Despite multimodal treatment, it is not possible to cure high-grade glioma (HGG) patients. Therefore, the aim of treatment is not only to prolong life, but also to prevent deterioration of health-related quality of life as much as possible. When the patient’s condition declines and no further tumor treatment seems realistic, patients in the Netherlands are often referred to a primary care physician for end-of-life care. This end-of-life phase has not been studied adequately yet. The purpose of this study was to explore specific problems and needs experienced in the end-of-life phase of patients with HGG. We retrospectively examined the files of 55 patients who received treatment in our outpatient clinic and died between January 2005 and August 2008. The clinical nurse specialist in neuro-oncology maintained contact on a regular basis with (relatives of) HGG patients once tumor treatment for recurrence was no longer given. She systematically asked for signs and symptoms. The majority of the patients experienced loss of consciousness and difficulty with swallowing, often arising in the week before death. Seizures occurred in nearly half of the patients in the end-of-life phase and more specifically in one-third of the patients in the week before dying. Other common symptoms reported in the end-of-life phase are progressive neurological deficits, incontinence, progressive cognitive deficits, and headache. Our study demonstrates that HGG patients, unlike the general cancer population, have specific symptoms in the end-of-life phase. Further research is needed in order to develop specific palliative care guidelines for these patients.

Keywords: end-of-life, high-grade glioma

Patients with high-grade glioma (HGG), the most frequently occurring primary malignant brain tumor, have a poor prognosis and cannot be cured. Despite aggressive multimodality treatment with surgery, radiation therapy, and chemotherapy, median survival ranges from <1 to 5 years depending on histological subtype, tumor grade, cytogenetic analysis, age, and performance status at the time of diagnosis.1,2 Focal neurological deficits, symptoms of increased intracranial pressure, epilepsy, and cognitive dysfunction are prominent symptoms in HGG patients which may arise in any stage of the disease.3–5 Furthermore, fatigue, mood disturbances, and anxiety are often reported.6 These factors all negatively affect health-related quality of life (HRQOL) of patients and their relatives.7–9 Antitumor treatment as well as supportive medication [often steroids and antiepileptic drugs (AEDs)] may cause side effects which may further diminish HRQOL.10,11 Since HGG patients cannot be cured, the aim of treatment is not only to prolong life, but also to maintain quality of life as long as possible. In this respect, HRQOL is included as a secondary endpoint in a growing number of randomized clinical trials evaluating antitumor treatment.12,13

When the patient’s condition declines due to tumor progression and further tumor treatment is not an option, the end-of-life phase begins. In this phase, only supportive treatment is given.14 In the Netherlands, patients in this phase often no longer visit the neuro-oncology outpatient department and become dependent on care provided by primary care physicians. Depending on where the patient resides, the general practitioner, the nursing home specialist, or the hospice doctor is the coordinating physician. In the Netherlands, only a minority of cancer patients dies in
hospitals, which probably also holds true for HGG patients.\textsuperscript{15,16}

Patients and their relatives often are anxious about what will happen in the last phase of life. Until now, there are limited data on the end-of-life phase of these patients.\textsuperscript{4,17–19} The few existing reports identified symptoms related to increased intracranial pressure (headache and drowsiness), as well as progressive neurological deficits, epileptic seizures, confusion/delirium, fatigue, and dysphagia as the most prominent symptoms.\textsuperscript{17–19}

A better knowledge of the clinical issues for this specific group of patients in the end-of-life phase will improve the information given to future HGG patients and their families as well as the care supplied. We therefore explored the incidence of specific symptoms in the end-of-life phase in a group of HGG patients.

\section*{Patients and Methods}

\subsection*{Patients}

Adult (\textgtr 18 years of age) glioma patients, who had died between January 2005 and August 2008 after being treated for their tumor at the VU University Medical Centre, Amsterdam, were considered for inclusion in the analysis.

Patients with either an initial histological diagnosis of HGG (glioblastoma multiforme, high-grade astrocytoma, high-grade oligodendroglioma, or high-grade mixed glioma) or a histological confirmed low-grade glioma (LGG), with clinical and radiological progression suspected for a high-grade tumor following initial treatment, were included. According to our definition, the end-of-life phase started once patients presented with progressive disease for which there were no further tumor treatment options, or if patients refused further tumor treatment. Patients who died during tumor treatment were therefore excluded.

