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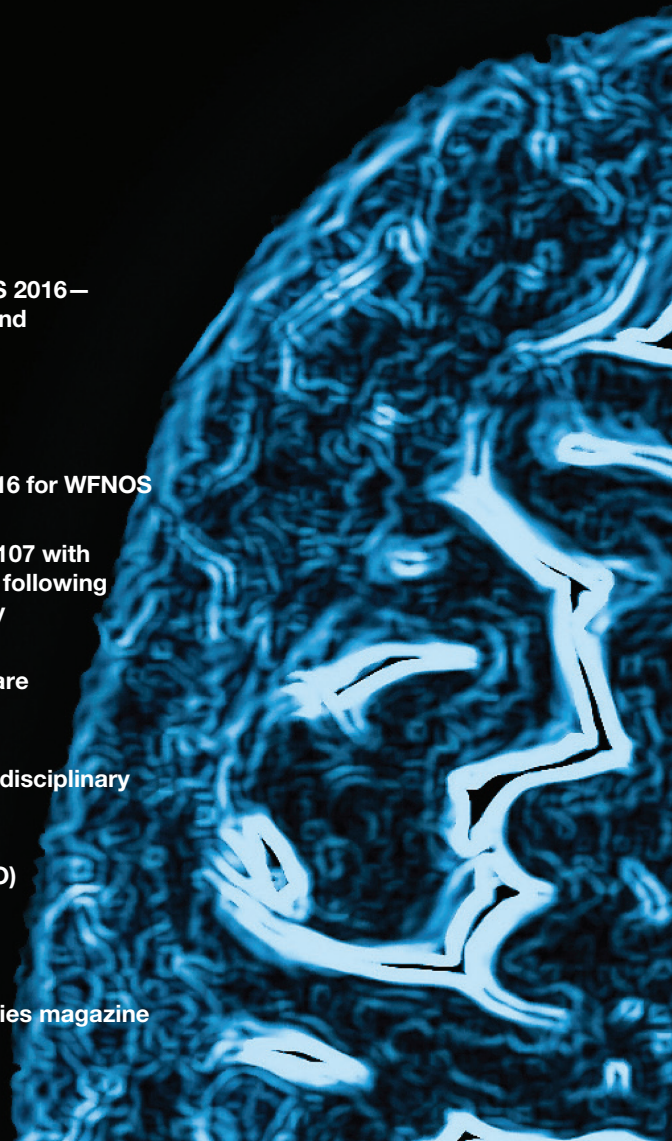

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Editorial

Dear colleagues,

This is the third issue of the *World Federation of Neuro-Oncology Societies Magazine* (WFNOS), the last for this year and the last to be coordinated by Christine Marosi, our managing editor.

We invite you to read on the attempt to identify trigger symptoms for brain tumor patients entering the end of life phase by Andrea Pace, Dario Benincasa, and Veronica Villani from Rome, who have huge experience in these problems, accumulated since more than twenty years by running the exemplary Neuroncological Palliative Home Care Service. Then, Torsten Pietsch and Guido Reifenberger will continue his presentation of the new WHO classification of CNS tumors with his article on the changes in pediatric brain tumors. Christine Marosi has written a short recapitulation on prevention and therapy of thromboembolic complications in brain tumor patients. The snapshot presentation of current trials summarizes the multipeptide vaccination trial STING exploring the vaccine known as ICT-107 for patients with newly diagnosed glioblastoma. Ingela Oberg suggests in the nurse's corner an integrated support for brain tumor patients and their proxies, beginning at diagnosis through the whole course of the illness—a forward looking initiative! A step toward this goal is presented by Anita Granero from Toulouse, a patient advocacy initiative, supporting children with brain tumors and their families.

The Neuro-Oncological society presented in this issue is the Korean Society of Neuro-Oncology.

Riccardo Soffietti presents his Highlights of Neuro-Oncology and Hugues Duffau & Brigitta Baumert responded in the Interview to questions on the management of patients with low-grade gliomas.

We thank all contributors for their articles and in particular acknowledge the engagement of our first managing editor, Christine Marosi, from Vienna, Austria.

Kind regards,
on behalf of EANO & SNO

Michael Weller, MD
President, EANO & WFNOS

E. Antonio Chiocca, MD, PhD
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Trigger symptoms at the end of life in brain tumor patients

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Abstract

Background: In brain tumor patients the provision of supportive and palliative care often occurs late and the timing and the role of palliative care in brain tumor patients remain to be better defined. Earlier identification of people approaching the end of their life may lead to earlier planning and better care**.** Recently, trigger symptoms have been identified as potential predictors of the entering in the last stage of disease in cancer patients and in patients affected by neurological degenerative diseases. The aim of this study was to identify trigger symptoms as early predictor of end of life stage in a population of BT patients. Methods: We retrospectively analyzed a population of glioma patients deceased from 1 June 2014 to 31 January 2016. Neurological and general medical symptoms occurring in the last three months of life and time of onset before death were collected.
Results: 46 patients (31 GBM; 14 progressive grade II-III glioma; 1 anaplastic meningioma) were included in this study. Among neurological symptoms the most frequent were neurological deterioration and dysphagia occurring in 67% of patients. Drowsiness was reported in 46%, agitation and/or delirium in 27% and seizures in 19% of patients. Among general medical symptoms reported the most frequent was fatigue (30%) and hyperglycemia (19%). The earliest symptoms were neurological deterioration and fatigue occurring respectively at a mean time of 4,8 and 5,3 weeks before death. Dysphagia was the most late symptom, occurring at 2,1 weeks before death. Conclusion: The results of our study do not permit the identification of trigger symptoms helping to define the beginning of end of life in this population of patients. The cluster of symptoms observed in our study confirms the end of life symptoms reported in previous studies and shows that the decline in physical and cognitive functions is rapid in the last 4-6 weeks before death. Future research should focus on the definition of the best timing and the appropriate palliative care model to assure a better quality of life in the last stage of disease.

Keywords: brain tumor, palliative care, end of life, trigger symptoms

Introduction

Primary malignant brain tumors (BTs) have a low rate of incidence with annual incidence of 5.8 males and 4.1 females per 100,000 in developed countries[1]. Although current multimodality treatment including surgery, radiotherapy and chemotherapy, the prognosis of patients with primary or metastatic brain tumors (BTs) still remains poor. Malignant gliomas have the worse outcome, with a median survival ranging from 12 to 15 months for glioblastoma and from 2 to 5 years for anaplastic gliomas[2]. While development of more active treatments are ongoing, physicians looking after BT patients have the important role of providing effective and adequate palliative care in the last stage of disease.

The concept of palliative care is an emerging field in neuro-oncology. The WHO 2012 definition of Palliative Care (PC) affirms that palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual [3].

There is a general consensus about the fact that PC should start early and not only in the last stage of disease. Early integration of palliative care into the ongoing care of patients living with BT may improve quality of life and symptom management. Recent studies report that early integration of palliative care approach with standard oncologic care in cancer patients may have a beneficial effect on quality of life and mood disorders[4].

In BT patients the provision of supportive and palliative care often occurs late and the timing and the role of palliative care in brain tumor patients remain to be better defined[5].

The identification of the beginning of the dying phase is crucial to avoid sub-optimal care. However, there is currently no validated instrument for determining the beginning of the dying phase and no common definition of end of life exists.

Recently, pathways that can support clinicians in the process of identifying the beginning of the dying phase have been developed in cancer patients and in patients affected by neurological degenerative diseases[6,7]. The knowledge of early predictors of end of life stage and the assessment for changes in signs and symptoms that may suggest a person is dying, could help clinicians to plan and deliver appropriate care that integrates active and palliative management.

In general cancer populations several symptoms have been identified as potential predictors the entering in the last stage of disease and particularly: changes in breathing, general deterioration, lowering of consciousness, caregivers' clinical judgment, lowered oral intake[8].

Table 1: symptoms in BT at the End of Life reported in the literature

Symptoms	Confusion	Headache	Dysphagia	Drowsiness	Agitation, delirium	Seizures	Fatigue
Sizoo 2010	33	33	71	87	–	45	25
Pace 2009	–	36	85	85	15	30	–
Faithfull 2005	39	72	10	–	31	56	44
Koekkoek 2014	44,7	34,6	24,5	75	45	25,9	–
Oberndorfer 2008	–	38	79	90	–	48	–

In patients with progressive neurological disease trigger symptoms have been suggested for the recognition of end of life such as swallowing problems, recurring infections, marked decline in functional status, first episode of aspiration pneumonia, cognitive difficulties, weight loss and significant complex symptoms[7]. There is evidence that these triggers may help in the recognition of the end of life and that early recognition of the final stage can be useful in allowing the focus of care to be clarified and a palliative care approach initiated.

Nevertheless, several studies showed that End of Life phase of Brain Tumor (BT) patients is quite different in respect to the expected trajectory observed in general cancer population[9]. Additionally, disease history and needs of care in the last stage of BT patients have few similarities with other progressive neurologic diseases[10].

In recent years some studies have reported the symptoms observed in the last weeks/months of life of BT patients (Table 1). Most frequent symptoms are consciousness alteration, dysphagia and seizures. However, symptoms before death have been described in small, retrospective and single-site studies and in different setting of care[11–15].

The aim of this study was to identify trigger symptoms as early predictor of end of life stage in BT patients.

Methods

We retrospectively analyzed a population of glioma patients deceased from 1 June 2014 to 1 January 2016. All patients received home assistance by the Neuroncological Palliative Home Care Service provided by our Institution (Regina Elena National Cancer Institute of Rome, Italy). This study is part of a larger project to develop a model of palliative and supportive home care for BT patients. The description of the pilot project of Neuroncological Home Care model was previously published[16,17].

Home clinical records of patients who died in the period of observation were retrospectively analyzed. Records contain demographic and clinical information on each clinical modification during home care assistance. Neurological and general medical symptoms occurring in the last three months of life and time of onset before death were collected.

Statistical analysis

We applied descriptive statistics to define the population and symptoms. Moreover, we tested whether there was a difference in the prevalence of each symptom and time of onset before death. Two-tailed tests were performed, using a significance level of 0.05. We used SPSS version 21.0 software for all analysis.

Results

From June 2014 to January 2016, 92 patients were assisted by our service of neuroncological palliative home care. Among these 37 patients were still alive in January 2016, 1 patient was lost to follow-up. We identified 54 patients who had died before January 31, 2016. Among these patients 8 have not complete clinical data so they were excluded. 46 patients were included in this study. All patients were assisted until death. Median time of home care assistance before death was 6 months (range 3-17).

Characteristic of patients

Patients were affected by GBM in 31 cases and by progressive grade II-III glioma in 14. One patient was affected by anaplastic meningioma. The median age was 67 years and 52% were male (24/46). Median survival time from diagnosis in GBM patients was 16 months (range from 5 to 43), in no GBM patients was 32 months (range from 8 to 83). Place of death: 32 patients have died at home (71,8%), 14 in a Hospice (28,2%).

Symptoms

Symptoms were dichotomized in neurological and general medical symptoms. A total of 11 symptoms emerged from the analysis. Among neurological symptoms the most frequent were neurological deterioration and dysphagia occurring in 67% of patients. Drowsiness was reported in 46%, agitation and/or delirium in 27% and seizures in 19% of patients.

Among general medical symptoms reported the most frequent was fatigue (30%) and hyperglycemia (19%). Less

Table 2: Incidence and time of onset of neurological and medical symptoms in 46 patients

Neurological Symptoms	%	Median time before death in weeks (SD)
Confusion	26	4.3 (1.7)
Neurological deterioration	67	4.8 (2)
Headache	13	3.8 (1.3)
Dysphagia	67	2.1 (1.2)
Drowsiness	47	4.2 (2)
Agitation/delirium	28	4.5 (1.8)
Seizures	19	3.7 (3.8)
Medical Symptoms		
Fatigue	30	5.2 (2)
Hyperglycemia	19	4.2 (2.1)
Pneumonia	6	5 (2.6)
Urinary infection	2	2 (2)

frequent were pulmonary and urinary tract infections (6%).

