Editorial

Review of nintedanib plus pemetrexed/cisplatin in patients with malignant pleural mesothelioma: phase II results from the randomized, placebo-controlled LUME-Meso trial

Pyng Lee

Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Correspondence to: Pyng Lee. National University of Singapore, Yong Loo Lin School of Medicine, 1E Kent Ridge Road, Singapore 119228.
Email: pyng_lee@nuhs.edu.sg.

Provenance: This is an invited Editorial commissioned by the Section Editor Zhenying Guo (Department of Pathology, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China).

Comment on: Grosso F, Steele N, Novello S, *et al.* Nintedanib Plus Pemetrexed/Cisplatin in Patients With Malignant Pleural Mesothelioma: Phase II Results From the Randomized, Placebo-Controlled LUME-Meso Trial. J Clin Oncol 2017;35:3591-600.

Submitted Jun 28, 2018. Accepted for publication Jul 23, 2018.
doi: 10.21037/jtd.2018.07.105
View this article at: http://dx.doi.org/10.21037/jtd.2018.07.105

Burden

Malignant pleural mesothelioma (MPM) is an aggressive cancer of the pleura associated with asbestos exposure. MPM accounts for 10 cases/million in USA and up to 29 per million in Australia and UK (1). Although MPM has reached a plateau in USA (2), MPM is expected to peak in 2020 for Europe due to the long latency period between asbestos exposure and diagnosis (30–50 years), and use of asbestos until 1970 (3). Asbestos is not banned worldwide, mining and use continue in countries like China, India, Russia and Kazakhstan, which according to the World Health Organization (WHO) could lead to asbestos related diseases and MPM of epidemic proportion into the next decade (4).

Pathogenesis

Asbestos fibers when inhaled can cause chronic inflammation of the lung and pleura. Overexpression of growth factors (VEGF), genetic and epigenetic alterations and mutations of mesothelial cells like BRCA-associated protein (BAP-1), neurofibromatosis type 2 (NF-2) and p16 INK4A or CDKN2A can lead to cell proliferation, resistance to apoptosis and local immunosuppression. These provide the basis for novel drug development and therapy for MPM (5,6).

Treatment

Management of MPM requires multi-disciplinary approach, to date there are 2 therapeutic strategies; surgery with curative intent or palliative cytotoxic chemotherapy. MPM is diagnosed at advanced stage due to non-specific symptoms with only a minority suitable for surgical resection. Surgical eligibility (extrapleural pneumonectomy, pleurectomy or decortication) depends on tumour stage, performance status (PS), histology (epithelioid subtype) and nutritional status. Surgery as part of multimodality therapy that includes chemotherapy with or without radiation therapy should be performed at highly specialized centers with multidisciplinary expert teams or within a clinical trial (6-8). In asymptomatic patients with epithelial histology and minimal pleural disease who are not surgical candidates, a trial of close observation may be offered prior to chemotherapy (8).

Median OS of patients with advanced MPM is dismal at 12 months (9). Systemic chemotherapy is recommended for patients with PS <3 since it improves survival and quality of life (QOL) (7,8). First-line chemotherapy combining pemetrexed and cisplatin or pemetrexed and carboplatin is the standard of care (7-9). Raltitrexed could be an alternative to pemetrexed in combination with cisplatin (10).

Data from a phase III randomised trial (7,9) show that median OS with pemetrexed and platinum does not

exceed 13–16 months with best outcome in patients with epithelioid MPM subtype. Patients with PS 2 may be offered single-agent chemotherapy while those with PS 3 or greater should receive palliative care (8,11).

Pain arising from chest wall invasion can be controlled by radiotherapy, and new modalities such as intensity modulated radiotherapy, proton therapy and stereotaxic radiotherapy are under investigation (7-9,11,12). Prophylactic radiotherapy to chest wall incisions after surgery however remains controversial and not recommended in the 2018 American Society of Clinical Oncology guidelines since SMART trial has shown no benefit (8,13).

To date, there is no therapy approved for disease progression except to repeat pemetrexed-based chemotherapy if the patient has had a long progression-free survival (PFS) (14). Drugs such as vinorelbine and gemcitabine have been tested in MPM trial but less than a third experienced disease control after 12 weeks of treatment, and median OS is 6 months or less (15,16). New treatments are therefore urgently needed for MPM.

