Decision making in the treatment of gliomas

Treatment modalities for malignant gliomas have not changed greatly in recent years, but we are learning much more about how to tailor treatments to patients. This overview looks at the role of age, tumour size, performance status and various predictive and prognostic biomarkers in guiding treatment in newly diagnosed and recurrent disease.

The treatment modalities for malignant glioma have not changed a great deal over the past few years, and remain: surgery, radiotherapy and chemotherapy. Surgery is the first step and backbone in the treatment of glioma. Complete resection, debulking or biopsy allows for precise histopathological and molecular characterisation, which is essential if we are to tailor and personalise the therapy. Radiotherapy has been used for thirty years, and we know that it prolongs survival when compared with nitrosourea-based chemotherapy or best supportive care. Chemotherapy used to be the 'new kid on the block', but is now the standard of care in newly diagnosed glioblastoma, concomitantly with radiation. Its value in the upfront treatment of other subtypes is more controversial and the data are not yet conclusive. We commonly use chemotherapy (nitrosoureas and temozolomide) to treat recurrent glioma and as second- and third-line treatment.

Decision making in first-line treatment

Decisions in first-line treatment are not only about how to treat but also who to

European School of Oncology
e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*.
In this issue, Roger Stupp, from the University Hospital of Lausanne, Switzerland, provides an update on factors that can be used in decision-making, focusing on practical aspects and everyday questions in treating patients with malignant glioma.
Olavo Feher, of the Instituto do Cancer do Estado de São Paolo, São Paolo, in Brazil, poses questions sent in by participants during the e-grandround live presentation.
It is summarised here by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net

treat and when to treat. Prognostic and predictive markers are used to guide treatment to ensure we get the most out of it. These factors include performance status, age, tumour size and location, and resectability. There are not a lot of data on resectability, but we know resected patients do better. There are also molecular markers such as *MGMT,* LOH 1p/19q (t 1:19), and *IDH1* mutation. But to what extent do these parameters help us in everyday decisions in managing glioma ?

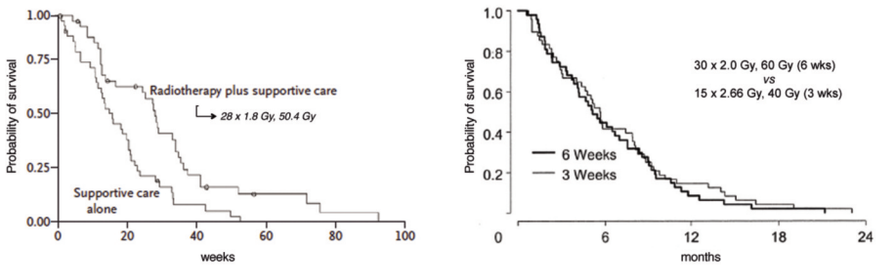
Performance status

Both WHO and Karnofsky's performance status scales are commonly used. The WHO scale has largely replaced Karnofsky in oncology because it is more reproducible; in neuro-oncology both scales remain in use. In practical terms it does not matter which one uses. Most benefit from treatment can be achieved in patients in reasonably good shape, who are alert and largely independent, and are able to come to the outpatient clinic.

Age

When we started the pivotal trial with temozolomide and radiation more than 10 years ago, patients over the age of 70 years were not considered for combined modality therapy on the grounds that their poorer prognosis and short survival would not justify a lengthy course of treatment. But a recent trial conducted by the French neuro-oncology group ANOCEF (*NEJM* 15:1527–1535) looked at the value of radiation versus supportive care in elderly patients aged over 70 years. The trial was closed early because radiation therapy improved survival over supportive care in patients even though they were considered to have poor prognosis (see figure above). A second, Canadian, randomised trial showed that hypo-fractionated radiation gives equivalent results to standard fractionated radiation in the elderly (see figure). The findings mean we can reduce exposure to radiation and the number of hospital visits for therapy in elderly patients.

