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Antiepileptic and antitumor treatment in brain tumor patients: Impact on clinical and radiological treatment

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Introduction

INTRODUCTION

Gliomas are the most common primary malignant brain tumors in adults.[1] They arise from glial cells, the supportive tissue of the brain. Gliomas are categorized by histological tumor type, WHO tumor grade and molecular biomarkers based on the revised criteria of the World Health Organization (WHO).[2,3] Based on both genotype and phenotype, adult brain tumors are classified into astrocytoma, oligodendroglioma and glioblastoma including the molecular markers isocitrate-dehydrogenase (IDH) and combined loss of heterozygosity (LOH) on chromosomes 1p and 19q. IDH mutations and the presence of 1p/19q co-deletion are both correlated with an improved survival in glioma patients.

Treatment of low-grade gliomas (WHO grade II) consists, when technically possible, of an early maximal safe resection.[4,5] In high risk low-grade glioma patients with unfavorable prognostic factors, postsurgical adjuvant treatment is advised. Unfavorable prognostic factors include age > 40-50 years, residual tumor, astrocytic subtype, diameter tumor ≥ 4-6 cm, neurological deficits or refractory seizures.[6] The postsurgical adjuvant treatment of IDH mutant WHO grade II oligodendroglioma (1p/19q- codeleted) and astrocytoma consists of radiotherapy and, depending on molecular biomarkers, chemotherapy with procarbazine, lomustine and vincristine (PCV) or temozolomide.[7,8] Anaplastic (WHO grade III) IDH mutant astrocytoma and oligodendroglioma (1p/19q- codeleted) are treated with a maximal safe resection followed by radiotherapy and temozolomide respectively PCV chemotherapy.[9,10,11] IDH wildtype astrocytoma can have an aggressive disease course and is treated conform WHO grade IV glioblastoma patients. In glioblastoma the standard treatment is a maximal resection followed by chemoradiotherapy with temozolomide.[12,13]

Estimates of prognosis based on histopathologic diagnosis prior to the 2016 WHO classification ranged widely: patients with low-grade tumors had a median survival of 5-15 years and with high-grade glioma ranging from 14 months to 10 years.[6] Longer follow-up data of trials indicate that survival of 1p/19q- codeleted oligodendrogliomas treated with radiation and PCV is actually closer to 20 years for grade II tumors and 15 years for grade III tumors.[14,15] Patients with a WHO grade II IDH-mutant astrocytoma have a median survival of approximately 11 years.[16] The median survival of WHO grade III IDH mutant astrocytoma is 5-10 years compared to approximately 1.5 years for the IDH-wildtype subtype.[17,16] Glioblastoma patients have a median survival of 14 months, but when the IDH mutation is present median survival is approximately two times longer than that of IDH-wildtype tumors.[16]

Of the intracranial tumors brain metastases represent the most frequent tumors. The incidence of brain metastases has increased over time, as a result of advances in detection of brain metastases and longer survival of cancer patients. In adults, lung (36-64%) and breast (15-25%) tumors and melanoma (5-20%) are the most common sources of brain metastases.[18] The median survival of patients with brain metastases is about nine months,

highly depending on tumor type and patient characteristics.[19] Treatment may involve resection, radiotherapy, systemic treatment, or a combination of these.

To evaluate the effect of brain tumor and cancer therapies on patients functioning, well-being and clinical status, several clinical outcomes can be used like imaging, epilepsy, health-related quality of life (HRQOL), cognition and activities of daily living. Epilepsy may be a sign of cancer either as manifestation of a primary brain tumor or from systemic cancer that presents with brain metastases. It is of major importance to achieve seizure control, as uncontrolled seizures may negatively influence HRQOL.[20] Seizures in brain tumor patients are treated with antiepileptic drugs (AEDs) and are generally initiated after the occurrence of a single seizure attributable to the tumor.
This thesis encompasses questions from the neuro-oncologist's daily practice regarding how to evaluate and define clinical outcomes, particularly with respect to epilepsy and imaging. We aimed to improve patient's clinical outcomes by optimizing AED treatment and improving the radiological assessment after antitumor treatment. To optimize AED treatment, more knowledge about the effects of AED treatment on for example, seizure frequency, side effects, tumor progression and survival is necessary. Another aspect of optimizing AED treatment is the avoidance of overtreatment and side effects, by studying the necessity of continuation of AED treatment after long-term seizure freedom.
Furthermore, to better treat brain tumor patients, improvement of the radiological assessment of tumor progression and pseudoprogression needs more attention. Obtaining high levels of diagnostic certainty is relevant, as tumor progression and pseudoprogression ask for a different treatment approach. The interpretation of neuro-imaging, hampered by treatment-related radiological effects, is still a challenge in neuro-oncology care. Improvement of advanced magnetic resonance imaging (MRI) techniques is therefore of great importance.

