Mesothelioma and Small Cell Lung Cancer

Anne S. Tsao, MD, and J. Heymach

In the mesothelioma section, two presentations were given. First, Dr. Donington delivered an overview of the most common targeted pathways and agents studied in malignant pleural mesothelioma (MPM). As described, the current front-line standard of care for unresectable MPM patients remains platinum pemetrexed, and numerous targeted agents have been investigated in combination with front-line chemotherapy and in the salvage setting. Although mesothelioma has the highest secreted levels of VEGF of any solid tumor, adding bevacizumab to cisplatin-gemcitabine did not improve PFS or OS in the ITT population from a large phase II randomized trial.[1] Nevertheless, targeting the VEGF pathway may still be relevant in MPM, because patients with serum VEGF levels below the median who received bevacizumab had a superior OS ($p = 0.028$). In the salvage setting, several phase I and II studies that targeted angiogenesis (VEGFR, PDGFR), EGFR, TRAIL-R1,2, Bcl-2, tRNA, immunotherapy, and mesothelin were discussed. In general, only modest results from these studies (negative results from the monotherapy EGFR tyrosine kinase inhibitor and imatinib mesylate studies) were reported. In terms of promising new agents under investigation, a large international phase III trial of vorinostat versus placebo in second- and third-line therapy was discussed.[2] This trial has completed its accrual of 660 patients and will have the results presented later this year. If positive, this will potentially alter the treatment landscape in the salvage setting for MPM.

In the second presentation, a phase I neoadjuvant dasatinib trial being conducted at MDACC was presented. This study is the first neoadjuvant targeted therapy study to be conducted in MPM and consists of tissue harvesting from multiple areas of the tumor at two time points, before and after 4 weeks of neoadjuvant dasatinib therapy. The preliminary results suggest that Src kinase Tyr419 IHC overexpression may be a valid biomarker at baseline that predicts for a response to dasatinib therapy and is a consistent pharmacodynamic marker.[3] A phase I trial in the unresectable MPM patients using cisplatin-pemetrexed-imatinib mesylate was presented which seemed to stabilize the cancer more than achieve a response. Nevertheless, this trial provided the rationale for SWOG 0905, a phase I/II trial in chemonaive MPM patients evaluating cisplatin-pemtrexed + cediranib (VEGFR, PDGFR inhibitor). S0905 is open for enrollment and has completed the phase I portion and has established the phase II cediranib dose as 20 mg po daily.

Small Cell Lung Cancer

Although standard therapy for extensive stage SCLC remains chemotherapy, several new therapeutic approaches for SCLC are currently under investigation.

VEGFR pathway inhibitors

SCLC is known to overexpress ligands for the VEGF and PDGF receptors and frequently harbor c-KIT amplifications. Cediranib, an inhibitor of all three receptor tyrosine kinases, is being investigated in combination with etoposide and cisplatin (EP) chemotherapy. In phase I testing, cediranib demonstrated promising activity in combination with EP, with a median progression-free survival of 8.9 months and a objective response rate of 70%, results that compare favorably with historical controls. A phase II/III trial is currently in development. In phase II, promising activity has also been observed for bevacizumab in combinations with EP[4] or irinotecan/carboplatin.[5]

BCL-2 inhibitors

BCL-2 is frequently overexpressed in SCLC and is associated with resistance to chemotherapy-induced apoptosis. The BCL-2 inhibitor ABT-263 was tested in patients with SCLC and other solid tumors. Among 29 patients with SCLC or pulmonary carcinoid, one patient had a durable partial response, whereas eight had prolonged stable disease. Progastrin-releasing peptide was identified as a surrogate for Bcl-2 amplification. ABT-263 is currently undergoing further testing in combination with EP.

Other agents

Amrubicin is an anthracycline inhibitor of topoisomerase II. Randomized phase II studies in refractory SCLC suggest that it may have comparable or greater activity than topotecan. Phase III studies of amrubicin monotherapy in second-line SCLC is currently in progress. It is also being tested in combination with cisplatin for first-line SCLC.

SVV-001 is a picornavirus with selective tropism for tumors with neuroendocrine features. Phase I testing suggest that it has activity in SCLC. A phase II trial in SCLC patients conducted by the North Central Cancer Treatment group is currently in development.

Future Directions

The development of novel agents in both mesothelioma and SCLC is promising. Several classes of agents have demonstrated preliminary benefit in these notoriously difficult to treat thoracic tumors. For both tumor types, the results

Department of Thoracic/Head and Neck Medical Oncology, M.D. Anderson Cancer Center, University of Texas, Houston, Texas.

Disclosure: Anne S. Tsao reports an honorarium from Genentech and Roche, and research support from Merck and BMS.

Address for correspondence: Anne S. Tsao, MD, Department of Thoracic/Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd. Unit 432, Houston, TX 77030. E-mail: astsao@mdanderson.org

ISSN: 1556-0864/11/0611-1825

from early trials using antiangiogenic agents are noteworthy; and additional larger prospective trials will hopefully define their role in mesothelioma and SCLC. The standard of care in salvage mesothelioma may change depending on the final results of the phase III vorinostat versus placebo trial. Both fields require efforts to cultivate predictive biomarkers and improved screening modalities.

REFERENCES

1. Karrison T, Kindler HL, Gandara DR, et al. Final analysis of a multicenter, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin (GC) plus bevacizumab (B) or placebo (P) in patients with malignant mesothelioma. *Proc Am Soc Clin Oncol* 2007; 18s:(abstract 7526).
2. Paik PK, Krug LM. Histone deacetylase inhibitors in malignant pleural mesothelioma: preclinical rationale and clinical trials. *J Thorac Oncol* 2010;5:275–279.
3. Tsao AS, He D, Saigal B, et al. Inhibition of c-Src expression and activation in malignant pleural mesothelioma tissues leads to apoptosis, cell cycle arrest, and decreased migration and invasion. *Mol Cancer Ther* 2007;6:1962–1972.
4. Horn L, Dahlberg SE, Sandler AB, et al. Phase II study of cisplatin plus etoposide and bevacizumab for previously untreated, extensive-stage small-cell lung cancer: Eastern Cooperative Oncology Group Study E3501. *J Clin Oncol* 2009;27:6006–6011.
5. Spigel DR, Greco FA, Zubkus JD, et al. Phase II trial of irinotecan, carboplatin, and bevacizumab in the treatment of patients with extensive-stage small-cell lung cancer. *J Thorac Oncol* 2009;4:1555–1560.