\subsection*{Materials and Methods}

In the end-of-life phase, patients no longer visited the outpatient clinic on a regular basis. The clinical nurse specialist, however, kept in touch with the patients and/or their families via a telephone service. Patients and caregivers were invited to call the clinical nurse specialist in the case of questions and problems. Otherwise, the clinical nurse specialist contacted the patients and/or their main informal caregiver(s) on a biweekly basis and asked for signs, symptoms, and problems encountered. In these telephone contacts, using a checklist, the clinical nurse specialist investigated the occurrence of pain, headache, focal neurological deficits, confusion, cognitive disturbances, seizures, and incontinence, as well as the level of consciousness, changes in medication (antiepileptics and steroids), and problems with intake of medication, fluid, and food (Fig. 1).

Furthermore, in the month following death, the course of the disease in the last week before dying was enquired after with the family or the primary care physician.

Symptoms, signs, and treatment in the end-of-life phase as a whole were retrieved from medical files and the chart of the clinical neuro-oncology nurse specialist. Symptoms and problems arising in the week before death were recorded separately.

\subsection*{Statistical Analysis}

We used SPSS software 15.0 for statistical analysis.

\section*{Results}

\subsection*{Demographic and Clinical Data}

Seventy-five consecutive adult HGG patients, who ended all tumor treatment while being treated at our centre, and died between January 2005 and August 2008, were identified. Seventeen (relatives of) patients did not use the telephone service. Nine of these 17 were referred to another institution in the end-of-life phase and had a contact person there. The other 8 declined the service. Fifty-eight patients were included in this analysis. Of these 58 patients, 12 patients had been diagnosed with an LGG before dedifferentiation to an HGG.

Table 1 shows demographic and clinical data.

\subsection*{Symptoms and Signs in the End-of-Life Phase}

Three of the 58 cases were lost to follow-up in the end-of-life phase and therefore excluded. Two of these patients died in a nursing home, and 1 passed away at home. In Table 2, symptoms and signs occurring anytime in the end-of-life phase are depicted.

The most frequently reported symptom was decreased consciousness (87\% of the patients) which, however, was not reported until the last week before death in the majority of patients (73\% of these patients). The second most common symptom was dysphagia. This occurred in 71\% of the cases and often coincided with decreased consciousness. Fifty-two percent of the patients experienced progressive neurological deficits...
Seizures were reported in 45% of all patients in the end-of-life phase. Of patients who already had seizures during the course of disease, 53% also had seizures in the end-of-life phase. Conversely, of patients who had been free of seizures so far, 11% had their first seizure in the end-of-life phase. Thirteen (52%) of the 25 patients who had seizures in the end-of-life phase had more than 1 seizure in this phase. All patients with seizures received AEDs. Among the patients who were on anticonvulsive drugs, there were no patients who never had epileptic seizures. In 40% of the patients, incontinence was reported to occur before the patients were bed-ridden. Headache, progressive cognitive deficits (memory loss, personality changes, apathy, and problems in executive functioning and understanding), and agitation/confusion all were reported in one-third of the patients. Next to headache, 25% of the patients reported bodily pain, often related to immobilization.

**Additionally Reported Symptoms**

In addition to the symptoms and signs structurally asked for, other symptoms and signs which were additionally reported by the patients and their caregivers are given in Table 3. Twenty-five percent of the patients experienced severe fatigue and 20% of the patients suffered from nausea or vomiting. Dyspnea was reported in 9 patients (16%): in 5 cases, this was most likely due to pneumonia, in 1 patient due to pulmonary embolism, whereas in the remaining 3 cases, the cause of dyspnea was unclear. Constipation, probably due to morphine use, was severe enough to be reported in 5 cases. In 5 patients, symptoms of anxiety and/or depression were mentioned. One patient had severe vertigo due to tumor infiltration in the 8th cranial nerve. Severe side effects from steroid use were reported in 4 cases: 2 patients suffered from steroid myopathy, 1 patient developed hyperglycemia, and 1 patient had a bowel perforation while using steroids. Overall, 44 (80%) patients used steroids in the end-of-life phase.

### Symptoms in the Week Before Dying

Although drowsiness was only present in 13 patients (24%) at the start of the week before dying, this number increased to 48 patients (87%) during the last week. This also holds true for dysphagia: the number increased from 5 patients (9%) to 39 patients (71%). In the last week, 28% of all patients experienced at least 1 seizure.

