Towards the Real Interdisciplinary Approach in Treating Brain Tumors: Report from the Neuro-Oncology Scientific Club opening meeting - NOSC 2011-13 October- Mashhad, IR Iran

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NOSC (The Neuro-Oncology Scientific Club) is a professional forum for the exchange of experts’ experience and updates on brain tumors in an interdisciplinary fashion. NOSC plans to act as a guideline definition group in Mashhad and meanwhile has no competing interest to disclose.
Towards the Real Interdisciplinary Approach in Treating Brain Tumors: Report from the Neuro-Oncology Scientific Club opening meeting - NOSC 2011-13 October- Mashhad, IR Iran


Abstract

To strategize interdisciplinary approaches in neuro-oncology and guideline definitions, there has always been a room for having joint meetings in practical fashion in our country. For forging relationship within various neuro-oncology professional bodies in Mashhad, Khorasan Province, Iran, the original concept of Neuro Oncology Scientific Club (NOSC) was formed. The NOSC great emphasis has been placed on building bridges between different groups in the field (i.e Radiation Oncology, Neurosurgery, Neuroradiology, Neurology, Pathology and Molecular Genetics). Following comprehensive round table discussions and “faculty speaks” we arrived at bottom line conclusions including:

1. Collecting and contemplating 10 year data of our patients so that to be incorporated in to the e-data registry.
2. Developing the initial format of the electronic data registry system for brain tumors in close conformity with the needs of the Oncology Research Center (ORC), Mashhad Medical University.
3. More engaging experts from allied fields including Psychiatry, Physical therapy and rehabilitation, Psychology and Nursing.

The forthcoming NOSC session will have two main issues on its agenda:

1. To discuss the preliminary draft of the local guideline (at least to define the diagnosis and referral algorithm in a real interdisciplinary approach).
2. Having the web based brain tumor data registry system launched.

The faculty speaks at NOSC 2011 - Mashhad, Iran

Introduction:
This session was the first of a kind in our country having experts from different disciplines involved in the managements of brain tumors come together. This interval meetings concept was proposed as a form of a scientific club (Neuro-Oncology Scientific Club /NOSC). This club is believed to be a facility to let the neuro-oncology experts of the field (Mashhad-Khorasan Province, Iran) discuss current topics in CNS tumors in a round table format and sharing ideas and experiences to more efficiently approach brain tumors in daily practice. The novelty of this club is mainly its multidisciplinary character.

The prospective aims that the interval meetings of the NOSC is heading for is something more than just having series of talks and presentations communicated. Although one of our aims is to share recent updates in neuro-oncology, more importantly we plan to arrive at consensus to develop local guidelines on diagnosis, treatment and follow-up of CNS tumors through an interdisciplinary viewpoint. NOSC also plans to have all the communicated discussions composed as written reports for publication to seek other domestic or international experts’ comments. The communicated ideas in a transparent atmosphere will let us benefit from the readers know-hows to improve this practice. This can also have implications for health policy, practice, research and medical education.

We would have the glial brain tumors as our initial focus, however other kinds of CNS tumors with totally separate treatment paradigms can be discussed in our following sessions in long-term.

The other idea is to arrive at the team work spirit in management of CNS tumors. Experts from different fields not limited to radiation oncology, radiology, neurosurgery, neurology, pathologoy, psychiatry, physical medicine and rehabilitation and nursing, would be involved to allow their standpoints be applied in brain tumor patients’ health and quality of life. Consequently, we may be able to capture data from the field to form a databank for brain tumor patients in...
our province, Khorasan. The data registry can be a pivotal tool to design clinical trials and critical researches to come into new insights both in fundamental and clinical aspects of neuro-oncology in Mashhad. We also can work on a tissue bank as a platform for molecular studies and so on.

NOSC tries to stay unbiased when discussing therapeutic options and other related issues. All comments are open to debates with no restrictions. Other than facilitation to run NOSC meeting which is by Behestandarou, NOSC has no conflict of interest to disclose. Having said this, NOSC above all, aims at improving our brain tumor patients’ health and quality of life through an interdisciplinary team work.

