**Points on the report from PenTAG**

I think the PenTAG statistical analysis of results are first rate, awesome in detail and understandable, however, I am very concerned by the final conclusion related to the cost effectiveness drawn by the PenTAG group and some of the further suggestions made. I say this as one of the two clinicians who PenTAG have approached for clinical views!. This is no more obvious than in the 1.6.1 and 1.6.2 Discussion section. The suggestion that "The impact of specific tumour type needs to be further explored to identify which, if any patients are likely to benefit from chemotherapy" ignores decades of prospective work, in different countries using chemotherapy of all types, in many situation all pointing at the same factors!

a. From a clinical viewpoint, there is plenty of evidence for response to chemotherapy and who are more likely to respond.:
    i. When chemotherapy is given alone (neoadjuvant) – young patients have a greater chance of response to chemotherapy than more elderly patients and younger patients have more prolonged responses, and fewer side effects.
    ii. When chemotherapy is given at relapse we see shrinkage when following up by sequential scanning. The duration of benefit is better in younger patients with a good performance status. When scans do deteriorate then the treatment is stopped and either nothing or further experimental therapy is used.
    iii. Elderly patients almost never respond to chemotherapy (unless they have an anaplastic oligodendroglioma) and are more likely to have side effects.

The suggestion that the selection for these studies don't reflect those we would consider treating and results are not generalisible is disingenuous!. The authors of this report seems to suggest that the treatments under study would be run out irrespective of age or performance status. This is not clinically sensible and no neuro-oncologist would defend

this. To try to imply that these trials are “not generalisible” or that this is a flaw of some sort is ridiculous!

I think this should be made perfectly clear because it is important for funders to realize that these drugs would only be suitable to be used in small percentages of patients (Gliadel – approximately 25% of all Grade IV patients). Indeed in clinical practice in this country it is likely that the selection criteria for the use of chemotherapy, would be even tighter than that used in these studies, as neuro-oncologists in this country have a more pessimistic view of treatment than colleagues in the rest of Europe. Narrowing the window of prescription for use, as I believe the neuro-oncologists in the UK would do, would improve the cost-effectiveness.

Other points re: Summary

1. Summary 1.1 - “Hitherto, existing approaches to chemotherapy have not convincingly demonstrated a survival benefit and may be associated with considerable adverse effects.” – The emphasis of this is again misleading. A meta-analysis of RCTs (Stewart) has shown that chemotherapy increases median survival by 2 months. In addition the improvement in median survival is much greater for younger patients with HGG and virtually all studies show an increase in percentage of longer-term survivors. The option is to have nothing and die or have chemotherapy and accept risk of side effects.
2. The report implies minor possible non-significant biases between the groups and makes a lot of these to play down the significance of the main results as if there is a bias to find the results as negative as possible.
3. 4.1.1 Presumably the authors mean “ **exclusion of over 65 year olds**” and those with a KPS < 60. It should be acknowledged that these results should be generalisible within the selection criteria. UK clinicians would not treat patients outwith these selection criteria, because of the realization that it would not be in the patient’s best interest as AGE and PERFORMANCE are important prognostic factors. In fact in the UK we are more restrictive!.

4. 1.4.2 This subtle negative bias within the report to find is further identified here where the “non-significance” statistical result is given; but not the long term significant statistics result using unstratified analysis. It then goes on to try and downplay the relevance of the result.
5. They state the only significant adverse event was raised ICP (yet see point 1 – re: “**considerable adverse effects”)**
6. Modeled cohort of 1000 patients, using the figures in this report (frequency 3.6/100,000 and knowing that only 25% of patients would be suitable for Giadel based on entry criteria) would take at least 2 years to treat 1000 in the UK with a cost of 3 million pounds/year.
7. The base case incremental cost-effectiveness ratio (ICER) is £57,000/QALY, which seems significantly better than Beta-interferon in MS if I am not mistaken. (The net cost per quality adjusted life year (QALY) gained from treatment with beta-interferon was £1,024,393 (95 per cent CI £276,191 to £1,484,824).
8. If the comment that “median survival benefit would need to increase to 25 weeks (from the 10 weeks modelled from trial data), or progression-free survival to 20 weeks (from none in the modelled trial data)” means that these drugs are disallowed, then the general feeling in the neuro-oncology community is that, particularly younger, patients with HGG would be missing out on effective treatment which has few serious side effects.

**Temozolomide**

2. “The RCTs may not be widely generalisible due to the exclusion of those with lower performance status and, in the larger RCT, those older than 70”. This statement again suggests a negative bias to these drugs, from rather naive non clinicians, as from a clinical viewpoint all clinicians realize that chemotherapy is ineffective in patients with a poor performance status or who are elderly and are more likely to have serious side effects (whereas younger patients and those with a good performance status are more likely to respond (imaging and

clinically) and treatment in the younger group will be more effective in terms of survival and quality of life!

3. 1.6.1 Suggestion that “The impact of specific tumour type needs to be further explored to identify which, if any patients are likely to benefit from chemotherapy” ignores decades of prospective work using chemotherapy of all types in many situation. This is known. No further research needs to be done on this. Anaplastic oligodendrogliomas do better with chemotherapy than anaplastic astrocytomas (AA) and AA do better than GBM. When patients benefit it can be seen by clinical and radiological response.

**In summary:**

1. The statistics are well done. – No problems
2. The interpretation of the statistics seems negatively biased and naive suggestions are made about how things should be researched in future. These did not come from me and I doubt very much that they came from Prof Brada.
3. I do not have sufficient expertise to comment on the costings /cost effectiveness, but some of the suggestions e.g. “median survival benefit would need to increase to 25 weeks (from the 10 weeks modelled from trial data), or progression-free survival to 20 weeks means we are very unlikely to have the benefit of any new drugs in neuro-oncology in future in the UK. Drug companies are unlikely to wish to spend their resources in finding drugs for these patients, as I don’t think anyone believes these sorts of treatment effects are ever likely in this disease in the foreseeable future.
4. Funders must realize that only a small proportion of patients would be eligible for these treatments and indeed the selection may be tighter in the UK than that used in these European Trials.
5. For the future of neuro-oncology in this country, some compromise must be made to allow limited use of these drugs or some sort of system similar to Beta interferon.

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