Concerning the time of symptoms onset the earliest were neurological deterioration and fatigue occurring respectively at a mean time of 4,8 and 5,3 weeks before death. Agitation and drowsiness occurred respectively at 4,5 and 4,2 weeks before death. Dysphagia was the later symptoms, occurring at 2,1 weeks before death.

Most of patients showed high prevalence of symptoms with more than 3 symptoms in 85%.

Symptoms list and time of onset before death are reported in table 2. We excluded symptoms such as death rattle, fever and coma because they usually occur in the last hours/days of life so too late to allow early identification of terminal phase.

Discussion

Palliative care approach should be offered to every patient with incurable disease and the early integration of palliative care have been demonstrated to be significantly related to better quality of life[4,19].

However, substantial unmet needs in BT end-of-life care still remain and continued efforts are needed to improve the quality of end-of-life care and neuroncologists education.

A crucial question is how to recognize the end of life phase and when to refer a patient to palliative care.

The results of our study do not permit the identification of trigger symptoms helping to define the beginning of end of life in this population of patients. Most symptoms observed in BT patients approaching death occur in the last month of life and do not allow plan in advance the appropriate end of life care. One of the most frequent symptoms is dysphagia but it occurs in the last 2-3 weeks of life and cannot be utilized as early predictor. The cluster of symptoms observed in our study confirms the end of life symptoms reported in previous studies and shows that the decline in physical and cognitive functions is rapid in the last 4-6 weeks before death.

However, the present study was performed at a single neuroncological center and may reflect the practice patterns provided by our Institution, somewhat limiting the generalizability of the results.

Disease trajectory of BT appear to be very different in respect to the trajectory of general cancer population and from neuro-degenerative diseases, and is characterized by fluctuating episodes of neurological deterioration often followed by period of improvement or stability. Also, the process of dying has been reported to not be well predictable in respect to general cancer patients[20,21]. Considering the complexity of supportive care needs, the very short life expectancy and the presence of specific symptoms related to neurological deterioration, BT patients need a specific palliative approach.

From these findings, it is important to consider model of care that should incorporate earlier palliative care referral, to facilitate the timing provision of adequate supportive and palliative care in BT patients and their families[22].

Future research should focus on the definition of the best timing and the appropriate palliative care model to assure a better quality of life in the last stage of disease.

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Updated WHO Classification of Embryonal Tumors of the CNS 2016—Toward Precision Diagnostics by Integration of Histological and Molecular Features

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Keywords: embryonal tumor, medulloblastoma, atypical teratoid/rhabdoid tumor, integrated diagnostics, World Health Organization (WHO) classification

Since the last version of the World Health Organization (WHO) classification of tumors of the CNS in 2007, knowledge on genetic events and biological features of embryonal tumors of the CNS comprising the 3 main groups—medulloblastoma, atypical teratoid/rhabdoid tumor, and other CNS embryonal tumors (formerly known as CNS primitive neuroectodermal tumors [CNS-PNET])—has rapidly increased by genome- and trancriptome-wide studies. In particular, RNA expression studies and DNA methylation profiling has led to the identification of "biological" entities of embryonal tumors defined by predominant signaling pathways and DNA methylation patterns associated to their cellular origin and/or location in the CNS. These classifiers overlap with histological features in some cases but are disconcordant in others. While the WHO classification 2007 relied on histological features only, the challenge of its update in 2016 was to integrate meaningful genetic/biological information to enable a more precise classification of embryonal CNS tumors without disrupting the continuity of the classification system. Continuity is especially needed for (i) longitudinal comparisons of outcome data of clinical studies, (ii) the comparison of associated research data, and (iii) a reliable basis for epidemiological information on the incidence of the disease entities.

This challenge was elegantly resolved by the application of the integrated diagnosis concept in the WHO classification 2016.[1] By this approach, the traditional histological diagnosis (eg, "classic medulloblastoma") and the histological grade of malignancy ("WHO grade IV") are combined with defined molecular genetic/biological features (eg, "Wnt activation"). In daily diagnostic practice, the histological part of the diagnosis can be made in the same short time-frame as before, the molecular diagnostic part requires additional tests which may or may not need more time for analysis, but finally, an integrated diagnosis of "classic medulloblastoma, Wnt activated, WHO grade IV" can be signed out, now precisely describing a well-defined disease entity. In many CNS tumor entities, the definition in the 2016 classification is still based on histological features only, but in most CNS embryonal tumors (as in diffuse gliomas) the definition of disease entities requires an integration of additional molecular information. This approach now defines the embryonal CNS tumors more narrowly, reduces the interobserver variability in diagnostics, and allows for a better selection of patients for treatment stratification as well as more improved prediction of treatment response and prognosis.

Some limitations for the integration of molecular characteristics come from a technical aspect. The methods that have to be employed for proper classification of the different embryonal tumor types of the CNS have to be (i) available or accessible in most neuropathological units wordwide and (ii) certifiable as diagnostic test systems. At the time when the 2016 update process of the WHO classification started, there was a lack of information on the availability of immunohistochemical and various molecular methods in the laboratories involved in

neuropathological tumor diagnostics in the different countries. This was discussed during the Congress of the International Society of Neuropathology (ISN) in Rio de Janeiro in 2014, and with the support of the ISN these data were collected by a worldwide Internet-based survey.[2] The data showed that most neuropathological units use immunohistochemistry and genetic tests; however, the latter are mostly restricted to fluorescence in situ hybridization and single gene–based methods, while genome-wide techniques that are more costly and require extensive laboratory equipment are only available in a few countries with a high human developmental index. While in the WHO classification 2016 no recommendation for the use of specific test systems or methods is given, care was taken that the implementation of molecular markers for classification is possible in daily diagnostic practice in most laboratories.

WHO Classification of Medulloblastomas

Although the 5 histological entities of medulloblastomas according to the 2007 classification (Table 1) could be validated as prognostic and useful in the stratification of patients for risk-adapted treatment in clinical studies, in particular in young children, the histological subtyping had several limitations. For example, interobserver variability in the assessment of certain histological features caused problems, such as the differentiation of "true" desmoplastic medulloblastoma variants versus cases with desmoplastic (reactive) changes due to superficial growth, or the differentiation between large cell and anaplastic medulloblastoma variants in cases showing both cytological components. The histology was often found related to certain genetic/biological features of the tumors but considered to be not as distinctive as a definition by mRNA expression or DNA methylation signatures. To improve the precision of medulloblastoma diagnostics, the histological typing is now combined with genetic information to allow for an informative diagnosis. For the histological part, only one adaptation was made in the WHO classification 2016: the large cell and anaplastic medulloblastomas are now jointly diagnosed as large cell/anaplastic medulloblastomas because it was felt difficult to differentiate these rare entities that often show a mixed cellular composition. This term had also been used in the 2000 WHO classification before. The definitions of the histologically defined medulloblastoma variants otherwise did not change significantly compared with the WHO classification 2007 (Table 1). Regarding the genetically defined component of the diagnosis, 4 main entities were newly defined. One entity is "medulloblastoma, WNT-activated." These tumors cannot be securely identified on hematoxylin-eosin stained sections alone; most of them have classic morphology but immunohistochemically show nuclear accumulation of ß-catenin protein as a surrogate biomarker for Wnt activation caused by *CTNNB1* activating mutations or, rarely, mutations in *APC* or other genes encoding components of the Wnt signaling pathway. The precise identification of these tumors is important because of their excellent prognosis in the pediatric age and the possible qualification of the patients for current trials aiming to provide evidence that reduction of treatment intensity might be possible in these patients. In the setting of clinical trials, it is widely recommended to use 2 independent methods for reliable identification of these patients, such as immunohistochemistry for ß-catenin and sequencing of *CTNNB1* exon 3 or alternative methods.

Tumors showing mRNA expression and DNA methylation profiles suggesting activation of Sonic hedgehog (SHH) signaling are considered to represent 2 very different disease entities, depending on the *TP53* genetic status. Therefore, 2 genetically defined entities are "medulloblastoma, SHH-activated and TP53-mutant" and "medulloblastoma, SHH-activated and TP53-wildtype." The latter occur mostly in adolescents/adults and young children who have a good prognosis if adequately treated. In contrast, *TP53*-mutant SHH medulloblastomas occur in older children and have a dismal prognosis. SHH activation is caused by mutations in *PTCH1*, *SUFUH*, *SMOH*, or other components of the SHH signaling pathway. Fortunately, SHH activation can be reliably assessed by different methods, including a panel of antibodies against SHH target proteins (see below). On the other hand, if an SHH-activated tumor is identified, the TP53 genetic status has to be determined for a precise classification. Proper identification of these cases is also important because a significant fraction of young children with SHH-activated medulloblastomas have underlying germline mutations of *PTCH1* or *SUFUH* (Gorlin syndrome). These patients and their families should be offered genetic counseling. The same is true for patients suffering from *TP53*-mutant SHH medulloblastomas indicating possible *TP53* germline mutations (Li–Fraumeni syndrome) or other germline defects.

The fourth genetically defined entity represents the majority of medulloblastomas lacking either WNT or SHH pathway activation (non-WNT/non-SHH medulloblastomas). These tumors seem to lack recurrent mutations but show frequent chromosomal copy number alterations such as isochromosome 17q. They can be further subdivided with DNA methylation profiling or mRNA expression studies in "group 3" and "group 4" medulloblastomas. These variants have so far only been considered as provisional subentities because it is not absolutely clear if they represent distinct diseases or variants of a single entity. There are no robust simple technologies (eg, immunohistochemical methods) available for their precise distinction. There also is a "gray zone" between groups 3 and 4, with tumors switching groups if different algorithms for data analysis are employed. From a clinical point of view, "group 3" non-WNT/non-SHH medulloblastomas contain standard-risk medulloblastomas (not behaving differently from

Table 1. Changes in the World Health Organization (WHO) classification of CNS embryonal tumors from 2007 to 2016

WHO classification 2007	WHO classification 2016
Medulloblastoma	***Medulloblastoma — histologically defined***
Medulloblastoma, classic	Medulloblastoma, classic
Medulloblastoma, desmoplastic/nodular	Medulloblastoma, desmoplastic/nodular
Medulloblastoma with extensive nodularity	Medulloblastoma with extensive nodularity
Medulloblastoma, anaplastic	Medulloblastoma, large cell/anaplastic
Medulloblastoma, large cell	
	Medulloblastoma — genetically defined
	Medulloblastoma, WNT-activated
	Medulloblastoma, SHH-activated and *TP53*-mutant
	Medulloblastoma, SHH-activated and *TP53*-wildtype
	Medulloblastoma, non-WNT/non-SHH
	*Medulloblastoma, group 3**
	*Medulloblastoma, group 4**
	**Medulloblastoma, NOS
CNS primitive neuroectodermal tumours (CNS-PNET)	***Other CNS embryonal tumours***
Ependymoblastoma	Embryonal tumour with multilayered rosettes (ETMR), C19MC-altered
	*Embryonal tumour with multilayered rosettes, NOS**
Medulloepithelioma	Medulloepithelioma ***
CNS neuroblastoma	CNS neuroblastoma
CNS ganglioneuroblastoma	CNS ganglioneuroblastoma
CNS-PNET, NOS	CNS embryonal tumour, NOS
Atypical teratoid/rhabdoid tumour	***Atypical teratoid/rhabdoid tumour***
Atypical teratoid/rhabdoid tumour	Atypical teratoid/rhabdoid tumour ****
	*CNS embryonal tumour with rhabdoid features**

In both classifications, all embryonal tumor entities are graded as WHO grade IV. Entities in the WHO classification 2007 that have been renamed in the updated WHO classification 2016 are printed in red. Blue indicates the new names used in the 2016 classification for entities defined by histological features. Entities defined by molecular features in the WHO classification 2016 are printed in green. For medulloblastoma entities, the diagnosis according to the WHO classification 2016 is composed of a histological as well as a genetic component (integrated diagnosis). *Provisional entities are printed in italics. **Medulloblastoma NOS should only be used for cases with insufficient material for proper classification or inconclusive molecular testing. ***Medulloepithelioma according to the 2016 classification is restricted to tumors showing the characteristic histological features but lacking *C19MC* alteration; medulloepitheliomas carrying *C19MC* alterations are diagnosed as ETMR, C19MC-altered. ****Atypical teratoid/rhabdoid tumors must show *SMARCB1* or *SMARCA4* alterations to be diagnosed as such; if this cannot be demonstrated in an otherwise histologically typical tumor, the descriptive term "CNS embryonal tumor with rhabdoid features" (provisional entity) should be used. NOS, not otherwise specified; SHH, sonic hedgehog; TP53, tumor protein 53.

