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SHORT COMMUNICATION

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Treatment of glioblastoma in Greenlandic patients

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ABSTRACT

Glioblastoma (GBM), WHO grade IV, is the most common primary malignant brain tumour among adults with a devastating overall survival of 14–22 months. Standard treatment of GBM includes maximum safe resection, radiotherapy plus concomitant and adjuvant temozolomide (TMZ), given over a period of approximately 9 months. Treatment and follow-up for Greenlandic patients with GBM are managed at Rigshospitalet (RH), Copenhagen. Greenlandic GBM patients, therefore, travel back and forth to RH, often unaccompanied, and challenged by cognitive failure or other symptoms from their disease and/or treatment. Few Greenlandic patients are diagnosed with GBM annually, but considering the poor prognosis and short remaining lifespan, it would be preferable to limit their travels. TMZ is administrated as capsules. Health personnel at Queen Ingrid's Hospital (DIH), Nuuk, are trained in treating other oncological diseases and handling side effects. Hence, it could be investigated whether administration of adjuvant TMZ at DIH could be feasible after personnel education as well as economic consideration and compensation, in close collaboration with neuro oncologists at RH. In this article, we describe the Greenlandic cancer treatment, and the typical workflow from diagnosis of GBM to treatment to progression.

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Introduction

Cancer treatment in Greenland

Greenland is part of the Arctic area and is the world´s largest island with an area of 2.166.000 square kilometres. The population number is 56.000, with the majority of 19.000 living in the capital of Nuuk. In the two second and third largest cities, Sisimiut and Ilulissat, the population is 5.600 and 4.700, respectively. Greenland is divided into four municipalities, and cities are mainly situated on the west coast. There are no roads between cities and intercity travel is by boat, helicopter, or airplane. There are two cities on the east coast, Tasiilaq and Ittoqqortoormiit, and travel to Nuuk from these cities can take several days. Weather conditions can also cause severe delay in patient transportation. Therefore, transportation and housing of patients require highly specialised logistic competencies. The national hospital of Greenland is in Nuuk, the Queen Ingrids Hospital (DIH) and the cities on the coast have different health care facilities serviced by travelling consulting medical doctors. Sometimes, no medical doctors nor nurses are available. Accessibility to analyses and radiological examinations vary. Cancer treatment was taken home to Greenland in 2004 and is only given at DIH where a team of dedicated medical doctors and nurses treat lung cancer, breast cancer and colorectal cancer. Treatments include chemotherapy, targeted treatment, anti-hormonal treatment and since 2023, also immunotherapy. With the current setup, experimental treatment is not an option for Greenlandic patients, unless they move to Denmark. There is a well-established collaboration with Department of Oncology at Rigshospitalet (RH), Copenhagen, Denmark where a team of medical doctors have the daily contact to DIH concerning the Greenlandic patients. This is also where majority of patients with other cancer diagnoses than the above mentioned receive medical oncological treatment. If radiotherapy is needed, the patients go to RH, as radiotherapy is not an option in Greenland. Due to the large distances, Greenland uses telemedicine to a high extent. The Covid period further developed this progress and today, consultation and treatment of patients on the coast can be done through virtual consultations. This enables a more favourable use of resources as medical specialists do not need to travel up and down the coast and use travel time to the same extent as before telemedicine. This also enables the possibility of getting medical specialists treating more rare diseases to

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consult patients, e.g. in haematology [1], and in the future, maybe in neurooncology.