Neuro-Oncology; A decade of experience with chemoradiation and beyond.

Reviewing the clinical aspects of high grade glioma treatment and its standard of care some concepts worth to re-emphasize. High grade gliomas (HGG) mainly include grade III (anaplastic astrocytoma-AA) and grade IV (glioblastoma multiforme-GBM). GBM constitute more than 50% of malignant gliomas and generally has a poor survival. One third of GBM patients survive more than a year and only 5% live over 5 years, while AA patients have a 5 year Overall Survival (OS) of 27% [1-3]. The prognostic factors in malignant gliomas which define the outcome include histologic diagnosis (GBM with the worst prognosis followed by AA and other types of malignant glial brain tumors), age and performance status (most trials are carried out on patients with favorable PS) [2].

Evidence show that over the past decade the prevalence of these malignant tumors are nearly doubled. One reason could be a more widely use of neuro-imaging which results in efficient diagnosis [4]. There are two types of GBM: (1) Primary or de-novo GBM which arises from astrocytes within almost 3 months in average, (2) secondary GBM which originates from a low-grade astrocytomas. This transformation process may take 1-10 years [4, 5].

Many molecular studies denote that these two types of GBM should be considered as separate entities while others stress on the commonalities these two types have in nature [5].

Imaging of GBM represents a distinct feature on MRI. GBM has a ring enhancement with gadolinium as well as a central hypo-intensity representing necrosis on T1 weighted MRI. In radiation oncology T2 image is the one used for planning. Since GBM has an infiltrative nature, tumor cells nested in the edematous area should be included in radiotherapy field [6].

One of the crucial therapies for malignant glioma and GBM in particular is surgery. Surgical removal of the tumor is recommended in many instances and even if not successful in some cases, can provide adequate tissue for pathologic diagnosis. Patients’ symptoms arising from high ICP and pressure effect of the tumoral mass are improved post surgery. Some studies postulated the benefit of surgery in survival. Tumor surgery has decreased the need for steroids in the course of the tumor management [2,7, 8].

In a prospective study data showed that surgery vs. biopsy can improve survival. Based on this evidence, an optimal resection of the tumor bulk is now considered as an important prognostic factor in patients’ long-term outcome [9, 10].

Due to the infiltrative character of GBM, surgery can hardly result in complete resection of the tumor with no risk of recurrence [8, 9].

The other standard treatment of the malignant glial tumor is the external beam radiation which has been proven to increase survival in prospective randomized trials [6, 11]. The conventional dose of radiotherapy is usually 6000 cGy-fraction; 200. All the efforts done to define new radiotherapy protocols rather than the conventional, have failed to increased survival more than what is achieved by the conventional RT[6]. Methods such as brachytherapy or radiosurgery boosts have added no value in terms of survival compared to conventional protocols of RT, however recent advances in radiotherapy technology and planning have significantly decreased the neurological consequences caused by irradiation and this has resulted in more efficient use of radiotherapy [12]. The systemic chemotherapy which is initially used concurrently with radiotherapy and then continued as adjuvant, had a marginal role before, but recently with the availability of newer chemotherapeutic agents like Temozolomide (TMZ), there has been a revolutionized trend in using chemotherapy in GBM treatment over the past decade. Old trials were trying to evaluate the effect of nitrosurea agents’ benefits in improving GBM patients OS and QOL. Many of these trials showed no survival benefit while few indicated minimally added survival rate when nitrosurea regimens were added to RT [13, 14]. The glioma meta-analysis critically analyzing data from 12 trials with cumulative patient number of over 3000, reported a 6% increase in one year median survival when nitrosurea regimens were added to RT. Since these data were not so impressive in terms of OS, other treatments such as local systemic chemotherapies through implantation of BCNU wafers were tried. These implants with sustained delivery of the chemo-agents to tumors were first tried in recurrent GBM cases and were shown to increase the OS [15]. Applying these implants for initially diagnosed GBM patients also showed survival benefits. BCNU wafers were then
approved by FDA. Although these wafers are currently used in some centers, there is no global consensus on their routine use [16]. There might be a need to use the standard of care chemoradiation with TMZ, so there will be cautions for TMZ interaction with BCNU. Based on the above evidence, this protocol is yet far from standard in therapeutic decision making. Furthermore, core scientific panels such as NCCN have not recommended this in high level category. Addition of TMZ to RT vs. RT alone, gross resection vs. subtotal resection and the use of BCNU wafers could improve patients’ survivals in different levels (Fig-2).

