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The "new normal" for glioblastoma adjuvant treatment in a COVID-19 pandemic scenario

„Nový normál" pro adjuvantní léčbu glioblastomu v podmínkách pandemie COVID-19

Abstract

Multidisciplinary treatment of brain tumors has been severely affected by the COVID-19 pandemic. In the context of a decrease in the number of neurosurgical interventions by over 50% in most centers from the countries affected by the pandemic, the setting of treatment priorities becomes essential. Due to the poor prognosis and biological particularities related to rapid progression, grade IV malignant gliomas are a priority in treatment. The severe limitations of hospitalization possibilities in intensive care units and the reduction of the possibilities of administration of adjuvant treatment leads to the necessity to take into account the possibilities for timely administration of adjuvant treatment in the decision for the neurosurgical treatment in new glioblastoma multiforme cases. Multidisciplinary team evaluation of each case is mandatory in order to make a rational decision. Isocitrate dehydrogenase (IDH) mutation and methylation status of O6-methylguanine-DNA methyl-transferase (MGMT) should be assessed as far as possible. IDH wild-type status should be a decisive factor in prioritizing the treatment. For young patients with a favorable performance status, the standard treatment includes long-course radiotherapy with concurrent temozolomide treatment, followed by 6-cycle adjuvant treatment with temozolomide, even in a COVID-19 pandemic scenario. The optimal therapeutic choice in the case of elderly and/or frail patients includes a moderate hypofractionated radiotherapy regimen of 40 Gy in 15 daily fractions over 3 weeks, or a hypofractionated protocol with 25 Gy in 5 daily fractions, taking into account the age and Karnoffsky performance status. Also, the MGMT methylation status must be taken into account for the decision to omit chemotherapy and for the delivery of a short-course radiotherapy regimen (25 Gy in 5 fractions). Omission of chemotherapy should consider both the additional risk of SARS-CoV-2 infection and the limited benefit of temozolomide treatment in the case of unmethylated MGMT status.

Souhrn

Multidisciplinární léčba nádorů mozku je v závažné míře narušena pandemií COVID-19. V souvislosti s poklesem počtu neurochirurgických operací o více než 50 % ve většině center v zemích postižených touto pandemií je nezbytné nastavit priority v léčbě. V důsledku nepříznivé prognózy a biologických charakteristik, se kterými je spojena rychlá progrese, jsou prioritou v léčbě gliomy ve stadiu IV. Ze závažného omezení možností hospitalizace na jednotkách intenzivní péče a z omezených možností pro podávání adjuvantní léčby vyplývá nutnost při rozhodování o neurochirurgické léčbě nového případu glioblastoma multiforme vzít v úvahu také možnosti včasného podání adjuvantní léčby. Pro správné rozhodnutí je nezbytná evaluace každého případu multidisciplinárním týmem. Pokud je to možné, měla by být stanovena mutace izocitrát dehydrogenázy (IDH) a metylační stav O6-metylguanin-DNA-metyltransferázy (MGMT). Pro stanovení priorit v léčbě by měl být rozhodující stav „wild-type" IDH. U mladých pacientů s příznivým performance statusem standardní léčba zahrnuje dlouhodobou radioterapii a současné podávání tenozolomidu, po kterém následuje 6 cyklů adjuvantní léčby temozolomidem, a to i v podmínkách pandemie COVID-19. V případě starších a/nebo křehkých pacientů je jako optimální terapie volen střední hypofrakcionovaný režim radioterapie s denní dávkou 40 Gy v 15 frakcích s dobou trvání 3 týdny nebo hypofrakcionovaný protokol s denní dávkou 25 Gy v 5 frakcích, a to po zvážení věku a performance statusu podle Karnoffského. Metylační stav MGMT musí být také brán v úvahu při rozhodování, zda vynechat chemoterapii a zda nasadit krátkodobou radioterapii (25 Gy v 5 frakcích). Při vynechání chemoterapie v případě nemetylované MGMT by mělo být bráno v úvahu jak další riziko infekce SARS-CoV-2 tak omezený prospěch z léčby temozolomidem.

