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Gac Med Mex. 2015;151:376-87

First Mexican consensus on recommendations of the multidisciplinary care of patients with glioblastoma multiforme (GBM): Mexican Interdisciplinary Group on Neuro-Oncology Research (GIMINO)

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Abstract

Glioblastoma multiforme is one of the most aggressive central nervous system tumors and with worse prognosis. Until now, treatments have managed to significantly increase the survival of these patients, depending on age, cognitive status, and autonomy of the individuals themselves. Based on these parameters, both initial or recurrence treatments are performed, as well as monitoring of disease by imaging studies. When the patient enters the terminal phase and curative treatments are suspended, respect for the previous wishes of the patient and development and implementation of palliative therapies must be guaranteed. (Gac Med Mex. 2015;151:376-87)

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KEY WORDS: *Glioblastoma multiforme. Brain malignant neoplasms. Brain tumor. Bevacizumab. Astrocytoma Grade IV.*

Introduction

Glioblastoma multiple (GBM) is the most common tumor of the encephalon; its main feature is predominant astrocytic differentiation, although GBM secondary forms can be the result of astrocytic, oligodendroglial or mixed tumours transformation.

This is the first problem we find when adressing primary tumors of the nervous system, since morphological classification appears to be insufficiently satisfactory to understand the biology of tumors and to know the therapeutic implications and prognosis for each case in advance.

Histopathological definition of GBM, however, follows the criteria proposed by the World health Organization (WHO), which defines it as "the most common encephalon primary tumor with predominating astrocytic differentiation". It is basically characterized by atypia, pleomorphism, mitotic activity, vascular thrombosis, microvascular proliferation and necrosis.

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Date of modified version reception: 06-10-2014
Date of acceptance: 20-10-2014

Malignant glioblastoma accounts for a very important percentage of intracranial neoplasms, although there is no established record of cases. As up to date, gliastoma is known to account for 12-15% of intracranial neoplasms and 60-75% of astrocytic tumors.

The prevalence of glioblastoma in the USA and Europe is 3-4 new cases per 100,000 inhabitants per year, although these data may vary according to the country. In the case of USA, for example, the number of new cases is 2.96, whereas in Switzerland it is around 3.55. A population-based study conducted in Zurich (Switzerland) reported a glioblastoma incidence peak at 61.3 years of age, and it also found that more than 80% of affected patients were older than 50 years. On the other hand, only 1% of glioblastoma-diagnosed subjects were younger than 20 years. This study also concluded that this type tumor was more common in men than in women[1].

Glioblastoma can appear in two forms: primary, with no evident precursor lesions, or secondary, owing to transformation of a diffuse, lower grade glial tumor.

Due to its infiltrative nature and relationship with cerebral functions, this type of tumor is characteristically not amenable to complete resection; due to its high capacity for spreading, survival is less than one year in 50% of cases.

Once the primary or secondary glioblastoma diagnosis has been established, survival is similar, although, in the latter, total survival depends on the grade of the original lesion that generated the glioblastoma.

If we analyze aspects related to the genetics of the tumor, we observe a large number of mutations occurring; on one hand, oncogenic factors are gained and, on the other, oncogene-protecting factors are lost. The list of gene mutations is long, both for primary and secondary gioblastoma.

With regard to its location, glioblastomas can be observed in the subcortical region, in any of both hemispheres. Tumor location varies according to the cerebral region: 31% of cases are found in the temporal lobe; 24%, in the parietal lobe; 23%, in the frontal lobe; and 16%, in the occipital lobe. The presence of glioblastoma in the fronto-temporal area is also frequent.

From its original location, the tumor infiltrates through the white substance tracts and, through the corpus callosum, it invades the contralateral hemisphere. In children, it is not infrequent for glioblastomas to locate in basal ganglia and the thalamus. Other rare locations of the tumor are the ventricles, the brainstem, the cerebellum and the spinal cord, which correspond to exceptional regions where gliblastomas can be found.

Clinical manifestations of patients affected by glioblastoma are varied. Many of the symptoms that can occur are the consequence of intracranial hypertension (headache, nausea, vomiting, alertness disturbances) or locoregional involvement by compression, invasion and edema (seizures, neurological deficit, changes in higher mental functions or any other data consistent with neurological focalization).

Clinical evaluation of the patient with glioblastoma

Clinical evaluation of patients affected by glioblastoma is integrally performed taking into account general, neurological and higher mental functions examination.

When the patient presents with data consistent with intracranial hypertension, a quick and efficient intervention must be implemented in order to ensure the patient's wellbeing, by offering diagnostic auxiliary studies and early therapeutic measures.

After these measures have been established, an improvement of the patient's clinical status can be observed, both in intracranial hypertension and in neurological focalization data; hence, assessment of the patient should be dynamical according to the response, not to initial management.