Over the recent years, a breakthrough alkylating chemotherapeutic agent known as TMZ is introduced (Stupp et al. 2005) to be the standard of care regimen for GBM and refractory AA patients who have a favorable PS and are.

The final analysis of this study published in Lancet Oncology in 2009 reported the 5 year OS of these patients to be 10% compared to 2% in RT/TMZ vs. RT alone arm respectively [20].

In a sub-analysis performed on the molecular basis of the tumor for an enzyme known as Methyl Guanine Methyl Transferase (MGMT), which plays a role in DNA repair, it was shown that positive methylation status of this enzyme causes a chemosensitivity to TMZ [20]. Although solid evidence indicate the significance of the impact of MGMT methylation status on OS, current guidelines do not recommend routine assessment of this enzyme’s methylation status in everyday practice (Fig-3) [18,19,20]. There are other agents which are mainly used in recurrent GBM. Bevacizumab as an anti vascular endothelial growth factor monoclonal anti body (anti VEGF MAb) has been approved for this indication since 2009. Other agents which can be used as salvage in recurrent GBM include TMZ, platinum based regimens, PCV and Irinotecan [21]. There are ongoing studies assessing the combination of bevacizumab and TMZ with radiotherapy in recurrent GBM. Dose dense (21/28) use of low dose TMZ is also under investigation. These are expected to be introduced as available options while approaching recurrent GBM.

Frequently faced issues in high grade glioma management. Looking for practical answers.

There are consensus and controversies on some frequently encountered issues while managing brain tumors. For many of these questions there is no straight forward reply or recommendation. In the EORTC-NCIC study by Stupp et al., which resulted in definition of the standard regimen for the treatment of GBM (75 mg/m2 daily ,7days per week from the first to the last day of RT, up to a maximum of 49 days concomitantly with RT -RT/TMZ-,followed by monthly adjuvant TMZ -5/28 days- for at least 6 cycles) (Fig-4) [22,23], one critical question can be about the optimal duration of adjuvant TMZ treatment in GBM.

To date, prolonged maintenance therapy with cytotoxic chemotherapeutic agents has not been shown to confer a benefit in many diseases. In glioma patients even though no trial has ever been designed specifically to evaluate the duration of maintenance chemotherapy, the available data with Carmustine (BCNU) or PCV used for up to 12 months failed to demonstrate a significant survival advantage. Those who are with the idea of prolonged adjuvant chemotherapy in glioma, depend on the radiological response however response may also be seen after therapy has been discontinued. Stupp et al., who have introduced the standard protocol for chemoradiotherapy with TMZ, recommend not to exceed 6 maintenance doses [17, 26-30]. This is for a number of reasons: (1) Although this treatment is usually well tolerated, cumulative bone marrow toxicity may limit the possibility to administer subsequent salvage chemotherapy in case of recurrence. (2) There is a theoretical risk for development of myelodysplastic syndrome or secondary leukemia after chronic exposure to TMZ. This is like any other alkylating agent. (3) Quality of life could be improved following a treatment free interval (less fatigue for instance). (4) When adjuvant doses are withheld, patients can have the option of re-exposure to the same treatment at a later stage. Currently the evidence to let the patients on 12 cycles rather than 6, in adjuvant chemotherapy in GBM is scant [23]. Nevertheless and short of class I evidence, prolongation of TMZ maintenance for up to 12 cycles is exceptionally used for patients who show continuous tumor response on MRI and a favorable clinical evolution [23]. Other than the Stupp protocol there are suggested dose intense regimens which allow a more intense exposure of the methyl diazonium ion to the DNA to more efficiently methylate the promoter segment of the MGMT gene. Other than the standard adjuvant protocol (5/28d) there are recommendations for dose intense regimens which are out lined in the illustration (Fig-5) [26, 31-34]. The rationale behind these suggested schedules is more effective depletion of the repair protein MGMT following the continuous exposure to TMZ. In a phase II randomized trial by Greek et al., there has been no added survival benefit of the intensified adjuvant TMZ therapy (150 mg/m2 for 5 days given every 2 weeks instead of every 4 weeks) over the standard Stupp protocol compared to RT alone. However cross trial comparison should be made with caution [17, 27].
another ongoing trial the standard dose adjuvant TMZ chemotherapy is being compared with a dose-dense regimen (75-100 mg/m2 daily for 21 days in a 28 day cycle). Although this study has reached to initial results in 1100 patients, the final analysis is pending (EORTC 22033-26033).