"group 4" patients) as well as *MYC*-amplified tumors showing mostly a very poor prognosis. *MYC* amplification is considered as an important prognostic biomarker within non-WNT/non-SHH medulloblastomas but not as a diagnostic marker defining an own entity.

As all combinations between histological and genetic parts of the medulloblastoma classification scheme are theoretically possible, there are frequent associations. For example, most WNT-activated medulloblastomas are of classic histology (as are most non-WNT/non-SHH

medulloblastomas) and most SHH-activated cases with *TP53*-mutation show an anaplastic phenotype. Almost all desmoplastic/nodular medulloblastomas and those with extensive nodularity are SHH-activated. The term "medulloblastoma, not otherwise specified (NOS)" should be restricted to cases with insufficient material for further analysis or inconclusive results of molecular testing.

In summary, the concept of an integrated diagnosis is used for WHO classification of medulloblastomas and allows a precise assignment of patients for risk-adapted stratification. It also allows comparison to results of study cohorts in the past and provides a robust basis for further refinement.

WHO Classification of Atypical Teratoid/ Rhabdoid Tumors

More than 90% of atypical teratoid/rhabdoid tumors show mutations/deletions of the *SMARCB1* (*SNF5* / *INI1*) gene on chromosome 22. Rarely, alternative mutations can be found in *SMARCA4* encoding another component (Brg1) in the same chromatin remodeling complex. Both alterations lead to a homogeneous complete loss of these nuclear proteins, which can be easily detected by immunohistochemistry or alternatively by genetic methods. Therefore, one of these 2 alterations should be demonstrated. Only for those cases that lack these characteristic mutations leading to loss of nuclear expression but morphologically resemble atypical teratoid/rhabdoid tumors, the term "CNS embryonal tumor with rhabdoid features" has been introduced in the WHO classification.

WHO Classification of Other CNS Embryonal Tumors

In this group of rare, mostly pediatric tumor entities, extensive renaming of entities occurred. First, the term "CNS primitive neuroectodermal tumor" ("PNET") was deleted in the WHO classification 2016 because it was felt that this term has led to misuse as a basket term for malignant tumors not fitting into other categories or to misinterpretation. Indeed, the meaning of "PNET" has significantly changed over the years. The term was originally introduced by Michael N. Hart and Kenneth M. Earle in 1973, and the PNET concept was then developed in the 1980s by Lucy B. Rorke and comprised undifferentiated neuroepithelial tumors occurring ín various locations of the CNS. The hypothesis at that time was that such tumors may show similar biological behavior independent of their location. This hypothesis was not proven and pineoblastoma as well as medulloblastoma were identified as separate entities. This then led to the term "supratentorial PNET" for a group of non-medulloblastoma/ non-pineoblastoma primitive tumors. As such tumors can also occur in non-supratentorial (cerebellar or spinal) locations, finally in 2007, the term "CNS-PNET" was coined, also to clearly differentiate these CNS neoplasms from peripheral PNET of the Ewing tumor family that are biologically distinct. In the 2007 classification, "CNS-PNET" was an umbrella term for (i) ependymoblastoma, (ii) medulloepithelioma, (iii) CNS neuroblastoma, (iv) CNS ganglioneuroblastoma, and (v) "CNS-PNET, NOS." Ependymoblastomas are characterized by multilayered rosettes of proliferating cells forming a central lumen ("ependymoblastic rosettes"). Another tumor entity with similar rosettes but of lower cellularity was described as "embryonal tumors with abundant neuropil and true rosettes (ETANTR)" some years later. In both, amplifications and/or translocations of the oncogenic micro-RNA cluster *C19MC* on the long arm of chromosome 19 were found as characteristic features in addition to Lin28 expression. Moreover, clinical and radiological features overlap, so that ependymoblastoma and "ETANTR" are now considered to represent facets of the same entity. This entity also embraces some cases with histological features of medulloepithelioma. Because the *C19MC* alteration is very characteristic, it is now integrated in the diagnosis of this entity, which has been termed "embryonal tumor with multilayered rosettes (ETMR), *C19MC* altered." Rare cases which show the morphology of ependymoblastomas/ETANTR but lack *C19MC* alterations are provisionally termed "ETMR, NOS." The diagnosis "medulloepithelioma" can now only be used for cases lacking C19MC alterations. Cases that represent primitive embryonal tumors of the CNS but cannot be classified in one of the defined categories are termed "CNS embryonal tumors, NOS" in the WHO classification 2016 instead of "CNS-PNET, NOS" in 2007. This diagnosis should only be used if other tumor entities such as undifferentiated gliomas and sarcomas have been excluded by adequate histological and molecular analyses. In fact, recent molecular profiling data indicate that the group of embryonal CNS tumors may in fact be composed of molecularly distinct subentities that can only be distinguished by sophisticated molecular profiling (eg, based on large-scale DNA methylation profiling).[3]

Practical Consequences of the WHO Classification of CNS Embryonal Tumors 2016

The implementation of the WHO classification system in the routine diagnostic setting has important implications.

First, neuropathological units have to broaden their repertoire of diagnostic methods to be able to assess the required molecular markers for diagnosis but also differential diagnosis. Most markers such as nuclear ß-catenin, SHH target proteins (like p75-NGFR or Gab1), Ini1, Brg1, and Lin28 can be assessed by immunohistochemistry. Other markers need genetic methods such as the analysis of *C19MC* amplification by fluorescence in situ hybridization or alternative DNA-based methods. For each marker assay, appropriate controls have to be used for validation of the method. A false result of a molecular test can lead to incorrect diagnosis of the tumor and hence inadequate treatment of the patient. In particular, PCR methods used for amplification of DNA fragments for sequencing are sensitive to possible contaminations. These have to be excluded by rigorous separation of pre- and post-PCR laboratories and equipment. Certain molecular tests, such as DNA sequencing (eg, *TP53* mutational assessment in SHH-activated medulloblastomas) may prolong the time required to establish a final diagnosis. The treating physicians should be aware of the status and timing of additional molecular tests because longer time for diagnostics should not lead to an inadequate delay of postoperative treatment that may put the patient at unacceptable risk.

Conclusions

The updated WHO classification 2016 has integrated key molecular markers into the classification of CNS embryonal tumors that allow for a more precise and reproducible diagnosis as well as improved stratification of patients for a risk-adapted treatment. Without disrupting the connection to past classifications, it enables future clinical trials with precisely defined patient cohorts. The WHO classification 2016 provides a robust basis for further refinements and a major step forward toward precision medicine for patients suffering from highly malignant embryonal tumors of the CNS.

Key points

- The updated WHO classification of embryonal tumors of the CNS has added genetic markers to histological features for a more precise classification of these highly malignant tumors.
- Novel diagnostic assays have to be established for daily routine diagnostics and appropriate validation procedures must be implemented.
- An integrated diagnosis is used for medulloblastoma that is composed of a histological component and an additional genetic component (WNT-activated, SHH-activated and *TP53*-mutant, SHH-activated and *TP53*-wildtype, non-Wnt/non-SHH). Further markers provide additional prognostic information and may also facilitate treatment decisions (eg, *MYC* amplification).
- Atypical teratoid/rhabdoid tumors can only be diagnosed if mutation or loss of *SMARCB1* or *SMARCA4* is demonstrated.
- The term “CNS-PNET” has been deleted.
- The entity of “embryonal tumor with multilayered rosettes (ETMR)” comprises the former ependymoblastomas and histologically similar tumors sharing characteristic alterations of the oncogenic *C19MC* micro-RNA cluster.

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Thromboembolic Complications in Patients with Gliomas

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Abstract

Abstract: the incidence of thromboembolic complications (VTE) in patients with gliomas is very high. This short Review summarizes available evidence on incidence of VTE in glioma patients and on the current standards for prophylaxis and treatment of VTE episodes. Both are still based on the use of low molecular heparin, as there are to date no trials with the new oral anticoagulants.

Keywords: venous thromboembolism, glioma, low molecular Heparin

Patients with diagnoses of malignant glioma have to face an aggressive cancer accompanied by increasing neurological deficits, but also a medical condition predisposing them to various complications negatively impacting their quality of life.[1] Among those potential complications, ranging from epileptic seizures to the highly variable side effects of corticosteroids, complications of venous thromboembolism (VTE) are a burdensome and potentially fatal medical threat.

It has long been known that malignant tumors lead to a systemic activation of coagulation and fibrinolysis, varying with cancer entities, time since tumor diagnosis, and tumor treatment. Cancer-associated thrombosis was described as early as 1823 by Bouillard and Bouillaud in France but is more well known as "sign of Trousseau," commemorating the French internist who described the association of cancer and thrombosis in 1865, shortly before dying of this complication himself.[2] Since these pioneering observations, the mechanisms of the increased risk of VTE in cancer as well as the efficacy and safety of prophylactic and therapeutic measures in cancer patients have been studied. In this short survey, the particular features of VTE complications in patients with malignant gliomas are summarized and new developments are presented.

Epidemiology of Venous Thromboembolism in Patients with Malignant Gliomas

VTE incidence in patients with malignant gliomas is among the highest in all cancers, just below the rates of patients with pancreatic and gastric cancer.[3–6] Although a peak is observed during the first year of survival, VTE can occur at any time—and as personal observation is frequently diagnosed at the time of a relapse. Whereas the risk of VTE is just around 1 / 1000—thus less than 1/1000—the observed incidence in glioma patients varied from 7.5% to 39% in retrospective studies, whereas recent prospective studies found 13%–17%.[7–11] This high variability is due to the definition of the starting point, with or without inclusion of the perioperative period and of the screening methods, whether only symptomatic patients are included or whether sensitive screening methods are used. Sawaya et al[12] were able to detect deep venous thromboses by radiolabeled fibrinogen scans in up to 60% of glioblastoma patients during the postoperative period.