With clinical status improvement, the patient's management can advance to more complex studies, such as neuropsychological evaluation, language studies or studies where the patient's participation is definitory, such as functional magnetic resonance imaging (MRI).

The more complete the work-up of a patient, the more the data available for a therapeutic proposal to be made, as well as for research projects.

General status of the patient is reported by consensus based on the Karnofsky performance status (KPS); also by consensus, a patient in "good shape" is considered to me that with a KPS higher than 70, or with a score in the Eastern Cooperative Oncology Group (ECOG) scale of 0 to 1, which means the patient maintains his autonomy and is able to engage in daily activities normally[29,30].

Clinical assessment and follow-up

Neurological clinical evaluation is the basis for assessment of the status of the patient who bears a tumor lesion. From this assessment, performance status and quality of life are deducted. The neurological evaluation has to be objectively recorded, in addition to the previously mentioned performance and general status scales.

The patients also have to undergo a survey on quality of life and an examination on neurocognitive aspects, i.e., those neurocognitive manifestations associated with the pre-treatment status and after all modalities of complementary treatment must be assessed[3,4].

The objective is double: on one hand, to assess quality of life with progressive disease (PD) and complementary treatment, and on the other, to assess the patient's neurocognitive status. To carry out this clinical evaluation and follow-up, we have a neurocognitive assessment battery, where tests such as the Hopkins test, the trail making test or the multilingual aphasia examination are performed.

Treatment profiles

In the choice of treatment, it is essential making a differentiation depending on the age, performance status of the patient (KPS), general medical status, size and location of the lesion, possibilities of maximum safe resection and the patient's willingness according to the probabilities of survival and functional risks.

Surgical considerations

In the treatment of glioblastoma, surgery has three objectives:

- Source of a sample for histopathological analysis. Either by open surgery or navigation- or stereotaxis-guided biopsy (minimal invasion); useful material should tried to be obtained (in terms of quantity and quality) for histopathological diagnosis. In case of minimally invasive biopsies, efforts should be made to try taking the sample from sites that, according to imaging studies, more information will provide on the biopsied lesion. Samples taken from necrotic areas, areas with cerebral edema, areas near the subarachnoid space or any other area with direct involvement or bleeding that puts the patient's life or function at risk. Participation of all members of the multidisciplinary neuro-oncology group is highly important in the selection of the best region to be biopsied.
- Decrease of intracranial pressure and compression on adjacent cerebral structures. Resection of the lesion is indicated when its compressive effect compromises the patient's life or function. Surgery has been shown to be able, and should offer an improvement of the patient's condition versus minimally-invasive biopsy[28,7,8]. Improvement of the patient's clinical conditions by means of surgery, as well as reduction of the size of the lesion, allow having access to other complementary therapeutic methods better opportunities of response[27].
- Improvement of the overall survival prognosis. The term maximum safe resection encompassess the concept of resecting the most amount of tumor possible while preserving the patien's function. An aggressive resection at the expense of clinical and functional deterioration of the patient is not justified. Necessary studies have to be performed and make use of the necessary surgical techniques to attain this objective. The probabilities of resection, the type of preparation and the approach have to be multidisciplinarily discussed in order to reach this goal. In case of not having the necessary technological and human resources available, the patient should be referred to an adequately equipped center.

Data that lead to assume that a diagnostic and therapeutic functional approach of the lesion is required are:

- Closeness to eloquent areas (motor, language, sensory, visual).
- Data consistent with neurological focalization of the patient.
- Deep location of the lesion (basal ganglia, ventricles, brainstem).

Glioblastoma primary treatment

Patients younger than 70 years with autonomy (KPS > 70)

Tumor resection

The choice of treatment in patients younger than 70 years is based on American guidelines' recommendations[5]. In the first place, surgical excision or resection is practiced as extensively as possible. Although years ago, the prognostic impact of surgery was questioned[6], different studies confirm that, in high grade gliomas, extensive surgery is related to a better prognosis[7-9].

After surgery, recommendation 2B (non-standard) can be followed, with the placement of carmustine wafers in the post-operatory cavity[10]. This step is carried out only in those patients in whom complete resection was possible. It is not carried out in patients with partial surgical resection, since cerebral edema-related problems can be produced, leading to intracranial pressure increase.

Glioblastoma complementary treatment

After surgery, in patients younger than 70 years with KPS higher than 70%, the pharmacological treatment to be used is determined based on the results of Stupp et al. classical work of 2009[12], where the results of an international, multi-center open, randomized, controlled phase III clinical trial were published. The conclusions of this work allowed for what is considered to be the standard treatment for glioblastoma patients younger than 70 years and adequate autonomy to be defined, according to the results of the KPS. In the study, the patients were divided in two arms: the first was treated with radiotherapy, and the second, with radiotherapy concomitant with temozolomide at a 75 mg/m^2 dose, and then with six cycles of temozolomide at 150-200 mg/m^2 doses.

