Are we done with dose-intensive temozolomide in recurrent glioblastoma?

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In this month’s issue of Neuro-Oncology, Han et al present another sobering result of dose-dense chemotherapy in a series of 40 recurrent glioblastoma patients failing chemo-irradiation with temozolomide (TMZ). In a well-designed trial the investigators avoided patients with pseudoprogression by not excluding patients relapsing within three months from the end of radiotherapy (RT), and also took O6-methylguanine-DNA methyltransferase (MGMT) status into consideration. They report a progression-free survival (PFS) at 6 months (PFS-6) of just 10%, with a trend towards improved outcome in MGMT promoter methylated cases (median PFS 12 weeks versus 8 weeks for unmethylated cases, \( P = .06 \)). Taken together with the first results of the DIREKTOR trial (NCT00941460) presented at ASCO 2014, it seems fair to ask if there is any role left for these dose-dense temozolomide schedules given to glioblastoma patients at progression after combined chemo-irradiation with TMZ.2,3

After the early phase I and phase II studies on TMZ in recurrent glioblastoma using the now classical schedule of day 1–5 every 28 days that led to its licensing, a variety of different dosing regimens were developed. Initially, the major driving force behind the development of alternative TMZ regimens was dose intensification. Schedules now known as ‘three weeks on-one week off’, ‘one week on-one week off’, ‘continuous dosing over 6 weeks’, etc., resulted in a doubling of the temozolomide dose intensity with acceptable toxicity.4,5 At least one of the earliest explored schedules made a difference for patients: the data on a six-week continuous daily 75 mg/m² temozolomide administration led to the incorporation of this schedule into the combined temozolomide chemo-irradiation scheme that subsequently was found to improve outcome in newly diagnosed glioblastoma patients.6–8 Once temozolomide became standard of care for newly-diagnosed glioblastoma, the pattern of care for relapsing patients had to be redefined. Until then, temozolomide was the most commonly used regimen for glioblastoma relapsing after radiotherapy, but now the obvious question was whether that made any sense in patients relapsing during or after temozolomide chemotherapy. Moreover, it had become clear that patients with a methylated MGMT promoter gene were less sensitive (if sensitive at all) to temozolomide (or nitrosoureas). This led to the development of MGMT depleting agents like O6-benzylguanine as well as the investigation of regimens that combined nitrosoureas and temozolomide, which if used together also more effectively deplete MGMT.9–12 A paper by Tolcher et al that described more pronounced depletion of MGMT in peripheral blood mononuclear cells after protracted, dose-dense temozolomide schedules further boosted the development of these dose-intense temozolomide trials in recurrent glioblastoma.13 The argument was no longer limited to dose intensification but now also included more effective depletion of MGMT and thus held promise to overcome MGMT-mediated resistance to temozolomide. Since then, a large number of trials have been reported, and some of these generated significant interest because of promising results, with reports of PFS-6 of up to 44% in one trial.14 With a PFS-6 of just 10%, the prospective study conducted by Han et al questions once again the effectiveness of these temozolomide dose-intensification schedules.

In clinical oncology, uncontrolled trials are subject to biases of various and often-unknown sources, and that bias is even further increased in retrospective reports. In one important meta-analysis of studies on recurrent glioblastoma the impact of factors such as age, performance status and need for steroids was clearly demonstrated and allowed separation into groups with completely different outcomes: 4.9 months for the poor prognosis group and 10.4 months for favorable prognosis patients in overall survival.15 In neuro-oncology, we assume that this will not impact PFS-6, which is the primary endpoint of many studies on recurrent glioblastoma, but whether that is true remains to be seen. As an example, a meta-analysis of the European Organization for Research and Treatment of Cancer (EORTC) studies on recurrent glioblastoma found that both performance status and the number of target lesions were associated with PFS.16 It is of interest that two other studies with a total 107 relapsed glioblastoma patients treated with the ‘one week on-one week off’ regimen reported PFS-6 rates of more than 40%.16,17 One of these was retrospective, the other did not exclude patients relapsing within three months from RT and had a young patient population (median age of 51 years in the glioblastoma cohort) with good performance status (72% of patients having a Karnofsky performance status of 90 or 100). Interestingly, in this last study median PFS was 24 weeks, whereas the same regimen investigated by...
the same investigators but in a prospective multicenter trial setting (the DIREKTOR trial, see also below) resulted in a median PFS of only 8 weeks.\textsuperscript{2,11} A third study using the one week on-one week off regimen reported a PFS of 27% in 24 patients.\textsuperscript{18} In this study (and despite the fact that this was the second treatment in 79% of patients) the median interval between the end of RT and the start of dose-dense TMZ was no less than 19 months, with a range of 8 to 75 months. All of this points to the importance of patient selection, explaining the more favorable outcome in comparison with the pivotal temozolomide trials in recurrent glioblastoma, for example.\textsuperscript{19}

