

## The End-of-Life Hospital Setting in Patients with Glioblastoma

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### ABSTRACT

Despite aggressive treatment, outcome of patients with glioblastoma is poor. Several distinct clinical problems arise in the terminal stage of this disease. The purpose of this study was to evaluate the end-of-life phase in a hospital setting in patients with glioblastoma. Twenty-nine consecutive patients with glioblastoma, who died in our department, were included in this analysis regarding symptoms, medication, diagnostics, and interventional procedures. The patients were comparable with respect to age, gender, and overall survival with data from the literature. Relevant clinical symptoms, medications, diagnostics, well as interventional procedures increased continuously toward end of life. Pain, epileptic seizures, and symptoms of brain edema were the most frequent clinical symptoms. According to this, most patients were on antiepileptic drugs (AED), steroids, and analgesics. In the last phase, symptoms from brain edema, fever, decrease of vigilance, dysphagia, and pneumonia were the prominent clinical features. Our study demonstrates that the end of life in patients with glioblastoma has several periods with different clinical aspects with respect to symptoms and treatment.

### INTRODUCTION

**D**ESPITE AGGRESSIVE TREATMENT, outcome of patients with glioblastoma is poor. During the diagnostic period and causal tumor treatment such as surgery, radiotherapy, and chemotherapy, patients are followed closely by different specialties. Radiologists, neurologists, neurosurgeons, radiotherapists, and medical oncologists are involved in the patient's care. It is the effort of all medical interventions to prolong life, maintain function for everyday living, and improve quality of life as long as possible. However, when the patient's condition deteriorates and no further surgery, radiotherapy, or chemotherapy seems reasonable, several clinical problems may arise in this terminal phase

of the disease. Seizures, headache, dysphagia, progressive neurologic deficits, and personality changes are common.<sup>1</sup>

In the terminal phase of the disease, as a result of social, economic, individual, and cultural reasons, some patients are admitted to the hospital, where they finally die. Regarding this terminal phase of the disease, there is a lack of relevant articles in the neurologic literature, providing recommendations for supportive care in patients with brain tumors.<sup>2-4</sup>

The purpose of this study was to evaluate the end-of-life phase in patients with glioblastoma with respect to the time course of symptoms, drug treatment, frequency of diagnostic and interventional procedures.

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METHODS

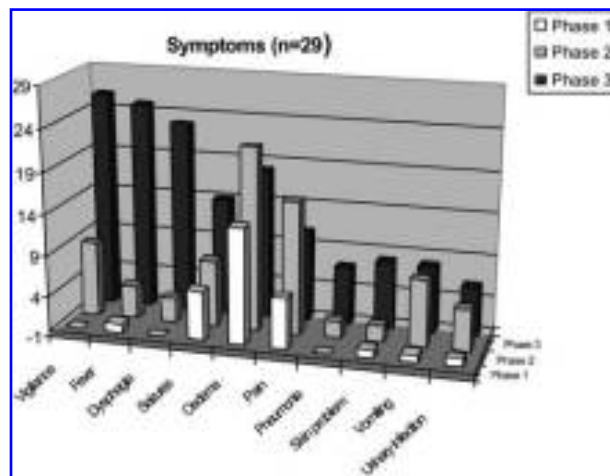
Data from 29 consecutive patients with glioblastoma were obtained retrospectively from inpatient and outpatient records by physicians according to a specifically designed protocol. The protocol contained demographic data, information regarding symptoms, treatment, diagnostics, and interventions in each phase, as well as data concerning glioma treatment, Karnofsky Performance Status (KPS), and overall survival.

The last 10 weeks before death were divided into three periods. Phase 1, from 10 to 6 weeks before death; phase 2, 6 to 2 weeks before death; and phase 3, the last 2 weeks before death. The division into the three phases was done up front, based on clinical experience in order to detect different aspects in the course of the disease and in the care of these patients.

