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

Sizoo, E.M.

2013

document version
Publisher's PDF, also known as Version of record

Chapter 1.1 General introduction and outline

Introduction

Epidemiology of brain tumours

Primary brain tumours account for approximately 2% of all cancer types[1]. The large majority (85%) of all histologically confirmed primary brain tumours are gliomas[2]. In the Netherlands, the annual incidence is stable with approximately six per 100.000, corresponding with approximately 1000 new cases[2, 3]. Men are more often affected with a male/female ratio of 1.6[2]. Gliomas are classified according cell type and tumour grade using World Health Organization (WHO) criteria (table)[4]. Grade I and II gliomas are denominated low grade, grade III and IV high grade. Most gliomas (70-75%) are high-grade at time of diagnosis[2]. Increasingly, molecular features of glioma cells are important for diagnosis and prognosis[5, 6]. In this thesis, we focus on patients with high-grade glioma (HGG).

Table 1 WHO classification of gliomas

Grading	**Histological characteristics**		
Grade I	Pilocytic astrocytoma		
Grade II	Astrocytoma	Oligodendroglioma	Oligoastrocytoma
Grade III	Anaplastic astrocytoma	Anaplastic oligodendroglioma	Anaplastic oligoastrocytoma
Grade IV	Glioblastoma multiforme		

High-grade glioma

High-grade glioma (HGG) patients present with neurological or cognitive deficits related to the localization of the tumour (motor functioning, speech, personality), with epileptic seizures and/or with signs of increased intracranial pressure (e.g. headache, vomiting, visual disturbance, drowsiness)[4].

Until date, patients with HGG cannot be cured and median survival is poor: approximately 42 months for patients with anaplastic oligodendroglioma[7, 8], 19 months for patients with anaplastic astrocytoma[7] and 5 to 14 months for patients with glioblastoma multiforme[7, 9]. Age, WHO performance status and the need for dexamethasone before the start of treatment are independent prognostic factors[10].

At diagnosis, the main aim of treatment in HGG patients is to prolong life, but since the treatment of primary brain tumours is not curative, morbidity during the remaining survival time is of utmost importance for both the patient and his or her relatives. Thus, the potential

benefit of any treatment should be weighed against the impact on health-related quality of life (HRQOL) of that treatment.

Treatment in HGG patients consists of surgery, followed by radiotherapy, often in combination with chemotherapy. The goal of surgery is histological verification of the tumour and cytoreduction aimed at alleviation of symptoms. Moreover, several (non-randomized) studies suggest that more extensive resection increases overall survival[11]. Surgery may cause neurological deficits and focal cognitive deficits negatively affecting HRQoL short after the operation. However, these deficits are often transient and more extensive resection is associated with improved HRQoL over time[12]. Radiotherapy has long been acknowledged as effective in HGG treatment[13-16], without having a negative effect on HRQoL[16]. The role of chemotherapy was recognized more recently. Chemoradiation (radiotherapy with temozolomide chemotherapy) followed by six adjuvant cycles of chemotherapy has proven to increase median and two year survival in glioblastoma (grade IV) patients in comparison with radiotherapy alone[9]. The addition of concomitant and adjuvant temozolomide in glioblastoma patients in good condition at the start of treatment had no negative effect on health-related quality of life[17]. Whether there is an effect of this combined modality treatment in anaplastic astrocytoma (grade III) patients is currently evaluated in a randomized controlled trial. In patients with recurrent HGG, temozolomide chemotherapy improves time to progression, but not overall survival[18]. In patients with anaplastic oligodendoglioma, the addition of six cycles of procarbazine, lomustine and vincristine (PCV) chemotherapy to radiotherapy has proven to improve both progression free[19] as overall survival[8]. PCV chemotherapy has proven to have a negative effect on health-related quality of life (domains nausea, loss of appetite, drowsiness) during and shortly after treatment, but no long-term effects were reported[20].

