**C5-02** **Mesothelioma, Wed, 10:30 - 12:15**

**A randomized trial of active symptom control (ASC) with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma. First results of the Medical Research Council / British Thoracic Society MS01 trial**

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**Background:** Mesothelioma is invariably fatal and virtually all treatments are given with the primary aim of relieving symptoms. Although chemotherapy is now widely used it has never been compared in a randomized trial with ASC alone. Two chemotherapy regimens were chosen for investigation: MVP and vinorelbine which had both shown good palliation in phase II studies.

**Methods:** Patients with malignant pleural mesothelioma were randomized to (a) ASC alone, (b), ASC+MVP (4 x 3-weekly cycles of mitomycin 6mg/m$^2$, vinblastine 6mg/m$^2$, and cisplatin 50mg/m$^2$), and (c) ASC+N (12 x weekly injections of vinorelbine 30mg/m$^2$). ASC was defined as regular follow-up in a specialist clinic and treatment could include steroids, analgesics, bronchodilators, palliative radiotherapy, etc. The primary endpoint was overall survival, and secondary endpoints were response, toxicity, palliation, and quality of life (QL). QL was assessed by patients completing the EORTC QLQ-C30. Slow accrual forced a re-design from a 3-arm to a 2-arm trial by combining the 2 chemotherapy arms and aiming to accrue 420 patients, to reliably detect a 3 month improvement in median survival (76% power, 5% significance level).

**Results:** Between 2000 and 2006 a total of 409 patients were accrued from 80 centres in the UK and Australia (136 ASC, 137 ASC+MVP, and 136 ASC+N). The median age of the patients was 65 years, 91% were male, 23% performance status (PS) 0, 63% PS 1, 73% epithelial histology, 33% stage III and 48% stage IV. The main symptoms at the time of randomization (reported by the clinicians as being moderate or severe) were: lethargy (54%), chest pain (51%), breathlessness (41%) and sweating (30%). In the MVP arm 61% of patients received 4 cycles and in the N arm 49% received at least 10 weekly cycles of vinorelbine. All 3 treatment groups resulted in good palliation (defined as prevention, control or improvement) at 6 months: lethargy 59%, 51% and 52%, chest pain 61%, 68% and 60%, breathlessness 29%, 22% and 33%, and sweating 59%, 91% and 73% for ASC, ASC+MVP and ASC+N respectively. No differences between treatments or over time were observed in 4 pre-defined QL subscales (physical functioning, dyspnoea, pain and global QL). A total of 349 patients have died, and a small, but non-significant, survival benefit was seen for ASC+CT (HR 0.89, 95% CI 0.72, 1.12, p=0.32). The median and 1 year survival for the ASC arm was 7.6 months and 30%, and applying the HR to this, gave 8.5 months and 34% for the ASC+CT arm. Exploratory analyses by chemotherapy group suggested a survival advantage for vinorelbine compared with ASC (HR 0.81, 95% CI 0.63, 1.05).

**Conclusions:** The MRC/BTS MS01 trial is the 2nd largest ever randomized trial in mesothelioma and is the first, and likely to be the only, trial to compare ASC with or without chemotherapy. Although overall the addition of chemotherapy to ASC did not result in a statistically significant survival benefit, there was a suggestion that vinorelbine should be investigated further.

**C5-03** **Mesothelioma, Wed, 10:30 - 12:15**

**Open-label study of pemetrexed alone or in combination with a platinum for previously treated patients (pts) with malignant pleural mesothelioma (MPM): Outcomes from the International Expanded Access Program (EAP)**

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**Background:** Prior studies have demonstrated the efficacy of pemetrexed (P) alone or in combination with a platinum drug for the treatment of chemonaive MPM pts (Scagliotti 2003; Vogelzang 2003). Recent data suggests P might also be efficacious for pre-treated pts with MPM. The P arm in a phase III study of pre-treated MPM pts yielded an 18.7% response rate (40.7% with stable disease, SD), 3.7 mo (95% CI 3.0, 4.4) median time to progressive disease (TtPD), and median survival time of 8.4 mos (95% CI 6.2, 10.5) (Jassem 2006). The EAP provided 3312 pts with access to P alone, P plus cisplatin (Cis), or P plus carboplatin (Cb) in 13 countries. In this abstract we report on the safety and efficacy data of previously-treated pts with MPM.