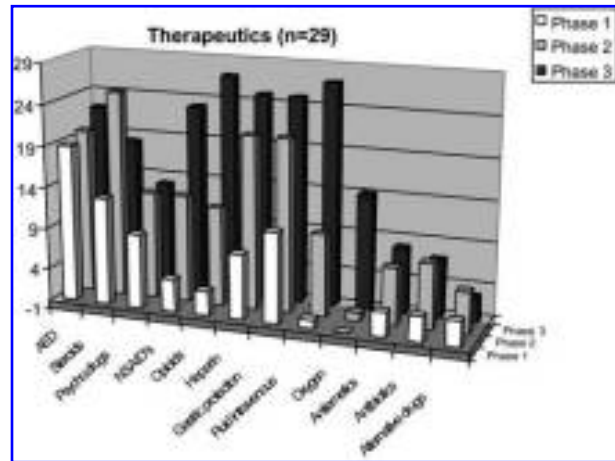
RESULTS

The patients were comparable with respect to age (mean, 59; standard deviation [SD] ± 9), and overall mean survival (48 weeks, SD ± 11) with data from the literature. The male predominance was probably due to the small sample size. (9 females/20 males). In the investigation period (last 5 years), a total of 162 patients with glioblastoma were registered and treated in our institution. Of these, 18% died in our department.

Mean KPS at the beginning of phase 1 was 70%



**FIG. 1.** Symptoms of 29 patients with glioblastoma according to phase 1–3. The number of patients from phase 1/2/3: Vigilance decrease (0/9/26), fever (1/2/25), dysphagia (0/3/23), seizures (6/8/14), \*edema (14/22/18), headache (6/16/11), pneumonia (0/2/7), skin problems (1/2/8), vomiting (1/8/8), urinary infection (1/5/6). \*Symptoms clinically suspected brain edema.



**FIG. 2.** Drug treatment in 29 patients with glioblastoma according to phase 1–3. The number of patients from : phase 1/2/3 AED (19/20/22), steroids (13/25/18), psychopharmacological drug (9/13/13), NSAIDs, (4/13/23), opioids (3/12/27), heparin (8/21/25), gastric protection (11/21/25), intravenous fluids (1/10/27), oxygen insufflation (0/1/14), antiemetics (3/7/8), antibiotics (3/8/7), alternative drugs (3/5/53). AED, antiepileptic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs.

(SD ± 10), and subsequently decreased from phase 2 to 50% (SD ± 8), and in phase 3 to 20% (SD ± 4). Mean time between end of antitumor treatment and death was 10 weeks (SD ± 4), which reflects the beginning of phase 1.

The most frequent treatment regimen was surgery plus radiotherapy and subsequent chemotherapy (first-line chemotherapy; *n* = 10, more than one chemotherapy; *n* = 12). Seven patients had surgery only (*n* = 4), or biopsy (*n* = 3). Treatment regimens were applied subsequently after diagnosis in an adjuvant setting.

Reasons for hospitalization were difficulties in maintenance of home care due to immobility (13/29), acute deterioration of clinical condition (8/29), seizure (4/29), infection (2/29), and one deep veinous thrombosis (1/29).

Relevant clinical symptoms, such as decrease of vigilance, seizures, fever, dysphagia, as well as vomiting, skin problems and pneumonia, increased from phase 1 to 3. Pain had a peak in phase II and decreased again in phase III (Fig. 1).

Drug treatment generally showed a continuous increase from phase 1 to 3 except steroids, which declined in phase 3. Most pronounced increase was detected for the treatment of pain, prophylaxes of venous thromboses (heparin), fluid substitution, and gastric protection. The majority of patients in period 3 received transdermal or subcutaneous opioids, intravenous fluids, anticoagulation, anticonvulsants, gastric

protection. Intermittent oxygen insufflation was used almost exclusively in the terminal phase (Fig. 2).

