Evaluating the Impact of Neoadjuvant Chemotherapy and Surgery on Quality of Life (QL) in Patients with Early Stage NSCLC: A Prospective Analysis as part of the GINEST Project

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Abstract # 8092

Background: The assessment of the impact of combined modality therapy on QL has rarely been prospectively planned and evaluated. The modest but significant survival gains reported with both neoadjuvant and adjuvant approaches need to be viewed in terms of the added risks and toxicities associated with two or three modalities of treatment. Validated QL instruments are available, such as the LCSS (Lung Cancer Symptom Scale), used in this study.

Methods: The objective was to compare patient-determined QL ratings from baseline (prior to neoadjuvant chemotherapy) with those 6 months post-op. All patients had clinical Stage I or II NSCLC, and participated in one of the two similar randomized protocols of the GINEST Project to receive pre-operatively: three every 3-week cycles of gemcitabine plus carboplatin or paclitaxel in one trial (Study S235), or gemcitabine plus carboplatin or cisplatin in the second (Study S236). Patients completed the LCSS at baseline, every 3 weeks pre-op, and every 3 months post-op.

Results: Full QL data over the 9 month evaluation period are available in this ongoing study on 33 patients: 52% women; median: age = 63, PS = 0. 94% had complete resections. Pathologic staging: 76% Stage I, 15% Stage II, 9% Stage III. Surgery: 12% pneumonectomy, 15% bilobectomy, and 73% lobectomy. Patients rated their QL as stable or improved in 78% (95% CI: 64% - 92%) of cases at 6 months post-op. A subgroup of patients (7 of 33) reported worsening of QL (> 1 decile), with a mean decrease of 44% in these patients. An average of 5 of the 9 LCSS symptom parameters also declined in these 7 patients; no single symptom was associated with the QL decline. Worsening QL appeared more likely in those having more than a lobectomy and in Stage III extent. It did not appear to be related to the chemotherapy regimen or baseline QL score.

Conclusions: In this evaluation of patients 6 months post-op with early stage NSCLC given neoadjuvant gemcitabine-containing chemotherapy, most patients (78%) reported improved or stable quality of life. Prospectively planned QL assessment is feasible to carry out with combined modality trials and adds useful information not otherwise attainable.

Background

- Phase II and Phase III trials[1,2,3,4] have indicated advantages for giving chemotherapy prior to surgery, in terms of:
  - *Resectability*
  - *Survival*
- The majority of trials have been conducted in patients with Stage III extent. A recent randomized study, including patients with Stages I, II, and IIIA found a greater magnitude of benefit in patients with earlier stage disease. [4]
- In addition to the above randomized Phase III study, neoadjuvant Phase II trials in early stage disease have indicated feasibility in this population of patients. [5]
- Among the issues in neoadjuvant treatment in both early- and late-stage extent are:
  - Can more effective chemotherapy regimens be identified?
  - Are frequently used regimens for advanced disease safe when given preoperatively?
  - How does this aggressive combined modality approach affect patients' Quality of Life (QL) after the completion of treatment?

References: [1] Martini *Ann Thorac Surg* 1993; [2] Rosell *NEJM* 1994; [3] Roth *JNCI* 1994; [4] Depierre *JCO* 2002; [5] Pisters *Proc ASCO* 2003.

Objectives

- Objectives of the GINEST Project overall, are to identify efficiently the activity of chemotherapy regimens in early stage non-small cell lung cancer, in terms of:
  - Major Response – Focusing on complete response as a surrogate for survival
  - Safety – Focusing on pulmonary and hematologic endpoints
  - Quality of Life – Focusing on the long-term effects on patients completing aggressive combined modality therapy
- This report is the initial analysis examining Quality of Life results in patients six months after the completion of all treatment (3 cycles of gemcitabine-contain chemotherapy followed by resection of the primary lung cancer).
- Additional reports at this meeting outline GINEST results dealing with:
  - Response and Resection Rates (abstract #7215)
  - Safety based on pulmonary function (abstract #7227)

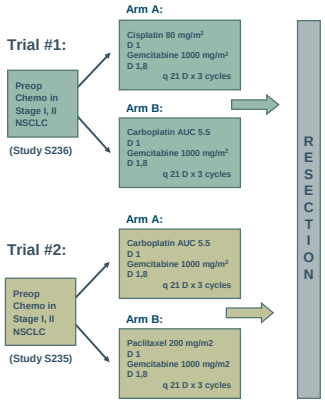
Study Design

INCLUSION CRITERIA

- Stage I or II NSCLC confirmed with biopsy
- Negative mediastinum by CT, PET, or mediastinoscopy
- No prior chemotherapy or radiation for NSCLC
- ECOG performance status of 0-1, adequate hematologic function
- No patients with Pancoast tumor presentation

GINEST TREATMENT PLAN

All patients participated in one of the two similar protocols of the GINEST Project:



Quality of Life Instrument (LCSS) Features

- **Instrument Description[1]:**
  - Designed for clinical trials and patient management
  - Requires only 2 - 4 minutes for patient completion
  - Good psychometric properties[1]
  - Patient-completed form: 9 visual analog scales including:
    - Summary Items: Global QoL; Symptom Distress; Effect on Activities
    - Thoracic Subscale: Dyspnea, Cough, Hemoptysis
    - General Subscale: Fatigue, Pain, Anorexia
- **Assessment Plan:**
  - Administered at baseline, every 3 weeks preoperatively, then every 3 months
    - Analysis plan compared baseline values with those at 6 months after completion of all treatment*