During the disease process, the aim of treatment gradually shifts from mainly life-prolonging, to mainly maintaining HRQoL by means of supportive treatment. Towards the end of life (EOL), (nearly) all treatment will be supportive.

End-of-life phase

The EOL phase in HGG is generally referred to as the period when the patient starts to deteriorate and tumour-directed treatment is no longer possible. Furthermore, it is most often confined to the last three months of life. In this EOL phase, symptom burden is generally high and palliative care is of utmost importance[21]. The main goals of palliative care are to improve or maintain the HRQoL of the patients facing a life-threatening illness and their relatives by the prevention and relief of suffering[22] and to facilitate a dignified death[23]. EOL care is aimed at maintaining HRQoL as long as possible, but it also may require medical EOL decisions for the prevention and relief of suffering. In some instances these decisions may hasten death. EOL decisions include the withholding or withdrawing of life-prolonging

treatment, and the administration of drugs with a potential or certain life-shortening effect[24]. Examples of EOL decisions in HGG are withdrawal of chemotherapy or dexamethasone, withholding artificial food and fluid administration, non-admittance to the hospital or intensive care unit for treatment of infections, and palliative sedation. In the Netherlands 57% of deaths are preceded by an EOL decision[24]. In some European countries (The Netherlands, Belgium, Luxemburg and Switzerland), physician-assisted death such as euthanasia or physician-assisted suicide are allowed under strict conditions upon a well-considered request.

In the Netherlands, patients are often no longer seen by the clinical specialist after ending tumour directed treatment and referred to the GP or a palliative care setting (hospice, nursing home) for EOL care. Guidelines for EOL treatment in these patients are lacking and EOL treatment depends on the involved physicians' expert opinion. At the start of this research project in 2008, data about the EOL phase of HGG patients were scarce[21, 25, 26] and it was unknown how long patients live after ending tumour-directed treatment and what EOL care and treatment they receive.

Outline of this thesis

In this thesis, we will focus on the end-of-life phase of HGG patients: what do HGG patients experience, how is their quality of life, do they die with dignity and how is the quality of care and the EOL decision-making process?

We use various methods to answer our questions: *a systematic review* (chapter 1.2), a *chart review* (chapter 3.1) and a *retrospective cohort study* in which we collected data about the EOL phase of deceased HGG patients from physicians (chapter 2.2 and 4) and relatives (chapter 3.2, 4 and 5).

In Chapter 1.2 we review all literature published on the EOL phase of HGG patients before April 2012. Articles are reviewed on: symptoms and signs, HRQoL and quality of dying, caregiver burden, organization and location of palliative care, supportive treatment and EOL decision-making.

Chapter 2 focuses on symptoms and signs of patients in the EOL phase. In chapter 2.1 we report on our first pilot study to explore this EOL phase in which signs and symptoms are summarized. In chapter 2.2, we report on the prevalence and predictors of the development of seizures in the EOL phase. Moreover, we describe the use and (dis)continuation of anti-epileptic drugs in the last week of life according to physicians of a cohort HGG patients.

Chapter 3 focuses on quality of life in HGG patients. In chapter 3.1, we review the current knowledge on quality of life in HGG patients. In particular, we focus on the concept of health-related quality of life (HRQoL), available instruments to measure this HRQoL and the

influence of various treatment modalities on the patients' HRQoL. In chapter 3.2 we describe the development of a proxy-reported questionnaire to measure HRQoL in the EOL phase in retrospect. Furthermore, we describe HRQoL of HGG patients in the EOL phase.

Chapter 4 describes the EOL decision-making process in HGG patients. We assess in physicians and relatives of a cohort deceased HGG patients whether patients express EOL preferences, how often they discuss these preferences with their treating physician, until what time patients are competent to participate in decision-making and how often EOL decisions are taken.

In chapter 5 we address dying with dignity in HGG patients. Dying with dignity can be regarded as an overarching goal of palliative care. We assess how often HGG patients die with dignity as perceived by their relatives and what disease- and care factors correlate to dying with dignity in these patients.