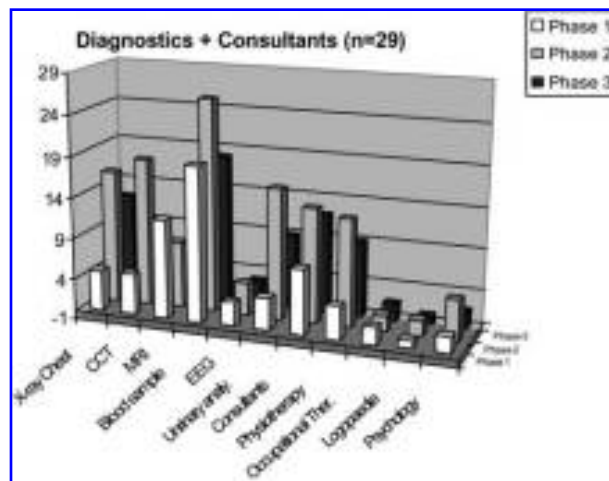
Diagnostics such as cranial computed tomography (CCT), electroencephalogram (EEG), X-ray of the chest, blood tests, and urinary analysis most frequently appeared in phase 2. Only the number of magnetic resonance imaging (MRI) investigations of the brain declined over time. Regarding consultants, phase 2 was the busiest period. Physiotherapy, occupational therapy, logopedia, psychologic assessment, directed to mobilize the patient and to strengthen his remaining function, was only marginal in all three phases (Fig. 3).

Interventions, such as urinary catheter and venflon increased from phase 1 to 3. Most patients required an airbed in phase 3, and only few had a nasogastric tube (Fig. 4).

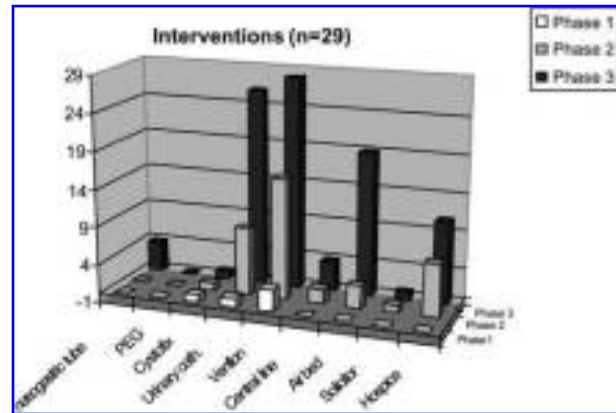
The majority of patients, as documented in the reports, died due to tumor progression 62% (18 patients), as well as respiratory distress 14% (4 patients). Pneumonia as a cause of death was diagnosed in 21% (6 patients), and 1 patient died due to a treatment complication.

## DISCUSSION

Providing adequate palliative care to dying patients with glioblastoma is an important, but from the scien-



**FIG. 3.** Diagnostic procedures and consultants in 29 patients with glioblastoma according to phase 1–3. The number of patients from phase 1/2/3 who had: chest x-ray (5/16/12)\*, CCT (5/18/7),\* MRI (12/8/4), blood tests (19/26/18),\* EEG (3/4/3), urinary analysis (4/16/9), consultants (8/14/12),\* physiotherapy (4/13/9), occupational therapy (2/2/2), logopedia (1/2/1), psychologist (2/5/2). \*Ratio of investigations per patient: chest x-ray (1,3/1,4/1,5), CCT (1/1,2/1), blood tests (1,9/2,8/2,1), consultants (1,4/2/1,6). CCT, ; MRI, magnetic resonance imaging, EEG, electroencephalogram.