RADIOTHERAPY: ELDERLY PATIENTS DO BENEFIT



Trials looking at more elderly patients have shown that this group (>70 years) does benefit from radiotherapy and that elderly patients (>60 years) can gain equivalent benefit from a lower overall dose given in fewer sessions

Source: Keime-Guibert for ANOCEF: *NEJM* (2007) 15:1527–1535

Roa et al. *JCO* (2004) 22:1583-1588. Reprinted with permission. © ASCO. All rights reserved

An analysis of subgroups from the EORTC/NCIC pivotal trial comparing temozolomide and radiation with radiation alone in patients aged 60–65 years and those aged 65–70 years shows benefits in both age groups in favour of combined treatment. The hazard ratio in the 65- to 70-years age group was less favourable than in the younger group (0.78 vs 0.64, compared to 0.63 in the whole trial population). These results do not suggest there is no value in combined modality treatment in the more elderly group, but may indicate the need to select patients who will benefit from a more aggressive approach.

The interest in elderly patients is illustrated by two randomised trials, NOA-08 and the Nordic trial, reported at ASCO last year. The NOA-08 trial compared an intensive temozolomide regimen (week on/week off) with radiation in patients aged over 65 (median age 72 years). The objective, which was to show that temozolomide is not inferior to radiation, was not attained, and toxicity with the dose-dense temozolomide regimen was higher than anticipated. With initial radiation alone a median survival of 10 months was achieved, which was reasonably good in an elderly population compared to other trials (Wick et al. ASCO 2010, abstract 2001).

The Nordic trial compared two radiotherapy regimens with temozolomide (5/28 days) in patients aged over 60 (median 70 years). Hypofractionated radiation and temozolomide seemed to be somewhat equivalent (Malmstrom et al. ASCO 2010 abstract 2002). The verdict is still out, but these studies show that if you select the right patients, radiation should be given. However, they also show that chemotherapy alone may be an alternative for some patients, such as those living far away from the hospital and those who are not in a condition to travel. The ongoing NCIC/EORTC intergroup randomised trial is looking at combined modality treatment, and as this approach worked in younger patients, I think it should also work in elderly patients, if selected correctly.

The role of surgery

Several trials have shown that patients who have complete tumour resection do better than patients who only have a biopsy. For example, the EORTC trial demonstrated that patients who had complete resection had longer survival than those undergoing only partial resection or

biopsy (see below, upper figure). A German trial aimed at increasing the complete resection rate by using fluorescent lights in the operating theatre. Results showed improved progression-free survival after complete resection, and higher rates of complete resection using this approach (see lower figure). This trial did not show longer overall survival, but at least it provided further evidence for the role of surgery. However, the extent of surgery needs to be balanced against the risks.

Question: *Considering the data in the elderly – the results of the EORTC/NCIC and the German and Nordic trials – what is your current approach in elderly fit patients with good performance status today, without results from the randomised trials?*

Answer: *If I have a fit elderly patient, I would give them combined modality treatment, possibly temozolomide chemotherapy combined with hypofractionated radiation. I would consider exclusive temozolomide chemotherapy in a patient with a methylated tumour requiring a large radiation field, particulary in an elderly and cognitively frail patient. In short, I would go with combined modality treatment outside a clinical trial if I do not have a clinical trial available.*

Question: *Would you be afraid to combine temozolomide with hypofractionated radiation?*

Answer: *No.*

Molecular markers

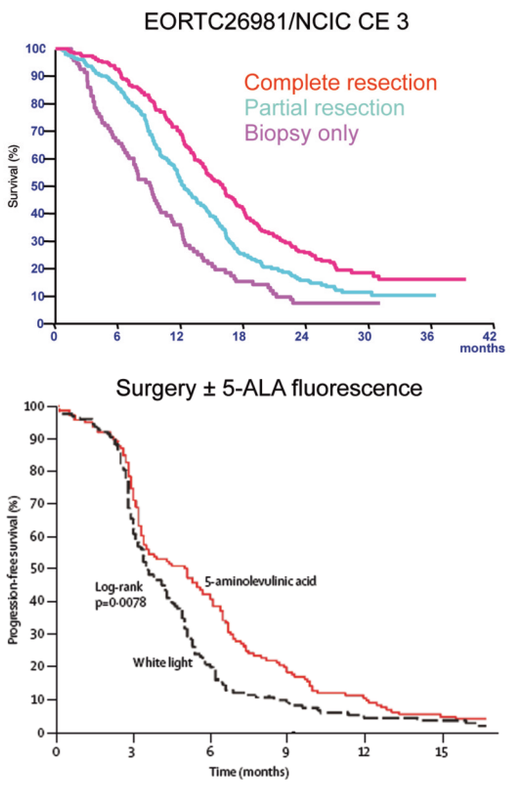
So far, we have seen that clinical factors can give a gut feeling about how to treat a patient, but we have few objective factors to use in deciding who we should treat and how. I think experience has a role here, and my answer to the last question illustrates that we sometimes deviate from the established standard of care for specific reasons, while in other situations a contemporary standard does not exist as it has never been investigated.