**Methods:** Eligible pts had histologic or cytologic diagnosis of MPM and were previously treated with ≥1 line(s) of chemotherapy. Pts pretreated with P were allowed if they had experienced clinical benefit from the prior P. P 500 mg/m$^2$ alone, or in combination with either Cis 75 mg/m$^2$ or Cb AUC 5, was given on day 1 of each 21-day cycle with standard pre-medication consisting of vitamin B12, folic acid, and dexamethasone. Investigator-determined best response (RR) and survival data (with censoring) were recorded at the end of study participation. Myelosuppression data (NCI CTC, version 2.0) were also collected.

**Results:** In this nonrandomized, open-label study 988 previously treated pts received ≥1 dose of P (493 pts), P+Cis (168 pts) or P+Cb (327 pts) and were evaluable for safety. Among the study participants, 396 P pts, 151 P+Cis pts and 285 P+Cb pts were evaluable for efficacy. Baseline characteristics, and efficacy and safety data are summarized in the table.

**Conclusion:** This large study suggests that previously treated MPM pts can benefit from treatment with P, P+Cis, and P+Cb.

| | P | P+Cis | P+Cb |
|---|---|---|---|
| Median age (range) (years) | 63.0 (31, 85) | 59.5 (26, 77) | 61.0 (25, 80) |
| Male (%) | 75.9 | 75.6 | 81.3 |
| Karnofsky performance status ≥ 80, % of pts* | 74.5 | 81.8 | 81.7 |
| RR, % of pts (95% CI) | 12.1 (9.1,15.7) | 23.8 (17.3, 31.4) | 16.8 (12.7, 21.7) |
| Disease control rate (responders +SD), % of pts, (95% CI) | 58.1 (53.0, 63.0) | 67.5 (59.5, 74.9) | 66.3 (60.5, 71.8) |
| One-year survival rate, % (95% CI) | 54.7 (42.6, 66.8) | 67.9 (48.6, 85.5) | 65.5 (54.6, 76.5) |
| Median TtPD (months) (95% CI) | 4.9 (4.2, 5.8) | 7.4 (5.6, 10.4) | 6.9 (6.2, 7.4) |
| Leukopenia, Gr 3/4, % of pts | 13.9 | 11.0 | 18.6 |
| Neutropenia, Gr 3/4, % of pts | 15.6 | 19.9 | 31.8 |
| Thrombocytopenia, Gr 3/4, % of pts | 4.9 | 12.9 | 18.6 |
| Anemia, Gr 3/4, % of pts | 9.2 | 10.4 | 12.4 |

*Approximately 95% of pts in each treatment arm contributed PS data.

**C5-04** **Mesothelioma, Wed, 10:30 - 12:15**

### Exploring alternate methods to monitor therapy in Malignant Pleural Mesothelioma (MPM): comparing Radiological Response with Pulmonary Function Tests (PFTs) and Patient-reported Outcomes (PROs) using the LCSS-Meso Instrument. A study based on 410 patients from the EMPHACIS trial

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**Background:** Tumor growth in MPM presents technical challenges in measuring tumor volume or response radiographically even when using advanced imaging techniques. Additionally, MPM is highly symptomatic with nearly all patients presenting with three or more symptoms. Of major symptoms, dyspnea is rated by patients as having the greatest severity (Gralla ASCO 2003). Prior analyses indicated that improvement in Forced Vital Capacity (FVC) correlated with improvements in patient-reported dyspnea (Gralla WCLC 2005) and that radiological response correlated with improvements in FVC (Paoletti ASCO 2003). This analysis was undertaken to determine whether dyspnea and other PROs of the 8-item LCSS-Meso and PFTs can enhance or replace radiological evaluation in monitoring response to therapy.

