Optimizing antiseizure medication treatment in glioma patients with epilepsy

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CHAPTER 10

Summary, general discussion, and future directions

Summary and general discussion

The aim of this thesis was to assess the efficacy (part 1) and tolerability (part 2) of antiseizure medications (ASMs) in glioma patients with epilepsy. In addition we aimed to get insight into the ASM prescription behavior and treatment policy in brain tumor-related epilepsy (BTRE [part 3]).

In **chapter 2** we showed that based on the available evidence levetiracetam, phenytoin, and pregabalin seemed to be most effective as ASM monotherapy in glioma patients, of which levetiracetam had the lowest treatment failure rate (at 12 months: 24% for levetiracetam, 34% for phenytoin, and 41% for pregabalin). This conclusion was based on the results of a total of k=66 studies that have been conducted up to July 2020 and evaluating the efficacy of ASMs in glioma patients with epilepsy. The number of studies conducted regarding this topic has increased immensely over the past decades. No studies have been conducted prior to the '90s and only k=3 during the '90s. In the subsequent decade, during 2001-2010, a total of k=21 studies were conducted, while this doubled during 2011-2020 with k=42 studies. The exponential growth of publications assessing ASM efficacy in BTRE seems to follow the same trend as is seen in the general academic publishing world with an exponential rising of publications each decade.[1] Despite all these publications, only two of these k=66 studies were randomized controlled trials (RCTs), although underpowered. In the observational studies that were identified, methodological issues (e.g., taking into account potential confounders and presence of death as competing risk) were insufficiently taken care of, hampering reliable interpretation of results. It was remarkable that only k=2 studies were conducted evaluating the efficacy of lamotrigine, despite lamotrigine being a frequently prescribed ASM in glioma patients. Key message from our systematic review is the lack of high-quality comparative ASM efficacy studies in glioma patients. Apart from RCTs, observational studies can be of high value to inform clinical practice for glioma patients with epilepsy, provided that they are well conducted and adjusted adequately for confounders.

In **chapter 3** we demonstrated the superiority of first-line levetiracetam compared to valproic acid in terms of efficacy. In the decade of 2001-2010 valproic acid was the ASM of choice in glioma patients, at least in the Netherlands. In the beginning of the subsequent decade levetiracetam began to replace valproic acid as ASM of choice in glioma patients, although no (high quality) comparative ASM efficacy studies had been published. The commonly held perception among neuro-oncology professionals was that levetiracetam had a better tolerability compared to valproic acid, while efficacy was probably similar. A lack of drug-drug interactions contributed to the popularity of levetiracetam among neuro-oncology professionals as first-line agent. Although levetiracetam demonstrated to be superior compared to valproic acid, the underlying reason is different than previously thought. We showed that tolerability seemed to be similar between the first- and second-

generation ASM, but levetiracetam showed favorable efficacy. The latter was established by showing both a significantly longer time to treatment failure due to uncontrolled seizures and time to recurrent seizure for levetiracetam. Retrospective observational studies, including our study, are susceptible to bias, but previous studies evaluating the efficacy of ASMs in glioma patients took few measures to reduce this bias. In our study we matched the two ASM groups on measured potential confounders (e.g., antitumor treatment), which resulted in mimicking an RCT design as far as possible and thus resulting in more reliable results. Importantly, our study was also the first comparative ASM efficacy study in glioma patients estimating outcomes with a competing risk model, taking into account death as competing event. As a result effectiveness and efficacy outcomes could be estimated more reliably. Due to the dismal prognosis of several subtypes of glioma a substantial proportion of patients die before the event of interest (e.g., treatment failure) has occurred. Censoring patients who have died instead of accounting for them in a competing risks model potentially leads to overestimation of the event of interest. Therefore, effectiveness and efficacy outcomes could be more reliably estimated with a competing risks model. Arguably, time to treatment failure is the most appropriate primary outcome in BTRE patients, especially in observational studies. It encompasses both ASM efficacy and tolerability and has therefore great clinical utility. A change in ASM treatment regimen and the reason for this change is well recorded in the medical charts and thus can be obtained reliably. This would be less true for the exact number of seizures as would be necessary with the regularly used ≥50% seizure reduction outcome. Number of seizures is difficult to assess both retrospectively as prospectively in glioma patients for a variety of reasons, including neurocognitive deficits, behavioral problems, and recall bias.[2] Preferably, time to treatment failure is accompanied by a seizure severity scale in prospective studies.