Glioblastoma

Glioblastoma (GBM), WHO grade IV, is the most common malignant brain tumour among adults worldwide, and approximately 300 Danes are diagnosed with the disease every year [2,3]. GBM is an aggressive and invasive brain tumour with infiltrating tumour cells spreading far from the site of the primary tumour [4]. Histologically, the tumour is characterised by diffusely infiltrating astrocytic tumour cells, microvascular proliferations and/or palisading necrosis [3]. Symptoms at debut may include convulsions, focal neurological deficits, continuous headache, changed mental state, and is often combined with symptoms of increased intracranial pressure [3]. Standard therapy for GBM comprises maximal safe resection followed by radiotherapy plus concomitant and adjuvant Temozolomide (TMZ) [5]. Radiotherapy is given 5 days a week (Monday-Friday) for a period of 6 weeks, at a dose of 2 Gy per fraction, for a total dose of 60 Gy. Concomitant TMZ is administrated as capsules, with a dose of 75 mg per square metre per day from the first to the last day of irradiation. After a 4-weeks break, patients receive up to 6 cycles of adjuvant TMZ with 150–200 mg per square metre per day for 5 days followed by a 23-days break [5]. Despite intensive treatment, GBM is incurable. Recurrence is inevitable with a median time to recurrence of approximately 7 months and a median life expectancy of 14–22 months, depending on prognostic and predictive factors [5–7]. The prognostic and predictive role of O6-methylguanine-DNA methyltransferase (MGMT)-methylation was identified in 2005 and guides treatment decisions with TMZ [8]. To this day, MGMT promotor methylation, resulting in lack of MGMT-mediated DNA-repair is the only known predictive factor for treatment response to TMZ. Several phase III studies have shown that the presence of MGMT promotor methylation in GBM tumours among patients treated with TMZ increases the median survival with up to 50%, thereby reaching a median overall survival of approximately 22–24 months and few surviving more than 5 years [5,8,9]. Prognostic factors associated with poor prognosis include increasing age, poor performance status (PS), the use of corticosteroids, multifocal tumour and low degree of surgical resection of the tumour [10]. Few cases arise as a result of hereditary genetic syndromes, germline mutations and/or risk factors such as single nucleotide polymorphisms or previously irradiation of the brain. For the majority, the cause of the disease remains unknown [3,11]. New studies suggest that the malignant transformation of neural stem cells to GBM stem cells might contribute to the development of GBM, treatment resistance and recurrence [12]. Further studies are needed to understand the mechanisms of tumorigenesis and elucidate whether GBM stem cells may be a target for future treatment. The role of molecular testing is now part of the standard treatment setup in many centres worldwide, including at RH [13]. Several international studies are running using a targeted approach in umbrella and basket designs [14,15] and new studies are being designed with incorporation of the genomic results, including experimental treatment in the first line setting [16].

Diagnosis and classification

Diagnosis and classification of brain tumours have changed throughout the last decades in accordance with the growing availability and implementation of molecular testing. Historically, the classification of GBM has been based on the histologically characteristics that could be identified by light microscopy including presumed cell line (e.g. astrocyte, oligodendrocyte etc.) and the grade of cellular differentiation [17]. The improved understanding of how molecular mutations may affect tumorigenesis and clinical presentation of brain tumours resulted in WHO integrating the molecular parameters into the 2016 *WHO Classification of Tumors of the Central Nervous System* [17]. With this classification, the molecular parameters determine the diagnosis when the histological pattern is indeterminate. Until recently, GBM has been divided into GBM *isocitrate dehydrogenase (IDH)*-wildtype, GBM *IDH*-mutant and GBM not otherwise specified (NOS). *IDH* exists in three different subtypes (*IDH1*, *IDH2* and *IDH3*), all of whom are intracellular enzymes of importance to energy production and cell growth. *IDH*-mutations within tumour cells decrease the normal *IDH*-activity resulting in decelerated tumour growth when compared to *IDH*-wildtype tumours [18,19]. Subsequently, *IDH*-mutations are associated with better prognosis [18,20]. In the latest *WHO Classification of Central Nervous System Tumours* from 2021, all diffuse astrocytic tumours with *IDH*-mutations are considered a distinct type, Astrocytoma *IDH*-mutant, and are then graded as CNS WHO grade 2, 3 or 4, thereby eliminating the term Glioblastoma *IDH*-mutant [21]. When grading *IDH*-wildtype diffuse astrocytic tumours, several studies show that the presence of one or more of three specific genetic parameters are sufficient to assign the highest WHO grade. These genetic parameters include *Telomerase Reverse Transcriptase (TERT)* promotor mutation, *Epidermal Growth Factor Receptor (EGFR)* gene amplification or combined gain of chromosome 7 and loss of chromosome 10 (+7/-10) [22,23]. As a result of these studies, WHO recommend that the diagnose GBM

IDH-wildtype, WHO grade 4, is used for *IDH*-wildtype diffuse and astrocytic tumours among adults with microvascular proliferation, necrosis, *TERT* promotor mutation, *EGFR* gene amplification or + 7/-10 chromosome copy number variations [21].

Recurrence and follow-up

GBM recurrence is inevitable and the treatment strategies at time of recurrence depends on the localisation and extension of the tumour, the molecular characteristics, the patient's physical state and preferences [24]. Re-resection is recommended when tumour localisation and the patient's state allow operation. If possible, the patient is recommended to be included in clinical trials due to the sparse effect of the current available second line treatments. Currently, there is no standard second line treatment, but in Denmark we use the chemotherapy Lomustine (CCNU). Since 2016 the Department of Oncology at RH, Denmark, has offered patients with GBM a thorough genomic sequencing of their tumour tissue in attempt to identify patients eligible for experimental treatment at time of recurrence [13]. For patients with GBM, treatment and follow-up are based on an interdisciplinary effort, that demand close cooperation between the departments of Neurology, Neurosurgery and Oncology. In parallel with the oncological therapy, Danish patients with primary brain tumours are guaranteed neurological follow-up at a neurology department, including treatment for the disease-specific epilepsy- and pain-management, neurorehabilitation and -palliation as well as psychosocial support [25]. If the patient during or after the oncological therapy develops neurologic symptoms that require hospitalisation, such as epileptic seizures, increasing intracranial pressure or onset of focal neurologic deficits, the patient is admitted to the local neurology department. Only patients with symptoms caused by the oncological therapy, for example febrile neutropenia, are admitted and treated at the oncology department.