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Introduction

The new coronavirus (SARS-CoV-2) spread around the world has generated a pandemic that severely affects health systems in all countries, requiring a relocation of resources with possible limitation of medical services, with cancer patients being one of the most affected categories. Even though the neurological manifestations are not specific to the clinical spectrum of COVID-19 disease and the specialists in neurology and neurosurgery were not relocated to the units destined for this new and unpredictable infectious disease, the treatment protocols of brain tumors were affected indirectly by the necessary precautions to protect the staff and patients, especially by severely limited hospital beds in intensive care units (ICUs), often reserved for COVID-19 patients. Among brain tumors, glioblastoma multiforme (GBM), a grade IV malignant glioma, is the most aggressive type of high-grade glioma (HGG), with the median survival after diagnosis estimated at 12–15 months. The survival at 5 years is approximately 3–7%, even if the maximal standard treatment has been administered according to the current guidelines. The basic potential curative treatment of HGG is surgery, usually followed by radiation therapy and chemotherapy with temozolomide. In this epidemiological context generated by the COVID-19 pandemic, most centers report a reduction in the number of operated cases, given the need for triage, in order to protect the staff and patients against a possible SARS-CoV-2 infection. Most of the neurosurgergical departments reported a drop of more than 50% in the operating volume. Thus, there is a major risk of unacceptable delays of the treatment in patients diagnosed with GBM. In order to balance the risks between the possible progression of the tumor and COVID-19 infection associated with hospital visits, which may expose patients to an additional risk, it is necessary to develop recommendations for prioritizing the urgency of treatments, adapted to this condition of "new normal", in the context of possible long-term coexistence with the new coronavirus. Krenzlin et al reported a fall of 48.1 ± 4.44% in cranial emergency hospital admission after the declaration of the new pandemic [1–3].

"The new normal" recommendation for GBM multidisciplinary treatment

Given the current COVID-19 pandemic, a new strategy for prioritizing the treatment of patients with GBM must be designed, adapted to the way we manage our neuro-oncological patients, in order to offer a maximum benefit of the treatment and a limitation of the infectious risk. The aim of this article is not to detail the standard measures applied in all departments to limit the risk of infection with the new coronavirus. The staff wearing personal protective equipment and face masks, ensuring social distance, limiting the time spent by patients in the waiting room of each medical department, and using alcohol-based solutions for hand sanitization are the measures already implemented after the declaration of the pandemic in the vast majority of hospitals. The use of telephone consultations or videoconferences and the maximum limitation of patient's visits at the departments do not solve the possible problem of the lack of available hospital beds. Postponement and prioritization strategies must take into account the effect on the progression of the disease. Given the aggressiveness and ability of glioblastoma to grow rapidly, GBM cases should be discussed individually in a multidisciplinary team (MDT) in order to correctly assess the urgency of treatment and the possibilities of its administration according to current guidelines. In the case of neurosurgical interventions, it is recommended to review the operating lists for the next 12 weeks in order to assess the benefit and risk in each case, but the prioritization must be dynamic, requiring continuous review of the current capacity of departments. The evaluation of capacity in neurosurgery, neurology, oncology, radiology, pathology, and radiotherapy before starting the treatment is essential. There is a consensus for the postponement of the treatment of low-grade meningiomas, which are purely elective, and for the individual analysis of cases of high-grade tumors, that cause neurological deficit, in terms of urgent surgery. The decision to perform the intervention must also consider the possibility of providing timely adjuvant treatment. In terms of treatment priorities, large benign tumors with acute symptoms and tumors in the posterior fossa, both causing hydrocephalus or having life-threatening potential, are considered a high priority, regardless of their histological type. Medulloblastoma and grade 3 gliomas in young patients are included in the 2nd class with "high-intermediate" priority. An intermediate priority is given to HGG in young patients with a good performance status. A lower priority is given to low-grade gliomas, small benign tumors or to HGG in elderly patients. Neurosurgical treatment is the cornerstone of the treatment with curative potential in GBM. A limitation in neurosurgical resources will severely compromise the ability of these patients to be treated with the best treatment according to the guidelines. The extension of resection plays an essential role in prognosis and for subsequent adjuvant therapy decisions. In the case of GBM patients with poor performance status, older age has also a prognostic role and a decision of intensive adjuvant treatment must take into account the fragility of these patients and the risks associated with intensification of the treatment in terms of potential death in case of SARS-CoV-2 infection.