What of molecular markers? *MGMT* (O-6-methylguanine-DNA methyltransferase) predicts outcome – at least that's the hypothesis. It is a DNA repair protein that removes the methyl group that had been transferred from temozolomide onto guanine If the gene promoter is methylated, which is an epigenetic phenomenon affecting gene regulation, the gene is silenced. In other words, the gene is not expressed and the cell does not have the toolbox to repair the DNA damage. If this hypothesis were true, patients with a methylated *MGMT* promoter would benefit most from temozolomide chemotherapy.

Studies show that *MGMT* status predicts benefit from combined treatment. Patients with an *MGMT* methylated promoter, who are missing the tools to repair DNA damage, show most of the benefit of the addition of temozolomide, while in patients with non-methylated *MGMT,* temozolomide seems to have no, or marginal, effect on outcome (see figure overleaf).

This initial retrospective observation has recently been prospectively validated (RTOG0525; Gilbert et al. ASCO 2011, abstract 2006). We can conclude that there are two populations of tumours: those with a methylated promoter and others with a non-methylated promoter, and they may merit a different treatment strategy. In tumours with methylated *MGMT*, I think that temozolomide plus radiation should be the backbone of any proposed treatment, and should also be the backbone of any clinical trial investigating the addition of new drugs. For tumours with a non-methylated *MGMT*, we should think of options other than temozolomide, because drugs with a different mechanism of action are needed to treat these patients optimally. The difficulty is that we do not yet have a better alternative for these patients; and even the best test is never 100% predictive. Until better treatments are established, even patients with an unmethylated *MGMT* promoter will receive temozolomide and radiotherapy.

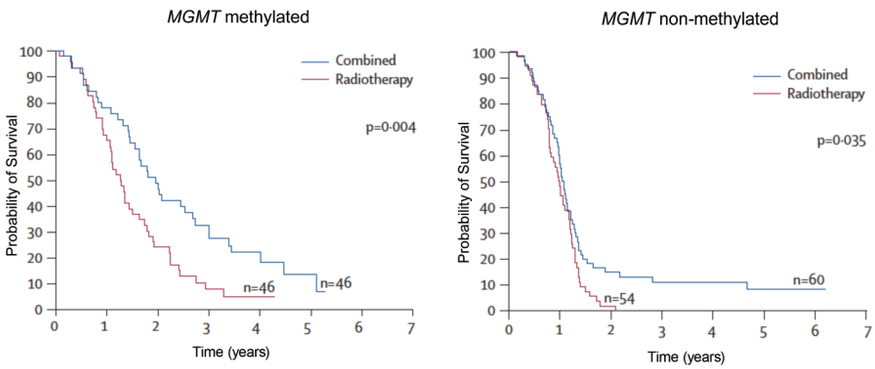
SURVIVAL AND THE EXTENT OF RESECTION



Complete resection was associated with better survival in the EORTC trial. In the German trial, fluorescence-guided surgery led to more complete resections, but complete resection was associated only with delaying disease progression and not with improved survival

Source: (top) Adapted from R Stupp et al. *Lancet Oncol* (2009) 10:459–466 (figure unpublished)
(bottom) Reprinted from Stummer et al. *Lancet Oncol* (2006) 7:392–401 © 2006, with permission from Elsevier

MGMT PREDICTS BENEFIT FROM COMBINED TREATMENT



If these results are confirmed, an alternative to temozolomide should be used in patients with non-methylated *MGMT*

Source: Reprinted from R Stupp et al. *Lancet Oncol* (2009) 10:459–466 © 2009, with permission from Elsevier

THE CURRENT STANDARD OF CARE

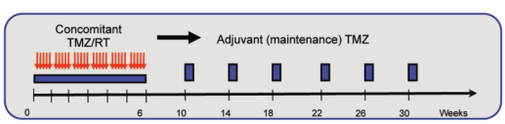
Temozolomide is given seven days a week, including weekends (tumours do not observe Sundays), while radiation is given five days a week (see figure below). With concurrent chemoradiation therapy, daily antiemetic prophylaxis is often not needed. We use a 5-HT3 antagonist only for the first few days of treatment (to avoid constipation associated with prolonged administration), before moving to a simple antiemetic like metoclopramide or domperidon.