**FIG. 4.** Interventions in 29 patients with glioblastoma according to phase 1–3. The number of patients from phase 1/2/3: nasogastric tube (0/0/4), PEG (0/0/0), cystofix (1/1/1), urinary catheter (1/9/26), venflon (3/16/28), air bed (0/3/19), solicitor (0/1/1), hospice (0/7/11). PEG, percutaneous endoscopic gastrostomy.

tific literature, neglected aspect of treatment. No evidence based recommendations are provided on this topic. Most of the literature in this field is focused on general cancer patients,<sup>5,6</sup> or based on principal statements concerning neurologic disease.<sup>3,7,8</sup>

Among patients in a general palliative unit most frequent clinical symptoms were, pain, dyspnea, increased respiratory secretion, nausea and vomiting, confusion, bowel and bladder problems.<sup>9</sup> In a study by Hall et al.,<sup>10</sup> investigating the last 48 hours in long-term palliative care patients (patients with cancer only 14%) respiratory distress was the most prevalent symptom, pain was second, and delirium was third. In general patients with cancer only, pain was equally prevalent with respiratory distress.<sup>1,10</sup>

Patients dying from brain tumors seem to have special clinical features in the terminal phase of their disease. Epileptic seizures, progressive neurologic deficits, symptoms from brain edema, headache, personality changes, and restlessness are most prominent.<sup>1</sup> Our study confirmed some of these characteristic clinical features for patients with brain tumors, such as seizures, symptoms from brain edema, and pain. Additionally we detected symptoms such as fever, dysphagia, and vigilance decrease, which increased dramatically in phase 3. Moreover, our study demonstrates that there are different periods in the end-of-life phase of patients with brain tumors.

In phase 1, pain, epileptic seizures, and symptoms from brain edema were the leading clinical features. According to these symptoms, antiepileptic drugs (AED), steroids, and analgesics were administered, but heparin and gastric protection were also. Heparin,

probably because of progressive neurologic deficits and immobilization, and gastric protection was used concomitantly with steroids.

In phase 2 only pain and treatment of symptoms from brain edema increased substantially. This might be because steroids are used in order to control headache by treating symptoms from brain edema. In our experience, this clinical decision is not always based on radiologic findings. Also, the administration of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids increased, which might indicate a polypragmatic approach with respect to pain treatment. There was also a peak regarding diagnostics (blood samples, CCT, x-ray of the chest, urine analysis), which can be explained by the desire to justify the clinical deterioration from phase 1 to phase 2. This holds also true for the increased number of consultants in phase 2.

In the terminal phase 3, most frequent clinical symptoms were decreased vigilance, fever, dysphagia, seizures, and pain, which explains that almost all patients received transdermal or subcutaneous opioids, AED, gastric protection, a venflon, and intravenous fluids. Anticoagulation, urinary catheter, skin problems, and an airbed can be attributed to the fact that most of the patients were bed-bound in phase 3, which however is nonspecific for patients with brain tumors. Also pneumonia and intermittent oxygen can be seen in this context. With focus on phase 3, all medication should be promptly available and possibly given by a nonoral route because dysphagia is present in the majority of patients.

Symptom control, especially with respect to pain, seizures, and symptoms from brain edema requires adequate drug treatment. Recommendations for the use of steroids,<sup>11,12</sup> and AED<sup>11,13</sup> in patients with brain tumors are available, however, not specifically for the terminal phase of the disease. Little is known about drug treatment of pain in patients with brain tumors, which might also be due to several pathogenetic factors (hydrocephalus, swelling caused by tumor mass, cranial nerve infiltration, or infiltration of the meninges, treatment-related diffuse pain resulting from immobilization, plateau waves, etc.).<sup>14–17</sup> Opioids seem to be appropriate in the treatment of respiratory distress in cancer patients in the terminal phase of the disease.<sup>18–20</sup> This might be also true for equivalent symptoms in brain tumor patients, however no valid data are available.<sup>21</sup> Neuroleptics and benzodiazepines for sedation purposes was administered in half of the patients in phase 2 and 3. Practice of sedation in terminal ill patients has a wide divergence among palliative care specialists and no clear guidelines are available.<sup>22,23</sup>

Although the terminal phases of this disease have turned out to be a symptom- and drug-intensive period, the management is up to the individual experience of personal engaged in the patients care. This requires further clinical research to develop evidence-based guidelines.

It is hoped that this compilation may provide a basis for future research in the palliative setting of patients with glioblastoma.

