Evaluating Improvement in Patient-Reported Dyspnea and Pulmonary Function Tests (PFTs) in Patients with Malignant Pleural Mesothelioma (MPM): An Analysis as part of the 448-Patient Randomized Pemetrexed + Cisplatin versus Cisplatin Trial

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Abstract

Background: MPM is a highly symptomatic disease: over 90% of patients report dyspnea and nearly all patients present with three or more symptoms. Of the major symptoms (dyspnea, pain, cough, fatigue, anorexia), dyspnea is rated by patients as having the greatest severity (Gralla Proc ASCO 2003). Of these symptoms, only dyspnea also has a physiologic correlate - measured by PFTs. Prior analysis indicated that Forced Vital Capacity (FVC) correlated with objective response and is not difficult to perform in this MPM population (Paoletti Proc ASCO 2003). However, it has not been determined if FVC improvement associated with chemotherapy treatment is perceived by patients as resulting in improved patient-rated dyspnea scores. In a multicenter randomized trial with 448 patients, those assigned to pemetrexed + cisplatin demonstrated significant advantages in survival (p=0.02) and radiologic response (p<0.001) over those receiving cisplatin monotherapy (Vogelzang JCO 2003).

Methods: We analyzed the data of the patients in the randomized Vogelzang MPM study for change in dyspnea and FVC. 75% (n=334) of the patients were prospectively evaluated with both PFTs (including FVC) and dyspnea (part of the LCSS-Meso validated MPM quality of life scale). Patient characteristics included: Stage III and IV (78%); 81% men; median KPS=90% (range 70%-100%); median age=61 (range 21-85). 93% of patients presented with ≥ 3 symptoms; 92% reported dyspnea with a mean severity score of 68% on the LCSS-Meso (0=most symptomatic, 100=least symptomatic).

Results: The FVC scores for all patients were divided into two groups (change from baseline less than the median improvement – poorer FVC group; or change greater than the median improvement – better FVC group). As seen in the table, patients in the better FVC group rated their improvement in dyspnea (absolute change in %) as superior to those with less change in FVC (p<0.001). When examined by randomized chemotherapy treatment assignment, those receiving pemetrexed + cisplatin reported moderately greater improvement in dyspnea than those given cisplatin; this was especially apparent in the poorer FVC group. More patients on the pemetrexed arm achieved improvement placing them in the better FVC group (57% vs. 43%, p=0.05).

	Improvement in Patient-Rated Dyspnea Scores* (All Patients, and by Randomized Treatment Group)		
% Improvement in FVC from Baseline	All Patients	Pemetrexed + Cisplatin	Cisplatin
≤ 3.05% (poorer FVC group)	5.3 (n=167)	8.0 (n=72)	2.6 (n=95)
> 3.05% (better FVC group)	13.3 (n=167)	13.5 (n=96)	13.2 (n=71)

Conclusions: 1) An important correlation is found between patient-perceived improvement in dyspnea and standard PFT scores expressed as FVC improvement. 2) Patients randomly-assigned to pemetrexed + cisplatin were more likely to achieve PFT improvement sufficient for placement in the better FVC group (also associated with greater patient-rated dyspnea improvement), than those receiving cisplatin. 3) Effective chemotherapy for MPM not only results in improved survival and response, but also in less patient-reported dyspnea. 4) The dyspnea score, as rated by patients using the LCSS instrument, is a valuable and accurately-determined endpoint which should be evaluated in future studies including MPM and other malignancies in which dyspnea is a frequent symptom.

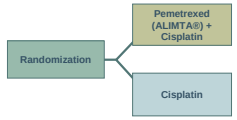
Background

- Dyspnea is one of the most severe and frequent symptoms in thoracic malignancies. Improvement of this key symptom is a major goal of therapy.
- Therapeutic approaches should be judged on their ability to benefit patients in symptom control as well as survival. These goals are often related; however, each parameter must be tested to ascertain the value of a new treatment.
- Of the common symptoms in malignant pleural mesothelioma (MPM), only dyspnea has a measurable physiologic correlate, pulmonary function tests (PFTs).
- Both patient-reported dyspnea and PFTs were assessed in a large multinational phase III trial in patients with MPM.
- This report reviews the effect of a new chemotherapy combination on symptom control, with a focus on patient-reported dyspnea and its correlation with PFT changes.

Clinical Trial Design

Major Eligibility Criteria:

- KPS ≥ 70%
- Unresectable MPM
- No prior chemotherapy
- Primary objective: survival
- Secondary objectives included:
  - Tumor response rate
  - Pulmonary function tests (forced vital capacity [FVC], slow vital capacity [SVC], forced expiratory volume in one second [FEV_1])
    - Assessed at baseline and every other cycle
    - Reported as actual (liters) and % predicted
  - Patient-reported outcomes (PROs) using LCSS-Meso
    - Assessed at baseline and weekly while on study
    - Scores range 0 to 100 (0=best)



Quality-of-Life and PRO Assessment

LCSS-Meso Features

- **Practical**
  - Designed for clinical trials and patient management
  - Requires only 2 - 4 minutes for patient completion
  - Available in more than 40 languages
- **Well-tested**
  - Good psychometric properties for MPM
  - Captures all dimensions while focusing on physical and functional

❖ Patient form: 100-mm visual analogue scale - 8 items
❖ Observer form (optional): 5-point categorical scale - 5 items

Patient Characteristics: Demographics

	Pemetrexed + Cisplatin N=226	Cisplatin N=222
Age (years) Median (range)	61 (29-85)	60 (19-84)
Gender Male	81%	82%
Stage III	32%	31%
Stage IV	45%	48%
Karnofsky Performance Status 70 - 80	48%	44%
Karnofsky Performance Status 90 - 100	52%	56%