Anti-angiogenic drugs

Owing to the high expression of angiogenic growth factors and receptors in MPM, various anti-angiogenic drugs have been investigated as monotherapy, in combination with chemotherapy (cisplatin plus pemetrexed), maintenance treatment or both.

A phase III randomised trial did not show benefit of thalidomide as maintenance therapy after first-line chemotherapy with cisplatin plus pemetrexed (17). A phase II trial of cisplatin plus gemcitabine combined with bevacizumab (an anti-VEGF monoclonal antibody) or placebo showed no difference in median PFS (6.9 months bevacizumab *vs.* 6.0 months placebo). Although median OS for bevacizumab group was encouraging, it was not significantly increased compared with placebo group (15.6 *vs.* 14.7 months) largely confounded by patients receiving second-line pemetrexed in the placebo group (18). MAPS trial (19) of 448 patients with MPM demonstrated small but significant benefit in median OS when bevacizumab was added to cisplatin plus pemetrexed and continued as maintenance therapy versus chemotherapy alone (18.82 *vs.* 16.07 months). Median PFS was also significantly increased by 2 months in the bevacizumab group with tolerable mild toxic effects that did not affect QOL. Thus, this study suggested a new approach to unresectable MPM, however bevacizumab is not approved by the US Food and Drug Administration (FDA) or European Medicines Agency for use since MAPS trial was not designed as a registration trial. It is probable that the large size and design of MAPS trial provided the power to show significant survival benefit of bevacizumab in combination with first line chemotherapy.

In the issue of *Journal of Clinical Oncology*, Grosso *et al.* reported results of LUME-Meso trial, a phase II/III randomized, double-blind trial designed to assess efficacy and safety of nintedanib plus chemotherapy as first-line treatment of MPM (20). Chemotherapy-naive patients with unresectable, non-sarcomatoid (epithelioid or biphasic) MPM and ECOG (Eastern Cooperative Oncology Group) PS 0 to 1 were recruited. The intervention group received up to six cycles of pemetrexed and cisplatin plus nintedanib 200 mg twice daily while the control group received chemotherapy plus placebo. Nintedanib and placebo were continued until disease progression. The primary end point was PFS.

Eighty-seven patients were randomly assigned 1:1 ratio. The median number of chemotherapy cycles received for both groups was six; and the median treatment duration with nintedanib was 7.8 and 5.3 months with placebo. Primary PFS favoured nintedanib, hazard ratio (HR) 0.56 (95% CI, 0.34–0.91; P=0.017). There was a trend toward improved OS with nintedanib (HR, 0.77; 95% CI, 0.46–1.29; P=0.319) especially epithelioid MPM subtype where median OS gain was 5.4 months (nintedanib 20.6 months *vs.* placebo 15.2 months; HR, 0.70; 95% CI, 0.40–1.21; P=0.197) and median PFS gain was 4.0 months (nintedanib 9.7 months *vs.* placebo 5.7 months; HR, 0.49; 95% CI, 0.30–0.82, P=0.006). The effect of nintedanib on PFS and OS was consistent across all subgroups expect those with biphasic MPM where more than half (nintedanib 64% *vs.* placebo 70%) received subsequent therapy. Tumor response was objectively superior with nintedanib than placebo.

Adverse events (AE)

All patients experienced at least one AE. More patients in the nintedanib group experienced grade ≥3 AE (79.5% *vs.* 53.7% placebo). Neutropenia was the most frequent grade 3 AE (nintedanib 43.2% *vs.* placebo 12.2%), however rate of febrile neutropenia was low (4.5%) and not reported with placebo.

Incidence of AEs associated with anti-angiogenic agents was not different (nintedanib *vs.* placebo), of interest were bleeding (11.4% *vs.* 12.2%), GI perforation (0% *vs.* 2.4%), thromboembolism (9.1% *vs.* 17.1%) of which (6.8% *vs.* 14.6%) were due to venous thromboembolism, no arterial

thromboembolism.

Serious AEs occurred in 18 patients (40.9%) on nintedanib and 17 patients (41.5%) on placebo. The most frequent SAEs (all grades; nintedanib v placebo) were neutropenia [9.1% (n=4) *vs.* 2.4% (n=1)], diarrhoea [6.8% (n=3) *vs.* 0], pyrexia [6.8% (n=3) *vs.* 4.9% (n=2)], and pulmonary embolism [2.3% (n=1) *vs.* 9.8% (n=4)] respectively. Three patients on placebo died of SAEs: one patient from disease progression, one patient from general physical health deterioration, and one patient from disease progression and nephrotic syndrome. One fatal SAE with nintedanib where the patient died of disease progression unrelated to treatment.

