering contents, standardization, and availability, the BS product H15 (350 mg; Hecht Pharma, Stinstedt, Germany) was selected for use in the study. H15 does not contain any other ingredients apart from BS. The capsules were bought by the pharmacy of the University Hospital Freiburg. Lot numbers of the product were exactly listed. The manufacturer was not informed about the trial.

After consulting with a pharmacologist, the dosage in the active treatment group was set at 4200 mg/day (3×4 capsules/day), primarily because of potential difficulties associated with swallowing a large number of capsules. Because BS is available as a dietary supplement and no considerable adverse effects have been reported, there was no defined maximum dose. It is noteworthy that Boeker and Winking[2] reported better results with 3600 mg BS extract than with 2400 mg and reported no effects with 1200 mg.

Placebo capsules contained the excipient lactose.

Blinding and Randomization

Randomization was performed by a pharmacist using a computer-generated randomization schedule over 48 treatment numbers. Allocation was performed using balanced blocks of 4 distributing BS/placebo 1:1. A consecutive treatment number was allocated to the individuals included in the trial.

For blinding, H15 capsules were sealed in another capsule in the pharmacy. Using these double-layer capsules, the characteristic smell of BS could not be perceived. Placebo capsules containing lactose were produced with the same coating. Supply for 1 week was transferred into plastic boxes, which were labeled with the individual patient treatment number.

The BS/placebo capsules were delivered to the Department of Radiation Oncology at University Hospital Freiburg. For security reasons, envelopes for emergency decoding were also transferred to blinded staff. The randomization code was kept in the pharmacy until the study ended and the database was closed. No emergency envelope was opened. This procedure ensured that all

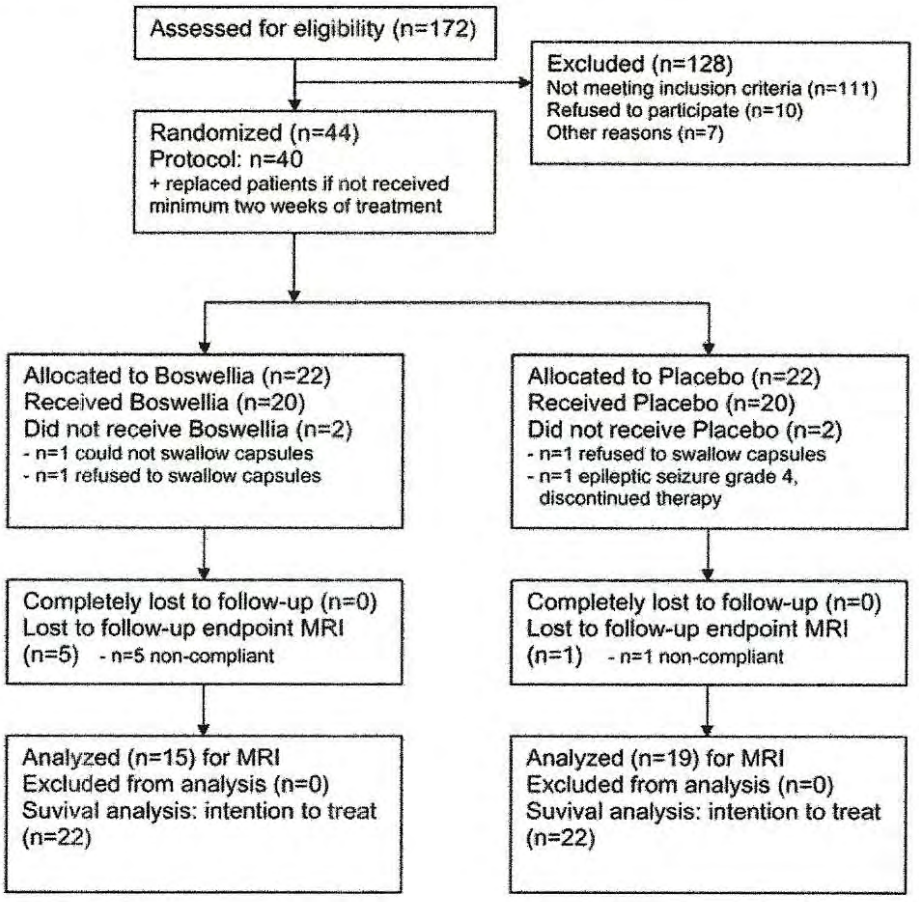

Figure 1. A CONSORT flow diagram for the study is shown.

patients and staff were blinded. Additionally, the primary endpoint was rated by an independent neuroradiologist who did not know the patients and only disposed of the magnetic resonance images.

