Re: A Multicenter Phase II Study of Gemcitabine and Oxaliplatin for Malignant Pleural Mesothelioma

I would like to compliment Schuette and colleagues, who have begun to address the problem of mesothelioma and asbestos-related malignancy in Eastern Europe. Sadly, we can expect to see large numbers of such patients from the formerly Communist countries. The poor environmental pollution control record of the impoverished Eastern European countries will certainly contribute to the risk. Unfortunately, with the 30-40–year period of latency from time of asbestos exposure to development of mesothelioma, we will be facing a tragic legacy in many countries where asbestos exposure was not carefully regulated until very recently.[1]

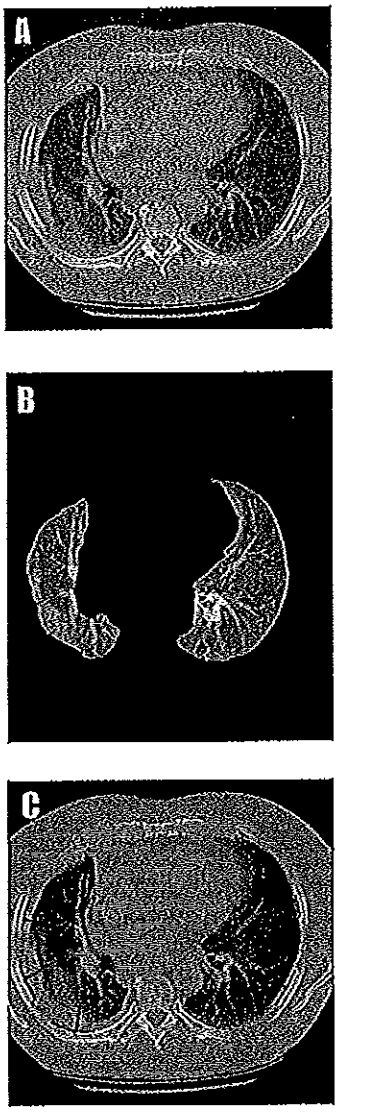
These authors in eastern Germany recruited 25 patients in a 2.5-year period to a multicenter trial of a novel regimen of gemcitabine and oxaliplatin.[2] Oxaliplatin was given on days 1 and 8 of a 21-day cycle for a total of 6 cycles and gemcitabine was given on days 1 and 8 of the 21-day cycle. The authors observed a high partial response rate of 40% and also a good median survival of 13 months. These figures compare well to the best available regimens, namely pemetrexed/ cisplatin[3] and gemcitabine/ cisplatin.[4] Recently, the raltitrexed/ oxaliplatin doublet has been reported to have a similar level of activity.[5] Each of these platinum-containing doublet regimens seem to achieve a median survival of approximately 12 months.

The major differences between the various platinum-containing regimens include not only the toxicities associated with cisplatin, carboplatin, and oxaliplatin, but also the cost of the drugs. At the University of Chicago, the cost of oxaliplatin at 130 mg/m^2 is $3415, the cost of carboplatin at an area under the curve of 5 every 21-28 days is $2480, and the cost of cisplatin at 70 mg/m^2 is $58 (personal communication, S. Parsad, PharmD, March 2003). Thus, decisions about which is the best platinum agent to use should be based in part on economics. Certainly, in many physician practices in the United States, the cost of chemotherapy includes the cost of the patient-occupied chair for the necessary 6-8 hours to administer high-dose cisplatin. This is a substantial cost, and therefore carboplatin is widely used. Schuette et al suggested that oxaliplatin could be an alternative to the carboplatin regimen but did not compare the costs.[2]

The other issue in selecting doublet-based therapy for mesothelioma is the chronic toxicity spectrum of the platinum portion of the doublet. Oxaliplatin causes cumulative neuropathy, as does cisplatin. Neither cisplatin nor oxaliplatin are particularly myelosuppresive, which is a favorable characteristic for combination chemotherapy. Carboplatin, likewise, has minimal neuropathy but is associated with slightly more myelosuppresion. Thus, non–platinum-containing doublet combinations such as gemcitabine/ pemetrexed are attractive to clinicians and patients because they do not apparently cause chronic toxicities (such as neuropathy and renal dysfunction).[6]

Another issue raised by the investigators revolves around their use of a standard radiologic definition of measurable disease and regression (S. G. Armato, PhD, unpublished data, 2003). However, it is now increasingly clear that mesothelioma cannot be measured using such standard definitions that have been used since the 1980s.[7] I would strongly recommend, based on data from Byrne et al[4] and Vogelzang et al,[3] that mesothelioma clinical investigators measure the perpendicular thickness of the pleural rind at 1-3 points (Figure 1) on 3 separate computed tomography levels (ie, slices). By consistently using this method in all chemotherapy trials, clinical investigators will be able to better compare response

Figure 1 Computed Tomography Scans Showing Perpendicular Thickening of Pleural Rind



The computer-based lung segmentation software assists in measuring the thickness of pleura from a computed tomographic (CT) image of a patient with mesothelioma. Standard CT image shows a right pleural mesothelioma (A). CT scans (B) show the pleural margins (in red; C) developed using lung segmentation software. *Figure provided courtesy of Sam Armato, PhD, of the University of Chicago Department of Radiology.*

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rates among various doublet regimens.

Despite this variability in measuring technique, it is my opinion that these platinum-based doublet regimens—pemetrexed/cisplatin,[3] gemcitabine/cisplatin,[4,9] gemcitabine/carboplatin,[8] raltitrexed/oxaliplatin,[5] and gemcitabine/oxaliplatin[2]—are each capable of producing similar rates of tumor response and stable disease.[10] Decisions for therapy should be made based on local preferences for therapy, availability of drug supply, incidence of chronic and acute toxicities, and the economics of drug administration.

1. Peto J, Decarli A, La Vecchia C, et al. The European mesothelioma epidemic. *Br J Cancer* 1999; 79:666-672.
2. Schuette W, Blankenburg T, Lauerwald K, et al. A multicenter phase II study of gemcitabine and oxaliplatin for malignant pleural mesothelioma. *Clin Lung Cancer* 2003; 4:294-297.
3. Vogelzang NJ, Rusthoven J, Symanowski J, et al. A phase III study of pemetrexed in combination with cisplatin vs. cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003. In press.
4. Byrne MJ, Davidson JA, Musk AW, et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: a Phase II study. *J Clin Oncol* 1999; 17:25-30.
5. Fizazi K, Doubre H, Le Chevalier T, et al. Combination of raltitrexed and oxaliplatin is an active regimen in malignant mesothelioma: results of a phase II study. *J Clin Oncol* 2003; 21:349-354.
6. Adjei AA. Preclinical and clinical studies with combinations of pemetrexed and gemcitabine. *Semin Oncol* 2002; 29(6 suppl 18):30-34.
7. Pass HI, Temeck BK, Kranda K, et al. Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 1998; 115:310-317.
8. Hughes A, Calvert P, Azzabi A, et al. Phase I clinical and pharmacokinetic study of pemetrexed and carboplatin in patients with malignant pleural mesothelioma. *J Clin Oncol* 2002; 20:3533-3544.
9. Nowak AK, Byrne MJ, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002; 87:491-496.
10. van Haarst JW, Burgers JA, Manegold CH, et al. Multicenter phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma (MPM). *Lung Cancer* 2000; 29(1 suppl 1):18 (Abstract #56).