The impact of this study allowed for a survival increase to be observed in patients of the second treatment arm (14.6 vs. 12.1 months). Although this improvement was not too large, the choice of this treatment as standard is because the conclusions of the study by Stupp et al. yielded other important results. On one hand, 1% of the patients who followed this treatment were still alive at 5 years of the glioblastoma diagnosis, whereas, on the other hand, 2-year survival was achieved by 25% of the patients. Additionally, the impact on survival was greater in those patients who had methylation in the O6-methylguanine-DNA-methyltransferase (MGMT) promoter[13].

Anti-angiogenic therapies as primary treatment

Other of the possibilities studied in recent times has been the use of treatments whose pharmacologic goal is to target the arrest of angiogenesis. In particular, the AVAGLIO study is a multi-center, international, randomized phase III clinical trial that has shown good results in patients with newly-diagnosed glioblastoma[31,32]. Patients participating in the study were randomly assigned to two treatment arms. In the first, they received the standard therapy established in the study by Stupp et al., together with placebo, at a dose of 10 mg/kg intravenously (i.v.) every two weeks, to continue with a treatment with placebo for 3 additional weeks. The second arm followed Stupp et al. standard treatment, together with a concomitant dose of bevacizumab of 10 mg/kg i.v., to continue the treatment with this drug for 3 additional weeks.

The results demonstrated an improvement in the patient's progression-free survival, as well as in quality of life-associated parameters, largely due to a reduction in the use of steroids associated with the treatment with bevacuzumab. However, no improvement in global survival was observed; therefore, according to American guidelines, it should be considered as an alternative therapy in some cases, but it should be regarded as standard treatment[31-33].

Currently, bevacizumab is recommended for the treatment both of newly-diagnosed glioblastoma and recurrent glioblastoma. In the first case, the dose of Avastin, in combination with temozolomide and radiotherapy for 6 weeks, is 10 mg/kg body weight administered once every two weeks. After interrupting the treatment for 4 weeks, bevacizumab therapy is resumed (10 mg/kg body weight administered once every two weeks) in combination with temozolomide up to 6 four-week cycles. Once these 6 treatment cycles are completed, Avastin (15 mg/kg body weight given once every three weeks) continues to be administered as monotherapy until PD.

Avastin is also indicated for the treatment of recurrent glioblastoma, at a dose of 10 mg/kg body weight administered once every 2 weeks or 15 mg/kg body weight administered once every 3 weeks. In this case, maintaining Avastin treatment is recommended until PD of the underlying condition.

Patients older than 70 years

Patients older than 70 years with KPS > 70

In the case of the treatment of elderly patients preserving their autonomy (i.e., with a KPS score higher than 70), standard therapy follows the proposal of the RSP/ANOCEF[14] clinical trial (national, multi-center, randomized, open, controlled phase III trial). Following this treatment is also recommended if the glioblastoma has been recently diagnosed.

Standard therapy for these patients is based on radiotherapy (50 Gy); without temolozamide having to be added to the treatment, individuals participating in this trial had a survival improvement[14].

Other clinical trials assessed the possibility of reducing the radiotherapy dose (in the standard case it is 60 Gy). A national, multi-center, randomized, open, controlled phase III clinical trial conducted in Canada, which recruited people older than 60 years with KPS > 50, assessed, as treatment arms, using radiotherapy at 60 Gy in 30 sessions on one hand, and on the other, 40 Gy in

15 sessions[15]. The results showed no significant differences between both treatment groups and steroids requirements were lower in the group undergoing the accelerated radiotherapy course.

A second clinical trial conducted by the NORDIC group (international, multi-center, randomized, open, controlled phase III trial) recruited patients older than 60 years to test three therapy options: 60 Gy in 30 sessions, 34 Gy in 10 sessions and 6 temozolomide cycles. The results of this study, where the use of standard radiotherapy was compared with the hypofractioned use of radiotherapy against temozolomide, also failed to demonstrate significant differences. Something that remains clear is that standard treatment in this type of patients is essentially based on radiotherapy[34].

Patients older than 70 years with KPS < 70

In the case of individuals older than 70 years with no personal autonomy (KPS < 70), the treatment will be different to that for previously quoted cases. Conventionally, standard therapy was based exclusively on palliative care. However, currently, it appears that the most appropriate treatment consists in using temozolomide. The use of this chemotherapy offers global survival of 6 months; additionally, in 25% of cases the patients recover their autonomy[34].

Other chemotherapeutic alternatives

There are other alternatives of chemotherapeutic drugs that can be considered. For example, the procarbazine, lomustine and vincristine (PCV) combination protocol[16], used in the treatment of anaplastic glioma, is considered the most favorable alternative, although lomustine is not directly available in Mexico.