Study Course

After providing written informed consent, patients received the BS/placebo in consecutive order following the randomization list in a box containing 84 capsules for 1 week (3×4 capsules/day starting with the first day of radiotherapy). Baseline examinations and weekly study visits (physical examination, EORTC-QLQ 30, mini-mental state, Common Toxicity Criteria [CTC], dexamethasone medication) were performed by a physician. On every study visit, each patient returned the empty box and received the BS/placebo for the next week. After considering the clinical status of each patient, the necessary dexamethasone dose was defined. At the end of radiotherapy, BS/placebo was discontinued. The first follow-up visit occurred 4 weeks after the end of radiotherapy.

Study Endpoints

The primary study endpoint was cerebral edema volume on T2-weighted magnetic resonance imaging (MRI) after therapy compared with volume at baseline (ie, before the start of radiotherapy). Edema volume (cm^3) was calculated by multiplying the edema extent in 3 directions (x, y, z). Midline shift and size of ventricles were also measured. MRI imaging was performed at 3 time points: before the start of therapy, at the end of therapy, and 4 weeks after the end of radiotherapy (plus BS/placebo).

The secondary endpoints of the study were dexamethasone medication (mg/week), toxicity (RTOG/EORTC-CTC score), quality of life (average functioning scales of the EORTC-QLQ 30), cognitive functioning (mini-mental state examination), and progression-free

survival. In addition, serum levels of boswellic acids were measured via high-performance liquid chromatography combined with mass spectrometry.

Dexamethasone dose was determined by each patient's clinical situation before and during therapy. The dose was increased when symptoms of intracranial pressure occurred; it was decreased when the patient was asymptomatic. Because the study was a double-blind one, the physicians responsible for the dexamethasone dose did not introduce a bias. Dexamethasone doses were given as median and range, because the mean values were biased by single outliers. Data about the duration of steroid therapy prior to beginning radiotherapy were not collected.

Serum Levels of BS

Serum levels of boswellic acids have been shown to reach a peak 1-2 hours after oral ingestion and plateau 2 hours later.[4] The specified pharmacokinetic profile was verified in a test with a male subject; after oral ingestion of 1750 mg BS (H15), serum levels of the boswellic acids AKBA and KBA were measured hourly for 6 hours. This test proved that it was possible to take patients' blood samples during the plateau phase at any time of the day.

Extracts from different *Boswellia* species consist of different boswellic acid compounds.[5] The BS preparation used (H15) is known to contain AKBA and KBA in relevant concentrations.[6] In the test subject, KBA serum levels up to 34.23 ng/mL were found. AKBA was found in low serum concentrations, with a maximum of 2.83 ng/mL and a minimum of 1.16 ng/mL, which is near the detection limit. AKBA could not be shown in the study patients' serum. This may be due to concentrations below the detection limit of 1 ng/mL.

Measurement of boswellic acid concentrations was performed in the Central Laboratory of German Pharmacists (Eschborn, Germany). The blood samples were centrifuged, and the serum was frozen at −80°C immediately. The high-performance liquid chromatography/tandem mass spectrometry method for analysis has been published elsewhere.[4]

Statistics

In addition to descriptive statistics, the Wilcoxon rank test (BS group versus placebo group) for significance ($P < .05$) was performed. For 2-sided testing, a power of 80% and $\alpha = 0.05$ a sample size of $n = 19$ for each group was calculated and rounded up to $n = 20$ per group. For better demonstration of the results, edema response was classified according to the following groups: (1) increase of edema, >105% of baseline (5% error); (2) constant edema, 75%-105% of baseline; (3) slight decrease of edema, 25%-75% of baseline; (4) large decrease of edema, <25% of baseline. The raw data were the basis for statistical testing.

