The end-of-life phase of high-grade glioma patients

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Chapter 2.1

Symptoms and problems in the End-of-Life Phase of High-Grade Glioma Patients

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Abstract

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 (HRQoL) as much as possible. When the patient's condition declines and no further tumour treatment seems realistic, patients in the Netherlands are often referred to a primary care physician for end-of-life (EOL) care. This EOL 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 high-grade glioma.

We retrospectively examined the files of 55 patients who received treatment in our outpatients clinic and died between January 2005 and August 2008. The clinical nurse specialist in neuro-oncology maintained contact on a regular base with (relatives of) high-grade glioma patients once tumour 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. In nearly half of the patients in the end-of-life phase, and in one third of the patients in the week before dying seizures occurred. 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 EOL phase. Further research is needed in order to develop specific palliative care guidelines for these patients.

Introduction

Patients with high-grade glioma (HGG), the most frequently occurring primary malignant brain tumour, have a poor prognosis and cannot be cured. Despite aggressive multimodality treatment with surgery, radiation therapy and chemotherapy, median survival ranges from less than one year to five years depending on histological subtype, tumour grade, cytogenetic analysis, age and performance status at the time of diagnosis.[9, 73]

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.[4, 37, 74] Furthermore, fatigue, mood disturbances and anxiety are often reported.[75] These factors all negatively affect health related quality of life (HRQoL) of patients and their relatives.[76-78] Anti-tumour treatment as well as supportive medication (often steroids and anti-epileptic drugs) may cause side-effects which may further diminish HRQOL.[39, 79] 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 anti-tumour treatment.[17, 80]

When the patient's condition declines due to tumour progression and further tumour treatment is not an option, the end-of-life (EOL) phase begins. In this phase only supportive treatment is given.[81] In the Netherlands, patients in this phase often no longer visit the neuro-oncology outpatients department, and become dependent on care provided by primary care physicians. Depending on where the patients resides, the general practitioner (GP), the nursing home specialist or the hospice doctor is the coordinating physician. In the Netherlands, only a minority of cancer patients dies in hospital, which probably also holds true for HGG patients.[82, 83]

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 EOL phase of these patients. The few existing reports identified symptoms related to increased intracranial pressure (headache, drowsiness), as well as progressive neurological deficits, epileptic seizures, confusion/delirium, fatigue, and dysphagia as the most prominent symptoms.[21, 46, 48]

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 EOL phase in a group of HGG patients.

Patients and Methods

Patients

Adult (> 18 year of age) glioma patients, who had died between January 2005 and August 2008 after being treated for their tumour 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 tumour 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 tumour treatment options, or if patients refused further tumour treatment. Patients who died during tumour treatment were therefore excluded.

Material and Methods

In the EOL 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 case of questions and problems. Otherwise, the clinical nurse specialist contacted the patients and/or their main informal caregiver(s) on a bi-weekly 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 (anti-epileptics, steroids) and problems with intake of medication, fluid and food, using a checklist (Figure 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.

Figure 1: Checklist used in the telephone interviews

- □ Headache
- □ Pain
- □ Nausea/ vomiting
- □ Cognition
- □ Confusion or agitation
- □ Paresis and mobility
- □ Seizures
- □ Level of consciousness
- □ Intake and problems with intake
- □ Incontinence
- □ Dexamethasone use

Symptoms, signs and treatment in the EOL 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.

Statistical analysis

We used SPSS software 15.0 for statistical analysis.

Results

Demographic and clinical data

Seventy-five consecutive adult HGG patients, who ended all tumour 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 EOL phase and had a contact person over there. The other eight declined the service. Fifty-eight patients were included in this analysis. Of these fifty-eight patients, twelve patients had been diagnosed with a LGG before dedifferentiation to a HGG. Table 1 shows demographic and clinical data.

Table 1 Demographic and clinical data (n = 58)

Sex o Male o Female	 39 (67%)[a] 19 (33%)[a]	*** clinically and radiological evidenced** **** from diagnosis**
Age at diagnosis, years	52 (18-81)[b]	
Grade o Grade III o Grade IV o Unspecified*	 15 (26%)[a] 41 (71%)[a] 2 (3%)[a]	
History of low grade glioma	12 (21%)[a]	
Survival** in months o Grade III o Grade IV	 21 (11-86)[b] 12 (0.5-71)[b]	
Length of the end-of-life phase, days	46 (1-294)[b]	
Place of death o At home o Hospital o Hospice o Nursing home	 38 (66%)[a] 10 (17%)[a] 5 (8.5%)[a] 5 (8.5%)[a]	

number of patients (percentage) [a] or median (range) [b]

Symptoms and signs in the end-of-life phase

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

The most frequently reported symptom was decreased consciousness (87% of 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 cases and often coincided with decreased consciousness. Fifty-two percent of patients experienced progressive neurological deficits (motor deficit, coordination loss and/or aphasia). 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 EOL 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 EOL phase had more than one seizure in this phase. All patients with seizures received antiepileptic drugs. Among the patients who were on anticonvulsive drugs, there were no patients who never had epileptic seizures. In 40% of patients, incontinence was reported to occur before the patient was bed-ridden. Headache, progressive cognitive deficits (memory loss, personality changes, apathy, problems in executive functioning and understanding) and agitation/ confusion all were reported in one third of patients. Next to headache, 25% of patients reported bodily pain, often related to immobilization.