Another studied treatment alternative, which is interesting from the treatment economical costs point of view, is the use of carboplatin[17]. The poor results of a trial (partial response [PR] of 12%, stable disease [SD] in 19% of the patients or PD in 69% of the cases) lead to think that, in spite of being able to be regarded as an alternative treatment, using the PCV protocol should be preferred.

Treatment follow-up

Patients on complementary treatment must be followed with clinical assessments, MRI scans and laboratory tests and, in special cases, with positron-emission tomography (PET) scans. Follow-up starts with the post-operative control MRI scan (see section on neuroimaging assessment), which is highly useful to calculate the volume of residual lesion after surgery. Subsequently, the patients should be assessed with non-multimodal MRI every 2-3 months to find out treatment response and to evaluate the tumor's behavior.

While the patients remain on treatment with chemotherapy, they should be clinically assessed and by means of laboratory tests prior to every chemotherapy dose (every 3-4 weeks), in order to evaluate the absence of side-effects produced by chemotherapy.

In case of doubts on the behavior of the lesion in routine MRI scans, a multimodal MRI scan including diffusion, perfusion sequences (rCBV) and spectography of uncertain zones might be indicated. In addition, information of metabolic activity of the lesion can be complemented using PET with fluorothymidine or methionine, all this with the purpose of clarifying the nature of contrast enhancement in the T1 sequence or the hyperintensity zones in the T2 sequence.

Multidisciplinary neuro-oncological assessment is always advisable in controversial cases in order to determine, by consensus, the type of tumor evolution and the therapeutic behavior to be followed.

Secondary treatment of gliastoma with radiotherapy

Radiotherapy in patients younger than 70 years

Radiotherapy is a treatment that has been used since the seventies, once the surgical resection is completed. Although, as previously mentioned, the main prognostic factor in these patients is surgery, there was in fact empirical knowledge suggesting that radiotherapy offered good results. However, it is important mentioning that patient prognosis is different depending on the age and performance status, two parameters to be strongly considered both in the choice of treatment and subsequent follow-up.

Currently, radiotherapy is used as standard treatment and complementary to chemotherapy. As previously mentioned, standard therapy usually consists in radiotherapy at 60 Gy (this offered the best survival results, since morbidity was hardly considered)[18], although there are several studies trying to advance towards new radiotherapeutic approaches with different doses and fractionings.

It should be noted that tolerance to this secondary treatment has largely improved over the past few years

due to advances in the technique itself. In addition, the treatment with radiotherapy has been associated with chemotherapy for years, since nitrosureas have better response with alkylating agents.

On the other hand, in spite of standard radiotherapy being applied at 60 Gy, the fact is that in recent years, initiatives have emerged trying to demonstrate the likely efficacy of this secondary treatment at other doses. In particular, a study published in 2002 assessed radiotherapy dose escalation at 70, 80 and 90 Gy[19], with a mean survival (MS) of 12 months. No necrosis was observed and survival found was similar to that in previous studies. However, the pattern of failure was local in this case.

Another strategy is based on using hypofractioning, which entails increasing the biological dose by increasing the daily fraction. Dose escalation is interesting in this case, since acute effects are tolerated, but chronic effects are devastating. Over the last years there have been different studies testing the effect of hypofractioning up to a radiotherapy total dose of 60 Gy, by varying the fraction size. The results attained were interesting, since a 14-month improvement in MS was observed[20], and the research entered phase II. However, the conclusions of these studies, although good, do not indicate that this treatment approach has potential enough to become the standard treatment.

Radiotherapy for senile patients

In the treatment of patients older than 70 years considered as senile, the patient's autonomy status is strongly taken into account: if it is good (KPS > 70), conventional therapy is the most adequate, but if the patient has a KPS < 70, regardless of age and other possible treatments, radiotherapy emerges as a very interesting treatment alternative.

In these cases, radiotherapy is planned in accordance with the results obtained in neuroimaging studies, by MRI. European guidelines recommend for MRI to be practiced within 2-3 weeks in order to verify if there is edema or not; if this is the case, there will be two phases of treatment (the first targeting edema and the second the tumor). Conversely, American guidelines recommend for the MRI scans to be performed within the first 72 h after surgical intervention, in order to avoid edema to be visualized. The difference between both types of guidelines is not in different responses to the treatment, but rather in how easy the planning is for subsequent interventions.

Glioblastoma secondary treatment with radiosurgery

Introduction

When secondary treatment with radiosurgery is being considered, two important messages have to be interpreted. On one hand, radiosurgery is noth the ideal therapy, but in a small percentage of cases where tumor recurrence is also observed, this technique may be used as treatment strategy.

The principles of radiosurgery are basically two: reoxygenation and redistribution, although there are also other less important related factors (regeneration, radiosensitivity and repopulation).