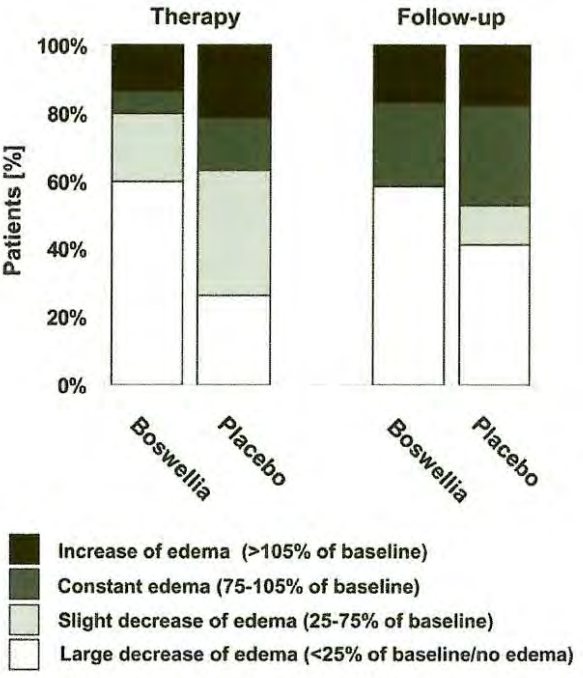

Figure 2. Results are shown for the primary endpoint: relative volume of cerebral edema compared with baseline for *Boswellia serrata* versus placebo after therapy and at follow-up (4 weeks after therapy).

Analysis of progression-free survival was performed using the Kaplan-Meier method and log-rank test. For data management and statistical calculations, Microsoft Excel 2002, jmp 5.01 (SAS Institute), and Sigma Plot 8.0 (SPSS) were used.

RESULTS

MRI Measurements

At the end of radiotherapy and at the first follow-up visit the relative changes of edema volume compared with baseline were evaluated. At the end of radiotherapy, 60% of patients who had received BS reached a decrease of edema to <25% of baseline values or showed no edema at all. In the placebo group, only 26% of patients reached this optimal outcome (Figure 2). At that point, 13% of BS group patients and 21% of placebo group patients had an increase of edema volume to >105% of the baseline value. At follow-up, 4 weeks after the end of therapy and

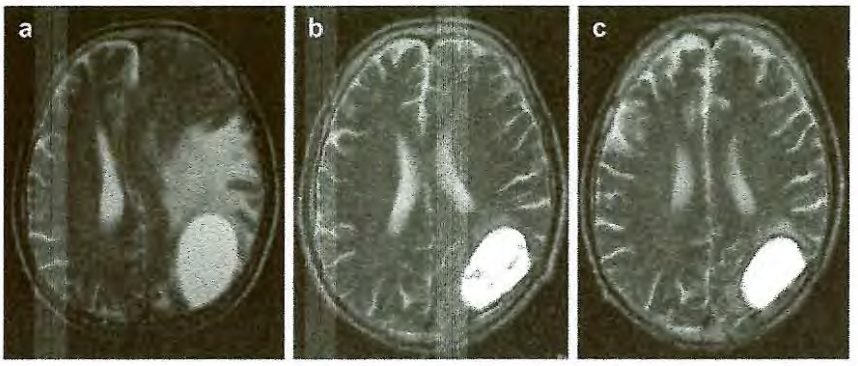

Figure 3. T2-weighted magnetic resonance images of a patient from the *Boswellia serrata* group with metastases from lung cancer (adenocarcinoma) are shown (a) at baseline, (b) after radiotherapy, and (c) at follow-up (4 weeks after radiotherapy).

after discontinuing BS or placebo, the changes of edema volumes in both groups converged again (Figure 2).