**Methods:** We analyzed data from 410 patients from the randomized MPM trial of cisplatin ± pemetrexed (Vogelzang JCO 2003). Changes from baseline in PROs and FVC were calculated at the time of response for patients with an investigator-determined radiological major response (PR), at first evidence of at least stable disease (SD) for patients with best response of SD, or at discontinuation for patients with best response of progressive disease (PD). PROs considered are reported in the table. Changes in PROs were summarized by radiological subgroup which were further restricted to patients with or without an FVC improvement of at least 5%. Discriminant analyses were conducted to classify patients into two groups: PR+SD vs PD using changes in PROs and FVC as predictors. Prediction rates from the discriminant analyses were calculated as the number of correctly classified patients divided by total sample size.

**Results:** PRs alone reported smaller PRO changes than those PRs with 5% improvement in FVC for dyspnea, pain, and symptom distress. Those with PD alone reported similar change to those with PD and  < 5% improvement in FVC. The highest prediction rate (78.4%) was achieved by a combination discriminant of patient-reported dyspnea and FVC; however, combining either two PROs (ie, dyspnea and activity level) or all PROs achieved nearly the same prediction rate (77% and 78%, respectively).

**Mean Changes from Baseline and Prediction Rates**

| Item | PR (n=125) (A) | PR and >5% FVC (n=49) (A) | PD (n=120) (A) | PD and <5% FVC (n=50) (A) | Prediction Rate (%) (B) |
|---|---|---|---|---|---|
| Dyspnea | 6.4 | 11.6 | -18.8 | -21.8 | 73.1 |
| Fatigue | 1.5 | 1.9 | -22.0 | -22.7 | 71.3 |
| Pain | 11.1 | 16.9 | -12.3 | -15.1 | 71.0 |
| Symptom distress | 5.8 | 9.2 | -16.5 | -16.2 | 67.3 |
| Activity level | 3.7 | 1.8 | -22.6 | -22.5 | 71.9 |
| Global quality of life | 4.6 | 1.9 | -21.6 | -20.4 | 72.5 |
| All PROs | - | - | - | - | **78.0** |
| FVC | - | - | - | - | 67.2 |
| Dyspnea/FVC | - | - | - | - | **78.4** |
| Dyspnea/ Activity level | - | - | - | - | **77.0** |

A. Visual Analogue Scale (0-100 mm) for each PRO item. Positive value indicates improvement.

B. Number of radiological PR+SD correctly classified by discriminant plus number of radiological PD correctly classified by discriminant divided by total sample size; sample sizes are approximately 410 for PROs and 296 for FVC.

**Conclusions:** Changes in patient-reported LCSS-Meso items correlate with radiological response to therapy. PROs appear to be at least as sensitive in predicting response to therapy as objective measures such as FVC. The LCSS-Meso may serve as an effective, inexpensive, and easy-to-administer alternative to radiological assessment for monitoring response to therapy for MPM. Prospective studies are needed to confirm these findings.

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### The yield of EUS-FNA in early stage malignant pleural mesothelioma

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**Background:** Selected patients with limited (cT1-3N0) malignant pleural mesothelioma are being considered for a multimodality therapy with induction chemotherapy followed by extrapleural resection and radiotherapy. Since invasion of the mediastinal lymph nodes is a negative prognostic factor, cervical mediastinoscopy is recommended for staging in these patients. Transoesophageal Endoscopic Ultrasound with a linear scanning ultrasound endoscope and real time guided fine needle aspiration (EUS-FNA) enables mediastinal lymph node staging with high accuracy in lung cancer patients.

 