The risk of VTE in glioma patients is variable with individual factors relating to the patient, the tumor, and the tumor treatment. Patient-related factors include age, previous history of thromboembolic events, blood group

A or AB, obesity, comorbidities, and decreased mobility. Most deep venous thromboses in glioma patients occur in a paretic limb. Tumor-associated factors include the grading of the tumor, tumor size greater than 5 cm, residual tumor after surgery, and detection of thrombotic veins in the surgical specimen. The treatment-associated factors comprise the postoperative hypercoagulable state, presence of venous access devices, chemotherapy, therapy with vascular endothelial growth factor antagonists, and hormonal therapies (dexamethasone, tamoxifen).[13,14]

Moreover, some biomarkers associated with increased risk of VTE in glioma patients have been identified in prospective observational studies. In the Viennese Cancer and Thrombosis Study started in 2003, >1700 patients with cancer were enrolled after cancer surgery, the earliest after a perioperative period of 2 weeks, 213 of them with malignant gliomas.[15] Blood samples were drawn at inclusion, before starting radiotherapy or chemotherapy, and 39 glioma patients participated in a small substudy with 7 further blood samples taken at monthly intervals.[11] The clinical follow-up for 2 years yielded to the identification of biomarkers potentially associated with VTE events, as elevated soluble P-selectin (sP-selectin), prothrombin-fragment 1 + 2, factor VIII activity, D-dimer, elevated leucocyte count, and interestingly decreased platelet count at the time of the first blood sample. Two risk assessment models (RAMs) were built on the basis of these results by attributing one point to each risk factor present in a given patient. The first included low platelet count (<25th percentile of the study population) and high sP-selectin (≥75th percentile). The cumulative VTE probability after 12 months was 9.7% for score 0, 18.9% for score 1, and 83.3% for score 2, respectively. The second RAM included only commonly available parameters, such as low platelet count (<25th percentile), elevated leukocyte count, and elevated D-dimer (≥75th percentile). The probability of VTE was 3.3% for score 0, 23.0% for score 1, and 37.7% for score >2, respectively. Both scores still require independent validation.[15]

The longitudinal assessment of coagulation parameters in the substudy showed a decrease of clotting factor VIII, sP-selectin, fibrinogen, and thrombin, whereas patients with a VTE event maintained elevated levels of these 4 parameters during the observation period.[11]

Prophylactic Anticoagulation in the Perioperative Period

Several guidelines recommend prophylactic anticoagulation with low molecular weight heparin (LMWH) in hospitalized cancer patients with an acute medical illness or reduced mobility.[16–21] These guidelines apply to glioma patients; exceptions due to the presence of intracerebral hemorrhage (ICH) or intratumoral bleeding, coagulopathies or bleeding disorders, and platelet counts below 50.10^9 G/L should be discussed individually. The timing of starting a perioperative prophylaxis with LMWH is different for brain tumors than for other cancers: prophylaxis should be started within 24h postoperatively, not during anesthesia to avoid increased ICH.[22,23] The prophylactic anticoagulation should be prolonged during the hospital stay or at least for 7–10 days, in case of functional impairment until full mobility is recovered.

To date, there are no studies proving an advantage by prolonging prophylaxis beyond the perioperative period. In a small phase II study using tinzaparin for 12 months, 2 of 40 patients developed ICH and 4 VTEs were recorded.[24] A small uncontrolled phase II study on 45 patients with high-grade glioma (HGG) showed no ICH, no VTE, and no survival gain when dalteparin was given for a median of 6 months.[25] The only placebo controlled trial exploring this issue, the PRODIGE trial, recruited 186/516 planned patients and had to be terminated early because of shortage of placebo.[26] There were 11% VTE in the dalteparin arm and 17% in the placebo arm and 5 cases of ICH in the dalteparin arm, versus 1 in the placebo arm, thus a signal in favor of prolonging the prophylaxis, but the result did not allow a definite answer.

Therapeutic Anticoagulation at VTE Events

In case of a VTE event, anticoagulation with LMWH at therapeutic dosage appears to be safe in HGG patients. Nevertheless, an individual assessment of bleeding risk and performing a cranial CT scan to exclude major ICH appears advisable for the documentation that contraindications were not present at the time of starting therapeutic anticoagulation. The detection of intracerebral blood products in asymptomatic patients may be interpreted as postsurgical residues or minor ICH and does not constitute a contraindication for therapeutic anticoagulation. Moreover, a rate of spontaneous ICH in primary brain tumors, such as in oligodendrogliomas, of 2%–8% has to be considered. The duration of the therapeutic anticoagulation (3–6 mo) and of the following secondary prophylactic anticoagulation has to be managed in analogy to other cancer patients, weighing the risk of recurrent thrombosis or pulmonary embolism against the risk of ICH and the wishes of the patient. For most patients with HGG this means considering lifelong prophylactic anticoagulation after a thromboembolic event, as their tumor mostly remains in an uncontrolled state.

For prophylactic and therapeutic anticoagulation in glioma patients, LMWH is the most commonly used drug. Oral vitamin K antagonists are slightly less effective, require compliance in diet, show significant drug interactions with

anti-epileptic drugs, and have a long half-life, making them less controllable and thus less safe than LMWH. Novel oral anticoagulants would offer the advantage of avoiding daily injection of LMWH and of frequent controls of coagulation parameters. So far, these drugs have not been tested and are not approved in patients with primary brain tumors, so their use cannot be recommended. Moreover, with the exception of dabigatran, no antagonists for these drugs are available, so their safety in a population with high risk of (intracerebral) bleeding is critical.

For glioma patients with a VTE event occurring during therapy with bevacizumab, experience has shown that anticoagulation with therapeutic doses of LMWH appears to be safe and effective, although a rate of ICH of up to 4% has been observed.[27,28] There are no established rules for the delay of reinstitution of bevacizumab after the start of therapeutic anticoagulation; so far individual decisions considering the risk of bleeding against the increase of neurological deficit due to brain edema have to be taken.[29]

To summarize, malignant gliomas are tumors belonging to the group of cancers with the highest risk of VTE. Mobility deficits frequent in glioma patients, as well as their increasing age and potential multimorbidities, further increase the risk of VTE events. The risk of ICH precludes the early start of prophylaxis of VTE perioperatively. There are no conclusive studies on the benefit of prolonging perioperative thrombosis prophylaxis in glioma patients.

There are risk assessment models to predict the individual VTE risk in a given patient that need to be validated. Current prophylactic and therapeutic antithrombotic therapy is based on LMWH. There are no studies using novel oral anticoagulants in this population.

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British Neuro-Oncology Society (BNOS) Conference Report 2016 for WFNOS

By Maryanne Roach

Approximately 250 people with an interest in neuro-oncology attended part or all of "Trials, Technologies and T-cells" in Leeds from Wednesday June 29 to Friday July 1, 2016. The conference opened with the Education Day.

Council would like to acknowledge the hard work of the Leeds team led by Professor Susan Short. As the strap line to the Conference title predicted, they certainly brought together the best of basic science and clinical research in neuro-oncology.

We were delighted to welcome as invited speakers: Bernhard Radlwimmer (German Research Center), Laura Evgin (Mayo Clinic), Nicola Sibson (Oxford Institute for Radiation Oncology), Stephanie Combs (ISAR Hospital, Munich), Richard Gilbertson (University of Cambridge), Luisa Ottobrini (University of Milan), Gelareh Zadeh (University of Toronto), and Sebastian Bradner (University College, London).

Methodological Techniques for Assessing Efficacy

Many presentations revolved around the setup, testing, and quality assurance of novel assay techniques designed for in vitro or preclinical use. These included the use of mathematics to model drug release/takeup from a polymer particle paste intended for intracavity implantation and the design of microfluidic chips which should maintain tissue viability/cancer cell proliferation, hence allowing practical and cost-effective testing of therapies in a near natural environment.

To date, a desire to use arterial spin labeling as a non-invasive MRI technique to quantify perfusion has been hindered by inconsistent results in preclinical experiments, so considerable work has been done to reliably determine changes in tumor perfusion in a rat model of brain metastasis.

Further developments are still required, however, when studying CNS metastasis, preclinical research being hindered by the lack of good models. In vitro techniques cannot reflect the tumor microenvironment, and reliance on spontaneous development of metastases in animals is impractical (except in melanoma, where, as in humans, a high incidence makes this feasible), although xenografts in a new strain of immunocompromised mice are an improvement (but still take up to 9 months for metastasis development). Another option being tested is that of seeding tumor cells onto brain slices.

An innovative concept is being used in Cambridge whereby the multidisciplinary team (MDT) concept has been transposed to the laboratory and candidate drugs are tested in mice in conjunction with surgery and radiotherapy (RT) in near-human randomized trials.

Metabolism

Due to the limited effectiveness of targeted therapies because of the inherent heterogeneity of glioma, an attractive alternative strategy is to exploit the altered metabolism exhibited by virtually all tumor cells (ie, their high dependence on glucose). It has also been shown that the glycolytic enzyme hexokinase 2 (HK2) is crucial for the Warburg effect, and as it has little or no expression in normal brain, it is an attractive target. However, in the absence of a known direct inhibitor, exploration of gene networks regulated by, or associated with, HK2 was necessary and has led to the identification of the azole class of antifungals as potential inhibitors of tumor metabolism.

Genomics Biomarkers

Next-generation sequencing is, of course, now central to research and diagnosis and will be in the future for choice of personalized therapeutics; streamlined paths are being devised to identify the relevance of the very large chromosomal copy number changes seen in brain tumors. Many speakers described the identification of particular genetic mutations present in subgroups of specific brain tumors, with some evidence of differential response to treatment, such as in pediatric high-grade gliomas and medulloblastoma.

The PARADIGM trials focus on the premise that "cells with stemlike features" upregulate the protein responsible for repair of RT-induced DNA damage. This potentially can be reversed by a poly-ADP ribose polymerase (PARP) inhibitor, with optimal radiosensitization occurring when combined with an inhibitor of ataxia telangiectasia mutated kinase.

Imaging and Radiotherapy

As full molecular characterization is not yet routinely available in clinical

practice, greater demands are being placed on traditional diagnostic techniques. The deduction of isocitrate dehydrogenase mutation status from MR imaging and spectroscopy can perhaps be made by study of degree of contrast enhancement, edema, sharpness of margins, path of growth, blood vasculature, and buildup of 2-hydroxyglutarate. In medulloblastoma, an imaging agent taken up preferentially by the leaky vasculature is being developed so that the good prognosis "wingless" (Wnt) subgroup can be identified on MRI, possibly precluding the need for total resection and thereby possibly reducing the risk of posterior fossa syndrome.

Seventy percent to 80% of neuro-oncology patients are treated by means of RT, but the potential of RT delivery techniques is greater than the accuracy of target definition; there is enormous planning variation among oncologists (although improved somewhat by concomitant use of PET scanning). Hence, attempts are being made to fuse CT with MRI, rather than use them as 2 separate RT planning procedures, or to use an MR-integrated LINAC (linear accelerator) so the patient doesn't have to be brought in for a prior planning session at all. And as immobilization can only currently be controlled to within 3 mm, there are also attempts being made to 3D print the mask from the MRI. The INSERT (INtegrated SPECT/MRI for Enhanced Stratification in Radiochemo Therapy) project has as its objective the development of a multimodality imaging tool for concurrent spectroscopy and MRI.

Immunovirotherapy

Despite the original belief that the CNS is immune privileged, it has been shown that an active immune response against intracranial tumors can be generated. Hence, there has been a rapid move into various types of immunotherapy: vaccines, oncolytic viruses, checkpoint inhibitory monoclonal antibodies, and adoptive cell transfer with CAR (chimeric antigen receptor) T cells. The great variety of mechanisms of action and targets ensures that an enormous number of combinations are possible, both with other immune-mediated therapies, of the same or different class, and with conventional chemoradiotherapy.

Particular attention was given to:

- ICT-107, a dendritic cell vaccine (as an aside, another research avenue being explored is the possibility that circulating myeloid dendritic cells may be more effective than peptide vaccines and laboratory-generated monocyte-derived dendritic cells).
- Reovirus, an oncolytic virus (which self-amplifies its dose specifically at the target cancer and not in normal cells) in phase I/II in pediatric high-grade glioma and in combination with standard of care chemoradiation in adult glioma. It was originally administered intratumorally, but intravenous administration is now possible, along with granulocyte-macrophage colony-stimulating factor pretreatment. There is also interest in convection-enhanced delivery via microcatheter in diffuse intrinsic pontine glioma.
- Nivolumab, ipilimumab, and other checkpoint inhibitors being used alone or in combination in the portfolio of so-called Checkmate clinical studies—although it was emphasized that there is a need to monitor patients carefully and intervene early if there are side effects.