The measured and calculated average volume of edema at baseline was 188.4 mL (range, 0-617.3 mL) in the placebo group and 159.3 mL (range, 0-506.2 mL) in the BS group ($P = .86$). During radiotherapy, these values changed to 97.4 mL (range, 0-346.8 mL) in the placebo group and 45.7 mL (range, 0-264.0 mL) in the BS group ($P = .023$). After 4 weeks of follow-up, the values were 83.3 mL (range, 0-352.7 mL) and 73.9 mL (range, 0-413.1 mL), respectively.

Typical MRI pictures of a patient receiving BS are shown in Figure 3. This patient did not need any dexamethasone while on radiotherapy.

Stratifying the patients into primary and secondary brain tumors did not change the results. Due to low patient numbers in the subgroups, stratified results were not significant.

Because tumor response on radiotherapy may have a remarkable effect on edema outcome, this endpoint was investigated carefully. In the BS patients, tumor volume (biggest lesion) changed from an average of 24.4 cm^3 before radiotherapy to 2.9 cm^3 after radiotherapy compared with 19.9 cm^3 to 16.1 cm^3 in the placebo group. This difference was statistically significant ($P = .008$). Tumor response was also evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST). In the placebo group, 18% of patients had progressive disease (PD), 36% stable disease (SD), 36% partial response (PR) and 10% complete response (CR). In the BS group, 0% had PD, 62% had SD, 25% had PR, and 13% had CR.

To investigate whether the BS group was experiencing primary edema reduction or secondary edema reduction via a decrease in tumor volume, the ratio of T1-weighted MRI tumor volume and T2-weighted MRI edema volume (T1/T2 ratio) was calculated. Before therapy, this ratio was 0.11 in the placebo group and 0.15 in the BS group. After therapy, it was 0.15 in the placebo group and 0.06 in the BS group. This may be a hint for the edema reduction by BS depending on an additional antitumor effect.

The MRI measurements of midline shift and the size of ventricles correlated with edema size but did not adduce significant results.

Use of Dexamethasone

In the placebo group as well as the BS group, the median value of dexamethasone dose was 0 mg/wk before and during therapy. The ranges before therapy were 0-84 mg/wk in the placebo and 0-112 mg/wk in the BS group. The ranges during therapy were 0-122 mg/wk in the placebo group and 0-84 mg/wk in the BS group. These differences were not statistically significant.

Adverse Effects

Common adverse effects of radiotherapy were the same in the placebo and the BS group (dermatitis, alopecia). Symptoms of increased intracranial pressure (nausea, vomiting, dizziness, epileptic seizures, and headache) recorded by RTOG/EORTC-CTC score are shown in Table 2. Two patients had grade 3 and 4 toxicity, both of whom were in the placebo group (nausea grade 3 in 1 patient and epileptic seizure grade 4 in 1 patient). The patient with the epileptic seizure had to discontinue radiotherapy and the study.

In 6 patients from the BS group, diarrhea grade 1-2 occurred compared with no patients from the placebo

Table 2. Intracranial Pressure Symptoms During Therapy, Numbers of Patients

	Boswellia					Placebo				
CTC grade	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Nausea	16	5	1	0	0	18	3	0	1	0
Vomiting	20	0	2	0	0	21	1	0	0	0
Dizziness	15	4	2	0	0	19	2	1	0	0
Epileptic seizures	22	0	0	0	0	21	0	0	0	1
Pain grade (VAS 0-10)	**0**	**1-2**	**3-4**	**5-6**	**>6**	**0**	**1-2**	**3-4**	**5-6**	**>6**
Headache	11	4	4	2	0	16	2	0	4	0

CTC indicates Common Toxicity Criteria; VAS, visual analogue scale.

group. There occurred no other adverse effect associated with the BS group or placebo group.

Many patients had a significant problem swallowing 12 relatively large capsules of BS or placebo per day, but most of the patients learned to cope with this problem. One patient who had metastases from esophageal cancer could not swallow the capsules. Two patients refused to further swallow the capsules and discontinued the study in the first treatment week.

Quality of Life and Mental Functioning

The median Karnofsky index of the BS and placebo patients at baseline was 70 and 80, respectively. It did not change remarkably during radiotherapy (80 and 70 at the end of radiotherapy). After 4 weeks of follow-up the median Karnofsky index was 80 in both groups. All differences were not statistically significant.