The main concern following the continuous exposure to TMZ is the induction of profound lymphocytopenia with decreased CD4 count. Based on the above, the available experience does not warrant the use of alternative TMZ regimens outside the widely accepted protocol [23].

The next question is to whether administer prophylactic antibiotic for Pneumocystis Carinii Pneumonia (PCP) in those receiving TMZ chemotherapy. Lymphocytopenia associated with continuous exposure to TMZ may enhance the risk for opportunistic infections not limited to Pneumocystis Pneumonia but Candida, and Listeria specially in patients receiving corticosteroids concomitantly [35,36].

The prophylaxis is usually with Trimetoprim-Sulfametoxazol 1 tablet three times a week. Other strategy could be to monitor patients' lymphocytes and CD4 count and to start antibiotics once the counts dropped below 500 and 300/mm3 respectively. There is another crucial question to address. Which setting of TMZ included treatment is more important, concurrent (with RT) or adjuvant?

In many of other solid tumors such as non-small cell lung cancer, esophageal carcinoma and cervical cancer, concomittant chemotherapy is shown to improve outcome. Currently there is no available report comparing the privileges of concomitant over adjuvant TMZ and vice versa [37-39].

There is an ongoing well designed trial (Van den Bent et al.) evaluating the efficacy of RT alone, concurrent RT/TMZ alone, adjuvant TMZ alone and standard protocol arms in treating non 1p/19q deleted anaplastic astrocytoma and oligosstrocytoma. The outcome of this trial would reply to the above question. For the time being experts recommend to adhere to the standard protocol without modifications in either dose or treatment duration.

TMZ was initially studied in recurrent anaplastic astrocytoma and the results of the randomized studies led to FDA approval for the use of TMZ in these patients. TMZ however is not yet studied for use in primary setting of AA treatment. In a large randomized trial by the Medical Research Council (MRC), no benefit of adjuvant PCV was documented compared to RT alone [40, 41].

There are some recent works in place focusing on some special subgroups of AA (i.e. those with co-deletion of 1p/19q, isocitrate dehydrogenase-IDH1-mutation) which are shown to have more favorable response to therapy. There might raise a question regarding the value of MGMT methylation status checking in routine practice. In Stupp trial, methylated MGMT was shown to drastically affect survival and treatment outcome (risk of death was reduced by 55% in 2 years)[20], however lack of reproducibility when interpreting the test plus inappropriateness of paraffin embedded blocks rather than fresh steriotactically obtained samples, make routine evaluation of MGMT of a questionable value. Since currently there is no alternative treatment available for those with unmethylated MGMT, globally renowned experts in neuro-oncology do not recommend routine assessment of MGMT methylation status when deciding to treat GBM or recurrent AA.

The role of molecular and chemical shift imaging in our decision making; the value of MRS.

