Pemetrexed disodium (Alimta™) For The Treatment of Mesothelioma

The main evidence supporting the use of pemetrexed for the treatment of mesothelioma consists of a randomised study which compared a combination of pemetrexed and cisplatin (PC) with cisplatin (C) alone in patients with mesothelioma and showed that the combination regimen extended median survival by nearly 3 months (Vogelzang et al 2003). On the basis of this study the US Food and Drug Administration approved pemetrexed for the treatment of mesothelioma and it has also been licensed for this indication in Europe including the UK.

Inclusion criteria included Karnofsky performance status (PS) >/= 70, corresponding to WHO or ECOG PS 0-1. Patients were excluded if they had had prior chemotherapy, a second primary malignancy, or brain metastases, or if they were unable to interrupt non-steroidal anti-inflammatory therapy which are not recommended for simultaneous use with pemetrexed because they may delay pemetrexed clearance.

Severe toxicity during the first part of the trial, with three possible treatment related deaths among the first 43 patients treated with pemetrexed was noted to be associated with high blood levels of homocysteine and methylmalonic acid, linked to reduced levels of folic acid and vitamin B12. Similar evidence from trials in other diseases led to use of folic acid and vitamin B12 supplements as described above. The change resulted in 3 patient subgroups: never supplemented (NS), partially supplemented (PS) and fully supplemented (FS). The sample size was substantially increased to ensure adequate statistical power of the FS subgroup. Dexamethasone was administered as described above. Dose adjustments could be made if haematological toxicity occurred.

Patients were recruited from 88 centres in 20 countries. 456 patients were randomised but eight who did not receive chemotherapy were excluded from analysis. Patients on the PC arm received a median of six cycles while those on the C arm received a median of four cycles. NS patients received a median of two cycles on each arm. In the whole group median survival was 12.1 with PC v 9.3 months with C (p=0.021). Among 331 FS patients median survival was 13.3 with PC v 10.0 months with C (p=0.051). The investigators reported a tumour partial response rate of 41.3% in the PC arm but a review by the Food and Drug Administration (FDA) confirmed only half of these (Hazarika et al 2005).

The PC arm showed higher rates of severe leucopenia, anaemia, thrombocytopenia, nausea, vomiting, diarrhoea, constipation, anorexia and mucositis. An abstract of quality of life (QoL) data presented at ASCO in 2003 reported a significant sustained improvement in QoL and symptom relief when compared with cisplatin alone. This differentiation in QoL and symptoms was reported to have occurred within the first 3 cycles and reached statistical

significance in most variables (global QoL, pain, dyspnoea, fatigue, anorexia and cough) by week 15, all in favour of the combination regimen (Gralla et al 2003).

There are several reason as for caution in interpretation of this study. The survival advantage was not quite statistically significant in the fully vitamin supplemented group of patients. The patients in the pemetrexed trial were younger and fitter than average for mesothelioma patients and it is possible that if there is a survival benefit that it might be fitness–related. The trial was confounded by large proportions of patients in both arms receiving second-line treatment and it is unclear what effect this had on the result. Finally for this group of patients a small increase in life expectancy may not be the primary aim for either the patient or the clinician. Symptom control and/or quality of life (QoL) are very important, and with the full QoL data from the pemetrexed study remaining unpublished, it is unclear how QoL balances with any change in the duration of survival. QoL differences will remain difficult to evaluate in this study even when data are published because the control arm consisted of relatively high dose cisplatin which is fairly toxic and ineffective treatment for MPM. It is possible that QoL advantages for pemetrexed may be at least partially a result of toxicity without relief of disease symptoms in the control arm.

A phase II study has suggested that efficacy may be approximately similar when carboplatin in a dose of AUC 5 is used instead of cisplatin in combination with pemetrexed (Hughes et al 2002). The substitution of carboplatin for cisplatin is associated with reduced symptomatic toxicity particularly with regard to nausea and vomiting, and increased ease of administration with less need for prolonged hydration with intravenous fluids. QoL may well be better if pemetrexed is used with carboplatin rather than with cisplatin although a randomised study is needed to investigate this.

Support for the efficacy of this class of drug is provided by similar results from a smaller study of cisplatin with or without raltitrexed, another anti-folate, in 250 patients with mesothelioma (Van Meerbeeck et al 2005). Median overall and 1 year survival with cisplatin vs raltitrexed were 8.8 (CI 7.8 – 10.8) months vs 11.4 (CI 10.1 – 15) months and 40% vs 46% respectively (p= 0.048). There was no detriment to QoL from raltitrexed. I understand that the manufacturers of raltitrexed have no intention of trying to have it approved for treatment of mesothelioma and in fact may stop making the drug altogether for economic reasons, so pemetrexed is the only drug of this type likely to remain available for treatment of mesothelioma in the short to medium term.

As yet there is no randomized trial evidence that demonstrates that chemotherapy confers better quality of life and survival than supportive care without chemotherapy, questions which continue to be addressed by the British Thoracic Society study MSO-1 comparing two alternative chemotherapy regimes, single agent vinorelbine and the combination of mitomycin, vinblastine and cisplatin with active symptom control alone (Muers et al 2004). This is due to

close to recruitment around the middle of this year and results may be available during 2007. The potential effects of this study on the perceived role of pemetrexed merit consideration. The problem with this study, with which I am involved as a designer of the trial and member of the trial steering committee, is that it has been slow to recruit and has to some extent been overtaken by events. If it should prove negative, the response from the oncology community is likely to be that it used less effective chemotherapy than pemetrexed, and so should not be taken as evidence against the use of pemetrexed, but rather as evidence against the use of the older regimes used in MSO-1. If it should be positive, the response is likely to be that it proves that chemotherapy prolongs survival so more patients should receive chemotherapy than currently, but on the basis of reported response rates pemetrexed is likely to be more effective than either regime used in MSO-1 and so should be the drug of first choice. Hence, whatever the outcome of MSO-1 it is not likely to reduce demand for pemetrexed but rather strengthen it. A decision on pemetrexed therefore should not be delayed because of MSO-1.

In summary, unless cisplatin alone actually shortens survival, which seems unlikely, the evidence from the pemetrexed and raltitrexed trials suggests that these drugs probably do confer a small median survival advantage, and as with any chemotherapy, patients whose tumours respond well to therapy are likely to gain more than average in terms of survival. The effects on quality of life are as yet not fully evaluated but at the least do not appear to be detrimental

Despite the need for caution in interpretation of the data, pemetrexed is an agent with demonstrable clinical efficacy in treatment of mesothelioma and as such it is to be welcomed. Our own experience with pemetrexed at Barts suggests to us that it has some advantages over alternatives in terms of lesser toxicity, particularly when used with carboplatin rather than cisplatin, and ease of administration, with a three weekly out-patient treatment schedule. It is a reasonable option for treatment of patients who prefer to receive chemotherapy after a discussion of the pros and cons of this form of treatment. Provision of pemetrexed at present in the NHS is very patchy, a return to the worst excesses of ‘post-code prescribing’ and guidance from NICE is urgently needed. In my view there is sufficient evidence for this drug to be recommended as cost effective treatment for mesothelioma.

References

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