With regard to reoxygenation, consideration should be paid to the fact that, due to tumor rapid growth and slowness of the neaoangiogenesis process, necrosis and hypoxia are produced in the central part of the tumor; therefore, oxygen is scarce and thus, the free radicals-mediated mechanism (indirect route for radiation action) does not function adequately. This is the reason these neoplastic cells are basically resistant to this treatment.

Taking into account the second parameter, redistribution, things happening in all different cell-cycles have to be analyzed, since each one of these stages also alters the outcome of radiation. A cell in the synthesis phase (S) is more resistant to the free radicals action than, for example, a cell in the mitotic phase (M).

In this context, if after surgical resection 1 cm^3 residual is left and radiation is applied, some cells will be treatment-resistant (in particular, those in the synthesis phase and with low oxygen level). Conversely, if several sessions of radiation are applied, it will be more likely for most cells to be in different phases and, therefore, more cells will be able to be eliminated than with a single session. This is the big difference between radiotherapy and radiosurgery and also, for this reason, radiosurgery is less recommended, except in very special cases.

Radiosurgery administration

To administer radiosurgery, some authors consider preferable considering a 2-cm planning-target volume (PTV), while others argue on the convenience of using a 4-cm PTV. Anyway, the standard measure currently used is the following: 2 cm beyond the formation of the edema itself.

In this sense, the utility of the technique known as PET should be highlighted (especially used with thymidine)[21], since it helps to reduce the field to be irradiated, by improving tumor location. Thanks to this innovative technology, healthcare professionals are able to define the most metabolically active region, in order to irradiate only the required zone, although this methodology can also cause for false positives to appear.

At the moment of considering treatment with radiosurgery, the same occurs as in the case of radiotherapy, since there are two guidelines depending on whether recommendations are European or American. In the case of the European school, up to 5 fractions are considered, whereas the American guidelines recommend a single dose. Anyway, radiosurgery can be applied either as initial adjuvant therapy or rather as treatment after tumor recurrence.

Initial therapy with radiosurgery

There is a large variety of studies with regard to time and doses to be applied, in addition to the volume considered to be irradiated. The design of the treatment with radiosurgery will be very different depending on these three parameters,

Different treatment combinations have been evaluated[22]. For example, success was analyzed after administering radiosurgery followed by radiotherapy, but this is no longer used because it doesn't provide beneficial results. A different approach, where radiosurgery would follow radiotherapy, seems to indicate that it also fails to be beneficial in the first 8 weeks of treatment. In other words, it's still too soon to clearly determine the role of radiosurgery and further clinical trials ar needed to confirm or refute these initial works.

So far, the studies are methodologically poorly designed, since they show selection biases. Such is the case of a trial comparing radiotherapy with radiotherapy plus radiosurgery. Survival was 13 versus 25 months[23], a difference that cannot be considered significant if the design of the study is not the most appropriate from the methodological perspective.

Treatment of tumor recurrence with radiosurgery

In the case of recurrent glioblastoma, once the neuroimaging study has been performed, radiosurgery can be applied (usually at 18 Gy doses); in those cases, survival has been observed to be of 8-10 months. However, it is important to consider that these are methodologically deficient studies, since they are not clinical trials and, ultimately, the volume to irradiate shows important variations depending on each case.

If the recurrent tumor has a small volume (less than 4 cm^3), the observed benefit of radiosurgery is larger. It is also true that the possibility of complications increases but, in exchange, the benefit surpasses the risk, given the bad prognosis for patients. Currently, there are several studies demonstrating the benefit of radiosurgery in combination with targeted therapy, but their results have to be further analyzed.

Inclusion criteria for the treatment with radiosurgery

As previously mentioned, therapy with radiosurgery is not very frequent, and patients receiving it should meet some requirements[24].

First, they must have a specific degree of autonomy (KPS > 60) and small tumor volume, which should always be smaller than 4 cm (longest diameter); in addition, subependymal dissemnation should not be observed and, finally, location should not be adjacent to the brainstem or optic tracts. This final criterion is recommended due to the potential risk of the patient suffering radionecrosis, which can considerably affect his/her quality of life.

In any case, radiosurgery may be considered as the last treatment option, and only in those cases where recurrence is local and surgical resection is not desired. For these reasons, the percentage of patients who benefit from this technique is really modest. Its prognostic impact is mainly focused on the survival factor, either administered alone or with a targeted therapy or with chemotherapy (clinical trials are needed in order to confirm any of these options).

Finally, there are also works underway on neoplastic growth mathematical reconstruction, which might help for a more accurate administration of radiosurgery. This way, extension to other encephalic regions might be prevented.

Neuroimaging assessment

Technical considerations

Control MRI schedule

The first post-operative MRI scan should be made within the first 48 h after the completion of surgery. In addition to the usual follow-up sequences, a diffusion

sequence is performed looking for the presence of zones with ischemia that might be source of subacute contrast enhancement and could be mistaken with progression and to be considered in case of starting treatment with anti-angiogenic drugs as first line of complementary treatment[25].