When brain tumors are primarily diagnosed and undergo treatment, the role of imaging will be evaluation of response to treatment vs. relapse. In many instances conventional imaging such as MRI is not conclusive to document or rule out relapse of glial tumors (Fig-6) [42]. One of the applicable imaging modalities to efficiently differentiate progression from pseudoprogression is Proton Magnetic Resonance Spectroscopy (1H-MRS). This method can also be used in primary diagnosis of the tumors. MRS output is a curve graph showing some peaks proportional to concentration of distinct microelements in an identified voxel [43]. The region of interest in MRI can be further analyzed using these techniques. Since each pathology changes the metabolites of a distinct region in a specific way, MRS can be of diagnostic value for tumors, infections, so on [43, 44].

MRS may succeed to decrease the need for biopsy taking in the future. That is the difference in proton spin larmor frequency which results in different chemical signaling in terms of metabolite concentration in MRS [44]. These differences are so small (0.0001%) that can be scaled as parts per million (ppm). On the MRS curve graph horizontal axis, zero is on the right. On the left extreme is the 4 ppm concentration. Like MRI, proton frequency is the basis for the routine MRS imaging (1H-MRS). MRS protocols which are based on Na, K, and Ph. are more being used for research purposes [44].

The micro-metabolites assessed in MRS include water (0-reference), Choline, Creatine, NAA (N-Acetyl Aspartate). There are few metabolites on MRS curve which are of diagnostic value in brain tumors. These are NAA (generated by normal neural cells), Choline (represents the cellular turn over. i.e. the higher the
mitosis rate, the higher the choline level is.), Creatine (corresponds to the baseline metabolism of the nerve cell) [44, 45].

When imaging for the brain tumors, Choline and NAA are of special note. Increased choline in presence of decreased NAA can suggest a tumoral composition of a point (Fig-7) [45]. Lactate is peaked when there is an anaerobic metabolism and lipid levels are increased when we have necrosis [45]. Having all these metabolites assessed and interpreted, a clear picture of the neurochemical composition of a voxel will be in hand. When at a distinct voxel, Choline in increased, NAA is decreased, Creatine is at mid level, with noticeable level of lactate, the necrotic nature of the tumoral tissue at that point is inferred. NAA is a marker for glial tumors, so if at a given tumoral voxel no NAA is noted, the tumor is most probably non glial [45, 46].

One of the cardinal implications for MRS is to differentiate tumor relapse (true progression) from post radiation necrosis [43]. Normally to detect the progression we apply Gad-MRI. Areas which are enhanced can represent progression; however radiation necrosis can likewise both induce a mass like picture and enhancement. Currently the best modality to mark a lesion as true or pseudoprogression of glial brain tumor is either Positron Emission Tomography (PET) scan or MRS [43, 47]. MRS at the pseudo progression zone does not show a choline peak. To differentiate glial brain tumors from metastatic lesions following points should be noted: (1) in glioma, Choline spreads outside the enhancement border. (2) In metastasis, we do not have a NAA peak. (3) Metastatic lesions do not have infiltrative extension to their surrounding [46, 47].

MRS can be done in a multi-voxel fashion, showing where we have tumoral infiltration and where we do not. MRS can also be color coded. For instance, there would be a color mapping to localize where Ch/NAA is increased (Tumor cells are nested) [47]. To specifically define pseudoprogression at a voxel, MRS is preferred over the diffusion weighted MRI. Based on what stated earlier, in at least two conditions such as granulation tissue and radiation necrosis, conventional imaging is not informative enough and molecular imaging modalities should address the unmet needs.

On the bottom line, based on the literature, the most preferred methods to differentiate necrosis from recurrence are PET and MRS. Other imaging methods even SPECT have their own shortcomings for this purpose.

There is a growing hope that an interdisciplinary collaboration and better application of the state-of-the-art molecular imaging would result in better planning for our brain tumor patients’ diagnostic and therapeutic measures.