Immunotherapy is another area where traditional endpoints are of limited value. There is a chronological disconnect between active cellular response (which may occur within a week) and clinical tumor response (unlikely to be evident for weeks or months) and, in any case, there is concern as to whether peripheral response is necessarily indicative of intracranial activity. In any case, the various types of assay still require harmonization and standardization, and the nature of the dynamic immune response is reflected in same-patient variations on different days. In addition, there may be an initial increase in tumor burden due to infiltration by immune inflammatory cells, an indicator of antitumor response, but which could be considered progression using traditional methods of assessment. These issues are being addressed by the newly devised Immune-related Response Criteria (irRC), but the fact that no single biomarker of immune response is ever likely to be available means that other types of assessment, such as neuro-oncology–specific Patient Reported Outcome Measures, need incorporation.

Clinical Advances

Attempts are being made to translate improvement in diagnosis time in children to the adult setting with a "Headache Plus" initiative which incorporates guidelines for identifying headache suspicious of cancer, coexistence of subtle behavioral or cognitive symptoms (possibly using a simple fast semantic verbal fluency screen done in the general practitioner's clinic), a past history of cancer, and visual signs confirmed by optometric evaluation of visual fields and fundi.

Initiatives like these are bringing more elderly sufferers into the potentially treatable pool, and while there is a gradual increase in active treatment of these patients as prognostic factors are elucidated, there is currently very little cognitive/frailty screening to predict their tolerance to therapy—although those practitioners who do

utilize such assessments find the results of value in making treatment decisions. As a result, there were calls for a multidisciplinary geriatric assessment tailored specifically for use in neuro-oncology.

Conclusions

It is not saying anything new to emphasize the enormous challenge that we face. We are not short of ideas—rather the opposite. There are a vast number of hypotheses as to the basis for the heterogeneity and plasticity of glioma and its invasive and migratory capacity. In addition, there are many (cause or effect?) interrelationships among genomics, proteinomics, and metabolomics to be considered, along with the impact of the tumor on normal brain metabolism and, vice versa, the effect of the tumor's microenvironment. There are a plethora of putative treatment targets, but we still seem so far off significant clinical progress.

Our search for the answer has us dancing to and fro. On the one hand, there is the search for ever more specific and highly targeted, personalized therapies (that the National Health Service may never be able to afford?) while, on the other hand, the heterogeneity of the disease soon renders these ineffective, meaning that research either moves back to broader epigenetic strategies or devises ever more complex combinations of modalities with differing, and often cascading, mechanisms of action.

Appendix

The best presentation prize was awarded to Dr Jason Adhikaree, Nottingham Enhancement of Myeloid Dendritic Cells, for "MAPK p38 Inhibition Promotes T Cell Proliferation and Restores Adaptive Immunity in GBM Patients."

The best scientific poster was by Chiara Moriconi, Cardiff University/ School of Pharmacy and Pharmaceutical Sciences: "Caveolin-1 Implicated as a Pro-Invasive Gene in High-Grade Glioma Cell Models: Implementation of a 3D Spheroid Matrix Invasion Assay."

The best clinical poster was that of Ingela Oberg, Cambridge University Hospital NHS Foundation Trust (Addenbrookes): "Nurse-led Telephone Clinics Improve Patient Satisfaction and Enhance Follow-up for Benign/ Low Grade Tumour Patients."

BNOS 2017 will be held 21–23 June in Edinburgh.

Abstracted from a report prepared by Maryanne Roach on behalf of the BNOS Council and BNOS 2016 organising committee. Full version on BNOS website http://www.bnos.org.uk

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A phase III randomized double-blind, controlled study of ICT-107 with maintenance temozolomide in newly diagnosed glioblastoma following resection and concomitant temozolomide chemoradiotherapy

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Phase: III

Study Design

This is a double-blind phase III study where patients with newly diagnosed glioblastoma, eligible for the study, are randomized 1:1 into 2 treatment arms following the standard of care primary treatment with chemoradiation (temozolomide/radiotherapy). Arm 1 will receive ICT-107 in combination with the standard of care, arm 2 will receive temozolomide with a blinded control consisting of autologous monocyte-enriched peripheral blood mononuclear cells.

ICT-107 consists of dendritic cells prepared from autologous mononuclear cells that are pulsed with 6 synthetic peptides derived from MAGE-1 (melanoma-associated antigen 1), HER-2 (human epidermal growth factor receptor 2), AIM-2 (absent in melanoma 2), TRP-2 (transformation related protein 2), glycoprotein 100, and interleukin-13 receptor alpha.

All subjects must be positive for human leukocyte antigen A2.

All subjects must have histologically confirmed glioblastoma and tissue available for assessment for O^6-DNA methylguanine-methyltransferase (MGMT) promoter methylation status prior to randomization (for stratification).

This study will enroll 414 subjects, using a 1:1 randomization. A sample size of 414 will allow detection of a hazard ratio of 0.71 for overall survival (OS), with 80% power and a 1-sided alpha of 0.025. This estimate assumes a median OS of 15.3 months in the control arm (based on the assumption that 35% of subjects will have MGMT promoter methylation), with an improvement to 21.5 months in the ICT-107 arm.

The primary efficacy endpoint is OS. The primary analysis will be conducted in the intent-to-treat (ITT) population and will use a stratified log-rank test, stratified by MGMT status.

The secondary endpoint, of progression-free survival (PFS), will be analyzed in the ITT population using a stratified log-rank test, stratified by MGMT status. In the absence of symptomatic clinical

study synopsis

progression, radiographic progression will be based on central radiologic review. Methods similar to those used for OS will be used for PFS analysis, including Kaplan–Meier estimates and Cox proportional hazards models.

Additional secondary endpoints are:

- OS in the subgroup of subjects with tumors with MGMT promoter methylation.
- OS in the subgroup of subjects with tumors without MGMT promoter methylation.

The trial is currently recruiting.

Understanding the Importance of Supportive and Palliative Care Needs for Glioma Patients and Their Carers

Ingela Oberg

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At recent conferences and through the proverbial neuro-oncology grapevine, there seems to be renewed vigor around quality of life (QoL) issues and the importance of supportive and palliative care needs for our glioma patients—but in reality, what does this really entail for our patient cohort and their carers?

This article aims to explore and condense the myriad of information regarding this topic and to try and create a platform for future discussions to aid collaborative workings across disciplines with the overall outcome of enhancing standards of patient care, leading to improved QoL for both our glioma patients and their carers for end-of-life treatments.

The European Association of Neuro-Oncology is currently looking to produce comprehensive guidelines for end-of-life and palliative care treatment for glioma patients, which will offer more comprehensive, detailed analysis of the whole end-of-life pathway—so watch out for these guidelines in due course!

Let's start with the obvious question . . . how is QoL defined? According to the World Health Organization (WHO),[1] this starts by defining health as "a state of complete physical, mental, and social well-being, not merely the absence of disease." It therefore follows that "the measurement of health and the effects of health care must include not only an indication of changes in the frequency and severity of diseases but also an estimation of well-being, and this can be assessed by measuring the improvement in the quality of life related to health care."

So, if QoL is an estimation of overall well-being, what can we do from a nursing/allied health professional perspective to best support our patients to achieve a good QoL toward the end of their lives? Are there any tangible aspects we as professionals need to consider incorporating into our daily practice when it comes to QoL and palliation? In short, yes—there is a lot we can and should be doing, but it may not be as clear-cut as one would think in regard to ensuring the provision of accurate, written information.

The overall theme emerging from the literature looking at QoL and palliation in glioma patients is to consider not only the needs of the patient, but moreover the needs of the caregiver, as patients' well-being is dependent on the caregivers' well-being.[2] Some caregivers overestimate their coping skills because they are more concerned with the patient's prognosis and QoL, leading to increased carer stress and heightened levels of anxiety.[3]

Philip et al[4] feel that standards of care (including those around palliation) may be enhanced by moving toward a proactive rather than a reactive approach, extending the goals of care beyond medical needs and broadening the focus of care to include family needs. Indeed, this is in line with the WHO,[5] as it stipulates that palliative care should improve the QoL of both patients and their families, something that has also been echoed by the National Institute of Clinical Excellence (NICE),[6] which advocates that both family and caregivers' needs should be assessed and addressed. A recent study by Flechl et al[7] lends further weight to this argument by stating that there is an urgent need for support and training dedicated to caregivers, as they feel there is insufficient information about what to expect, leading to high burnout rates and financial difficulties. The authors even argue that there is a strong case for urgent multidisciplinary support programs to face caregivers' problems, thus helping them to reduce their burden.

Maintaining QoL at the palliative phase of treatment requires a balance between the burden of illness and making resources available to patients to help them reduce that burden. When both these needs and QoL assessments are integrated into patient care, QoL also becomes a goal of care, as the primary focus is no longer on survival alone.[8] One way to help achieve this carer–patient balance is to continually reevaluate the information and support needs of the patients and their caregivers, as these needs change over time with disease progression.[9] Caregivers play a significant role in supporting patients and they in turn need special support themselves (including practical assistance) when symptoms progress and they find themselves transitioning from a family member to a caregiver.[10] This ongoing support may best be served by having one dedicated, authoritative, and central point of contact for continuity of communication with a health professional—most likely to be the specialist nurse.[9]

So, in reality, how are we to achieve this? Some recommendations from the literature are to include carer-specific information; an outpatient clinic to include allied health support; and access to specialized support services for carers of patients with extensive deficits or behavioral challenges.[4] Some of this is already in existence. In the UK, for example, there are already in existence holistic needs assessment clinics focusing on the patients as well as their carers. We have brain tumor support days aimed specifically at informing, educating, and supporting carers and family members. Currently in the UK, one big stumbling block seems to be the (lack of) provision of adequate, targeted neuro-rehabilitation for our glioma patient cohort. This issue remains a challenge in both practical and financial terms, due to the associated high mortality rates. As the condition is often progressive in nature, its cost-effective remit is very limited. However, research has shown that brain tumor survivors can improve function with specialist rehabilitation, with some gains maintained up to 6 months.[11]

Another aspect we must consider, and seemingly improve upon, is early referral to palliative care services and psychosocial support services. This may be influenced by negative attitudes to psychosocial support for which both the patients and health professionals are likely to play a part. Recent research has shown that approximately half of distressed cancer patients do not access psychosocial services, with some blankly refusing, as they see it as a sign of personal weakness.[13] Patients with primary malignant

gliomas are often referred late in the illness trajectory, with few patients getting the option to participate in important end-of-life decisions while they are cognitively and communicatively intact—this may include decisions about preferred place of death and detailing their advance directives.[12] Furthermore, comparatively low referral to and use of psychosocial services may limit patients' abilities to cope with their condition and the changes they experience through their disease trajectory.[13]

So it would seem we have some work to do as health professionals to enhance patients' QoL toward the end of their lives. Understanding glioma patients' use of these services, along with their physical and psychosocial experiences, is essential to developing service delivery models to help meet their needs.[13] Janda et al[14] have gone so far as to make 5 recommendations to improve service delivery for brain tumor patients and their carers: (i) assignment of a dedicated member of the care team or case manager; (ii) proactive dissemination of information, education, and psychosocial support; (iii) access to objective assessment of neuropsychological functioning; (iv) easier access to welfare payments; and (v) services facilitating communication about difficult illness-related topics.