Three patients (6.8%) on nintedanib and seven patients (17.1%) on placebo experienced AEs leading to permanent discontinuation of last study medication. AEs leading to discontinuation of nintedanib were upper abdominal pain and vomiting in one patient; liver dysfunction in another; and neutropenia, aplasia, and Klebsiella pneumonia in third patient. Fourteen patients (31.8%) on nintedanib and six (14.6%) on placebo experienced AEs requiring dose reduction. AEs leading to dose reduction of nintedanib were diarrhoea (9.1%), increased alanine aminotransferase levels (9.1%), nausea (4.5%), and neutropenia (4.5%).

Notably a multi-targeted anti-angiogenic kinase inhibitor nintedanib (VEGFR 1–3, PDGFR α or β, FGFR 1–3, SRC and ABL kinase pathways) combined with standard chemotherapy has demonstrated significant gain in median PFS and manageable toxicity profile especially for the epithelioid histology. A randomised phase 3 trial is underway with nintedanib in combination with cisplatin and pemetrexed (NCT01907100) for epithelioid MPM since benefit from the phase 2 trial was more substantial for epithelioid than non-epithelioid subtypes.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Robinson BM. Malignant pleural mesothelioma: an epidemiological perspective. Ann Cardiothorac Surg 2012;1:491-6.
2. Henley SJ, Larson TC, Wu M, et al. Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003-2008. Int J Occup Environ Health 2013;19:1-10.
3. Peto J, Decarli A, La Vecchia C, et al. The European mesothelioma epidemic. Br J Cancer 1999;79:666-72.
4. Kameda T, Takahashi K, Kim R, et al. Asbestos: use, bans and disease burden in Europe. Bull World Health Organ 2014;92:790-7.
5. Robinson BW, Musk AW, Lake RA. Malignant mesothelioma. Lancet 2005;366:397-408.
6. Andujar P, Lacourt A, Brochard P, et al. Five years update on relationships between malignant pleural mesothelioma and exposure to asbestos and other elongated mineral particles. J Toxicol Environ Health B Crit Rev 2016;19:151-72.
7. Scherpereel A, Astoul P, Baas P, et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. Eur Respir J 2010;35:479-95.
8. Kindler HL, Ismaila N, Armato SG 3rd, et al. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1343-73.
9. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-44.
10. van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005;23:6881-9.
11. Baas P, Fennell D, Kerr KM, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v31-9.
12. Perrot M, Wu L, Wu M, et al. Radiotherapy for the treatment of malignant pleural mesothelioma. Lancet Oncol 2017;18:e532-42.
13. Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled

trial. Lancet Oncol 2016;17:1094-104.
14. Zucali PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. Lung Cancer 2012;75:360-7.
15. Zauderer MG, Kass SL, Woo K, et al. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. Lung Cancer 2014;84:271-4.
16. Buikhuisen WA, Hiddinga BI, Baas P, et al. Second line therapy in malignant pleural mesothelioma: A systematic review. Lung Cancer 2015;89:223-31.
17. Buikhuisen WA, Burgers JA, Vincent AD, et al. Thalidomide versus active supportive care for maintenance in patients with malignant mesothelioma after first-line chemotherapy (NVALT 5): an open-label, multicentre, randomised phase 3 study. Lancet Oncol 2013;14:543-51.
18. Kindler HL, Karrison TG, Gandara DR, et al. Multicenter, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. J Clin Oncol 2012;30:2509-15.
19. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2016;387:1405-14. Erratum in: Lancet 2016;387:e24.
20. Grosso F, Steele N, Novello S, et al. Nintedanib Plus Pemetrexed/Cisplatin in Patients With Malignant Pleural Mesothelioma: Phase II Results From the Randomized, Placebo-Controlled LUME-Meso Trial. J Clin Oncol 2017;35:3591-600.

Cite this article as: Lee P. Review of nintedanib plus pemetrexed/cisplatin in patients with malignant pleural mesothelioma: phase II results from the randomized, placebo-controlled LUME-Meso trial. J Thorac Dis 2018;10(Suppl 26):S3124-S3127. doi: 10.21037/jtd.2018.07.105

