Two Stage Specific Prognostic Indices To Estimate Survival Of Patients With NSCLC

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Introduction

Both patients (Pts) with advanced non-small cell lung cancer (NSCLC) and their clinicians require accurate prognostic information to guide their decisions on therapy. A number of biomarkers are available in predicting clinical trials' outcomes and the results of overall clinical management. Inflammatory biomarkers, such as C-reactive protein (CRP) provide helpful prognostic information and prognostic indices centered around CRP have been developed.

Objective

To develop prognostic indices of survival for each of Stage 3 and Stage 4 that integrate both CRP and other prognostic biomarkers to improve the risk stratification of Pts with advanced NSCLC.

Methods

Population

- Since May 2001, clinical data of Pts with advanced NSCLC, seen at the Jewish General Hospital Pulmonary Oncology Clinic, in Montreal, Quebec, Canada, were prospectively recorded in a computerized database;
- Data of 269 (70%) out of 383 consecutive Pts, enrolled between April 9, 2002 and September 18, 2008, were available for these analyses; Follow-up ended on March 15, 2009.

Statistical analysis

- Descriptive analyses were used to compare Pts in both stages
- Univariate survival analyses using Kaplan-Meier method for Pts'characteristics;
- A multivariable model was developed using stepwise Cox's models;
- The prognostic score for each prognostic biomaker included in the model was derived by dividing the value of each statistically significant regression coefficient by the smallest statistically significant regression coefficient and the results were rounded to the nearest integer;
- A Prognostic Index was created by adding the prognostic scores to create 3 Risk Groups;

Ethic

- The study was approved by the Institutional Review Board of the Jewish General Hospital.

Table 1: Patient Characteristics

Variables	Number of Patients (266)		Results of Chi² Test
	Stage 3 Subjects n=67 (25%)	Stage 4 Subjects n=199 (75%)	
Age: Median (Range)	63 (43-79)	65 (38-87)	0.97*
Sex Male n (%)	35 (52)	101 (51)	0.83
Performance Status (ECOG)[a] 2: n (%)	8 (12)	50 (25)	0.03
Smoking: n (%)	63 (94)	163 (82)	0.02
Chemotherapy: single-agent n (%)	7 (10)	60 (30)	
double-agent n (%)[b]	60 (90)	139 (70)	<0.01
Diagnosis: adenocarcinoma n (%)	35 (52)	133 (67)	
Other types n (%)	32 (48)	66 (33)	0.03
C-reactive protein[c] ≥ 10mgL-1: n (%)	37 (55)	119 (60)	0.51
Albumin[c] ≤ 35: n (%)	4 (6)	32 (16)	0.04
Lactate Dehydrogenase[c] ≥ 300: n (%)	8 (12)	36 (18)	0.28
Calcium[c] ≥ 2.5: n (%)	16 (24)	30 (15)	0.10
Haemoglobin[c] < 110: n (%)	4 (6)	24 (12)	0.16
Absolute Neutrophil Count[c] ≥ 11: n (%)	7 (10)	20 (10)	0.93
Lymphocytes[c] < 1.2: n (%)	18 (27)	60 (30)	0.61
Weight Loss ≥ 5%: n (%)	26 (39)	73 (37)	0.76

a Eastern Cooperative Oncology Group
b All include platinum based chemotherapy
c Normal values: C-reactive protein ≤10 mg/L; Albumin 35-52 mg/L; Lactate dehydrogenase 110-210 U/L; Calcium 2.12-2.62 mmol/L; Alkaline phosphatase 56-120 U/L; Hemoglobin 140-180 g/L; Platelet 140-440x10⁹/L; Neutrophil counts 1.60-7.70 x10⁹/L; Lymphocytes 0.80-4.40x10⁹/L
* by t-test

- Pts with Stage 3 were significantly more likely to be smokers, diagnosed with adenocarcinoma, to have normal albumin levels and a better performance status than those with Stage 4;
- Interestingly, both groups had the same proportion of abnormal CRP and Lactate Dehydrogenase (LDH).