### Cause of Death

In 40 patients (73%), the presumed cause of death was brain herniation due to tumor progression. For 4 other patients, the cause of death was directly tumor-related; these patients died following a seizure (3 patients) or a hemorrhage in the tumor (1 patient). For 8 patients, the cause of death was indirectly tumor-related; 5 patients died due to an infection (in 2 cases, this concerned an aspiration pneumonia following a seizure), 1 died from bowel perforation while using steroids, 1 patient died from pulmonary embolism, and 1 suffered
traumatic brain damage following an accident and died from urosepsis. In 3 patients, euthanasia was performed under strict conditions upon a voluntary and well-considered request.

Discussion

The most commonly reported symptoms in the last phase of our cohort of HGG patients were drowsiness (87%), dysphagia (71%), progressive neurological deficits (51%), seizures (45%), incontinence (40%), progressive cognitive deficits (33%), and headaches (33%). Of these, drowsiness and dysphagia appeared to occur most frequently in the week before death.

One of the drawbacks of this study is the focus on symptoms specific for brain tumors. The more general end-of-life symptoms reported in extracranial cancer patients, such as fatigue, mood disturbances, nausea, and constipation, are probably underreported as these were not structurally asked for.20,21 Another restraint is the relatively small number of patients. Despite these limitations, our data are worth reporting, given the lack of studies in this field.

In 3 earlier studies in patients dying from brain tumors, comparable prevalence rates of increased intracranial pressure symptoms (drowsiness and headache), neurological deficits, seizures, and cognitive deficits were reported.17–19 The occurrence of dysphagia, however, differed among these studies. Dysphagia was reported in 70% of our cases, more or less comparable to the studies by Oberndorfer et al.17 and Pace et al.18 In contrast, Faithfull et al.19 described a prevalence of only 10%. This discrepancy in prevalence rates is probably due to the fact that we also denominated patients to be dysphagic if they were unable to swallow due to loss of consciousness. If these patients are excluded, only 14% had (true) dysphagia.

The high prevalence of swallowing difficulties in the last week of life may yield problems in taking medication. The majority of patients used AEDs and/or glucocorticoids (dexamethasone) in the last phase of life. About one-third of the patients suffered from seizures in the last week of life and these may be life-threatening as appeared to be the case in 5 patients. Since seizures are even a more prominent feature in the end-of-life phase than we had anticipated, continuation of AEDs should therefore be recommended, even if oral administration is no longer possible. In view of the fact that most patients stay at home or in a first-line care setting, a non-invasive administration route is preferred when patients are unable to swallow at the end of life. Rectal administration of carbamazepine, valproic acid, and phenobarbital is available. Otherwise, seizures may be treated with rectal diazepam, intranasal or subcutaneous midazolam or sublingual clonazepam.22 In the hospital setting, intravenous infusion should be considered.

Urinary incontinence has not been described in former reports concerning the end-of-life phase of brain tumor patients. In our cohort, it was a relatively early and prominent sign (before the patient was confined to bed) occurring in 41% of the cases. Incontinence has often been associated with immobilization, social withdrawal, body image distortion, and depression and thus has a major impact on quality of life.23 Urinary incontinence, specifically in brain tumor patients, can be caused by the tumor itself, such as may be the case in frontal tumors, or due to impaired cognition and consciousness. Other (reversible) causes may be urinary tract infection, hyperglycemia, and the use of sedatives.24 In a general cancer population, 29% of the patients were incontinent for urine in the end-of-life phase.24 Thus, the prevalence of incontinence appears to be relatively high in brain tumor patients.

Of further interest is to compare the prevalence of more “general” end-of-life symptoms in HGG patients with other cancer patients. The main symptoms reported in terminally ill cancer patients are fatigue and anorexia, followed by pain, nausea, constipation, delirium, and dyspnea.20,21 As noted before, these symptoms are probably underreported in our patients, since we did not ask for general symptoms. However, bodily pain was asked for and appeared to occur less frequently in glioma patients (25%) when compared with patients with systemic cancer, where prevalence rates of 60%–80% are reported.24 Despite the fact that we are still unaware of the prevalence of general symptoms in glioma patients in the end-of-life phase, the disease-specific symptoms are prominent. This indicates that the end-of-life phase of HGG patients cannot be compared simply with a general cancer population. Future studies prospectively exploring the end-of-life phase of HGG patients are mandatory in order to develop specific palliative care guidelines for these patients and their relatives.

Conflict of interest statement. None declared.

Funding

This work was supported by the St Jacobusstichting, The Hague (E.M.S., M.J.B.T).

References


