How best to treat recurrent glioma

Victor Alan Levin*: Victor Alan Levin received his medical degree from the University of Wisconsin (1966), was a Staff Associate in the Experimental Therapeutics branch of the National Cancer Institute (1967–1969) and completed a residency and fellowship in the Department of Neurology at Massachusetts General Hospital (1969–1972). After residency, he was recruited to the University of California, San Francisco in the Departments of Neurological Surgery, Neurology and Pharmaceutical Chemistry and the Clinical Pharmacology program. He was promoted to Professor of Neuro-oncology in the Department of Neurological

Surgery and Professor in the Department of Pharmaceutical Chemistry at the University of California, San Francisco. In 1988, he moved to the University of Texas MD Anderson Cancer Center as Professor and Chairman of the Department of Neuro-oncology to help develop multidisciplinary programs in neuro-oncology, pain management, cancer rehabilitation and cancer psychiatry. He was a founder of the Society for Neuro-Oncology and served as its first president between 1995 and 1997. He retired from MD Anderson Cancer Center in November 2009 and moved back to California where he works part-time at a Kaiser Permanente hospital and still sees neuro-oncology patients weekly. In addition to these accomplishments, he has published 375 peer-reviewed articles, chapters, editorials and books, including the multidisciplinary textbook, *'Cancer in the Nervous System'*. In his career, Dr Levin has received numerous awards including the gold medal award for extraordinary achievement (Society for Neuro-Oncology).

Q What are the features of recurrent glioma?

There is no unique group of neurological symptoms or signs that define recurrent glioma; everything depends on tumor location in the CNS. While headache can be a harbinger of tumor growth, it can just as easily be due to musculoskeletal contraction or imbalance unrelated to tumor growth and more related to activities. In a patient with weakness of a limb, greater weakness or involvement of leg or gait might indicate tumor progression. Likewise, in some with a stable speech problem (dysphasia), even greater difficulty with speech might indicate tumor progression. If one cannot rely on neurological symptoms and signs, what

can you rely on? Typically, neuroimaging with MRI or computed tomography imaging will define tumor progression, although sometimes progression is due to radiation damage to the CNS (radiation necrosis) or, if within 12–16 weeks of irradiation, the subacute effects of radiation on the CNS mimicking tumor growth (some call this pseudoprogression).

Q How does treating a recurrence differ from treating newly diagnosed glioma?

Today, high-grade gliomas, at presentation, are treated with surgical resection, external beam radiation therapy (EBRT) and chemotherapy during radiation therapy (chemoradiation) and/or after radiation

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therapy (adjuvant chemotherapy). For glioblastoma (WHO grade 4 tumors), therapy typically marches from maximal surgical resection to chemoradiation to adjuvant chemotherapy. For anaplastic gliomas (WHO grade 3 tumors) therapy still includes maximal surgical resection followed by EBRT and adjuvant chemotherapy. The drugs used in 2012 are primarily alkylating agents, such as temozolomide, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), 1,3-bis(2-chloroethyl)-1-nitrosourea and procarbazine.

For anaplastic gliomas with codeletion of chromosomes 1p and 19q, some practitioners will only use EBRT or chemotherapy at first and wait for progression to use the other modality. Tumors with chromosomes 1p and 19q codeletion are usually oligodendrogliomas and within this histology, approximately 70% will be codeleted tumors.

For recurrent high-grade gliomas, treatment can include the need for another surgical resection to reduce mass effect on the brain and/or to make a diagnosis of a higher grade glioma or to distinguish treatment effects from tumor growth. Re-irradiation is not normally used unless the time from last irradiation is 5–10 years or the lesion is small enough to be treated with stereotactic radiosurgery. In most cases, chemotherapy is a first choice for tumor recurrence or progression. Unfortunately, there is a dearth of drugs available to treat these tumors and, for the most part, they are the same alkylating agents used over the years for the initial treatment of high-grade gliomas.