## REFERENCES

1. Voltz R, Borasio GD: Palliative therapy in the terminal stage of neurological disease. *J Neurol* 1997;244:2–10.
2. Bernat JL, Goldstein ML, Viste KM Jr: The neurologist and the dying patient. *Neurology* 1996;46:598–599.
3. Borasio GD, Weltermann B, Voltz R, Reichmann H, Zierz S: Attitudes towards patient care at the end of life. A survey of directors of neurological departments. *Nervenarzt* 2004;75:1187–1193.
4. Carver AC, Vickrey BG, Bernat JL, Keran C, Ringel SP, Foley KM: End-of-life care: a survey of US neurologists' attitudes, behavior, and knowledge. *Neurology* 1999;22:284–293.
5. Lichter I, Hunt E: The last 48 hours of life. *J Palliat Care* 1990;6:7–15.
6. Cancer care during the last phase of life. *J Clin Oncol* 1998;16:1986–1996.
7. Voltz R, Bernat JL, Borasio GD (eds): *Palliative Care in Neurology* (Contemporary Neurology Series). New York: Oxford, 2003.
8. The American Academy of Neurology Ethics and Humanities Subcommittee: Palliative care in neurology. *Neurology* 1996;46:870–872.
9. Silbergeld DL, Rostomily RC, Alvord EC Jr: The cause of death in patients with glioblastoma is multifactorial: Clinical factors and autopsy findings in 117 cases of supratentorial glioblastoma in adults. *J Neurooncol* 1999;10:179–185.
10. Hall P, Schroder C, Weaver L: The last 48 hours of life in long-term care: A focused chart audit. *J Am Geriatr Soc* 2002;50:501–506.
11. Hildebrand J, Brada M (eds): Epileptic seizures. In: *Differential Diagnosis in Neuro-oncology*. New York: Oxford University Press, 2001, pp. 47–58.
12. Sinha S, Bastin ME, Wardlaw JM, Armitage PA, Whittle IR: Effects of dexamethasone on peritumoural oedematous brain: a DT-MRI study. *J Neurol Neurosurg Psychiatry* 2004;75:1632–1635.
13. Vecht CJ, Wagner GL, Wilms EB: Treating seizures in patients with brain tumors: Drug interactions between anti-epileptic and chemotherapeutic agents. *Semin Oncol* 2003;30:49–52.
14. Arcuri E, Ginobbi P, Tirelli W, Tirelli W, Frolidi R, Citro G, Santoni A: Preliminary in vivo experimental evidence on intratumoral morphine uptake. Possible clinical implications in cancer pain and opioid responsiveness. *J Pain Symptom Manage* 2002;24:1–3.

15. Hess B, Oberndorfer S, Urbanits S, Lahrmann H, Grisold W: Trigeminal neuralgia in two patients with glioblastoma. *Headache* 2005;45:1267–1270.
16. Pfund Z, Szapary L, Jaszberenyi O, Nagy F, Czopf J: Headache in intracranial tumors. *Cephalalgia* 1999;19:787–790.
17. Purdy RA, Kirby S: Headaches and brain tumors. *Neurol Clin* 2004;22:39–53.
18. Conroy JM, Harvey SC: Management of cancer pain. *South Med J* 1996;89:744–760.
19. Jennings AL, Davies AN, Higgins JP: Opioids for the palliation of breathlessness in terminal illness. *Cochrane Database Syst Rev* 2001;4:CD002066.
20. Thomas JR, Von Gunten CF: Treatment of dyspnea in cancer patients. *Oncology* 2002;16:745–750.
21. Quality improvement guidelines for the treatment of acute pain and cancer pain. American Pain Society Quality of Care Committee. *JAMA* 1995;274:1874–1880.
22. Morita T: Differences in physician-reported practice in palliative sedation therapy. *Support Care Cancer* 2004;12:584–592.
23. Jackson KC, Lipman AG: Drug therapy for anxiety in palliative care. *Cochrane Database Syst Rev* 2004;1:CD004596.

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