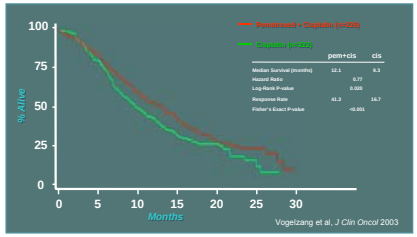
Patient Characteristics: Baseline LCSS-Meso Scores*

		Pemetrexed + Cisplatin n = 212		Cisplatin n = 219	
		% pts with	Mean score	% pts with	Mean score
Thoracic:	Pain	87%	72	90%	74
Thoracic:	Dyspnea	94%	69	91%	68
Thoracic:	Cough	81%	85	79%	86
General:	Fatigue	96%	65	95%	66
General:	Anorexia	91%	72	86%	75
General:	Activity	-	61	-	62

•Symptomatic defined as <100 on transformed scale where 100 = best score
• **93% of patients reported ≥3 symptoms**

Clinical Trial Design

Clinical Trial Results: Survival and Response



Vogelzang et al, *J Clin Oncol* 2003

Correlation of Tumor Response with Pulmonary Function Tests (PFTs)

Change in Lung Function by Tumor Response

(SVC = Slow Vital Capacity; FVC = Forced Vital Capacity; FEV1 = Forced Expiratory Volume [1 second])

	SVC (% predicted)			FVC (% predicted)			FEV_1 (% predicted)		
	N	Mean	SE	N	Mean	SE	N	Mean	SE
R	96	8.97	1.67	109	10.69	1.32	114	10.17	1.27
SD	130	3.36	1.33	147	3.26	1.03	150	3.20	1.00
PD	56	-2.78	2.15	65	-3.99	1.66	67	-6.03	1.58

R = major response; SD = stable disease; PD = progressive disease

For all PFT Parameters: R vs SD p < 0.009; R vs PD p < 0.001; SD vs PD p < 0.02

Adapted from Paoletti et al, *Proc ASCO* 2003

Quality of Life Results

Patient-Reported Scores by Response Outcome for ALL LCSS-Meso Parameters - Summary of Change from Baseline (model-based means) -

	Thoracic Symptoms			General Symptoms			Summary Items	
	Pain	Dyspnea	Cough	Fatigue	Anorexia	Activity level	Symptom distress	Global QoL
CR/PR (n=129)	12.01	10.13	9.20	5.60	6.50	6.80	7.30	7.90
SD (n=171)	8.97	8.50	7.40	5.20	5.30	4.30	7.60	5.80
PD (n=129)	3.40	-0.89	2.50	-5.20	-2.80	-6.80	1.50	-5.70
CR/PR vs SD*	0.254	0.515	0.382	0.892	0.634	0.346	0.902	0.413
CR/PR vs PD*	0.003	<0.001	0.003	<0.001	<0.001	<0.001	0.047	<0.001
SD vs PD*	0.034	<0.001	0.017	<0.001	0.001	<0.001	0.020	<0.001

*Analysis of variance (p-values)

When scores were compared between treatment arms for the CR/PR group, all scores were numerically greater for pemetrexed + cisplatin.

Adapted from Gralla et al, *Proc ECCO* 2003

Dyspnea-PFT Endpoint

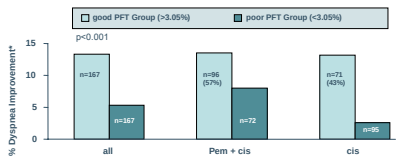
- This report evaluates whether changes in PFTs following treatment are perceived by patients as improving dyspnea
- If this correlation can be found, it would be useful in:
  - Demonstrating the value of a treatment regimen in aiding in palliation
  - Demonstrating the value of response to treatment as determined by patients
  - Illustrating that straight-forward patient-scored dyspnea is a useful treatment evaluation endpoint

Dyspnea-PFT Methods

- Analysis included all patients with both PFT and dyspnea assessments at baseline and after start of therapy
- For each patient, maximum improvement from baseline was calculated for each PFT parameter and dyspnea
- Patients were divided into poor and good PFT groups for each parameter based on median maximum improvement (change from baseline less than the median improvement – poorer PFT group; or change greater than the median improvement – better PFT group)
- Maximum improvement in dyspnea analyzed by PFT group and further by treatment group using two-factor analysis of variance
- Percent of patients in good PFT group compared between treatment arms using normal approximation for binomial

Dyspnea-PFT Results

Dyspnea improvement by improvement in FVC



* As measured by VAS LCSS-meso scales (in mm and in percent improvement)

Range of improvement in % predicted FVC: -75% to 83%
Comparison between treatments of % of patients in good FVC group: p=0.012

Nearly identical results were found for the other PFT parameters: FEV_1 and SVC

Conclusions

1) An important correlation was found between patient-reported improvement in dyspnea and pulmonary function test scores.
   - These findings indicate that this degree of change in PFTs is perceptible to patients and that such change can be of palliative benefit
2) Patients reported greater relief in dyspnea depending on the chemotherapy regimen received.
   - More patients treated with the combination regimen were classified as having greater improvement in PFTs
   - A previous report demonstrated that symptom improvement was greater in tumor responders receiving the combination regimen as compared to responders receiving monotherapy
3) Effective chemotherapy results in improved survival, response, and less patient-reported dyspnea.
   - This finding indicates a consistency in benefit related to antitumor effectiveness and demonstrates the patient-perceived value of effective chemotherapy
   - Symptomatic benefit is seen even with less than major tumor response; however, PFT improvement is greatest with major response
4) The dyspnea score is a valuable and accurately-determined endpoint.
   - The LCSS-Meso is well-accepted by patients, as well as by nurses and physicians.
   - This evaluation is inexpensive and non-intrusive. It should become a part of the clinical decision-making process.