Cancer Research UK response to NICE's consultation on their preliminary recommendation on pemetrexed disodium for the treatment of malignant pleural mesothelioma

Summary

Cancer Research UK does not support NICE's recommendation that the prescription of pemetrexed disodium should be limited to use in the NHS within clinical trials.

We urge the Committee to reconsider the cost effectiveness evaluations on which their recommendations are based, on the grounds that:

- Pemetrexed disodium is the only available and proven treatment for patients with mesothelioma, there is no viable alternative. The effectiveness of MVP and vinorelbine are unproven and thus these regimens are not appropriate comparators from the point of view of the cost analysis;
- The cost of supportive care is reduced by giving active chemotherapy contrary to the assumption made in the appraisal;
- Quality of life is improved by active chemotherapy not reduced as is the implicit assumption in this appraisal;
- There is a good rationale, based on the high expression of folate-receptor alpha in mesothelioma, for why antifolates should be more active than other agents.

General Comments

Cancer Research UK welcomes the opportunity to respond to this important consultation. We have concerns about a number of inconsistencies and assumptions made throughout the Appraisal Consultation Document. We therefore call on NICE to review and amend this appraisal prior to making their final recommendations.

Section 1: Appraisal Committee's preliminary recommendations

The appraisal document recommends pemetrexed disodium for the treatment of malignant pleural mesothelioma only as part of ongoing or new clinical trials that compare it with the current best practice or other promising treatments.

Cancer Research UK does not support this recommendation.

Section 2: Clinical need and practice

Pemetrexed disodium in combination with cisplatin is the only licensed therapy for the treatment of unresectable malignant pleural mesothelioma in the UK. This treatment has shown a survival advantage in randomised trials and is used throughout the world. Pemetrexed is also regarded as the standard treatment in many areas of the UK where funding for this treatment is made available.

Despite the acknowledgement in *Section 2.8* of the appraisal consultation document that pemetrexed in combination with cisplatin is the only chemotherapy regimen currently licensed for this indication, the document states that there is no standard chemotherapy treatment for MPM.

While *Section 2.6* states that: “there is no standard treatment pathway for MPM in the UK….a patient may receive a combination of treatments”, proposals for implementation and audit in *Section 7.2* refer to a “current best practice”, implying that a current standard treatment regimen is known.

The document recognises that **extrapleural pneumonectomy** is only an option for a very small proportion of patients (1-5%). This procedure carries a very high morbidity is not supported by any clinical trial data and is the subject of the ongoing MARS trial, which has only just started to recruit. It cannot therefore be regarded as a viable treatment option outside the context of this trial.

Section 5.2 in the document refers to **MVP** (mitomycin C, vinblastine and cisplatin combination) and **vinorelbine** as “standard care”. However, there is no randomised trial evidence to support this claim. In addition:

- The major published data supporting the use of MVP are derived from a selected case series collected over 16 years at the Royal Marsden Hospital. 244 patients were seen, 150 selected for treatment and a response rate of 15.3% reported in 131 of these.
- There are no published reports of formal Phase II studies reporting radiological response rates.
- All of the reports on MVP come from the same centre and group of collaborators. There are no independent or international trials supporting its activity.
- A single Phase II study of vinorelbine conducted in St Bartholomews Hospital published in 2000 reports a radiological response rate of 24% in 29 patients.
- There are no confirmatory studies of the efficacy of single agent vinorelbine from other centres.

We also note the statement in *Section 2.8* that: “To date there have been no reported randomised controlled trials comparing survival and symptom control in patients receiving chemotherapy with those receiving ASC/BSC.”

It is our considered view that such trials are no longer relevant following the EMPHACIS study and the EORTC/NCI Canada randomised trial of cisplatin alone, against cisplatin in combination with ralititrexed, in MPM. Both these trials showed a statistically significant survival advantage for the arm treated with the antifolate over those treated with cisplatin alone.

If chemotherapy does not increase survival, the only explanation for this result would be that the cisplatin reduced survival compared with best supportive care. However, there are no previous examples of treatment with cisplatin reducing survival. Cisplatin has been shown to increase survival in a large range of cancers (including non-small cell and small cell lung cancer, ovarian cancer, upper GI tumours, breast cancer, and cervical cancer) either in randomised trials or in meta-analyses. Survival of the control arms in the EMPHACIS trial and in the EORTC trial were both better than in historical survival reported for cohorts of mesothelioma patients.

Section 4: Evidence and interpretation

We call on NICE to reconsider the appropriateness of the use of MVP or vinorelbine as a comparator in a cost effectiveness study in the absence of evidence for a clinically beneficial effect, or to produce evidence to support the use of MVP as a plausible alternative treatment in this appraisal. In their consideration of appropriate

comparators with pemetrexed cisplatin the Committee accepts that cisplatin is not commonly used as a single agent in the UK, but in fact the Phase II data to support its use is more extensive than that for MVP. In addition, the toxicities for cisplatin noted in *Section 4.3.3* are surpassed by those of MVP, of which cisplatin is itself a component.

We also disagree with the Committees assumption that BSC/ASC costs would automatically be equivalent in patients receiving and not receiving chemotherapy. There are trials in other types of cancer, including lung and pancreatic cancer that show a reduction in best supportive care costs when cancer chemotherapy is used. Specific chemotherapy inducing a clinical response provides relief of tumour related symptoms. This allows for reduction, or cessation of opiates and other supportive measures, leading to a significant improvement in the quality of life for patients.

Section 5: Recommendations for further research

We consider the recommendation for trials comparing pemetrexed with MVP is inappropriate, given current paucity of evidence demonstrating that MVP is effective in treating MPM, and bearing in mind that the result of the MSO1 trial should be available soon.

Access to pemetrexed in Scotland

The Scottish Medicines Consortium in July 2005 ruled that pemetrexed in combination with cisplatin is accepted for restricted use within NHS Scotland for the treatment of chemotherapy-naive patients with stage III/VI unresectable malignant pleural mesothelioma. This decision is based on a prolongation of survival with pemetrexed in combination with cisplatin compared with cisplatin alone in patients with unresectable malignant pleural mesothelioma.

It seems incongruous that this decision should be reached in Scotland, and independently by the London Cancer New Drugs Group, but not by NICE in their evaluation.

Conclusion

We call on NICE to re-run this appraisal taking into consideration the reduced cost of supportive care following chemotherapy and that there is currently no effective alternative chemotherapy treatment for MPM.