What about anti-epileptics? These are only indicated in patients with a history of seizures and not as standard prophylaxis. It is also important to taper steroids. All too often we see patients who become weaker, not due to tumour progression but because of steroid myopathy.

THE PROGNOSTIC VALUE OF MRI

In clinical trials, MRI is usually performed four weeks after chemoradiation. However, results at this early time point are difficult to interpret and so this MRI may not have much value outside trials. The difficult issue is pseudoprogression after combined temozolomide and radiation therapy. After chemoradiation, and after radiation alone, images with increased contrast enhancement may falsely suggest tumour progression, while these changes of the blood-brain barrier reflect inflammation due to tumour breakdown and repair, and will normalise over the following months.

STANDARD OF CARE IN NEWLY DIAGNOSED GBM



RT	30 x 2 Gy, 5 days/wk	60 Gy	
TMZ	75 mg/m², 7 days/wk	max. 49 days	150-200 mg/m2 x 5 days, every 28 days, for 6 cycles
Antiemetics	5HT3 antagonist d1-3, then metoclopramide or no tx		5 HT3 antagonist (low dose) or metoclopramide
Antiepileptics	Only if seizure history		
Steroids	As needed, taper rapidly		
MRI		(X)	Approx. every 2-3 months

Six weeks of concomitant temozolomide (seven days a week, max 49 days continuously) and radiotherapy (five days a week) followed by intermittent adjuvant temozolomide is the current standard of care for all patients with glioblastoma multiforme, with supportive care to combat symptoms and side-effects and check-ups every two to three months (X = optional)

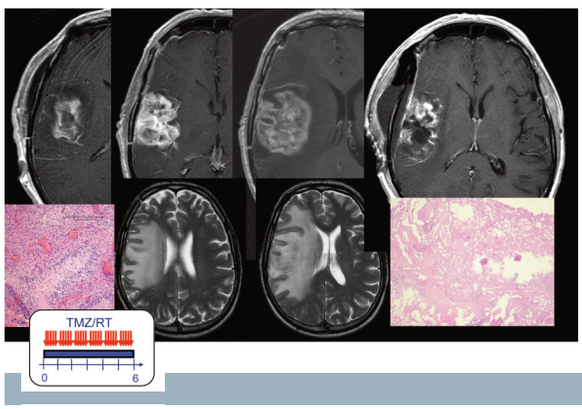
The figure opposite shows MRI scans for a patient with glioblastoma treated with temozolomide/radiotherapy in May 2008. The MRI for August 2008 shows a clear increase, with contrast enhancement, and some oedema, but we thought that it could be pseudoprogression. We continued, but an MRI in October 2008, after a longer period when we should be able to distinguish pseudoprogression from true progression, showed a further increase in tumour size, with more oedema. The patient was taken into surgery but there were no tumour cells to be seen, only necrosis. It is important to keep the phenomenon of pseudoprogression in mind, and not to take patients off treatment too early, particularly if they are clinically well.

MGMT may help in this situation. Brandes and colleagues (*JCO* 26:2192–2197) looked at patients who progressed after chemoradiation therapy but continued temozolomide further. Results showed that some patients continued to progress while others improved on MRI. Two-thirds of patients who subsequently improved had tumours with a methylated *MGMT* promoter, suggesting that pseudoprogression is more frequent in *MGMT* methylated tumours. In other words, pseudoprogression may be an expression of increased tumour breakdown rather than progression.

TREATMENT OF GRADE III (ANAPLASTIC) GLIOMA

Historically, the standard of care is radiation therapy and I think it is important to recognise that certain treatments used in the past may not have been evaluated with the same rigour as today. Data now show that we could start with chemotherapy first and then use

PSEUDOPROGRESSION ON MRI AFTER COMBINED TREATMENT



Follow-up MRI scans in patients treated with concomitant temozolomide and radiotherapy can be deceptive, and care must be taken not to assume patients are progressing when in fact they are responding

Source: MRI scans courtesy of Roger Stupp, University Hospital of Lausanne, Switzerland

radiation at progression. This could be considered for large tumours requiring extensive radiation therapy fields, or for oligos, which have a more favourable natural history and where you may want to delay radiation therapy. There are no data yet for combined modality treatment, but I know that this approach is used frequently.