Further evidence for this comes from the RESCUE trial, which examined continuous daily dosing of temozolomide in patients having relapsed after RT/TMZ.\textsuperscript{20} This trial analyzed outcome in relation to the interval between the end of initial chemotherapy and salvage temozolomide treatment. In the entire group, PFS-6 was 23.9%, but PFS-6 in the patients relapsing after the end of TMZ was 35.7% as opposed to only 7.4% in the patients relapsing during adjuvant temozolomide treatment. Of note, PFS-6 was 23.9% for patients relapsing during adjuvant TMZ, but here no minimum interval between the end of RT and study entry was specified. The good outcome in this last group is quite likely explained by the presence of pseudo-progression and radiation necrosis occurring early after the end of RT, with frequently spontaneous improvement over time even in the absence of treatment.\textsuperscript{21,22} The possible role of patient selection is further supported by the initial results reported at ASCO 2014 of the German randomized phase II DIREKTOR trial using the ‘one week on-one week off’ TMZ versus ‘three weeks on-one week off’ TMZ, which apparently did not yield a significant difference between the two groups in the entire study population. However, the analysis presented on MGMT promoter methylation status is particularly interesting and shows the same signal as the study by Han et al.: PFS-6 after dose-intensified temozolomide was 39.7% in patients with a methylated MGMT promoter gene vs. 6.9% in patients without MGMT promoter methylation. This suggests that if TMZ has activity in post-TMZ relapsing glioblastoma, this activity is in the methylated population.

Taken together, the data support a role for retreatment with temozolomide in carefully selected patients. The question is whether that should be some type of alternative regimen, or whether the standard regimen is good enough. There are two trials that have compared a dose-intense regimen versus standard dosing. First of all, RTOG 0525 compared in newly diagnosed glioblastoma the standard day 1-5 every 4 weeks regimen versus three weeks on-one week off.\textsuperscript{23} The trial was powered for comparison in both the unmethylated and the methylated tumors, and no difference in outcome was observed whatsoever. In a British study conducted before chemo-irradiation became standard of care PCV was compared to temozolomide in chemotherapy of naive relapsed high-grade glioma.\textsuperscript{24} In the temozolomide arm a further randomization was performed between two temozolomide schedules: the standard day 1-5/28 days schedule and the three week on/one week off schedule. No significant differences were observed, but patients treated with the standard day 1-5 every 4 weeks regimen tended to have a better survival compared with patients on the dose-dense schedule (median survival of 8.5 months versus 6.6 months for TMZ-21, $P = .056$). Assuming that even in those TMZ-naive patients 55-65% of patients have an unmethylated MGMT promoter, there is no indication that more TMZ delivers a better outcome. These trials deliver the message that no benefit of the dose-dense schedules has been demonstrated. Those that still want to use them should demonstrate the advantage of the alternative schedule in properly controlled trials, which would require a standard TMZ control arm.

To conclude, with yet another prospective, well-designed trial examining a dose-dense temozolomide regimen for recurrent glioblastoma failing to deliver a meaningful result in an all-comers cohort, it is clear that only in carefully selected patients is there a role for retreatment with for temozolomide at progression. Most likely, these are patients that relapse some months after the end of TMZ chemotherapy who have a methylated MGMT promoter (which are also the most likely patients to be still free from progression some months after the end of adjuvant TMZ). At present, there is no indication whatsoever that this requires a dose-dense TMZ regimen, but a well-designed randomized trial addressing this question would still be of interest. No uncontrolled trial on dose-dense schedules will deliver further informative data.

**References**