The interplay between neurosurgery, chemoradiation and radiodiagnosics

Getting to know how importantly neurosurgical intervention may contribute to improving lives of brain tumor patients, series of articles were briefly reviewed at NOSC and participants’ opinions were sought accordingly. Recent advances in brain surgical protocols as well as state-of-the-art functional neuroimaging techniques such as fMRI has significantly contributed to better surgical outcome. Pre-surgical planning for brain tumors using fMRI and Diffusion Tensor Imaging (DTI) has helped to decrease damage to eloquent cortical brain areas (rendering competent higher cortical functions, and cognition) as well as subcortical tracts (playing major roles in language and motor functions) [48].

Efficient tumor resection along with chemoradiation plays a pivotal role in treating brain tumor patients, by which patients can experience longer survival and more acceptable quality of life [20]. However only 10-15% of patients may have complete resection and majority of them have residual tumor and measurable disease after surgery. For many of high grade gliomas and GBM in particular, radiotherapy (fractionated to 60Gy) concurrently with TMZ (Stupp protocol [17]), followed by adjuvant TMZ is considered as the standard of care. TMZ oral capsules are administered at the dose of 75 mg/m2 concomitantly with RT for consecutive 42 days, followed by adjuvant regimen (after 4 weeks of break) at 150-200 mg/m2 dose. This protocol has not only shown to increase the 2 year OS of GBM patients (with WHO PS of 0 or 1 and appropriate hepatic and renal function) by 16% (26% vs.10% in RT/TMZ vs.RT alone arms respectively), but also resulted in a higher 5 year OS compared to RT alone. A few patients in favorable prognostic category can survive longer than 5 years [20]. MGMT status identifies patients most likely to benefit from addition of TMZ. Recursive Partitioning Analysis (RPA) with the EORTC system retains its prognostic significance over all as well as in newly diagnosed GBM patients receiving RT with or without TMZ. RPA class III patients are defined as those who are young, have intact cognitive performance, normal KPS and have experienced gross tumor resection rather than biopsy only. To sum up what is inferred from the recently published evidence:

(1) The survival advantages conferred by the addition of TMZ to RT in GBM remain significant and clinically relevant with long-term follow up.

(2) Observed a modest but significant proportion of
patients surviving at least 4-5 years with The RT/TMZ regimen.

(3) Patients in RPA III and with methylated MGMT benefit most from RT/TMZ regimen.

Important safety information for TMZ should be well known and observed in practice. These include but not restricted to hypersensitivity reaction to any of its components or DTIC, myelosuppression including prolonged pancytopenia which may result in anaplastic anemia. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. TMZ may carry fetal harm when administered to pregnant patients. Caution should be practiced when TMZ is administered to those with severe renal and hepatic impairment. Most of the constitutional untoward effects of TMZ are considered mild to moderate and well manageable. Where we stand with neuro-oncology in Mashhad and where we are planning to reach.

Reviewing the general status of neuro-oncology in Khorasan province (North eastern Iran) where the meeting experts are currently practicing- below points were re-emphasized:

The concept of the neuro-oncology working team and joint clinics should be strengthened in real practice. Brain tumor is the 10th most common amongst all malignancy types in Iran. In Khorasan province, CNS malignancies are at the 6th rank. Given their prevalence, we need to overcome pitfalls and challenges in diagnosis, treatment and follow up of these tumors.

The need for molecular and functional imaging, namely MRS, should be re-emphasized and their application must be exercised in our setting when indicated.

Molecular studies in collaboration with molecular pathology experts can be an exciting realm for research which we should plan for.

Stronger contribution of neurology, psychiatry, pathology, radioisotope, physical therapy, endocrinology and other allied disciplines experts in our future NOSC meetings should be more encouraged.

In relatively less common malignancies like brain tumor, the prerequisite for any research is a sound data registry system which allows data gathering and processing. This should be first launched in main radiation oncology centers which are currently active in the city of Mashhad (Khorasan).

NOSC’s first session conclusive remarks following plenary and round table discussions

The round table discussions went on to arrive at the conclusions outlined below. This was the group consensus of the first NOSC meeting in Mashhad.

A. NOSC, as an initiative step, is believed to be a valuable forum for lining up medium and long-term interdisciplinary strategies in neuro-oncology. Participants would adhere to its vision through participation in its interval meetings.