No doubt we all have a central part to play in helping our patients overcome the stigma surrounding psychological support services, and instead encourage them to utilize these services that are there to help and support them (and their carers) in the here and now, but also to help them plan for a dignified end to their lives. A lot of health care systems can seem quite fragmented, with services being widespread and underutilized by health care professionals. One suggestion made above would be to develop a role whose overarching responsibility it would be to assess, coordinate, and refer these patients and their carers to the appropriate support services. In my opinion, this would best be served by a lead neuro-oncology nurse, or nurse consultant.

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The Pediatric Neuro-Oncology Trained Volunteer: A New Multidisciplinary Team Member

By Anita Granero

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To strengthen and improve outcomes for pediatric brain tumor patients and increase patient, family, and staff satisfaction, multidisciplinary hospital teams now have a new ally: the professionally trained volunteer.

Oscar's Angels is a nonprofit charity based in France. The charity cares for and supports—emotionally and financially—families who have children hospitalized with brain and spinal tumors or severe neurological problems or who are in palliative care.

Oscar's Angels is officially certified by the French Ministry of Health's Agence Regionale de Santé (ARS) for its project "The Volunteer's Role in Pediatric Neuro-Oncology," an innovative program providing fully trained, specialist volunteers to work alongside medical teams helping families affected by a pediatric brain tumor.

The Diagnosis of a Brain Tumor: Living in a Parallel Universe

When a child, whatever the age, is diagnosed with a brain tumor, the lives of all the family members simply stop. Everyone is transported to a parallel universe inhabited by doctors, surgeries, drugs, and tubes. But at the same time, the family is expected to just carry on.

Even if the brain tumor journey has a happy ending, when successful treatment is achieved, the scars left by such a dramatic, life-changing experience are seldom completely healed.

Psychological distress associated with their child's cancer has been reported to occur among parents even many years after completed treatment. This is particularly true for the parents of children surviving brain tumors, since these children are frequently exposed to persisting sequelae, due to surgery, radiation therapy, and chemotherapy, but also as a consequence of the tumor itself.[1,2,3]

The quality of care the child receives and the quality of support the family is given during the time spent in the hospital will play a huge role in their future emotional and psychological states.

Feelings of "being alone" and not being properly supported are often reported by families of pediatric brain tumor patients and contribute greatly to their distress. They feel that their needs and concerns should be understood and addressed more effectively.

Parents often point out that during their child's long hospitalizations doctors and nurses are unable to spend real quality time with them. This may be due to the increase in doctors' workloads and to a shortage of specialist personnel.

The rapid evolution in the complexity of care for pediatric brain tumor patients also makes it very difficult for some families to communicate with health care staff and sometimes even to fully understand what is going on.

A New Member of the Hospital Multidisciplinary Team

The presence of professionally trained, specialist volunteers as part of the multidisciplinary approach to the care of pediatric brain tumor patients and their families has long been considered a very positive improvement. The use of volunteers doesn't just offer significant cost savings to hospitals, but it is also likely to enhance quality indicators such as patient satisfaction and safety.[4]

As the medical world evolves, so does volunteerism.

Together with the health care teams at the Children's Hospital of Toulouse in France, Oscar's Angels developed an innovative model of care using volunteers who are specifically trained to work in a hospital environment and are perfectly integrated into the medical teams. This has been particularly successful on the neuro-oncology wards, where children's pathologies are complex and demand a multidisciplinary approach. Holistic care and support for not only the patient but the whole family is often an urgent unmet need.

The Oscar's Angels volunteer program comes at no cost whatsoever for the family or the hospital.

Oscar's Angels–trained volunteers assist and support parents during the diagnostic and therapeutic processes and share with the medical teams all information necessary to care for the family in the best possible way.

The volunteers' primary task is to offer ongoing daily guidance and emotional support during a family's hospital stay and beyond—indeed, all through the child's illness, these volunteers help families understand complex medical information and provide financial assistance when necessary.

The volunteers also help parents deal effectively with the family disruption and turmoil caused by a brain tumor diagnosis, which can lead to marital, sibling, and peer conflicts. Oscar's Angels volunteers can help the family obtain the assistance they need from members of the psychosocial and pediatric teams at the hospital.

Giving an Effective Voice to the Families of Pediatric Brain Tumor Patients

This exceptional, unique, and innovative program is recognized by Toulouse Hospital as essential because it also brings to medical professionals a better understanding of the emotional stress faced by families when their child is in hospital.

The program highlights to health care staff the needs of these families who are experiencing a particularly challenging and difficult time in coping with their child's life-threatening illness.

An Oscar's Angels specially trained volunteer also works with the Pediatric Advanced Care Team (PACT) in Toulouse to provide emotional support for families embarking on end-of-life care for their child.

The volunteer's presence is highly reassuring for the families of pediatric brain tumor patients. Volunteers help families have an effective voice in the medical team. The volunteer is someone whom families can lean on any time they need to do so.

The introduction of a highly trained patient and family volunteer advocate as a legitimate hospital multidisciplinary team member is an additional step forward to professionalized volunteerism, more empathic care, and better outcomes for those whose lives have been touched by a brain tumor.

For more information about Oscar's Angels, see http://www.oscarsangels.com/03_volunteer.php

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Introduction of the Korean Society for Neuro-Oncology (KSNO)

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For the purpose of academic development in the field of neuro-oncology, the Korean Brain Tumor Society (KBTS) was founded in 1991 by neurosurgeons in Korea. The KBTS has played a pivotal role as a place for communication among neuro-oncologists for as long as 25 years. However, the emergence of needs for multidisciplinary approaches to management and research in neuro-oncology offers a new forum for exchange among experts of various fields. With that backdrop, the Korean Society for Neuro-Oncology (KSNO) was founded in 2011 under the banner of a mission to establish the principles of neuro-oncology and provide the best possible care to Korean neuro-oncology patients based on interdisciplinary cooperation and exchange. Currently, a total of 350 members from diverse fields of clinical and basic neuro-oncology research are actively participating in various academic activities.

The KSNO has held regular academic meetings twice a year since March 2011. The spring meeting aims to exchange updated knowledge on neuro-oncology research areas, while the autumn meeting is for educational purposes. The KSNO has provided platforms to run nationwide clinical research and to construct the database for multidisciplinary research funded by government. The KSNO also plays a role as a window of sponsored multi-institutional trials. The KSNO has an infrastructure of a peer-review system for protocols and research coordination, and of a disease-specific multidisciplinary research planning committee.

The KSNO (conjointly with the KBTS) publishes its own official journal, *Brain Tumor Research and Treatment*, which is an open access, peer-reviewed biennial English-language journal indexed on PubMed. The KSNO maintained close relationships with international allies such as the SNO, ASNO, and EANO. Based on a global framework of cooperation among the neuro-oncology societies, KSNO has won the bid to host the WFNOS 2021 meeting, which will take place between May 6 and 9 in COEX (the Convention and Exhibition Center) located in Seoul.

KSNO web: http://www.ksno.or.kr/

BTRT Journal web: http://www.btrt.org/

KBTS web: http://www.braintumor.or.kr/

Figure The memorial photo of the inaugural meeting of KSNO (March 19, 2011, Seoul St. Mary's Hospital, Seoul).

HOTSPOTS IN NEURO-ONCOLOGY

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• Kinetics of tumor size and peritumoral brain edema before, during, and after systemic therapy in recurrent WHO grade II or III meningioma

Furtner J et al, Neuro-Oncology 2016;18(3):401–407.

The efficacy of systemic antineoplastic therapy on recurrent World Health Organization (WHO) grades II and III meningiomas is unclear. The authors performed a retrospective multicenter analysis of serial cranial MRI in patients with recurrent WHO II and III meningiomas treated with different antineoplastic systemic therapies. Growth rates for tumor volume and diameter, as well as change rates for edema size, were calculated for all lesions. A total of 34 patients (23 atypical, 11 anaplastic meningiomas) with a total of 57 meningioma lesions, who had been treated at 6 European institutions, were identified. Systemic therapies included bevacizumab, cytotoxic chemotherapy, somatostatin analogues, and tyrosine kinase inhibitors. Overall, tumor growth rates decreased during systemic therapy by 51% for tumor diameter and 14% for tumor volume growth rates compared with the period before initiation of systemic therapy. The most pronounced decrease in meningioma growth rates during systemic therapy was evident in patients treated with bevacizumab, with a reduction of 80% in diameter and 59% in volume growth. Furthermore, a decrease in size of peritumoral edema after initiation of systemic therapy was exclusively observed in patients treated with bevacizumab (−107%).

Overall, this paper indicates that systemic therapy may inhibit growth of recurrent WHO grades II and III meningiomas to some extent. Bevacizumab had the most pronounced inhibitory effect on tumor growth, as well as some anti-edematous activity. Prospective studies are needed to better define the role of medical therapies in this tumor type.

• Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study

Habets EJJ et al, Neuro-Oncology 2016;18(3):435–444.

Stereotactic radiotherapy (SRT) is expected to have a less detrimental effect on neurocognitive functioning and health-related quality of life (HRQoL) than whole-brain radiotherapy (WBRT). To evaluate the impact of brain metastases and SRT on neurocognitive functioning and HRQoL, the authors performed a prospective study. Neurocognitive functioning and HRQoL of 97 patients with brain metastases were measured before SRT and 1, 3, and 6 months after SRT. Seven cognitive domains were assessed. HRQoL was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and BN20 questionnaires. Neurocognitive functioning and HRQoL over time were analyzed with linear mixed models and stratified for baseline Karnofsky performance status (KPS), total metastatic volume, and systemic disease. Median overall survival of patients was 7.7 months. Before SRT, neurocognitive domain and HRQoL scores were lower in patients than in healthy controls. At group level, patients worsened in physical functioning and fatigue at 6 months, while other outcome parameters of HRQoL and cognition remained stable. KPS less than 90 and tumor volume more than 12.6 cm^3 were both associated with worse information processing speed and lower HRQoL scores over 6 months' time. Intracranial tumor progression was associated with worsening of executive functioning and motor function.

In conclusion, prior to SRT, neurocognitive functioning and HRQoL are moderately impaired in patients with brain metastases. Lower baseline KPS and larger tumor volume are associated with worse functioning. Over time, SRT does not have an additional detrimental effect on neurocognitive functioning and HRQoL, suggesting that SRT may be preferred over WBRT.

• Circulating U2 small nuclear RNA fragments as a novel diagnostic biomarker for primary central nervous system lymphoma

Baraniskin A et al, Neuro-Oncology 2016;18(3):361–367.

Primary central nervous system lymphomas (PCNSLs) are highly aggressive tumors. Chemotherapy has improved prognosis significantly; however, early diagnosis is crucial for effective treatment. Presently, the diagnosis of PCNSL depends on histopathology of tumor biopsies. Based on promising findings about circulating U2 small nuclear RNA fragments (RNU2-1f) as novel blood-based biomarkers for pancreatic, colorectal, and lung cancer, the authors have investigated RNU2-1f in the CSF of PCNSL patients. CSF was collected from patients with PCNSL ($n = 72$) and control patients with various neurologic disorders ($n = 47$). Sequential CSF samples were collected from 9 PCNSL patients. RNU2-1f levels were measured by real-time polymerase chain reaction. As for results, measurement of RNU2-1f levels in the CSF enabled the differentiation of patients with PCNSL from controls by an area under the curve (AUC) of 0.909 with a sensitivity of 68.1% and a specificity of 91.4%. The diagnostic accuracy was further improved by combined determination of RNU2-1f and miR-21, resulting in an AUC of 0.987 with a sensitivity of 91.7% and a specificity of 95.7%. In consecutive measurements of RNU2-1f, which were performed in 9 patients at different stages of the disease course, RNU2-1f CSF levels paralleled the course of the disease.