Table 2
Results of Univariate Survival Analyses using Kaplan-Meier Method

Variables	Hazard Ratio (Confidence Interval 95%)	
	Stage 3 Subjects; N=67	Stage 4 Subjects; N=199
Age	1.01 (0.98 - 1.05)	1.00 (0.98 - 1.01)
Sex (male vs. female)	2.34 (1.21 - 4.51)	1.12 (0.79 - 1.59)
Performance Status (ECOG): (2 vs. 0-1)	1.42 (0.55 - 3.64)	1.96 (1.33 - 2.87)
Smoking: (ever vs. never)	4.08 (0.55 - 29.83)	1.84 (1.09 - 3.12)
Chemotherapy: (single vs. double)	1.82 (0.64 - 5.16)	1.54 (1.06 - 2.22)
Diagnosis: (adenocarcinoma vs. other)	0.81 (0.43 - 1.52)	1.06 (0.73 - 1.53)
C-reactive protein (≥ 10mgL-1 vs. < 10mgL-1)	2.67 (1.36 - 5.25)	2.05 (1.41 - 2.99)
Albumin: (≤ 35 vs. > 35)	3.32 (0.99 - 11.13)	2.28 (1.48 - 3.52)
Lactate Dehydrogenase: (≥ 300 vs. < 300)	3.01 (1.37 - 6.61)	4.34 (2.86 - 6.57)
Calcium: (≥ 2.5 vs. < 2.5)	1.63 (0.72 - 3.72)	0.99 (0.61 - 1.63)
Haemoglobin: (< 110 vs. ≥ 110)	0.77 (0.18 - 3.21)	1.79 (1.10 - 2.92)
Absolute Neutrophil Count: (≥ 11 vs < 11)	1.71 (0.61 - 4.84)	3.45 (2.10 - 5.68)
Lymphocytes: (< 1.2 vs. ≥ 1.2)	1.06 (0.52 - 2.17)	1.80 (1.25 - 2.60)
Weight Loss: (≥ 5% vs. < 5%)	1.31 (0.69 - 2.52)	1.32 (0.91 - 1.88)

- All Pts, regardless of stage, had poorer prognosis when CRP and LDH were abnormally high
- Only Pts with Stage 4 had poorer survival if their Albumin, Absolute Neutrophil Count, Lymphocyte Count or Haemoglobin levels were abnormal.

Developing a Prognastic Index for NSCLC Stage 3

Table 3
Multivariate Analysis of Prognostic Factors for Survival with corresponding Prognostic Score

Prognostic Factors	Hazard Ratio	Prognostic Score
C-reactive protein (≥ 10mgL-1 vs. < 10mgL-1)	2.56 (1.29 - 5.06)	1
Lactate Dehydrogenase (≥ 300 vs. < 300)	2.75 (1.24 - 6.08)	1

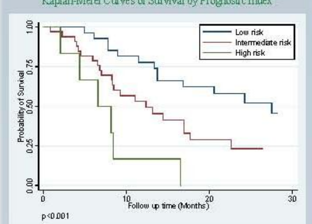
- Only CRP and LDH retained a significant and equally poor prognostic value for survival (score=1).

Table 4
Survival by Prognostic Index Group

Prognostic Index	Total of Prognostic Scores	No. of Patients	Survival (months) Median (95% CI)	2-year Survival
Low Risk Group	0	28	27.51 (13.71 - 34.71)	58 %
Intermediate Risk Group	1	33	12.8 (8.5 - 18.2)	23 %
High Risk Group	2	6	6.8 (2.1 -)	0 %

- The Low Risk Group included Pts with normal CRP and LDH;
- The Intermediate Risk Group included only Pts with high CRP;
- The High Risk Group included Pts with abnormal CRP and LDH;
- Increasing risk groups predicted a halving of the median survival and of the percentage of expected 2-year survival;
- All Pts in the High Risk Group died within 18 months.