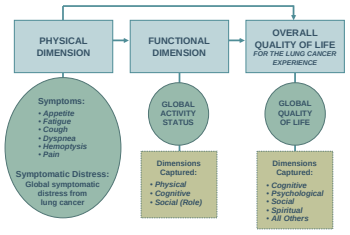
[1] For more information see: *www.lcss-ql.com*

* 33 patients assessed at 6 months (1 patient at 12 months, and 6 at 3 months, if 6 month data not available)

Study Design

QUALITY OF LIFE DIMENSIONS

- Conceptual Model for the LCSS and Clinical Trials



Results

PATIENT CHARACTERISTICS

	ALL PATIENTS (N = 87)	6 Month QL Group (N = 42)
Age (Median):	63	62
Percent Male:	53%	50%
ECOG Performance Status (median):	0	0
HISTOLOGY – Squamous Cell:	39%	33%
– Adenocarcinoma:	39%	48%
– Large Cell (or NOS):	22%	19%
STAGE – I:	71%	72%
– II:	24%	21%
– III:	5%	7%

CHEMOTHERAPY OUTCOMES

	Gem-Pac (N=35)	Gem-Carbo (N=40)	Gem-Cis (N=12)
Complete Response (cCR + pCR):	3%	0%	9%
Partial Response:	23%	20%	33%
Progressive Disease	17%	5%	0%
Major Response (CR + PR):	26%	20%	42%

Results

SURGICAL OUTCOMES

	Entered (N = 87)	Thoracotomy (N = 67)	Resection + QL at 6 mos (N = 42)
COMPLETE RESECTION:	73%	91%	97%
Lobectomy -		72%	72%
Pneumonectomy -		16%	14%
Bilobectomy -		12%	14%

QUALITY OF LIFE OUTCOMES

	Number of Patients	Percent
QL Evaluated 6 months after last treatment*	42	
Improved: (≥ 10% change**)	4	10% (or 33% of those eligible for improvement)***
Stable: (≤ 10% change**)	28	66%
Worsened: (≥ 10% change**)	10	24%

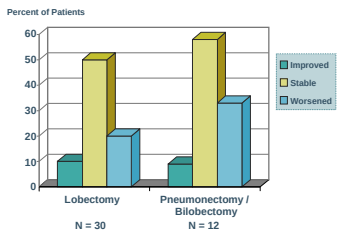
76% (95% CI: 63% - 89%)

(95% CI: 11%-37%)

* 33 patients assessed at 6 months (1 patient at 12 months, and 6 at 3 months - if 6 month data not available)
** Compared with baseline pre-treatment values
*** A total of 12 of 42 patients had baseline QL value > 10mm; these were thus the only patients who could improve by 10% or more

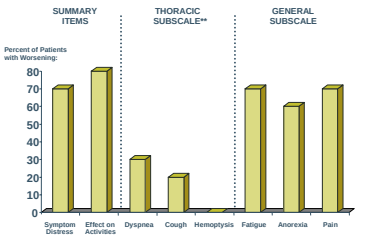
QUALITY OF LIFE OUTCOMES

Quality of Life at 6 Months After Completion of Treatment – By Resection Procedure



Results

Pattern of Symptom Worsening (%) in the Subset of Patients (24%) with Declined Quality of Life at 6 Months After All Treatment*



* Mean / median decrease in Quality of Life in this subset: 46% / 43%

** While worsening in both dyspnea and cough were seen as noted above, these symptoms were *more likely* to be improved in this patient group (30% and 40% of patients, respectively)

Conclusions

Quality of Life and Symptoms

- For the majority of patients (76%) with Stage I and II NSCLC undergoing neoadjuvant treatment with gemcitabine-containing chemotherapy, quality of life is preserved or improved when viewed at 6 months post-operatively.
- None of the following pretreatment aspects clearly identified patients at greater risk for poorer quality of life outcomes:
  - Randomly-assigned chemotherapy regimen
  - Baseline patient characteristics
  - Baseline quality of life and symptom parameters
- Of the subset of 24% of patients (95% CI: 11% - 37%) with worsened quality of life at 6 months after all treatment:
  - The mean quality of life was substantially less (- 46%) than for the whole group.
  - Thoracic symptoms were not particularly worsened, when compared with general parameters (fatigue, pain) and summary items (effect on activities and the distress of the symptoms).
  - There is a trend toward poorer QL outcomes in patients undergoing resections greater than lobectomy. While this difference was not significant, future studies should prospectively evaluate this factor.

Practice and Future Study Implications

- This analysis is one of the largest prospective studies evaluating quality of life in neoadjuvant therapy after completion of all treatment. Most patients are functioning well 6 months after these chemotherapy regimens and surgery. However, a subset of patients continue to have difficulties even at this time after treatment.
  - Physicians should be aware of these outcomes and discuss them with patients when considering combined modality approaches.
- This trial demonstrates that quality of life and "patient-reported outcomes" (PROs) can be assessed as part of a combined modality study. This evaluation produces information important to patients and physicians that cannot otherwise be obtained; however:
  - Patients accept this assessment easily; more emphasis among investigators to enhance their adherence is needed.
  - Continued investigation in the future may help identify patient parameters indicating greater risk for specific treatments.