Quality of life was measured using the EORTC QLQ-30 questionnaire at baseline, after radiotherapy, and after 4 weeks of follow-up. Using the functional scales (physical, role, emotional, cognitive and social functioning, and global health status), the patients in the placebo and the BS group at baseline reached an average score of 55.9 and 54.3 points, respectively (maximum, 100 points). After radiotherapy and after 4 weeks of follow-up, the BS group scored slightly better, with 58.6 and 61.3 points, respectively, compared with 56.2 and 53.8 points in the placebo group. The differences were not statistically significant. All patients had a comparatively low quality of life.

In addition to the EORTC-QLQ 30 questionnaire, the patients underwent a mini-mental state test (MMT). The average MMT score at baseline was 28 points in the placebo group and 29 points in the BS group (maximum, 30 points). At the end of radiotherapy and after 4 weeks of follow-up, the BS patients reached an average of 27 and 29 points, respectively, versus 28 and 26 points in the placebo group. The differences were not statistically significant.

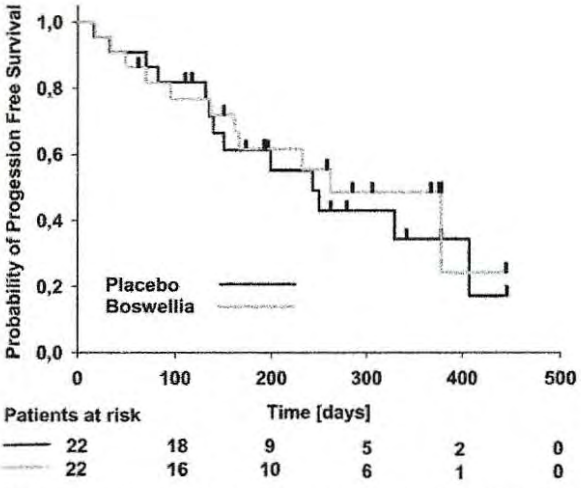

Figure 4. A Kaplan-Meier plot is shown for progression-free survival. Patients who failed died or had tumor recurrence; patients who were censored were alive and were recurrence-free at their last visit (log-rank test, BS versus placebo; $P = .68$).

At baseline, 100% of EORTC-QLQ 30 and MMT questionnaires in both groups were evaluable. After radiotherapy, 81% of the EORTC-QLQ 30 and 80% of the MMT questionnaires were evaluable. After 4 weeks of follow-up, 55% of the EORTC-QLQ 30 and 55% of the MMT questionnaires were evaluable. Missing questionnaires were due to patient noncompliance or death shortly after therapy. This may bias the quality of life results.

Progression-Free Survival

Progression-free survival, which could be a parameter for an antitumor effect of BS, did not differ between the 2 groups. This is shown by Kaplan-Meier plots in Figure 4

($P = .68$; log-rank test, BS vs placebo). The median follow-up time was 250 days.

Boswellic Acid Serum Levels

To prove BS uptake in the patients, the serum levels of the boswellic acids KBA and AKBA were measured. AKBA could not be shown in any of the 48 examined samples (concentration under the detection limit), and KBA was not shown in any of the 24 placebo patient samples. In 19 of the 24 BS samples, an average concentration of 64.9 ng/mL (range, 5.12-153.49 ng/mL) KBA was seen. In 5 of the BS samples, no KBA was found. Two of these samples came from patients who did not continue the study later on; 3 samples came from patients whose other samples were positive and who had difficulties with medication compliance.

In the patient with the highest BS serum levels (5 samples, all positive with an average KBA concentration of 123.1 ng/mL [range, 53.25-153.49 ng/mL]) one of the largest edema reductions was observed. His edema volume was reduced by more than 300 mL from baseline to the time after radiotherapy.