Part I of this thesis focuses on the role of antiepileptic drugs on several clinical outcomes, like seizure frequency, tumor progression and survival. Furthermore, the withdrawal of antiepileptic drugs in relation to the radiological follow-up and tumor progression in glioma patients will be discussed.

Part II focuses on the impact of antitumor treatment on clinical and radiological outcomes, with a specific focus on the differentiation between tumor progression versus pseudoprogression, in glioma and brain metastases patients.

PART I: The role of antiepileptic treatment in relation to clinical and radiological outcome

Seizures in patients with brain tumors are symptomatic and localization-related seizures, manifesting as focal seizures with or without bilateral tonic-clonic seizures. In brain metastases, seizures occur as the presenting symptom in 18% of patients; another 15% develop seizures later in the course of the disease.[21–23] In systemic cancer most seizures are associated with brain or leptomeningeal metastases.[22,24]

In low-grade gliomas, the risk of seizures varies between 65-85% and represents the first clinical symptom in 70% of patients. During follow-up, 6-11% of initially seizure-free patients will develop epilepsy later on.[25] In high-grade glioma patients the incidence of seizures is approximately 30-62%, with two-third occurring at presentation and one third during the course of the disease.[25–28] Low-grade gliomas have a stronger predilection for epileptogenesis than high-grade gliomas. The mechanism is incompletely understood, but it may be explained by the slow growth rate associated with low grade lesions, which favors development of seizure-prone changes like de-afferentation and disconnection of cortical areas leading to denervation hypersensitivity.[29] This slower rate of tumor growth may also permit adaptive change of the surrounding brain tissue to occur, thereby diminishing the development of focal neurological deficits.[23]

There are several pathophysiological mechanisms causing epileptic seizures due to the effect of the tumor itself and changes in the extracellular milieu causing cortical hyperexcitability. Alterations in micro-environment induce swelling and cell damage together with deregulation of sodium and calcium influx with generation of electrical impulses.[23,30] Molecular genotypes also contribute to the development of seizures. One of the first identified genetic factors is a combined loss of heterozygosity (LOH) on chromosomes 1p and 19q. Patients without a deletion of 19q seem to be more likely to present with seizures than those with the deletion.[31] Another biologic marker that has been associated with seizures is the presence of a mutation of IDH1 and IDH2. The more prevalent IDH1 is present in 70–80% of low-grade gliomas.[32] Under normal circumstances, the IDH1 enzyme, which takes part in the Krebs citric acid cycle, catalyzes isocitrate to a-ketoglutarate. If mutated, 2-hydroxyglutarate will be formed instead. This product shows structural similarity to glutamate and may activate N-methyl-D-Aspartate (NMDA) receptors and foster epileptogenesis. In several series of patients with low-grade gliomas, the presence of IDH1/2 mutations showed a higher chance of presenting with seizures as the initial clinical symptom.[27,32] It has also been found that seizure reduction may serve as a surrogate marker for tumor response and precede the radiological response after treatment with temozolomide.[33] Seizures may therefore be considered a prognostic marker for survival in glioma patients.

Chapter 2 focuses on the effect of valproic acid on survival in glioblastoma patients and on the impact of antiepileptic treatment on seizure frequency. Survival of patients

with high-grade glioma treated with chemoradiation has been argued to be positively impacted by the use of valproic acid.[34,35] Potential specific anticancer properties of valproic acid include its action as histone-deacetylase enzyme inhibitor leading to epigenetic modulation. It promotes hyperacetylation of DNA-binding histone proteins together with decondensation of chromatin, and a demethylation process of tumor suppressor genes.[27] Aside from the aforementioned hyperacetylation and demethylation effects, valproic acid may also affect cell differentiation, promote apoptosis and autophagy and lead to growth arrest in cancer cells and the sensitization of malignant cells to radiotherapy and chemotherapy.[27,36] There is also evidence that it downregulates MGMT expression, especially in temozolomide-resistant cell lines.[36]