In **chapter 4** we demonstrated the superiority of first-line levetiracetam compared to enzyme-inducing ASMs (EIASMs) in glioma patients. Efficacy was similar between both ASM groups, but EIASMs had a significantly higher risk of treatment failure due to adverse effects. Although EIASMs are generally discouraged by guidelines for use in glioma patients, they were found to be frequently prescribed. Our results support the statement to avoid prescribing EIASMs in the glioma patient population. Besides the high number of intolerable adverse effects, the drug-drug interactions with frequently prescribed medications in glioma patients (e.g., dexamethasone and lomustine) make EIASMs less than optimal candidates in the treatment arsenal of the neuro-oncology professional. Currently, EIASMs seem less and less prescribed in the glioma population, partly because of the high number of alternative available ASMs with better pharmacokinetic profiles.[3, 4] As a consequence it will be increasingly difficult in the future to compare (first-line) monotherapy levetiracetam versus EIASMs, making this study even more clinically relevant. The low number of patients in each specific EIASM group prevented a comparison of levetiracetam with specific EIASMs. There was quite a difference in treatment failure

between the specific EIASMs, ranging from 53% (oxcarbazepine) to 84% (phenytoin), but all treatment failure rates were substantially higher than levetiracetam. Based on our results there does not seem to be a place left for EIASMs in the daily treatment of seizures in glioma patients.

In **chapter 5** superior efficacy, but similar tolerability, of the dual therapy combination levetiracetam with valproic acid was shown compared to other dual therapy combinations with either levetiracetam or valproic acid. This suggests a beneficial synergistic effect when levetiracetam is combined with valproic acid in glioma patients and supports the proposed hypothesis of rational polytherapy as both ASMs have different mechanisms of action. Efficacy of fixed dual therapy combinations are notoriously difficult to evaluate given the large number of potential ASM dual therapy combinations. The high number of glioma patients on the fixed dual therapy combination levetiracetam with valproic acid (n=236 patients from an original cohort including n=1435 glioma patients treated with first-line monotherapy levetiracetam or valproic acid) is unique and to our knowledge no such study has been conducted in (non-)BTRE. Based on our results, evaluation of the efficacy/effectiveness of this dual therapy combination in non-BTRE deserves (more) attention. Simultaneously, the high number of different dual therapy combinations in the comparison group is an important limitation and different drug-drug interactions between ASMs (e.g., valproic acid and carbamazepine) or with other prescribed medications might have (negatively) influenced seizure outcomes. When combining two ASMs this can result in either: 1) synergy (i.e., supra-additivity, efficacy of the combination is greater than the expected efficacies of the individual ASMs separately); additivity (i.e., efficacy of the combination is equal to the sum of the individual ASMs efficacies); and antagonism (i.e., infra-additivity, efficacy is smaller than the sum of individual drug efficacies). Clearly, synergy with regard to efficacy is what the clinician intends to achieve when prescribing ASM dual therapy combinations. Alternative ASM combinations with levetiracetam resulting in synergy in mainly non-BTRE patients include lamotrigine and lacosamide.[5]

In **chapter 6** it appeared that the triple therapy combination of levetiracetam combined with valproic acid and clobazam has similar efficacy and tolerability compared to other ASM triple therapy combinations in glioma patients with refractory epilepsy. One month after triple therapy initiation the majority of patients in both ASM groups experienced a recurrent seizure and at 12 months almost half of triple therapy patients showed treatment failure for any reason. Finding the right dual therapy is already a challenge, thus finding the right triple therapy is even more challenging. With each additional ASM there is an increased likelihood of pharmacokinetic and pharmacodynamic ASM interactions, complicating treatment decisions. Furthermore, a smaller patient population receives triple therapy than dual therapy and a larger number of combinations can be made with three compared to two ASMs. A total of n=90 glioma patients (from the original cohort including n=1435 glioma patients) were included in our study, which is a reasonable large number

for this selective patient population, but too low to adjust adequately for confounders (e.g., systemic therapy). In order to determine the preferred triple therapy combination in glioma patients, with regard to efficacy and tolerability, a large collaborative international multicenter study would be needed in which it is possible to include a sufficient number of patients. Given the similar efficacy and tolerability across the ASM triple therapy combinations, other ASM characteristics (e.g., ease of administration) may play an important role in the choice of ASM. Due to the retrospective design of our study no additional outcomes were assessed, such as health-related quality of life (HRQoL) or seizure severity, which might contribute to determining the favorable treatment choice for an individual patient. However, at this stage with the currently available evidence, comparative efficacy ASM mono- and dual therapy studies have higher priority, given the lack of well-conducted ASM mono- and dual therapy studies and a smaller number of glioma patients with epilepsy will need ASM triple therapy.