A carefully conducted German trial looked at the sequence of treatment (*JCO* 27:5874–5880). It randomised patients between radiation first and chemotherapy at progression, or chemotherapy first and radiation at progression. The primary endpoint was progression the second time. Results showed no difference in overall outcome whether patients were initially treated with radiotherapy, followed by chemotherapy at first progression, or the inverse sequence. However, the use of concomitant chemoradiotherapy was not investigated (this is the subject of the ongoing EORTC-Intergroup CATNON trial). Based on these results, we may individually adapt the treatment strategy for each patient. Patients with a small tumour may best be treated with six weeks of radiation rather than a year-long chemotherapy regimen, while in larger tumours a primary treatment with chemotherapy may be considered.

MGMT in this trial was again a strong prognostic marker; however, while one might expect that tumours with a methylated *MGMT* promoter would benefit most from an approach starting with chemotherapy, time to first tumour progression was similar in these patients regardless of whether they were treated with radiotherapy first or chemotherapy first. The value of *MGMT* in grade III tumours is prognostic rather than predictive and does not readily help us chose whether to give chemotherapy or radiation therapy.

Chemotherapy for newly diagnosed anaplastic oligos

I deliberately use a term here that groups oligodendroglioma and mixed oligoastrocytoma together as 'oligos', because definition, reproducibility and trial results are not entirely consistent. As a general rule, pure oligodendroglioma, with a translocation of the gene 1;19 (LOH 1p/19q) have a distinct and prolonged natural history, and better responsiveness to both chemotherapy and radiotherapy. The above-mentioned German trial showed that patients who have an oligo component clearly do better in terms of time to first progression than patients who have anaplastic astrocytoma (*JCO* 27:5874–5880). Two randomised international trials evaluated the addition of PCV chemotherapy (procarbazine, lomustine (CCNU) and vincristine) in anaplastic glioma, including oligos, as a neoadjuvant (RTOG trial, *JCO* 24:2707–2714) or an adjuvant (EORTC trial, *JCO* 24:2715–2722). No benefit from the addition of chemotherapy could be demonstrated, even for the subset of the most chemosensitive oligos.

Individual treatment strategies should be based on tumour size, patient age and how aggressive a treatment one considers to be indicated. Primary chemotherapy may be an option for some patients with large tumours, but radiation therapy may be the best choice for small tumours; however, data do not support the unconditional preference for chemotherapy. More will be known when the ongoing international trials (CATNON coordinated by the EORTC, and CODEL, coordinated by NCCTG, and in Europe by the EORTC) have completed accrual and matured.

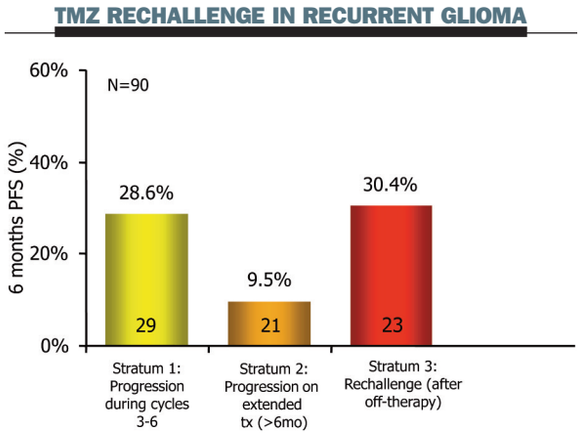
IDH mutations

IDH (isocitrate dehydrogenase) mutations were recognised a couple of years ago as an important prognostic factor for outcome. Patients with an *IDH* mutation, which usually occurs early in gliomagenesis, have a more favourable outcome than patients without this mutation. *IDH* mutation occurs in 70% or more patients with grade II and III glioma (*NEJM* 360:765–773; *JCO* 27:4150–4154). It gives us a way to identify whether a patient has a secondary glioblastoma. I would guess that many long-term survivors of recurrent glioblastoma, who do well with several lines of treatment, have *IDH* mutations.