Overall, these data suggest that the measurement of RNU2-1f in the CSF can be used as a diagnostic marker as well as a possible marker for treatment monitoring. These promising results need to be validated within a larger patient cohort.

• Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma—results from the DIRECTOR trial

Suchorska B et al, Neuro Oncology 2016;18(4):549–556.

The role of reoperation for recurrent glioblastoma multiforme (GBM) remains unclear. Prospective studies are

lacking. The authors have studied the association of clinical outcome with extent of resection upon surgery for recurrent GBM in the patient cohort of DIRECTOR, a prospective randomized multicenter trial comparing 2 dose-intensified temozolomide regimens at recurrence of GBM. Clinical and imaging data from the DIRECTOR cohort ($N = 105$) have been analyzed. Volumetric analysis was performed on gadolinium contrast-enhanced MRI as well as fluid attenuated inversion recovery/T2 MRI and correlated with progression-free survival after initial progression (PFS_2) and post-recurrence survival (PRS). Quality of life was monitored by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BN20 questionnaires at 8-week intervals. Seventy-one patients received surgery at first recurrence. Prognostic factors, including age, promoter methylation of O^6-DNA methylguanine-methyltransferase, and Karnofsky performance score, were balanced between patients with and without reoperation. Outcome in patients with versus without surgery at recurrence was similar for PFS_2 (2.0 mo vs 1.9 mo, $P = .360$) and PRS (11.4 mo vs 9.8 mo, $P = .633$). Among reoperated patients, postsurgery imaging was available in 59 cases. In these patients, complete resection of contrast-enhancing tumor ($N = 40$) versus residual detection of contrast enhancement ($N = 19$) was associated with improved PRS (12.9 mo [95% CI: 11.5–18.2] vs 6.5 mo [95% CI: 3.6–9.9], $P < .001$) and better quality of life. Incomplete tumor resection was associated with inferior PRS compared with patients who did not undergo surgery (6.5 vs 9.8 mo, $P = .052$). Quality of life was similar in these 2 groups.

Overall, surgery at first recurrence of GBM improves outcome if complete resection of contrast-enhancing tumor is achieved.

• A prospective trial of dynamic contrast-enhanced MRI perfusion and fluorine-18 FDG PET-CT in differentiating brain tumor progression from radiation injury after cranial irradiation

Hatzoglou V et al, Neuro-Oncology 2016;18(6):873–880.

The aim of this study was to assess the effectiveness of fluorine-18 fluorodeoxyglucose (FDG) PET-CT and dynamic contrast-enhanced (DCE) MRI in differentiating tumor progression and radiation injury in patients with indeterminate enhancing lesions after radiation therapy (RT) for brain malignancies. Patients with indeterminate enhancing brain lesions on conventional MRI after RT underwent brain DCE-MRI and PET-CT in a prospective trial. Lesion outcomes were determined by histopathology and/or clinical and imaging follow-up. Metrics obtained included plasma volume (Vp) and volume transfer coefficient (K_{trans}) from DCE-MRI, and maximum standardized uptake value (SUV_{max}) from PET-CT; lesion-to-normal brain ratios of all metrics were calculated. The study included 53 patients (29 treated for 29 gliomas and 24 treated for 26 brain metastases). Progression was determined in 38/55 (69%) indeterminate lesions and radiation injury in 17 (31%). Vp_{ratio} ($V_{P\ lesion}/V_{P\ normal\ brain}$, $P < .001$), $K_{trans\ ratio}$ ($P = .002$), and SUV_{ratio} ($P = .002$) correlated significantly with diagnosis of progression versus radiation injury. Progressing lesions exhibited higher values of all 3 metrics compared with radiation injury. Vp_{ratio} had the highest accuracy in determining progression (area under the curve = 0.87), with 92% sensitivity and 77% specificity using the optimal, retrospectively determined threshold of 2.1. When Vp_{ratio} was combined with $K_{trans\ ratio}$ (optimal threshold 3.6), accuracy increased to 94%.

In conclusion, Vp_{ratio} was the most effective metric for distinguishing progression from radiation injury. Adding $K_{trans\ ratio}$ to Vp_{ratio} further improved accuracy. DCE-MRI is an effective imaging technique for evaluating nonspecific enhancing intracranial lesions after RT.

• Supratentorial clear cell ependymomas with branching capillaries demonstrate characteristic clinicopathological features and pathological activation of nuclear factor-kappaB signaling

Figarella-Branger D et al, Neuro-Oncology 2016;18(7):919–927.

Clear cell ependymoma is one of the 4 main histological subtypes of ependymomas defined by the World Health Organization (WHO) classification of tumors of the CNS. DNA methylation profiling can distinguish 4 subgroups of intracranial ependymomas, including supratentorial (ST) ependymomas with Yes-associated protein 1 fusion, ST ependymomas with fusion of v-rel avian reticuloendotheliosis viral oncogene homolog A (RELA), posterior fossa ependymomas with balanced genome, and posterior fossa ependymomas with chromosomal instability. In addition, trisomy 19 is a genomic hallmark of ependymomas with rich branching capillaries. The relations of histological and molecular subtypes is still unclear. The authors have reported a series of 20 ependymomas histologically defined by clear cells and branching capillaries. A strong male predominance was observed. Median age at surgery was 10.4 years (range, 0.8–68.4). All cases were ST, cortical, contrast enhancing, and most often frontal, cystic, and calcified. All tumors qualified as WHO grade III. Some of them exhibited neuronal differentiation. Trisomy 19 was recorded in 13 cases. All samples strongly accumulated p65RelA protein within nuclei, indicating pathological activation of the nuclear factor-kappaB pathway. A causative C11ORF95-RELA fusion was detected in almost all cases. Median progression-free survival and overall survival were 11.4 years (95% CI: 5.1–17.8) and not reached, respectively.

In conclusion, ST clear cell ependymomas with branching capillaries display characteristic clinicopathological features and are associated with pathological activation of nuclear factor-kappaB signaling, which may indicate a potential novel target for therapy in these patients.

Interview for the World Federation of Neuro-Oncology Societies magazine

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How would you suggest treating these 2 patients with low-grade gliomas (LGGs)? We asked several specialists to give us their advice, the neurosurgeon Hugues Duffau from Montpellier, France; Brigitta Baumert, radiation oncologist from Bonn, Germany; and one of the principal investigators of the European Organisation for Research and Treatment of Cancer (EORTC) study 22033 that randomized patients with high risk LGG to get either radiation therapy or dose dense chemotherapy with temozolomide. Both responded to our invitation—in totally different ways.

Unfortunately, we did not get answers from 2 American colleagues who also were solicited—but commissioning articles for a "newborn" magazine cannot be a 100% success story. Our request most probably was not noticed among so many requests for contributions by so many journals. We therefore would welcome statements to the 2 cases also in further issues of the *WFNOS* magazine, to open a discussion of the management of challenging clinical cases.

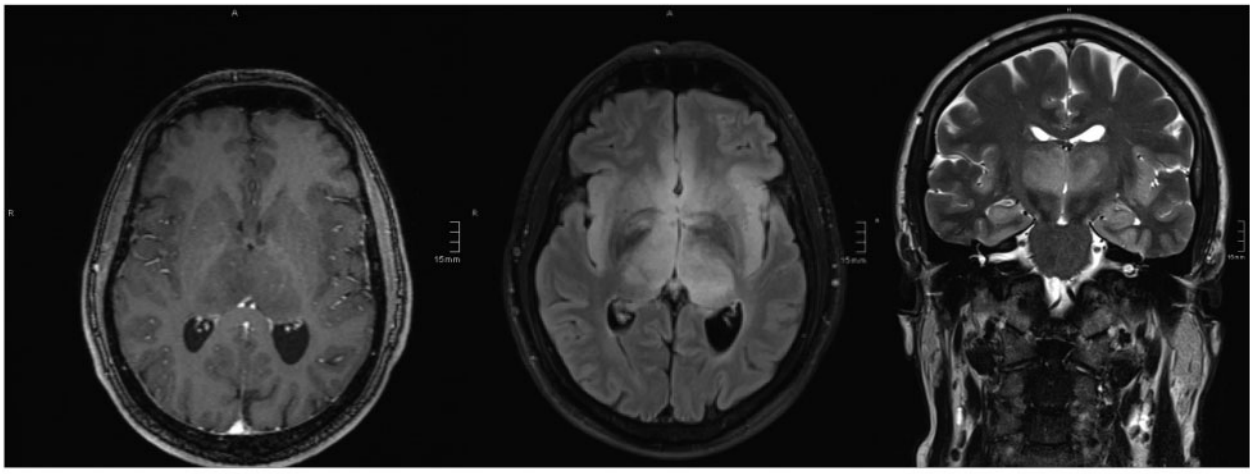
Our request was:

I would ask you to comment on the treatment options and your personal treatment or follow-up recommendations for 2 patients with LGG for which some MRI scan pictures and the neuropathology reports are attached.

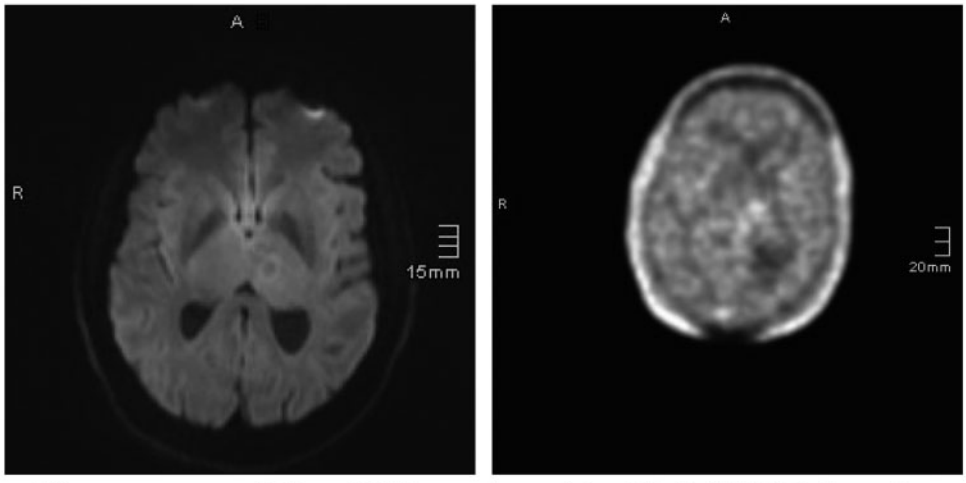
Low grade gliomas

Pat 1

Male patient, born 1964, brought by his colleagues
because he forgot his working tasks