In **chapter 7** (add-on) lacosamide was compared with (add-on) lamotrigine and the two ASMs showed a similar effectiveness in diffuse glioma patients, as both efficacy and tolerability were comparable. Despite the lack of studies evaluating the efficacy of lamotrigine as demonstrated in **chapter 2**, lamotrigine is a frequently prescribed ASM in the glioma population, probably stemming from the evidence of high efficacy in non-BTRE focal onset seizures. While valproic acid seems the preferred dual therapy combination with levetiracetam as shown in **chapter 5**, there might be reasonable grounds for not prescribing valproic acid as second-line agent. For example, the patient is a woman of childbearing age, has a hepatic disorder or is at high risk of thrombocytopenia. Both lacosamide and lamotrigine are potential effective alternative ASMs, which can be combined well with levetiracetam. Indeed we found that both agents were the most frequent combination in our study. As discussed above, when both tolerability and efficacy are comparable between ASMs other ASM characteristics become increasingly important and might play a decisive role in the treatment decision. A disadvantage of lamotrigine compared to lacosamide is the need for a more careful titration before an effective dosage is reached, making lacosamide the preferred choice if rapid initiation is desired. On the contrary, an advantage of lamotrigine is that it has mood-stabilizing properties, making it a rational choice in glioma patients with epilepsy who have a comorbid mood disorder. The role of the neuro(-onco)logist in the management of epilepsy is all the more important in case there is not clearly a preferred ASM, because numerous different factors have to be weighed in the decision.

In **chapter 8** we assessed the effect of ASMs on self-reported depression, anxiety, and cognitive complaints, frequently occurring neuropsychiatric symptoms in glioma patients. Our results indicated that ASM use did not seem to be independently associated with the concurrent presence of these neuropsychiatric symptoms. Neither was a difference found between levetiracetam and valproic acid on the outcomes. Alternative factors, such as a

history of mood disorder treatment and other prescribed medications than ASMs with a risk for depressive adverse effects seemed to play a more important role in the development of depression, anxiety, and cognitive complaints. Medical history of a patient cannot be changed, but alternative medications might be available for glioma patients with depression using medications with a risk for depressive adverse effects. Important to note is the lack of sufficient statistical power, which might have played a role in the absence of statistically significant differences between different ASM types. Levetiracetam is known for its psychiatric adverse effects in non-BTRE patients.[6] Therefore, the lack of a difference in anxiety and depression between levetiracetam and valproic acid was surprising and suggest that our results need to be interpreted with caution. However, we do think given the better efficacy of monotherapy levetiracetam compared to valproic acid and the lack of a difference in neuropsychiatric symptoms, the treating physician needs compelling reasons not to prescribe levetiracetam as first-line ASM in glioma patients. In **chapter 3** treatment failure due to adverse effects was similar between first-line monotherapy levetiracetam and valproic acid. However, 46% of the intolerable adverse effects were of psychiatric origin in levetiracetam and only 3% in valproic acid, a tremendous difference. In **chapter 5** levetiracetam was combined with valproic acid and this led to 17% of the intolerable adverse effects of psychiatric origin, suggesting possible antagonism of psychiatric adverse effects when combining levetiracetam with valproic acid. The latter may have ameliorated psychiatric adverse effects in glioma patients caused by levetiracetam. The total ASM load should be considered by the treating physician as a higher total ASM load seems to increase the risk of adverse effects in non-BTRE patients.[7] Nevertheless, we did not demonstrate this in this thesis as ASM dual therapy (at 12 months 11-13%) had comparable treatment failure due to adverse effects rates as monotherapy (at 12 months 14-15%) in glioma patients. This finding supports the general preference for starting ASM dual therapy instead of a subsequent trial with ASM monotherapy after failure of first-line monotherapy in glioma patients.

