Differential type and cost of treatment on disease progression (after TMZ vs. after radiotherapy only)

Under the original base case analysis it was assumed that on disease progression (i.e. tumour recurrence) patients who had received TMZ as first-line treatment, and those who had not, would have an equal (70%) chance of having active treatment with chemotherapy, and also that all having active treatment would receive PCV. This is represented diagrammatically below.

Original base case analysis:

After radiotherapy only as 1st line treatment

Get chemotherapy	70%	PCV: 100% TMZ: 0%
Palliative care only	30%	

After TMZ + RT as 1st line treatment

Get chemotherapy	70%	PCV: 100% TMZ: 0%
Palliative care only	30%	

This assumption was made on the basis that:

(a) according to our Expert Advisory Group, "current standard chemotherapy" on tumour recurrence in the UK is PCV, and approximately 70% of patients choose to receive it;

(b) there is a lack of robust data from the UK on the extent to which 1st line chemotherapy reduces the chance of having 2nd line (salvage) chemotherapy at tumour recurrence, or the extent to which receiving TMZ as 1st line chemotherapy reduces the chance of having TMZ a second time. Although our expert advisers noted that some centres were beginning to use TMZ at tumour recurrence on more patients, there are no data on the extent or speed of this change in clinical practice.

(c) The 2001 TAR (Dinnes et al) on TMZ for recurrent high grade gliomas found that there was no evidence that TMZ was more effective than current UK treatment of PCV. NICE advice was that TMZ may be used for recurrent disease if first line chemotherapy fails.

In retrospect our initial assumption may have introduced some bias, and the reviewers' comments suggest that there may be a broader consensus on the likely interrelationship between 1st and 2nd line chemotherapy treatment choices than we were aware, such that:

1. patients who have received chemotherapy as first-line treatment would be less likely to receive chemotherapy on tumour recurrence, and;
2. patients who had *not* received TMZ as first-line chemotherapy would be *more* likely to receive it on tumour recurrence.

However, as described below, the problem of how to *quantify* this interrelationship in a decision model remains. One alternative is to rely completely on the Stupp et al. (and Lamers et al.) resource use data from both trial arms. However, this may introduce other biases; if, for example, current UK clinical practice differs significantly from the control arm of the trial (in which 43% received TMZ as 2nd line 'salvage' therapy), or if 2nd line treatment choices following 1st line TMZ might be different in the UK.

Ways of tackling the problem

A number of analyses might be considered:

1. For simplicity, and in the absence of other firm data, assume treatment on tumour progression is as per current standard practice in the UK, and would be the same following radiotherapy-only or following TMZ plus radiotherapy. (i.e. the ORIGINAL PenTAG baseline analysis)

2. Keep the cost of 2nd line chemotherapy following radiotherapy-only as 70% getting PCV (i.e. current standard treatment), but also alter the effectiveness of the radiotherapy-only arm (because the Stupp et al survival estimate for control patients partly derives from 43% (72% × 60%) in the control arm getting TMZ on recurrence).

3. Assume that the effectiveness of 1st line treatment is restricted to extending progression-free survival, that the effectiveness of 2nd line treatment is restricted to extending survival *with-progression*, and therefore that a 'partitioned analysis' could be carried out (i.e. cost per progression-free QALY, excluding both costs and LYs that accrue after tumour recurrence).

4. Use the effectiveness and the resource use data from the Stupp et al trial and thereby assume that the pattern of 1st and 2nd line treatment choices: in the the *control arm* of the trial reflects what future standard UK clinical practice would be if TMZ were *not available* as an option for 1st line treatment, and the treatment choices in the *intervention arm* of the trial reflect what future standard UK clinical practice would be if TMZ were widely used as an option for 1st line treatment.

2nd line treatment in the Stupp et al. trial

After radiotherapy only as 1st line treatment

Get chemotherapy	72%	PCV: 40%
		TMZ: 60%
Palliative care only	28%	

After TMZ + RT as 1st line treatment

Get chemotherapy	58%	PCV: 75%
		TMZ: 25%
Palliative care only	42%	

1. The first option keeps the control arm post-progression costs in line with current UK clinical practice, but avoids the issue of estimating how post-progression costs might alter following 1st line TMZ .

2. The second option is not really feasible because we are unable to distinguish how much of the overall survival in the either arm of the Stupp trial is attributable to 1st line treatment and how much to different treatments at recurrence

3. The third option has been conducted for illustration in the original PenTAG report (section 5.3.5.6 on p.87) using the Stupp trial data on costs and life-years. For the analysis of the economic subgroup it increased the ICER from £[redacted]/LY to £[redacted]/progression-free-LY.

4. The fourth option, as stated above, involves assuming that the patterns of treatment choices and the resultant levels of resource use would be the same in the UK NHS as in the Stupp et al trial (which was conducted mainly in Canadian, Dutch and German treatment centres). We have conducted an additional analysis to assess the impact of making this choice.

Using the Stupp et al proportions having active (chemotherapy) vs. palliative management during progression, and – of those having active management – the different proportions having TMZ vs. PCV, produces the following incremental cost-effectiveness results from the PenTAG model:

Results with different treatment on progression between TMZ-plus-RT and RT only

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
RT only	20,055,237	794			
TMZ + RT	26,439,084	981	6,383,847	187	34,158
TMZ = temozolomide; RT = Radiotherapy; QALY = Quality-Adjusted Life-Year; ICER = Incremental cost-effectiveness ratio					

For comparison, the baseline results as originally reported by PenTAG, assuming the same treatments after tumour progression :

Original baseline results (Table 52)

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
RT only	17,086,676	794			
TMZ + RT	25,642,277	981	8,555,601	187	45,778
TMZ = temozolomide; RT = Radiotherapy; QALY = Quality-Adjusted Life-Year; ICER = Incremental cost-effectiveness ratio					

This lower ICER of £34,158 per QALY is mainly a result of:

1. (*Following RT-only* as 1st line treatment), 60% of those having active 2nd line treatment receiving TMZ instead of PCV (weekly cost £311 vs. £68 respectively)

   → COST↑↑↑

2. (*Following TMZ + RT* as 1st line treatment), 58% instead of 70% receiving 2nd line chemotherapy on tumour recurrence)

   → COST↓

3. (*Following TMZ + RT* as 1st line treatment), 25% (of the 58%) receiving TMZ as 2nd line chemotherapy instead of receiving PCV)

   → COST↑↑

This re-analysis leads to a 17% increase in the discounted cost of RT only (to £20.0 million), and a much smaller 3% increase in the cost of TMZ + RT (to £26.4 million). This in turn results in the lower incremental cost and ICER shown above.

Discussion

None of these options is unproblematic and it remains unclear which is the most realistic for UK practice. It is worth noting that the smaller RCT by Althanassiou showed a very different pattern of treatment for recurrent tumours, with 19% of those in the control arm receiving TMZ compared to none in the TMZ arm. The impact on effectiveness of different treatment regimens and orders is also unknown. Given this, it seems to us possible that the costs of "control" treatment may be artificially inflated by including costs for TMZ at recurrence when this treatment is not certain to improve survival, but is known to be expensive.