Figure 1
Kaplan-Meier Curves of Survival by Prognostic Index



Developing a Prognastic Index for NSCLC Stage 4

Table 5
Multivariate Analysis of Prognostic Factors for Survival with corresponding Prognostic Score

Prognostic Factors	Hazard Ratio	Prognostic Score
Performance Status (ECOG) (2 vs. 0-1)	1.85 (1.25 - 2.73)	1
C-reactive protein (≥ 10mgL-1 vs. < 10mgL-1)	1.82 (1.24 - 2.68)	1
Albumin (≤ 35 vs. > 35)	1.66 (1.06 - 2.59)	1
Lactate Dehydrogenase (≥ 300 vs. < 300)	4.33 (2.81 - 6.64)	3
Absolute Neutrophil Count (≥ 11 vs < 11)	2.80 (1.69 - 4.64)	2

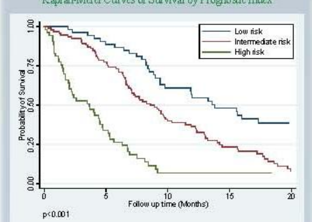
- Almost all prognostic biomarkers identified by univariate analysis (Table 2) retained independent significant predictive value;
- LDH and Absolute Neutrophil Count had the highest predictive value, while CRP, albumin, and Performance status had lower and equal predictive values

Table 6
Survival by Prognostic Index Group

Prognostic Index	Total of Prognostic Scores	No. of Patients	Survival (months) Median (95% CI)	1-year Survival
Low Risk Group	0	53	13.80 (9.39 - 24.84)	61 %
Intermediate Risk Group	1-2	93	8.61 (7.00 - 9.97)	38 %
High Risk Group	3-8	53	3.64 (1.97 - 4.71)	7 %

- The prognostic index was divided into three risk levels according to the total score;
- The Low Risk Group included Pts without poor prognostic biomarkers;
- The Intermediate Risk Group included Pts primarily with high CRP and either low Albumin or low Performance Status;
- The High Risk Group included Pts with high LDH and/or Absolute Neutrophil Counts, among a combination of the other prognostic factors;
- Between the Low to Intermediate Risk categories, there was a 35% decrease in survival and from the Intermediate to High Risk categories, a halving of 1-year survival.

Figure 2
Kaplan-Meier Curves of Survival by Prognostic Index



Discussion

- For each Prognostic Index, collections of stage specific poor prognostic biomarkers have been identified suggesting that such approach may improve the physician's prognostic ability;
- For Stage 3, among the identified biomarkers,
  - increased CRP identified a group of Pts with significantly reduced survival (Intermediary Risk Group) re-enforcing the importance of inflammation on survival and the need to measure it;
  - increased LDH (High Risk) identified a small group of Pts with very short survival suggesting that they may have been incorrectly staged (Stage 3 instead of Stage 4).
- For Stage 4, among the identified biomarkers,
  - increased CRP and low albumin or performance status identified a group of Pts with significantly decreased survival (Intermediary Risk);
  - increased LDH and other biomarkers identified a group of Pts with extremely short survival (High Risk Group) raising questions about the best treatment approaches for these Pts in terms of aggressive chemotherapy versus palliative care.
- Inflammatory biomarkers such as high CRP, low Albumin, high Absolute Neutrophil Count and high LDH are associated with shorter survival indicating that they should be measured on a routine basis for Pts' enrollement in clinical trials or when considered for chemotherapy.
- Increased LDH predicted poor survival independently of CRP, indicating that it is not related to inflammation. Upregulation of LDH-5 by cancer cells through HIF1α and HIF2α transcription factors favors a glycolytic metabolism independent of the presence of oxygen.[1]
- The Prognostic Index for Stage 3 is based on a small sample of Pts which limits the value of the conclusions drawn in our study.
- These findings need to be validated with another cohort of Pts with advanced NSCLC.

Conclusion

The use of these Prognostic Indices in advanced non small-cell lung cancer, for each of Stage 3 and Stage 4, may improve the treatment planning for these patients. Additionally, in the methodology of clinical trials, stratification or adjustment according to these Prognostic Indices should be considered so to improve the accuracy of the interpretation of the results

References

1. Koukourakis MI, Giatromanolaki A, Sivridis E, et al.: *Lactate dehydrogenase-5 (LDH-5) overexpression in non-small-cell lung cancer tissues is linked to tumour hypoxia, angiogenic factor production and poor prognosis.* Br J Cancer 89:877-885, 2003

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