Some practitioners will use alkylating agents in combination with other drugs approved for the treatment of cancer or might try alkylating agents with a newer experimental agent in the hope that it will be more active against the progression (growth) of the tumor. In addition, to these approaches, there are usually a number of Phase I (toxicity) and Phase II (efficacy) studies available to patients through academic centers. Sadly, of the many drugs tested over the past two decades, none of the so-called targeted agents have made it into the clinic. We remain hopeful that new drugs will eventually allow us to better treat patients with high-grade gliomas

and hopefully replace the alkylating agents we rely on today.

Q What factors are used to guide treatment decisions?

If a patient will benefit from another surgical resection and does not run a high risk of producing more neurological symptoms or complications, I will advocate surgery first. Typically, this is not common, since extensive resection for recurrent/progressive high-grade gliomas is not usually possible. Thus, most patients at recurrence will be advised to take chemotherapy. What chemotherapy to give is up to the medical team.

If the patient has never been treated with cytotoxic chemotherapy, then they will be offered temozolomide or lomustine as single agent or a combination with other approved cancer agents. If short of new drugs, I typically use combinations that incorporate drugs, such as 6-thioguanine [1,2], hydroxyurea [3], 5-fluorouracil [4,5], capecitabine [6], procarbazine or even isotretinoin [7]. Others might use dose-intense schedules or low-dose continuous dosing of temozolomide. Years ago we used procarbazine in various schedules for recurrent high-grade gliomas much the same way as has been done for temozolomide over the years. We have also used isotretinoin as a single agent with some activity in glioblastoma more so than anaplastic astrocytoma [8,9]. Lastly, vincristine was used in the past as part of the procarbazine, CCNU and vincristine combination but I stopped using it in the early 1990s, unless it was part of an approved clinical trial, because of poor penetration across the intact blood–brain barrier [10].

Since there is very little available to patients today aside from alkylating agents, the options are not many or too diverse. Sadly, of the more than 20 new drugs evaluated against recurrent high-grade gliomas over the past few decades, only temozolomide; a monofunctional alkylating agent, gained regulatory approval for the treatment of high-grade gliomas.

Q What is the current best practice for treating recurrence?

My colleagues and I approached this question for patients who failed temozolomide

and the reader might find our approach helpful [11]. We developed an algorithm to help clinicians treat these patients with available drugs. Our approach is reasonable and reflects our practice to a great extent. For anaplastic oligodendrogliomas that fail EBRT and/or temozolomide, I, for many years, used the TPC combination of 6-thioguanine, procarbazine, CCNU and hydroxyurea [12,13]. Since I could never convince myself that the hydroxyurea added to the combination and added complexity to the combination, I dropped it in favor of the TPC (6-thioguanine, procarbazine and CCNU) combination. For even less complexity, I use just lomustine plus 6-thioguanine. In almost no case do I use lomustine alone given the simplicity and value of adding 6-thioguanine to the nitrosourea [2,14].

Q When is combination therapy warranted?

In virtually all cancers where chemotherapy is effective to the extent of cure, the combination of anticancer agents will be found. This is logical from the perspective that attacking more than one target within tumor cells will be more likely to irreparably damage the tumor cells. In order for a combination to be used in the clinic, it needs to meet certain requirements of clinical trials to be judged efficacious. Unfortunately, clinical trials do not always yield the same results with drug combinations. This has been especially true of the procarbazine, CCNU and vincristine combination that I had a part in propagating over many years. Differences have, at times, not been appreciated owing to differences in diagnostic criteria, timidity in the use of the combination due to

toxicity concerns, reliance on nonradiographic criteria of treatment failure and failure to appreciate radiological treatment effects from tumor progression. It is my hope that in the years to come, every treatment I use today will be replaced by anticancer agents that will truly change the course and outcome of high-grade gliomas.

Q What research is required to improve the treatment of recurrent glioma?

Today we see an almost excessive effort to codify today's treatments with EBRT and alkylating agents, yet I believe that this is really not the work that is needed. What we needed are better anticancer drugs and not 'hand-me-downs' from the pharmaceutical industry. We need drugs that bind tightly to relevant tumor targets, drugs that are not metabolized, drugs that are not pumped by efflux pumps back into the tumor extracellular space or capillary plasma and we need better study designs that allow greater ease in the conduct of drug combination trials at the early stage of drug development. I have much more to say about this and hopefully will do so in an article in the near future.

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