Treatment options for recurrent glioma

While we have good data and prospective trials for the management of malignant glioma in the upfront setting, we lack large and solid trials in the recurrent setting. Decisions are individual, and depend on patients' and physicians' preferences, and availability of modalities and healthcare resources. Repeat surgery may be an option

in large tumours exerting a mass effect. A randomised trial would be needed to assess its true value, but I do not think that this is practically feasible, as it is hard to randomise patients between invasive surgery and a chemotherapy. Carmustine wafers (Gliadel) were approved for recurrent glioma undergoing repeat surgery, but the impact and use in daily practice remains limited. Approved chemotherapies include temozolomide, carmustine, lomustine and other nitrosoureas. Irinotecan (CPT11), cisplatin, carboplatin and etoposide are occasionally used, but not formally registered. Bevacizumab was recently approved in the US, but it was rejected by the European Medicines Agency (EMA). Re-irradiation is gaining in popularity, although it is not yet validated in prospective trials.



Studies exploring response to changing the dose/schedule, extending adjuvant treatment beyond the standard six cycles, or restarting temozolomide have found varying degrees of benefit

Source: Adapted from J Perry et al (for the Canadian Brain Tumor Consortium). *JCO* (2010) 28:2051-2057

Re-introduction of temozolomide, and alternative and dose-dense temozolomide schedules, are gaining in popularity. When temozolomide was approved, most patients were chemonaïve. They now all have temozolomide up front, so does it make sense to re-expose them?

A Canadian study re-challenged patients with progressive disease with temozolomide. It included patients who progressed in the early phase of adjuvant treatment, and then continued temozolomide on a different metronomic schedule (chronic non-interrupted temozolomide administration at 50 mg/m^2). Results showed almost 30% progression-free survival at six months. In patients who had been on temozolomide for more than the standard six cycles, only 10% seemed to gain benefit from staying on temozolomide. Patients who had been off treatment and then started again showed a 30% progression-free survival at six months (see figure above).

This was not a randomised trial, it was a practice treatment trial, but it tells us that patients who have been on temozolomide for a long while and progress may not benefit from re-treatment with temozolomide.

A British randomised trial looked at PCV versus temozolomide in recurrent chemonaïve (!) glioma patients not given chemotherapy during first-line radiation therapy. Results suggested that temozolomide was equivalent to PCV but not necessarily superior, although toxicity was lower (*JCO* 28:4601–4608). A second randomisation between two schedules of temozolomide – five days of 28 (standard administration schedule) and a dose-dense schedule for 21 (of 28) days showed slightly better outcomes with the five-day schedule. Similarly, the recently reported RTOG05025/EORTC/NCCTG -Intergroup trial failed to demonstrate superiority of a dose-dense temozolomide schedule in newly diagnosed glioblastoma (Gilbert et al., ASCO 2011, abstract 2006). We may have been overly optimistic about alternative temozolomide schedules.

What other alternatives do we have? A trial comparing enzastaurin with lomustine (*JCO* 28:1168–1174) provides data on lomustine in patients with recurrent disease who have failed on temozolomide and radiation. Results show overall survival of seven months, and progression-free survival of 19% at six months with lomustine – close to the 20% benchmark we set at the time with temozolomide. So, lomustine may be a better drug than we thought, often well-tolerated but with a substantial incidence of profound myelosuppression in previously treated patients.

VEGF inhibition for recurrent glioma

Use of agents targeting VEGF or VEGFR is the most recent strategy to be looked at. Data with two drugs – bevacizumab (Avastin) and cediranib (AZD2171) – have initially been particularly encouraging, giving us the kind of MRI images that get us excited! The figure opposite shows scans for a patient before and after treatment with bevacizumab and irinotecan (left-hand scans), and the tumour has almost vanished.

The right-hand scans in the same figure include similar findings from a trial by Batchelor and colleagues (*Cancer Cell* 11:83–95) for a patient treated with the VEGFR inhibitor cediranib. The scans show that the contrast enhancement disappears very rapidly. MRI scans the day before cediranib administration, the day after treatment, and after four weeks, show that the tumour had disappeared, or had started disappearing, 24 hours after giving cediranib. This is almost too good a result. It suggests that what we see with this VEGFR inhibitor is the normalisation of the vascular permeability and of the vasculature, but not necessarily a true anti-tumour effect, so some of this is a radiological

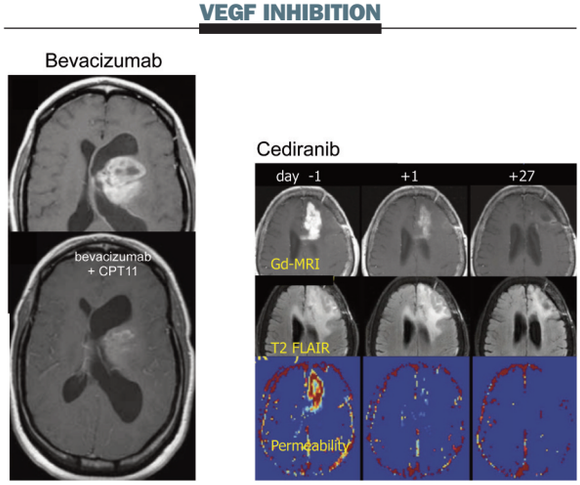
phenomenon of pseudoresponse rather than a true response. Nevertheless, regression of peritumoural oedema is real and often associated with a temporary improvement in patients well-being.