Table 2 Symptoms documented anytime in the EOL phase (n=55)

Symptoms	**Number of patients (percentage)**
Drowsiness/ progressive loss of consciousness	48 (87%)
Dysphagia	39 (71%)
Progressive focal neurological deficits (motor, dysphasia)	28 (51%)
Seizures	25 (45%)
Incontinence*	22 (40%)
Progressive cognitive deficits	18 (33%)
Headache	18 (33%)
Confusion	16 (29%)
Bodily pain	14 (25%)

*before the patient was confined to bed

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 patients experienced severe fatigue and 20% of patients suffered from nausea or vomiting. Dyspnoea was reported in nine patients (16%): in five cases this was most likely due to pneumonia; in one patient due to pulmonary embolism, while in the remaining three cases the cause of dyspnoea was unclear. Constipation, probably due to morphine use, was severe enough to be reported in five cases. In five patients, symptoms of anxiety and/or depression were mentioned. One patient had severe vertigo due to tumour infiltration in the 8th cranial nerve. Severe side-effects from steroid-use were reported in four cases: two patients suffered from steroid myopathy, one patient developed hyperglycaemia and one patient had a bowel perforation while using steroids. Overall, 44 (80%) patients used steroids in the end-of-life phase.

Table 3 Additionally reported symptoms (n=55)

Symptoms	Number of patients (percentage)
Fatigue	14 (25 %)
Nausea/vomiting	11 (20 %)
Dyspnoea	9 (16 %)
Constipation	5 (9 %)
Anxiety/depressive symptoms	5 (9 %)

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 (87%) of patients during the last week. This also holds true for dysphagia: the number increased from 5 patients (9%) to 39 (71%) patients. In the last week, 28% of all patients experienced at least one seizure.

Cause of death

In 40 patients (73%), the presumed cause of death was brain herniation due to tumour progression. For four other patients, the cause of death was directly tumour-related; these patients died following a seizure (three patients) or a haemorrhage in the tumour (one patient). For eight patients the cause of death was indirectly tumour-related; five patients died due to an infection (in two cases this concerned an aspiration pneumonia following a seizure), one died from bowel perforation while using steroids, one patient died from

pulmonary embolism, and another one suffered traumatic brain damage following an accident and died from urosepsis. In three patients, euthanasia was performed under strict conditions upon a voluntary and well-considered request.

Discussion

The most common 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%) respectively. 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 tumours. The more general EOL symptoms reported in extracranial cancer patients, such as fatigue, mood disturbances, nausea and constipation are probably underreported as these were not structurally asked for.[84, 85] 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 three earlier studies in patients dying from brain tumours, comparable prevalence rates of increased intracranial pressure symptoms (drowsiness, headaches), neurological deficits, seizures and cognitive deficits were reported.[21, 46, 48] The occurrence of dysphagia, however, differed amongst these studies. Dysphagia was reported in 70% of our cases, more or less comparable to the studies by Oberndorfer[46] and Pace[48], respectively. In contrast, Faithfull described a prevalence of only 10%.[21] 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 anti-epileptic drugs (AED) and/ or glucocorticoids (dexamethasone) in the last phase of life. About one third of patients suffered from seizures in the last week of life and these may be life-threatening as appeared to be the case in five patients. Since seizures are even a more prominent feature in the end-of-life phase than we had anticipated, continuation of AED's 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 EOL. 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.[65] In the hospital setting, intravenous infusion should be considered.

Urinary incontinence has not been described in former reports concerning the EOL phase of brain tumour patients. In our cohort, it was a relatively early and prominent sign (before the

patient was confined to bed) occurring in 41% of 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.[86] Urinary incontinence specifically in brain tumour patients can be caused by the tumour itself, such as may be the case in frontal tumours, or due to impaired cognition and consciousness. Other (reversible) causes may be urinary tract infection, hyperglycaemia and the use of sedatives. In a general cancer population, 29% of patients were incontinent for urine in the EOL phase.[86] Thus, the prevalence of incontinence appears to be relatively high in brain tumour patients.

Of further interest is to compare the prevalence of more 'general' EOL 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.[84, 85] 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%) as compared to patients with systemic cancer, where prevalence rates of 60-80% are reported[87]. Despite the fact that we are still unaware of the prevalence of general symptoms in glioma patients in the EOL phase, the disease specific symptoms are prominent. This indicates that the EOL phase of HGG patients cannot be compared simply with a general cancer population. Future studies prospectively exploring the EOL phase of HGG patients are mandatory in order to develop specific palliative care guidelines for these patients and their relatives.