In **chapter 9** ASM prescription preferences and treatment policy in patients with BTRE among European neuro-oncology healthcare professionals who treat these patients was surveyed. Our results showed that levetiracetam is considered the first choice with the perceived highest efficacy and least adverse effects compared to all other ASMs in BTRE patients. Commonly chosen alternatives if patients would show treatment failure due to uncontrolled seizures or adverse effects on levetiracetam included lacosamide, lamotrigine, and valproic acid. Notable differences of preference between countries were observed probably reflecting differing expert opinion per country. The majority of neuro-oncology healthcare professionals from Austria (100%), France (52%), Italy (56%), and Spain (55%) regarded lacosamide as equivalent first choice ASM, while only in the Netherlands a majority of healthcare professionals (75%) regarded valproic acid as equivalent first choice ASM. Potential adverse effects and interactions with antitumor treatments were the most

important factors for neuro-oncology professionals to choose a specific ASM. This corresponded to the fact that EIASMs are rarely favored as first choice or as equivalent alternative ASM. Given our results in **chapter 4** we think these outcomes are in good agreement with one another. The underlying reasons why levetiracetam is considered first choice and lacosamide, lamotrigine, and valproic acid as equivalent alternatives cannot be derived from the survey. It could be based on RCTs in non-BTRE, mainly observational studies in BTRE, clinical experience or other sources of information. With regard to ASM prescription preference, the results from **chapter 2 to 8** are in line with the results found in the survey as well as with the European Association of Neuro-Oncology (EANO) guidelines. This implies that the guidelines seem to be followed by the vast majority of European neuro-oncology professionals treating glioma patients with epilepsy, suggesting that patients are treated as optimal as possible.

Combining the evidence from **chapters 2 to 9**, levetiracetam seems the first-line ASM of choice in glioma patients in case the patient does not have any contraindications. If seizures are inadequately under control on monotherapy levetiracetam the combination with valproic acid is preferred. Appropriate alternative ASMs as add-on or ASM monotherapy are lacosamide and lamotrigine. No particular ASM triple therapy combination is favored, but clobazam seems a reasonable add-on ASM, which is easy to administer. Alternative ASM characteristics may play an important role in the choice of an ASM when initiating triple therapy given the absence of favorable triple therapy combination in efficacy or tolerability.

Future directions

The first part of this thesis focused on the efficacy of ASMs in glioma patients and showed that first-line monotherapy levetiracetam seems the preferred choice. If an add-on ASM is necessary due to inadequate seizure control, the combination of levetiracetam with valproic acid seems to give the highest efficacy, with lacosamide and lamotrigine as good alternative ASMs. However, all of these studies had a retrospective observational design and could potentially be affected by bias due to unknown confounders for which could not be adjusted for. In addition, the patient perspective on the impact of ASMs on their functioning and well-being is lacking, as no patient-reported outcomes could be assessed in these retrospective studies. Therefore, the results of the currently ongoing STING trial (first-line levetiracetam versus valproic acid in glioma patients with epilepsy, ClinicalTrials.gov Identifier: NCT030480) are much awaited as patient-reported outcomes (e.g., health-related quality of life) are measured besides seizure outcomes. Then it will be clear if the results found in **chapter 3** will be confirmed in an RCT design.

To our surprise only k=2 observational studies were found in **chapter 2** evaluating the

efficacy of lamotrigine in glioma patients, despite the ILAE establishing lamotrigine as class A evidence in their 2013 guideline for focal onset seizures in both adults and elderly.[8] In the SANAD II trial in patients with non-BTRE it was demonstrated that both first-line levetiracetam and valproic acid were found to be inferior compared to lamotrigine with regard to effectiveness.[9, 10] These results make it almost mandatory conducting a trial comparing first-line monotherapy levetiracetam (or valproic acid if valproic acid proves to be superior in the STING trial) with lamotrigine in glioma patients. Next, a trial in ASM dual therapy would be warranted to validate our results. The comparison between ASM dual therapy combination levetiracetam with valproic acid and the dual therapy combinations levetiracetam with lamotrigine or lacosamide would have priority as these seem effective rational alternative dual therapy combinations and are frequently prescribed. In addition, perampanel deserves a mention. Perampanel would be a rational dual therapy combination with levetircetam, given its mechanism of action is inhibition of glutamate, has shown good efficacy and tolerability in glioma patients, and has shown antitumor effects.[11, 12] International collaboration would be needed in order to have a large enough sample size and sufficient statistical power to detect clinically relevant differences in seizure outcomes. Tolerability of ASMs should be evaluated together with efficacy in these proposed studies in a manner as was done in **chapter 3 to 7** with ASM time to treatment failure as primary outcome. Based on both outcomes or combined as effectiveness it would follow what the preferred ASM (combination) is. Since the reign of Julius Ceasar and the life of Vincent van Gogh much has changed in the treatment of epilepsy. Indeed, a large number of ASMs have been developed improving the lives of millions of epilepsy patients around the world. Although there is still a long way to go, this thesis hopefully provides more direction for the neuro-oncology clinician in choosing the most appropriate ASM treatment strategy for his or her glioma patients.

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