We only have limited data with these agents in brain tumours. Although bevacizumab has been approved by the FDA, this is a conditional approval on the basis of phase II data. A randomised phase II trial in which patients were randomised to bevacizumab (with irinotecan added on progression) or to bevacizumab plus irinotecan showed that the majority of patients could be spared from using steroids by treatment with bevacizumab, which is less toxic than steroids. Tumour size – as measured by contrast enhancement – decreased in the majority of patients. Results showed an overall survival of around nine months, similar in both arms. Although survival appears slightly better than with historical controls, trials with cytotoxic agents alone have shown median survival durations of seven or eight months. So bevacizumab may have some value, but largely based on a steroid-like anti-inflammatory effect, while a clear antitumour effect remains to be demonstrated. It may improve quality of life in selected patients, without necessarily prolonging survival.

For cediranib, a pan-VEGFR tyrosine kinase inhibitor, a proper randomised phase III trial was conducted. The results of the REGAL study were presented recently at the ESMO meeting. This trial randomised patients to cediranib alone, cediranib and lomustine, or placebo plus lomustine. Results showed an overall survival of around nine months in the two lomustine-containing arms, and eight months in the cediranib alone arm (ESMO 2010 abstract LBA7). Disappointingly, no benefit was seen for the combination of cediranib and lomustine. Similarly to the bevacizumab, imaging showed improvement and there was less steroid use in patients on cediranib; however, it did not translate into improved survival. Overall, a VEGF-inhibiting strategy may be of some value; however, the target population (e.g. large tumours with important peritumoural oedema and mass effect), the optimal dose and frequency of dosing, and combination with cytotoxic chemotherapy remain to be determined.

Summary

In conclusion, we have a few clinical parameters on which to make decisions on when to treat and when to withhold treatment in patients with malignant gliomas. The nihilism we have had until recently, especially in elderly patients, may be questioned, and some elderly patients may benefit from active treatment. Complete tumour resection, if feasible, is associated with improved outcome.



Images showing recurrent gliomas before and after treatment with bevacizumab (left) and cedirinab (right) show dramatic tumour shrinkage, but this may not be true response

Source: (*left*) JJ Vredenburgh et al. *Clin Cancer Res* (2007) 13:1253–59, adapted and reprinted by permission from the AACR (*right*) Batchelor et al. *Cancer Cell* (2007) 11:83–95, reprinted with permission from Elsevier

In terms of molecular markers, *MGMT* methylation status predicts benefit from alkylating agent chemotherapy in glioblastoma and is prognostic in anaplastic glioma. LOH 1p/19q characterises a subgroup of patients and tumours with a protracted natural history. *IDH* mutations occur early in gliomagenesis and are characteristic for transformed lower-grade glioma, allowing us to identify secondary gliomas that have a different genetic makeup. They may indicate a more favourable prognosis, and tumours that are more likely to respond to treatment.

Question: *We have seen overall survival of glioblastomas converging at around 21 or 22 months in a couple of late phase II trials – the NABTT trials and the UCLA trial with bevacizumab and irinotecan, and temozolomide first-line trials with glioblastomas. Do you think the survival in glioblastomas is shifting to the 20 months hallmark?*

Answer: *I think it is shifting, because patients get better care. A lot of the benefits are due to better supportive care and the fact that we do not give up, and we do repeat surgery and multiple lines of chemotherapy. It is a conglomerate of many interventions rather than just one intervention. There is always some selection bias in clinical trials. We tend to include the better patients, because the ones with the worst prognosis may not even make it to a trial. A number of trials have shown a good number of patients progress even after chemoradiation, and never make it to any further lines of treatment. This underlines the need for randomised trials, because we cannot draw conclusions based on historical controls. This shift to improved survival means we need contemporary controls to help guide decisions. The answer is randomised clinical trials.*