There is controversy with regard to the need for a control MRI scan at the end of radiotherapy treatment, but performance of the first control MRI scan is considered mandatory after the 2nd-3rd cycle of coadjuvant chemotherapy. Subsequently, MRI controls should be practiced every 2 or 3 months to assess patient responses to the received treatments.

Technical characteristics of MRI

Control MRI scans should be performed with the same MRI equipment, the same sequence-acquisition protocol, the same amount of contrast and the same topographical anatomic references, all this in order for the scans to be comparable from the technical point of view.

The sequences used in usual follow-up controls are:

- T1 3D spoiled gradient recalled (SPGR) for 3-plane reconstruction and volume calculation by segmentation.
- Gadolinium-contrasted T1 3D spoiled gradient recalled (SPGR) for 3-plane reconstruction and volume calculation by segmentation.
- T2 or T2 fluid-attenuated inversion recovery (FLAIR) with fine cuts.

No additional sequences are required for usual follow-up of the patient under surveillance, unless it is justified by a clinical research protocol.

In case there are difficulties in differentiating between pseudo-progression, progression or radionecrosis, a multimodal MRI scan with perfusion (rCBV), spectroscopy (choline index) and diffusion (apparent diffusion coefficient [ADC] testing can be performed (cellularity), in addition to the usual sequences. Performance of a PET with fluorothymidine or methionine may prove being useful. It should be clarified that none if these tests has sensitivity or specificity enough to be considered the diagnostic standard in these particular situations.

Simple or contrasted computerized tomography has no place in the follow-up of patients, except for the detection of complications such as hydrocephalus or hemorrhage.

Response criteria/Response Assessment in Neuro-oncology (RANO) criteria

Response evaluation in neuro-oncology is made using the RANO criteria[26], which take as a basis the MRI assessment (formerly, they were based on computerized tomography results).

Radiological response to an agent is assessed by comparing the dimensions of the tumor in the baseline evaluation, just before the treatment is started, with the image of the tumor obtained after treatment administration, which will allow for tumor response to be determined[26].

It should be taken into account that the assessment of radiological response (especially with anti-angiogenic agents) is complex, mainly due to permeability changes. In this case, a confirmatory MRI analysis has to be performed 4 weeks after a radiological response is observed.

In neuroimaging studies, assessment standardization should be taken into account; in other words, the lesions should be measured using the same technique and, whenever possible, with the same MRI equipment used in the baseline evaluation.

With regard to the analysis by MRI, we will define a series of important terms to understand the development of the tumor and carry out its follow-up in the most adequate form:

- Complete response (CR): it is produced when all contrast enhancing lesions (measurable and non-measurable) have disappeared for at least 4 weeks and no new lesions occur; stability or improvement is observed in nonenhancing lesions on T2/FLAIR and the patient doesn't have to take corticosteroids (except if required as replacement therapy for a functional deficit). It is important taking into account that in case the confirmatory MRI is not performed at 4 weeks, the response is not to be understood as complete, and it only can be regarded as stable disease (SD).
- Partial response: when ≥ 50% decrease is observed in the sum of products of the longest diameters of all measurable enhancing lesions with regard to the baseline evaluation (at least for 4 weeks). Progression of non-measurable lesions should also not be observed, and it is important for new lesions not to appear. In addition, there should be improvement or stability of non-enhancing lesions on T2/FLAIR, clinical improvement or stability and reduction or maintainance of the corticosteroid dose in comparison with the baseline evaluation results. As with CR, if a confirmatory MRI is not performed at 4 weeks, the response is to be considered only as SD, and not as PR.
- Stable disease: when the criteria for CR, PR or progression are not met. For that, there must be

stability in nonenhancing lesions on T2/FLAIR, corticosteroids administered doses are to be lower than in baseline evaluation and patients must experience clinical stability or improvement. In particular, according to corticosteroid administration, in case doses have been increased due to the onset or worsening of symptoms and, however, no neuroimaging worsening is observed, MRI follow-up is to be made every 4 weeks. If, finally, radiological progression is demonstrated, the last assessment with corticosteroid doses equal or lower than the baseline dose should be regarded as SD.

- Progressive disease: when there is a ≥ 25% increase in the sum of the products of perpendicular diameters of contrast enhancing lesions with corticosteroids stable or increasing doses compared with baseline or a previous evaluation with documented reduced tumor volume. Another condition is a significant increase in T2/FLAIR nonenhancing lesions on stable or increased corticosteroid doses compared with baseline or a previous evaluation where smaller size of the tumor was demonstrated. If appearance of new lesions, increase of non-measurable lesions or clinical deterioration not attributable to causes other than tumor progression is observed, status should be regarded as PD. PD is also considered if an increased use of corticosteroids is observed and if scheduled evaluation is not performed due to serious deterioration or death of the patient.