For high-grade gliomas, radiotherapy and chemotherapy have a well-demonstrated role in the improvement of local control (LC) and overall survival (OS), but through prolonged exposure of the patient to repeated visits to the radiotherapy department associated with the immunosuppressive effect of temozolamide treatment, an increased risk in these patients has an unfavorable effect on the progression of the disease in case of their contact with COVID-19 infection. It is well-known that both temozolmide treatment and COVID-19 disease can be associated with severe lymphopenia. Intensified adjuvant treatment is associated with an increased risk, especially in elderly patients. The use of hypofractionated radiotherapy and the omission of temozolomide treatment may also be considered. For GBM, regardless of the age higher or lower than 65 years, treatment omission may be considered in patients with poor performance status, including Eastern Cooperative Oncology Group (ECOG) Performance Status of 2–4. The recommendation of active treatment exists in this context only if the performance status is 0 or 1. In the scenario of limiting the capacity of surgical treatment, it can be decided to administer the radiotherapy as the only method of treatment without requesting biopsy and shorter treatment using hypofractionated radiotherapy is recommended by most experts. According to the results of the trial performed by Stupp et al, a scheme of 45 Gy in 15 fractions over 3 weeks is proposed as an alternative for patients older than 65 years. The O6-methylguanine-DNA methyltransferase (MGMT) methylation status of GBM could be a criterion in favor of the administration of adjuvant chemotherapy [4–7].

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Discussion

The study performed by Stupp et al validated the addition of temozolomide to adjuvant radiotherapy treatment, demonstrating a significant survival benefit with low toxicity. When analyzing data of 573 patients from 85 centers, with a median follow-up of 28 months, the median OS was 14.6 months in the group that received only radiotherapy at a total dose of 60 Gy per week for 6 weeks and 5 days with concurrent administration of temozolomide (75 mg/m^2 per day, 7 days per week), followed by 6 cycles of adjuvant temozolomide. The median OS was 12.1 months in the group of patients treated with radiotherapy alone and 7% of patients treated with temozolomide developed grade 3 or 4 hematological toxicity. The study performed by Chinot et al, which proposed the addition of anti-angiogenic agents to temozolomide in adjuvant settings, did not demonstrate survival benefits. However, in vitro studies demonstrated the ability of GBM cell lines to proliferate after fractionated irradiation. Although reduced, repopulation capacity has been demonstrated and intrinsic radiosensitivity has been one of the factors involved. Budach et al evaluated the repopulation time ranging from 1 to 1.9 days, and these preclinical data demonstrate that, in some cases, standard fractionation is not sufficient to counteract the mechanisms of tumor progression.

These preclinical data justify the efforts to identify alternative fractionation schemes to overcome the mechanisms of radioresistance, hypofractionation having the advantage of obtaining an increased rate of cell death at higher doses per fraction, but also counterbalancing the effect of accelerated cell repopulation by reducing the total duration of the treatment. Attempts to change the fractionation have been associated with the use of possibilities offered by new radiotherapy techniques that allow escalation of doses to the radioresistant subvolumes with better sparing of surrounding healthy brain tissues [8–10].

Most hypofractionation regimens underlie the formalism of the quadratic linear radiobiological model (LQ), taking into account the biological effective dose (BED), a measure of the effect of each fractionation scheme. Usually, BED is used to compare the tumoricidal and toxic effects of different fractionation regimens. The concept started from this model and its purpose is to propose alternative schemes using a BED value comparable to that obtained by standard fractionation. Considering the value of α/β ratio = 8 Gy for the tumor, the BED for 60 Gy in a 30-fraction standard regimen has the value of 69.91 Gy. An alternative hypofractionation scheme should give a BED value around 70 Gy. Considering that the age and performance status as well as the extent of surgery have been identified as independent prognostic factors in GBM and age above 65 years is also associated with an increased risk of unfavorable development with possible death or admission to ICU and mechanical ventilation in the case of the contact with COVID-19 disease, a less aggressive and shorter treatment regimen should be considered for this category of patients. Analyzing the results of hypofractionation trials and radiobiological data underlying the proposed schemes, Hingorani et al concluded that the combination of temozolomide in addition to intensity modulated radiation therapy (IMRT) could increase the rate of LC and OS. Gupta et al analyzed the existing data 15 years ago and concluded that although there were more than 3 decades of experience in altered fractionation schemes (accelerated hyperfraction and hypofractionation) at that time, the results did not demonstrate a benefit of these radiotherapy protocols compared to standard 60 Gy in 30 fractions in patients with poor prognosis. It should be mentioned that at the time of the analysis by Gupta et al, temozolomide was not part of the standard protocol of the evaluated trials and IMRT was used less frequently. Also, there is no consensus in the uniformity of the delimitation of target volumes, especially regarding the inclusion of peritumoral edema in the radiation field [11–14].