A biopsy was done

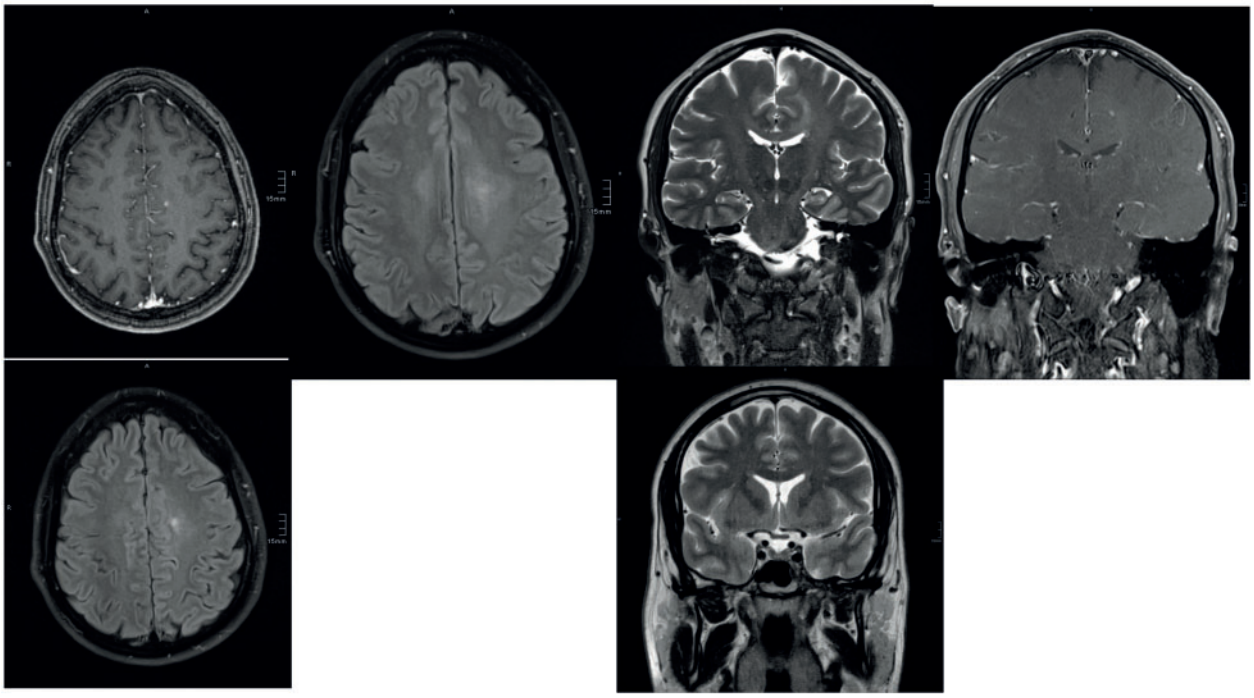


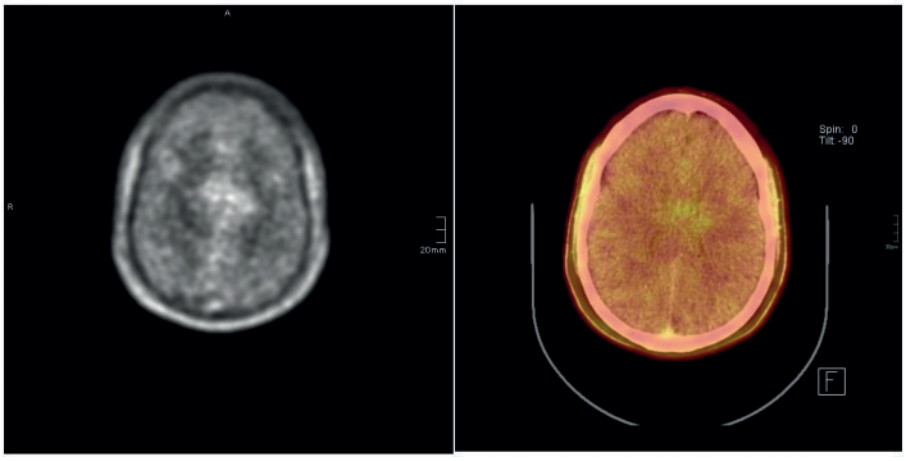
- Diffuse astrocytoma, IDH wt, H3K27 mutation positive, MIB-1: 15%, MGMT ongoing

Low grade gliomas

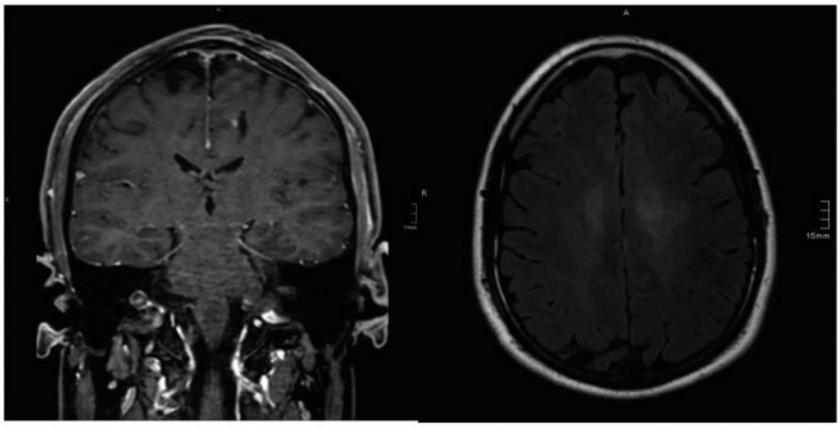
Patient 2

Male patient, born 1977,
completed two academic studies considered as one of the coming shooting stars at his university
grand mal seizure during night, no other symptoms





A biopsy was done

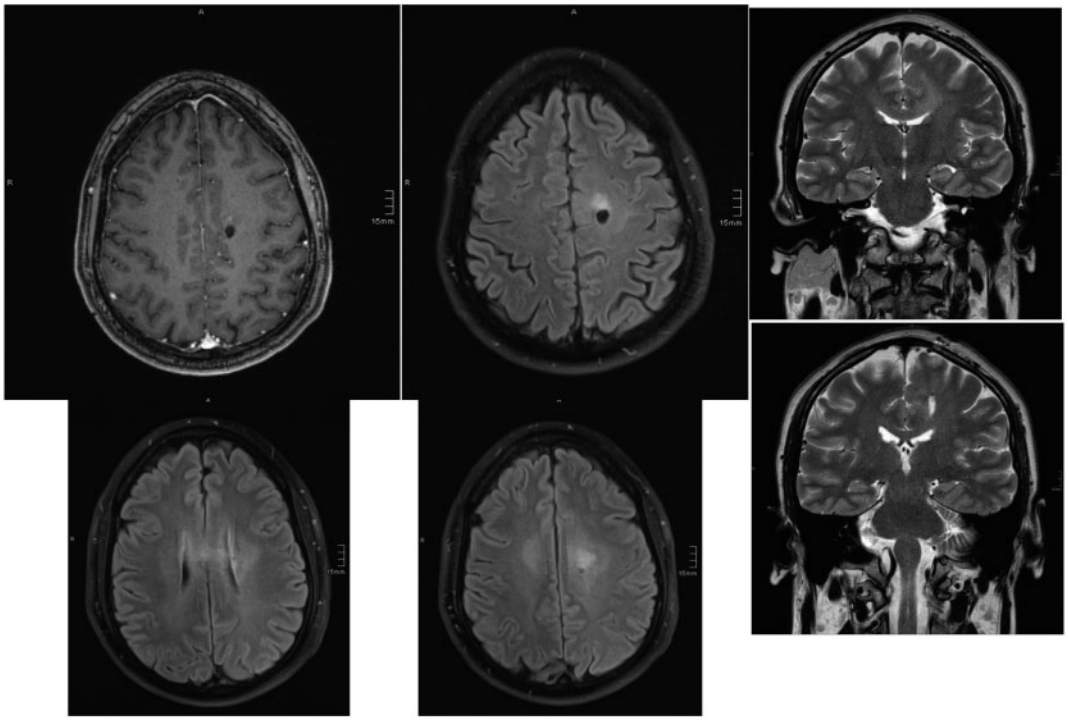


Diffuse astrocytoma, MIB 3.2%

NoIDH mutation, MGMT promotermethylation not methylated

How to treat this patient?

4 months later



Case Number 1

Summary: Patient 1 has a gliomatosis cerebri involving both hippocampal regions and shows tremendous forgetfulness, letting him miss his hospital appointments.

History: Male patient, born 1964, brought by his colleagues because he forgot his working tasks. A biopsy showed a diffuse astrocytoma, isocitrate dehydrogenase (IDH) wild-type, H3K27 mutation positive, methylation-inhibited binding protein 1 (MIB-1) 15%, O^6-DNA methylguanine-methyltransferase (MGMT) testing ongoing.

Treatment proposal by Hugues Duffau

Surgery is indicated in none of the two cases, due to a wide and bilateral diffusion in both patients.

Treatment proposal by Brigitta Baumert

This 52-year-old male patient suffers from extensive neurocognitive symptoms in the form of short-term memory dysfunction, which has resulted in a major impact on his daily life and work. MRI of the brain shows bilateral hypodensities in both hippocampal regions on T1-weighted images, no uptake of contrast media, and more extensive tumor infiltration beyond the hippocampal region on fluid attenuated inversion recovery (FLAIR) images. Histology classifies the tumor as a low-grade astrocytoma WHO grade II and IDH wild-type astrocytoma with a slightly increased MIB-1 index; alpha thalassemia/mental retardation syndrome X-linked (ATRX) was difficult to define. With the positive H3K27 mutation the tumor was classified as a mutant H3K27 diffuse midline glioma according to the new WHO classification of CNS tumors.[1] Earlier these were diffuse intrinsic pontine glioma, mainly arising in children, but sometimes also seen in adults. Reported molecular features of IDH wild-type and K27 mutation are worse prognostic markers leaning more toward the presence of a higher-grade glioma.[1,2]

In the absence of specific therapeutic options for K27 mutated midline glioma and the high MIB-1 index pointing to a higher-grade glioma, the presence of a higher age, >40–50 years, and present neurological uncontrolled symptoms, the therapeutic approach should be analogue a high-grade glioma with combined radiotherapy and chemotherapy with temozolomide (Stupp scheme) in analogy to the high-grade noncodeleted glioma. A potential positive MGMT methylation status would support this proposal. The radiation treatment fields would be relatively large and therefore I would propose to use a lower daily radiation dose with a 33 × 1.8 Gy fractionation scheme. As K27 mutations of thalamic tumors in younger adults transport a better prognosis than the same mutation in brainstem gliomas,[3,4] the total radiation dose could eventually be reduced to about 56 Gy seen the large radiation treatment fields needed to cover the whole tumor area.

Case Number 2

Summary: Patient 2 is a brilliant academic person, extremely busy in his career and has no complaints at all and no more seizures since the first, diagnostic seizure.

History: Male patient, born 1977, completed 2 academic studies and being considered as one of the up-and-coming shooting stars at his university, suffered a grand mal seizure during the night, no other symptoms. A biopsy showed a diffuse astrocytoma, MIB 3.2%, no IDH mutation, MGMT promoter methylation: not methylated.

Treatment proposal by Hugues Duffau

Surgery is indicated in none of the two cases, due to a wide and bilateral diffusion in both patients.

Treatment proposal by Brigitta Baumert

This 37-year-old male patient was diagnosed with a low-grade astrocytoma WHO grade II. Aside from a grand mal seizure suffered only once so far, he has no other symptoms and is not restricted in his daily life. However, molecular markers with the absence of an IDH1 mutation and MGMT methylation indicate a less favorable prognosis. On MRI, a small tumor on FLAIR images is seen with a very small area of contrast enhancement on T1-weighted images. The younger age of the patient, <45–60 years, the small tumor extension, and the oligosymptomatic presentation with a single seizure only are favorable prognostic markers. Based on the clinic presentation and the fact that this is an LGG, it can be decided to postpone treatment and decide on a wait-and-watch strategy. However, the tumor has no IDH mutation and is thus classified as a diffuse astrocytoma IDH wild-type. There are 3 prognostic subgroups within the group of LGG based on their molecular profile: IDH wild-type, IDH mutant, and 1p/19q noncodeleted and IDH mutant/codeleted, with increasing prognosis from the first subgroup.[5,6] For the middle group of IDH mutant/noncodel, radiotherapy had been shown to significantly postpone progression compared with chemotherapy with temozolomide alone.[6] Adjuvant chemotherapy after radiotherapy had been shown to result in a large survival benefit.[7]

This patient should therefore receive radiotherapy first, followed by adjuvant chemotherapy with with PCV (Procarbazine, CCNU, and Vincristine). Based on the clinical parameters (low-risk profile), treatment can be given at the time of progression—after having evaluated the possibilities of surgical resection.

References

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7. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med. 2016; 374(14):1344–1355.