B. This scientific club not only helps strategizing for maximal outcome in treatment of brain tumors but also serves as a scholarly forum which related neuro-oncology experts and trainees can benefit.

C. NOSC above all aims at improving brain tumor patients’ health and QOL through an interdisciplinary team work.

D. Other prospective aims that Mashhad NOSC should be heading for are:

1. Sharing updates on neuro-oncology in interval basis.
2. Taking steps to define local practice guidelines in neuro-oncology (Interdisciplinary).
3. Preparing databank with related tissue repertoire for neuro-oncology studies.
4. Establishing a stronger spirit for the team work in diagnosis, treatment and follow-up of brain tumor patients in khorasan province.
5. Publishing the consensus outcome of each meeting in forms of expert opinions or consensus report papers in neuro-oncology literature and web based discussion forums.

The panel later proposed to have the next NOSC meeting in 3 months (Jan 2012).

Main items on the following session agenda will be: (1) to discuss the preliminary draft of the local guideline (at least to define the diagnosis and referral algorithm in a real interdisciplinary approach). (2): having the web based brain tumor data registry system launched.

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References

2. Davis FG, Freels S, Grutsch J, Barlas S, Brem S. Survival rates in patients with primary malignant brain...


Illustrations

Illustration 1

Mashhad NOSC members, 2011

Illustration 2

Addition of TMZ to RT vs. RT alone, gross resection vs. subtotal resection and the use of BCNU wafers could improve patients’ survivals in different levels. Reproduced from [16].
Illustration 3

Kaplan-Meier estimates of overall survival by MGMT status. Patients with methylated MGMT (A). Patients with unmethylated MGMT (B). Reproduced from [20]

Illustration 4

EORTC/NCIC treatment scheme for glioblastoma . Adapted and reproduced from [24,25].

RT: focal radiotherapy, 60 Gy in 6 weeks to tumor volume + 3-3 cm margin

TMZ, Temozolomide (Temodar, Temodar®),
During RT: 150 mg/m² daily (including weekends) for up to 49 days.
Administration 1-2 hours before RT or in a.m. on days without RT.
Antiemetics: metoclopramide, usually needed only before initial doses.
Maintenance: 150-200 mg/m² daily x 5, for up to 6 cycles
Antiemetic prophylaxis with 5HT3 antagonist or metoclopramide

Pneumocystis carinii prophylaxis during continuous TMZ administration only (lymphocytopenia)
Pentamidine inhalations or trimethoprim/sulfamethoxazole 3x/week
Illustration 5

Standard and dose-dense temozolomide administration schedules. Adapted from [23].

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose: mg/m²</th>
<th>Dose intensity mg/m²/week</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
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<td>150–200</td>
<td>250</td>
<td>Brock et al. [20]</td>
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<tr>
<td>Daily for 42–49 days, repeat every 70 days</td>
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<td>515</td>
<td>Wick et al. [31], Tolcher et al. [32]</td>
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<td>Daily for 7 days, repeat every 14 days</td>
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<td>515</td>
<td>Tolcher et al. [32], Brandes et al. [33]</td>
</tr>
<tr>
<td>Daily for 21 days, repeat every 28 days</td>
<td>75–100</td>
<td>394–515</td>
<td></td>
</tr>
<tr>
<td>Daily for 3 days, repeat every 14 days</td>
<td>300</td>
<td>450</td>
<td>Herson et al. [34]</td>
</tr>
</tbody>
</table>

Illustration 6

Clinical course of pseudoprogression in a 65-year-old patient with glioblastoma. (A) Presurgical MRI scan. (B) Postsurgical MRI scan. (C) MRI scan performed 1 month after combined TMZ/RT; adjuvant TMZ was continued. (D) Four months later, during administration of maintenance TMZ. (E) Eight months later, during administration of maintenance. Reproduced from [23].
Illustration 7

A Normally expected MRS pattern (Right) An increased Ch/NAA ratio at a given point is proportional to tumoral cell composition (Left)
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