GBM in Greenlandic patients

Greenlandic patients with diseases requiring highly specialised treatments that are not available in Greenland, including treatment for GBM, are referred to treatment in Denmark [26]. The incidence of primary brain- and CNS tumours in Greenland is 5 per year [27] and the number of patients treated for GBM at RH annually is approximately 1–2. Greenlandic patients with newly onset of neurologic symptoms consistent with a brain tumour are initially examined with CT- or MRI-scan at DIH in Nuuk, Greenland. If the scan shows a brain tumour, the patient is referred to the Department of Neurosurgery at RH. Patients in need of acute intervention can be transferred by plane in agreement with the neurosurgeon at RH, and the transfer is planned in cooperation with the Patient Coordination in Nuuk. All subacute and elective referrals to RH are sent via the Patient Coordination in Nuuk and the Administration at the Greenlandic Patient House (GPH) in Copenhagen. GPH manages all information to the Greenlandic patient, e.g. scheduled appointments, booking of plane tickets, transport from the airport and accommodation and more [28]. At the time of departure, the patient is unaware of the exact duration of the stay in Denmark, and if the patient wishes a relative to accompany him or her, they can apply for economic support at the local municipality. After arriving to RH, the patient will be examined by the neurosurgeon, that will schedule for surgery or stereotactic biopsy to ensure diagnosis. If the patient is diagnosed with GBM, the patient is referred to the Department of Oncology at RH for evaluation for standard oncological treatment, following Danish national guidelines (www.DNOG.dk). First choice of treatment for patients in good PS is concomitant chemo/radiation and adjuvant chemotherapy. The oncologist informs the patient about the treatment, that is initiated approximately 4 weeks postoperatively [29]. Radiation and concomitant chemotherapy is given over a period of 6 weeks, followed by a 4-week break, after which the course of adjuvant chemotherapy begins. It is possible for the patient to travel back to Greenland in the 4-week break from treatment [30]. Adjuvant TMZ is given in cycles every 28th day. Prior to dispensation of TMZ capsules, blood samples are analysed, and the patient is examined by the oncologist. Between cycles, the patient can travel back to Greenland. Approximately three months after the last dose of radiation, the first evaluation with MRI is conducted, and in cases with regression or stable disease, adjuvant TMZ is continued to a maximum of six cycles. The patient is followed with MRI every third month during and after adjuvant TMZ (Figure 1). Due to the lower quality of the 0.4 tesla MRI-scanner at DIH, evaluation MRIs are performed with the 1.5 or 3.0 Tesla MRI-scanner at RH and described by in-house neuroradiologists according to the Response Assessment in Neuro Oncology (RANO) criteria [31,32]. A 1.5 tesla MRI is planned for DIH in the near future. In the follow-up period, the patient can be scanned with the MRI at DIH. At relapse, the patient will be evaluated for relapse surgery and/or second line chemotherapy.

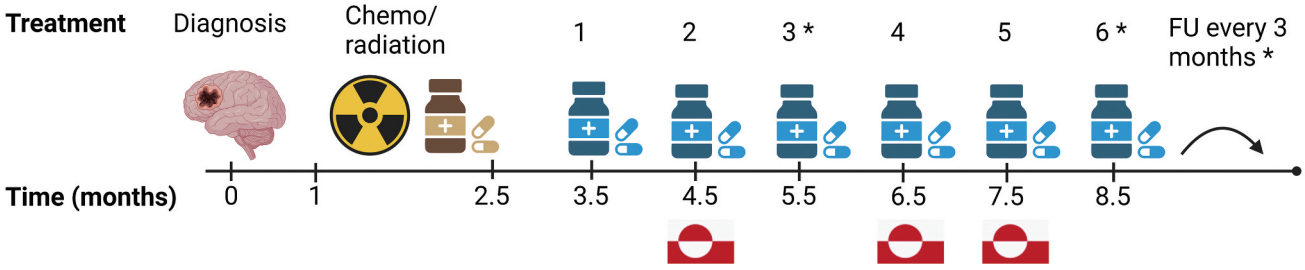

Figure 1. Illustration of a disease course of glioblastoma (GBM) from diagnosis through surgery to oncological treatment and follow-up (FU). Greenlandic flags illustrate cycles with adjuvant chemotherapy that may be administered at the Queen Ingrids Hospital (DIH), Nuuk and * illustrates when MRIs are performed. MRIs need to be performed at Rigshospitalet (RH), Copenhagen due to a higher tesla MRI at RH and are described by in-house neuro radiologists.