At the moment of evaluation and follow-up of the disease, some considerations are also necessary with regard to the type of lesions that can be found. In particular, it is important for the following definitions to be understood:

- Measurable disease refers to cases where the longest diameters, perpendicular to each other, of at least one 10-mm lesion visible in two or more 5-mm axial slices can be demarcated by means of MRI (best with this technique). The longest diameter is specifically chosen, and for the second measurement, a perpendicular line is drawn at the point of the longest diameter. It is important to clarify that the size of the measurable lesion in MRI has to be twice as large as the slice thickness. If a lesion appears surrounding a cyst or a surgical cavity, it is usually regarded as a non-measurable lesion, unless there is at least a nodular 10-mm diameter component (having in mind, on the other hand, that the cyst or cavity should never be included in the measurement).
- Non-measurable lesions are those where only one dimension can be calculated, as in the case of linear contrast enhancing or fine enhancing around a cavity. In addition, masses with no easily defined limits or those lesions not reaching a 10-mm size are considered non-measurable lesions.
- Satellite lesions found closer than 1 cm to the main lesion and within the same territory should be regarded as a single lesion (and its total size measured). In case there are multiple measurable lesions, at least the largest two should be measured. As previously mentioned, measurement of disease will consist in the sum of the products of the longest perpendicular diameters of each lesion. The maximum number of lesions to be measured will be five per case, including the largest, although occasionally, largest lesions are too confusing in form and their diameters cannot be accurately determined. In these cases, the next lesions in size able to be measured should be selected. In spite of the proposed criteria and definitions, there are several problems associated with these neuroimaging studies. For example, in the case of patients with recurrent disease to previous treatments and with several measurable lesions, those growing in size on the last MRI scans should be assessed. On the other hand, the rest of the lesions have to be reported, but should not be regarded as main or index lesions. In case there is significant growth of non-index lesions, this must be considered as tumor progression, even if the rest of lesions have not increased in size. Finally, it is important to highlight the existence of difficulties to demarcate the volume of radiotherapy treatment, although the most adequate technique is postoperative MRI weighted on T1.
- Pseudoprogression. When any of these features are observed:
  - Signs related to early tissue reaction (first three months) and associated with subacute treatment, together with edema, increased contrast enhancement, mass effects or suggestive symptoms similar to those of tumor progression.
  - All the above followed by clinical and radiological spontaneous resolution without intervention.
  - Presence of risk factors such as high radiation dose, concomitant administration of radiation or chemotherapy and MGMT-promoter methylated status.

Given the difficulty in the assessment of patients after radiotherapy administration, a 12-week post-radiation

period should be considered, having in mind that this time is a vulnerable period, where contrast enhancements are not easily regarded as progression. In other words, a high rate of pseudoprogression (about 20-30% of the cases) is observed, since some patients exhibit contrast enhancement, without this fact actually representing tumor progression.

Some factors that have to be taken into account to diagnose real progression are:

- Contrast medium enhancement appearing or continuing 12 weeks after radiotherapy conclusion.
- Contrast medium enhancement observed in a non-previously irradiated region.
- In case of anti-angiogenic drugs administration, such as bevacizumab, increase in nonenhancing and hyperintense areas on T2/FLAIR.
- Any underlying cause for changes on T2/FLAIR, such as ischemia, post-radiotherapy changes, seizure activity, infection or demyelination, must be ruled out.
- Changes on T2/FLAIR likely suggestive of tumor infiltration include mass effect, cortical ribbon infiltration and location outside the radiation field.

Advance directives

Rights of terminally ill patients

In Mexico, advance directives are regulated by Chapter II, Section Eight Bis of the General Statute of Health of 1984 (last reform was carried out in 2013), which determines the rights of terminally ill patients.

In particular, article 166 BIS 4 establishes that "any adult patient, being sound of mind, can, any time and regardless of his or her health status, express his or her wish, written in the presence of two witnesses, to receive or not any treatment, in case of suffering an illness and being terminally ill and being unable to express said will". This decision can be revoked any time.

Impossibility to express the last will is because the disease's own development may directly affect the subjects' mental capacities, from the legal point of view. This information is precautionary; it has no direct relationship with the patient's health status.

Section BIS 5 of the same article protects the "right to voluntary suspension of curative treatment, and as a consequence, to the initiation of strictly palliative care", which will entail, according to BIS 6, the suspension of any therapy directed to stop the development of the disease, maintaining only treatments exclusively intended to reduce pain and any other symptoms associated with the course of the disease.

This refers directly to direct suspension of curative treatment, and in a given moment, healthcare professionals and Bioethics Committees will be responsible for making a decision. However, this legal framework leaves several legal voids with regard to healthcare professionals' responsibility.