DISCUSSION

In addition to spiritual use, *Boswellia* or frankincense has been used as a medication for hundreds of years.[7] In recent years, mechanisms of action of boswellic acids have been identified.[8] Takada et al[9] showed that AKBA can potentiate apoptosis, inhibit invasion, and abolish osteoclastogenesis in different human cancer cell lines. The mechanism of these actions was found to be a suppression of nuclear factor κB (NF-κB) and NF-κB-regulated gene expression. It was further shown that boswellic acids possess potent anti-inflammatory properties in vitro by inhibiting 5-lipoxygenase, human leukocyte elastase, and the NF-κB pathway.[10,11] Cathepsin G was identified as another target of boswellic acids.[11]

In clinical research, positive effects of boswellic acids in the treatment of inflammatory diseases could be shown.[3,12] There exist clinical trials about the use of boswellic acids in asthma,[13] rheumatoid arthritis,[14] Crohn disease,[15] collagenous colitis,[16] and osteoarthritis of the knee.[17,18] To our knowledge, there exist only first clinical observation results for the treatment of cerebral edema by boswellic acids.[1,2]

In our study, patients taking BS extract had significantly less cerebral edema than patients taking placebo, whereas the median dexamethasone dosage was the same in the BS and the placebo group.

As cerebral edema and its inflammatory processes are major causes of morbidity in brain tumor patients the treatment of these phenomena has always been of high importance. The most effective medication for cerebral edema patients is steroids, in most cases dexamethasone. However, steroids have reasonable adverse effects as immunosuppression, mental changes, or even Cushing syndrome. Furthermore, there is evidence that dexamethasone influences cancer therapies through stabilization of blood-brain and blood-tumor barriers and reduction of tumor perfusion.[19] Several years ago, it was shown that the use of steroids influences vascular response to radiation[20] and directly inhibits apoptosis in human malignant glioma cells.[21] However, in spite of strong efforts, an adequate replacement medication for dexamethasone has not been found yet. Boswellic acids could be the basis for a new kind of anti-inflammatory and thus antiedema medication with decreased adverse effects, the additional induction of apoptosis, and no modulation of drug (and radiation) sensitivity.[19] In addition to the first clinical results,[1,2] our study may be a further step in this direction.

In this study, patients receiving BS showed a better tumor response to radiotherapy. This was not a planned endpoint, and therefore, it has to be considered carefully. Nevertheless, this observation may be a hint to a cytotoxic or radiosensibilizing effect of BS which will have to be investigated in further studies with long-time BS medication. It also has to be determined whether the impact of BS on cerebral edema may be caused by an antitumor effect.

The prospective, randomized, placebo-controlled, double-blind design of this study makes its results highly reliable. Nevertheless, the study will have to be confirmed by a phase 3 trial. In the design of such a study, some weaknesses of the reported trial should be considered. First, most of the patients had problems swallowing 12 large capsules a day; future trials should attempt to provide the boswellic acids in a more concentrated form.[22] Another possibility could be the development of a BS product with an isolated acting component and applicable intravenously. Second, considering the excellent toxicity profile of BS, a phase 3 study should use an even higher dose, particularly if the BS product can be more highly concentrated. Third, the food of the patients on study should be closely observed. It was shown by Sterk et al[23] that food intake can remarkably change the bioavailability of boswellic acids. By adding fat to normal nutrition, the

serum levels of BS could be further increased. Fourth, the measurement of quality of life should be better adapted to the situation of brain tumor patients; neither the MMT nor the EORTC QLQ 30 seems to be the best instrument for quality of life measurements in this context. A further study might use more individual instruments tested in palliative care, such as the SEIQoL.[24] Fifth, duration of dexamethasone medication before the study should be recorded, and an exact schedule for decreasing dexamethasone dose should be given. Finally, the effect of BS on the tumor should be included as a study endpoint.

A future phase 3 trial should consider the most important points for a potential clinical benefit of BS: an effect on cerebral edema with possible reduction of the necessary dexamethasone dose and an antitumor effect. It will have to be investigated whether both are reflected in patients' quality of life.

In our patients, BS significantly reduced cerebral edema measured by MRI. There were no severe adverse events concerning BS. The results of this study do not suggest the use of BS as a replacement of dexamethasone in patients treated with brain irradiation; nevertheless, they show that BS could allow for steroid sparing. The study will have to be confirmed by further investigations.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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