Discussion

Oncological treatment in small and/or remote communities can be challenged by many factors, e.g. low incidence and hence, lack of experience in the diseases, limited access to advanced treatments, long distance to the treating hospital and more. Therefore, we find it important for such communities to have a close collaboration with larger hospitals. It is also important to have a few dedicated medical doctors at the larger site that know the local conditions. DIH and RH have developed this collaboration, and the collaboration includes other medical and surgical specialities than oncology. Department of Oncology, RH also have a well-established collaboration with the Faroe Islands, where Danish oncologists travel to every two weeks [33]. Even though Greenland and the Faroe Islands have a similar population number, the distances in the Faroe Islands are not as far as in Greenland, making oncological treatment there less complex. The long distances in Greenland can influence treatment decisions, e.g. it is not feasible to prescribe a cancer treatment that requires intravenous injection weekly if you live in Tasiilaq, unless the patient wishes to stay in Nuuk for the whole treatment period. These treatment decisions are discussed with patients on a regular basis. Iceland has a similar collaboration with another hospital in Denmark and similar for all sites is the collaboration with a larger site, dedicated health care professionals locally and at the larger site and thereby the possibility to discuss patients, have access to new knowledge and treatments. GBM is a rare disease and despite improvements in genetic testing and greater understanding of the molecular pathogenesis of GBM, we have yet to experience groundbreaking advances in treatment strategy and survival. Therefore, the treatment of GBM is highly specialised and centralised. It is situated in only four centres in Denmark and the multimodal treatment of Greenlandic GBM patients is focused at RH, Copenhagen. 1–2 Greenlandic patients are treated for GBM at RH each year and with a median time to recurrence of seven months and median life expectancy of 16–24 months, we expect that the prevalence of GBM in Greenland will be approximately 4–6 patients. Due to small numbers, we do not report PFS and OS for Greenlandic GBM patients as one group. But as treatment follows Danish national guidelines, it is expected that PFS and OS is similar to the Danish survival data. During treatment and follow-up, Greenlandic patients are subjected to several travels back and forth to RH by plane. Some patients might live in remote places with several connecting flights or long journeys by boat and often travel without accompanying relatives to medical appointments, including when informed of results from evaluation MRIs. This can be particularly challenging as one of many symptoms in GBM is cognitive failure. Adjuvant TMZ is given over a period of 6 months, and the patient travels to Denmark every 28th day for blood sampling and medical appointments. As opposed to Danish patients with GBM, patients from Greenland are not guaranteed neurologic follow-up whilst in Denmark. It is possible for the patients to receive proper neurologic follow-up at DIH in Nuuk, but it can be complicated by lack of continuity when the patient is receiving treatment in Denmark. Given the low incidence of GBM in Greenland and since the TMZ is given as capsules, it might be possible to manage the adjuvant TMZ treatment at DIH, Nuuk, with close cooperation between the treating physician at DIH and the neuro oncologists at RH. This could be made possible by video consultations with a dedicated neuro oncologist on a regular basis and each time a Greenlandic patient is scheduled for adjuvant TMZ at DIH. Local adjuvant chemotherapy in the cycles not requiring MRI would spare the patient for up to four journeys to RH and hence, would result in more time at home with family and friends (Figure 1). When the 1.5 tesla MRI becomes operational at DIH, this might reduce travelling even more by two

journeys, hence six in total, in the treatment period, so the patients only need to travel to RH for diagnosis and surgery. In order to manage the adjuvant TMZ at DIH, it is essential for doctors and nurses to gain greater knowledge and training about the disease. DIH has a professional and well-established collaboration with Department of Oncology at RH. An appointed oncologist at RH is responsible for each disease category and the local physicians and nurses at DIH are well trained in handling chemotherapy and targeted treatment and in treating possible side effects from these. Therefore, a close collaboration already exists between DIH and oncologists at RH and it would be feasible to establish a similar setup for the neuro oncology speciality. However, the first steps to investigate the possibility of managing the adjuvant treatment of TMZ at DIH, is to estimate the subsequent increased expenses. This includes training of health care professionals, expenses for blood sample analyses, establishment of a standardised neurophysiological rehabilitation program etc., and a sufficient increase in health care professionals would need to follow.

Conclusion

The article describes how highly specialised treatment of cancer can be managed in Greenland through a close and professional collaboration between few dedicated health care professionals, also including the use of telemedicine. We have discussed advances and limitations for taking home the adjuvant treatment of GBM to DIH, Greenland. It is our hope that this article can contribute to a better understanding of GBM and the challenges the patients face.

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