Advanced directives

According to the *Reglamento de La Ley de Voluntad Anticipada* for the Distrito Federal, published in 2008 and amended several times (including in 2013), advanced directives can be defined as a "personal decision to undergo or not measures, treatments or medical procedures intended to prolong life when being in terminal stage and for medical reasons it is impossible to naturally preserve it, protecting all time the person's dignity". The advanced directives definition has a time-related gradient, placing quality of life and, of course, quality of death at the highest hierarchy.

In this document, the patient confirms his or her express wishes in case of experiencing and end-stage situation and was unable to express them by his or herself. This document can be revoked any time by the patient.

Given this situation, the legal framework itself defines the end-stage patient as that person "who suffers from a mortal disease, who has a life expectancy of less than six months and is unable to naturally preserve his or her life".

In any case, the objective of this legislation is to protect the person's dignity in the final stage and also warrant for the best physical, psychological and social conditions to be met in order for the patient to be able to have a dignified death.

After warranting strict fulfillment of the patient's advanced directives and in case he or she decided not to receive more treatments to stop the disease and prolong his or her life, the modality of palliative care, which will be described below, starts to be applied.

There are particular issues in several of the articles, but advanced directives are observed to involve many people and perspectives. It's not only about providing care and company to the patient, but also about healthcare institutions planning how the patient will be taking care of, with the responsibility, in any case, of providing for the patient to experience a dignified death.

Palliative care

Many of the clinical manifestations observed in patients fall within the area of neurosciences, and symptoms show a wide range of differences.

On one hand, there may be problems within the parenchyma, vascular disruption, cerebrospinal fluid alterations that may secondarily cause intracranial pressure increase. On the other hand, sometimes there are compression and irritation phenomena (sometines characterized as epilepsy or delusions), destruction fenomena (with focal deficit symptoms) or obstructive processes that may lead to the development of rostrocaudal deterioration. This type of symptoms ultimately leads to the patient's death.

Consequently, the goals of palliative care are really important: to ensure communication with the patient and his or her family, while trying to soothe and control the patient's symptoms, supporting his or her family environment.

In this last stage of the disease, interventions should be the least aggressive possible, by using drugs that produce the least adverse effects. Therefore, the transdermal route is usually recommended instead of the oral route (especially if there are problems with deglution), or the subcutaneous route (simple and painless administration route by means of which the patient can be administered drugs such as dexamethasone, morphine, haloperidol or paracetamol).

Once arriving to the palliative care phase, possible gastrointestinal effects and cognitive problems have to be prevented as much as possible, in order to select and regulate drug administration. The main symptoms to be treated include pain, which is assessed using the visual analogue scale, the most widely used assessment tool.

Associated respiratory problems are also to be treated, including dysnea, a condition where the patient experiences a sensation of choking and shortness of breath. In this situation, it is important offering the patient psychological support to prevent more anxiety, and in the case anemia is observed or problems at the respiratory level continue, morphine and oxygen should be administered. Treatment must be rapid and opportune, since this type of situations generates an important sensation of anxiety among patients and their families.

On the other hand, agitation and confusion symptoms cause problems with language, development of aggressive behaviors, etc. In this sense, medical intervention should evaluate first if there is a treatable cause that is producing these symptoms, such as fever, electrolytic imbalance, constipation or dehydration. Some palliative therapeutic approaches are based on the use of benzodiazepines and haloperidol or risperidone.

Other signs likely to occur are nausea and vomiting, wich are relieved with conventional therapies and are sometimes the consequence of the increased intracranial pressure itself. If fever appears, it is important not to empirically administer antibiotics, but rather using benzodiazepines, for example, in the treatment of insomnia (frequently, it is responsible for delirium). In the terminal phase, where palliative care is practiced, symptoms such as tiredness, anemia, diarrhea, or even problems with swallowing, can be seen, as well as the appearance of epilepsy episodes.

In this last situation, many times there is agreement with the family to sedate the patient, in order to provide the most quietness possible to the patient and the family in the last moments of the terminal phase of the person affected by glioblastoma. The final goal at that moment is, with no doubt, to provide and ensure the best conditions for a dignified death, as previously described.

Conclusions

GBM is one of the most common central nervous system neoplasms. Although, currently, its characterization is mainly histological, it is a fact that, in the future, genetical studies will acquire increasing importance.

The treatment of patients is selected based on age, performance status and cognitive status. This way, there is standard therapy with surgical resection combined with chemotherapy and radiotherapy in patients younger than 70 years with adequate cognitive status. In senile patients, radiotherapy and palliative care are used as a general rule. Finally, radiotherapy is only used in well selected cases.

Prognosis of this disease is very bad, given the aggressiveness of this type of cancer. Therefore, it is important ensuring not only PFS, but good quality of life as well. When the patient enters into terminal stage, it is essential for respect of his or her advanced directions to be warranted. In those cases where curative treatment is discontinued, palliative care should be implemented, which is intended to reduce some symptoms of end-stage disease and ensure a dignified death for patients and their families.

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