In chapter 3 we studied the impact of withdrawal of AEDs in glioma patients after long-term seizure freedom. Tumor directed treatments contribute to seizure control in glioma patients.[26,37] Some glioma patients who develop clinically and radiologically stable disease for years fortunately achieve sustained seizure freedom as well. In clinical practice most seizure free glioma patients nevertheless remain on treatment with AEDs. In patients experiencing long-term seizure freedom the question may rise whether AEDs should be continued lifelong or should be withdrawn to reduce side-effects and to eliminate the burden of taking daily AEDs. Other possible reasons to prefer AED withdrawal might be avoidance of teratogenic risk, reducing costs and decreasing the need for follow-up care concerning the epilepsy.[37] Currently, it is unknown if glioma patients and doctors are willing to withdraw AEDs after long-term seizure freedom. More importantly, no prospective data exist on the risk of seizure recurrence in glioma patients after AED withdrawal.

PART II: The impact of antitumor treatment on clinical and radiological outcome

The main radiological technique to analyze and monitor a brain tumor is standard MRI with T1-weighted sequence, T2 fluid-attenuated inversion recovery (FLAIR), gadolinium infusion and diffusion-weighted imaging. Although contrast enhancement is generally a strong surrogate for active brain tumor disease, there are restrictions as a result of different treatment related effects.[38] Changes in contrast-enhancement in posttreatment brain tumor imaging alone are non-specific for tumor response, as contrast-enhancement only reflects a disrupted blood-brain barrier (BBB). An increase of contrast-enhancement can be induced by tumor growth but also by several other processes, such as treatment-related inflammation, postsurgical changes, ischemia, radiation effects.[39] Pseudoprogression is a phenomenon of subacute imaging changes subsequent to radiochemotherapy suggestive of tumor progression, with or without clinical symptoms, which resolves spontaneously without further therapy. It is thought to be a treatment related local tissue reaction with inflammation, edema and disruption of the BBB. In 1979 pseudoprogression was first reported.[40,41] After the addition of temozolomide to radiotherapy for newly diagnosed

high-grade gliomas in 2005, pseudoprogression was more frequently encountered.[42] Pseudoprogression occurs predominantly within the first 3-4 months after completing treatment but it may occur from the first week up to 6 months after treatment.[43,44] It is most frequently seen in high-grade gliomas and brain metastases.[45] The incidence varies between 5.5% and 31% depending on the criteria used to define pseudoprogression.[39,46] It appears to be associated with favorable outcome and is more frequent in O6-methylguanine DNA methyltransferase (MGMT) promotor gene methylated GBM patients.[43] According to the literature the definition of pseudoprogression, treatment related effects and radionecrosis vary. Radionecrosis refers to the more severe reaction that occurs at a later stage after therapy and represents a more permanent tissue injury.[45] The distinction between pseudoprogression and tumor progression is critical for predicting prognosis and for future therapy. Changes related to pseudoprogression decrease over time, by definition, so the only way to discern tumor progression from treatment related effects is to perform follow-up examination. The difficulties in assessment of response to therapy have led to the revision of the criteria used to assess tumor response. Nowadays the Response Assessment in Neuro-Oncology (RANO) criteria in high-grade glioma for assessing response to therapy are used.[47,48] However, also with these criteria the conventional MRI is insufficient to reliably differentiate tumor progression from treatment related effects. Aside from brain biopsy being an invasive diagnostic, histopathology is in general not preferred in (asymptomatic) patients due to difficulties in interpreting post-radiotherapy biopsy samples, interobserver variations and inconclusive results due to heterogeneity of the tissue. Therefore, there is a great need for validated non-invasive techniques to assess tumor outcome. Of all advanced MRI techniques especially the quantitative dynamic susceptibility (DSC) perfusion MRI is used in daily clinical practice and shows promising results with high diagnostic accuracy.[49–51] Evidence for the widely used qualitative DSC perfusion technique is limited. Therefore, we studied the interobserver variability of the qualitative perfusion MRI in chapter 4.

With DSC perfusion MRI the angiogenesis can be assessed due to the T2 and T2* shortening effects of gadolinium-based contrast agents and involves rapid imaging to capture signal changes due to the first passage of intravenously administered contrast agent bolus.[45] One of the parameters derived from the DSC MRI is the relative cerebral blood volume (rCBV). It is thought that the rCBV is increased in tumors and decreased in treatment related effects such as pseudoprogression and radionecrosis. In chapter 5 and chapter 6, respectively, the value of perfusion MRI in high-grade glioma and patients with brain metastases is discussed.

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