The treatment of elderly patients currently includes temozolomide combined with hypofractionated radiotherapy at a total dose of 40 Gy in 15 fractions and is established as a standard. Trial NCT00482677 of the Canadian Cancer Trials Group performed in collaboration with the European Organization for Research and Treatment of Cancer (EORTC) and Trans-Tasman Radiation Oncology Group (TROG) demonstrated the benefit of temozolomide addition to the therapeutic protocol of GBM in 562 patients included, with OS of 9.3 vs. 7.6 months and progression free survival (PFS) of 5.3 vs. 3.9 months in the group of patients who received the combined treatment vs. radiotherapy alone, respectively. The methylated MGMT status significantly influenced the prognosis. In the group of patients with methylated MGMT, the median OS benefit of adding temozolomide was 5.8 months vs. only 2.1 months in cases with unmethylated MGMT, respectively. The International Atomic Energy Agency Randomized Phase III Study aimed to evaluate the optimal radiotherapy protocol for elderly and/or frail patients diagnosed with GBM. The study included 98 patients and the chosen radiotherapy regimens were 25 Gy in 5 fractions delivered for 1 week or 40 Gy in 15 fractions delivered for 3 weeks. The study demonstrated the non-inferiority of a 5-fraction scheme, with the median OS 7.9 vs. 6.4 months for a 3-week regimen and the median PFS 4.2 months in both arms. The quality of life was not different between the two study arms with a median follow-up of 6.3 months. The authors concluded that the radiotherapy scheme of 25 Gy in 5 fractions could be used in elderly and/or fragile patients in limited resources in COVID-19 pandemic era. IDH-wild type (IDHwt) is an important predictor of the rapid growth of GBM. IDHwt patients may be candidates for progression even during the treatment. Thus, the postponement of the treatment should not be taken into account in this category. Given these prognostic and predictive factors, including the status of MGMT methylation and IDH mutation, there is a possibility of refining patient stratification in terms of treatment priorities. In the light of these data and in the context created by the COVID-19 pandemic, patients who would certainly benefit from a de-escalation of the treatment by using a radiotherapy scheme limited to 5 fractions and omitting chemotherapy with temozolomide, include a group of frail patients aged ≥ 50 years with Karnoffsky performance status (KPS) between 50 and 70%, elderly and frail patients aged ≥ 65 years with KPS between 50 and 70% and the elderly, aged ≥ 65 years with KPS between 80 and 100% [6,15,16].

Conclusion

The severe limitations of hospitalization possibilities in the ICU and the reduction of the possibilities for the administration of adjuvant treatment leads to the necessity to take into account the possibilities of timely administration of adjuvant treatment in the decision for neurosurgical treatment in new GBM cases. MDT evaluation of each case is mandatory in order to make a rational deci-

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sion. IDH mutation and methylation status of MGMT should be assessed as far as possible and IDHwt should be a decisive factor in prioritizing the treatment. In young patients with a favorable performance status, the standard treatment includes a long-course radiotherapy with concurrent temozolomide treatment, followed by 6-cycle adjuvant treatment with temozolomide, even in a pandemic scenario. The optimal therapeutic choice in the case of elderly and/or frail patients must take into account the KPS and the age and includes 40 Gy in 15 fractions in a 3-week irradiation scheme, or 25 Gy in 5 fractions in a 1-week protocol. Also, the MGMT methylation status must be taken into account when deciding to omit chemotherapy and to use a short radiotherapy (25 Gy in 5 fractions). In the case of chemotherapy omission, both the additional risk of SARS-CoV-2 infection and the limited benefit of temozolomide treatment in the case of unmethylated MGMT status should be taken into consideration.

Conflict of interest

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study. All authors have contributed equally in the design and writing of the manuscript

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