



Standard therapy for the treatment of malignant pleural mesothelioma

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Almost all of the established cytotoxic agents have now been examined both as single-agents and in combination chemotherapy regimens as treatment approaches for malignant pleural mesothelioma (MPM). Until recently, only few agents have consistently produced objective response rates greater than 20%, and no agent has improved median survival beyond 10 months. The recent development of several new cytotoxic agents, such as the novel antimetabolite pemetrexed, has yielded encouraging results. In particular, pemetrexed produces response rates of up to 45%, and increases median survival to over 12 months when used in combination with cisplatin. This doublet-based chemotherapy regimen is now the standard therapy for the first-line treatment of MPM.
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The standard therapy for malignant pleural mesothelioma (MPM) began to change in 1999, following a key publication from a phase I study showing that the combination of pemetrexed plus cisplatin had clinical activity in patients with various solid tumors, including confirmed partial responses in five of the 11 patients with MPM [1]. These findings led to the design of a second phase I study in which carboplatin was combined with pemetrexed in patients with MPM [2]. This combination regimen resulted in an overall response rate of 32%, and 70% of patients noted an improvement in symptoms. A multicenter, phase II clinical study was then undertaken to confirm the promising results of phase I trials with pemetrexed in patients with MPM [3]. Single-agent pemetrexed was associated with a moderate re-

sponse rate of 14.1%, and a median overall survival of 10.7 months, which was about the best survival time reported to date. Dietary supplementation with low-dose folic acid and vitamin B₁₂ was shown to markedly improve the tolerability of pemetrexed, while maintaining clinical activity.

Based on the encouraging results of phase I trials with pemetrexed and cisplatin in MPM patients, in addition to early findings of a phase II trial of pemetrexed and cisplatin in patients with advanced non-small-cell lung cancer [4], a large, randomized, single-blind phase III study was conducted to compare the combination of pemetrexed with cisplatin versus cisplatin alone in patients with MPM [5]. Overall, 456 chemotherapy-naïve patients were randomized to either pemetrexed 500 mg/m² with, or without, cisplatin 75 mg/m² on day 1 every 3 weeks. After the enrolment of 117 patients, folic acid and vitamin B₁₂ were supplemented to limit toxicities. In the intent-to-treat analysis, median survival improved significantly from 9.0 months with cisplatin

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alone to 12.8 months with pemetrexed plus cisplatin ($p = 0.003$). At 18 months, there was still a statistically significant difference in survival between the two groups, and a trend for a survival advantage at 24 months with pemetrexed/cisplatin versus cisplatin alone. Furthermore, pemetrexed plus cisplatin achieved superior median time-to-disease progression (5.7 months versus 3.9 months, $p = 0.001$) and higher response rates (41.3% versus 16.7%, $p < 0.0001$) compared to cisplatin alone. More importantly, the pemetrexed/cisplatin doublet resulted in significant improvements in several dimensions of the Lung Cancer Symptom Scale (LCSS), including overall quality of life, pain, fatigue and dyspnea, and also improved pulmonary function compared with cisplatin alone. The results of this pivotal trial led to the approval of pemetrexed in combination with cisplatin for the treatment of patients with MPM. It is the only therapy for unresectable mesothelioma that is approved by the US Food and Drug Administration.

The survival benefit of a doublet-based regimen has been confirmed in another phase III trial comparing raltitrexed plus cisplatin versus cisplatin alone in 250 patients with mesothelioma [6]. Treatment with raltitrexed and cisplatin was associated with a trend towards improved survival and response rate compared to cisplatin alone, although this did not reach statistical significance.

The role of second-line chemotherapy in MPM has recently been evaluated in patients enrolled in a phase III trial of pemetrexed plus cisplatin versus cisplatin alone [7]. The most common drugs used in the second-line setting were gemcitabine and doxorubicin. Fewer patients in the pemetrexed/cisplatin arm received post-study chemotherapy than in the cisplatin-alone arm. However, the use of second line chemotherapy resulted in a statistically significant survival advantage when compared with patients who did not receive such therapy.

Several areas of investigation are currently being explored to further improve survival outcomes with chemotherapy for MPM. Encouraging results have been demonstrated in a multicenter, randomized, double-blind, placebo-controlled study of gemcitabine/cisplatin/bevacizumab versus gemcitabine/cisplatin/placebo in patients with unresectable MPM. Pemetrexed-based doublets and the possibility of using more frequent and/or high-dose pemetrexed is being investigated. Although there are currently no trials in mesothelioma of pemetrexed plus a targeted therapy, many potential combinations exist. Trials have been completed using the novel agents gefitinib, PTK 787 and erlotinib, but their activity appears limited. However, there is a plethora of new agents worthy of study, such as inhibitors of epidermal growth factor receptor, vascular endothelial growth factor receptor, and histone deacetylase.

Conclusions

The development of pemetrexed has led to a significant advance in the treatment of MPM. Pemetrexed in combination with cisplatin is the only treatment with activity proven in phase III trials. It is the first, and only registered chemotherapy for the treatment of MPM. Pemetrexed not only improves survival and response rate but also palliates symptoms and improves quality of life and lung function. Dietary supplementation with low-dose folic-acid and vitamin B₁₂ controls the toxicity of pemetrexed while maintaining efficacy. Whether other doublets, such as gemcitabine/cisplatin, are equivalent or superior to pemetrexed plus cisplatin remains unknown. The results using second-line chemotherapy are promising, and encourage future development of second-line trials in MPM. New, novel agents are under investigation, but early data are not yet promising. In conclusion, with the advent of combination chemotherapy using pemetrexed and cisplatin, MPM should no longer be considered a chemotherapy refractory disease.

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