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Role of Serum Carcinoembryonic Antigen (CEA) as a Predictive and Prognostic Marker of Response to Treatment in Patients with Advanced Non Small Cell Lung Cancer (NSCLC)

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Abstract: ***Background: The carcinoembryonic antigen (CEA) is an important tumor marker for malignant tumors including non small cell lung cancer (NSCLC). High serum CEA levels have been identified as a prognostic factor in both resected and metastatic NSCLC. The role of CEA as a predictive marker of response to chemotherapy have not been widely evaluated. So far only few prospective studies published in literature. The aim of the present study is to assess the role of CEA as predictive and prognostic marker of response to chemotherapy in advanced NSCLC. Methods: Seventy nine (79) patients with advanced NSCLC (stage IIIB or Stage IV), who had an raised serum CEA level (>10 ng/ml) at baseline and who had no more than one previous chemotherapy regimen, were included. Serum CEA levels were measured after three treatment cycles of platinum based chemotherapy (72%) or a tyrosine kinase inhibitor (28%). We assessed the change in serum CEA levels and the association with response measured by RECIS criteria. Results: A total of 168 patients with the diagnosis of advanced NSCLC were screened for CEA levels before the start of CT. Seventy nine patients finally evaluated according to criteria in the study After three cycles of chemotherapy, Patients with overall response (OR) had a CEA level reduction of 76.7% (95% CI 80.4-68.9); while patients with stable disease(SD) and progressive disease(PD) had an increase of 9.4% (95% CI 1.5 to 17.3) and 87.5% (95% CI 60.9 to 114), respectively. The ROC curve analysis for the changes in CEA levels in responsive patients had an area under the curve (AUC) of 0.803 (95% CI 0.67 to 0.93). Sensitivity and specificity were 85.4 and 86% (p < 0.003) respectively for a CEA level reduction of 28% or greater. Patients that achieved a decrease in CEA levels ≥28% presented an overall response in 76% of cases, stable disease in 13% and progression in 11%, while patients who did not attain a reduction ≥28% had an overall response of 14%, stable disease of 20% and progression of 66% (p < 0.006). The AUC in progressive disease was 0.840 (95% CI 0.72 to 0.95;fig 14), with a sensitivity and specificity of 86.7 and 87.2%, respectively, for a CEA level increase of 28% from baseline. The median follow up time was of 8.72 ± 3.97 months. PFS was longer in patients with ≥28% reduction in CEA (p <0.026). Reduction of CEA was not predictive of OS. Conclusion: A ≥28% reduction of serum CEA level from baseline after three cycles of treatment in advanced NSCLC is an accurate measurement of OR compared to RECIST, it has sensitivity and specificity and correlates with PFS. An increase of serum CEA levels from baseline is also an accurate measurement of PD. we demonstrated the predictive value of measuring CEA levels in NSCLC and we propose it to be part of the routine follow up of advanced NSCLC patients who have increase levels of CEA (>10 mg/dl) at baseline.***

Keywords: CEA (carcinoembryonic antigen), NSCLC (non small cell lung cancer)

1. Introduction

Lung cancer is the most common cause of cancer related death in men and the second in women worldwide(1). More than 60% of patients present with stage IIIB/IV disease(2). Among these more than half of the individuals treated with curative intent will relapse and eventually succumb to their disease. The efficacy of chemotherapy in advanced disease is limited with 20 to 35% response; and a 1-year survival rate of 35% (3,4).

Computed tomography is the most useful tool to evaluate response to chemotherapy (5). In addition positron emission tomography (PET) gives further information regarding metabolic activity of the tumor. But, not all the Non-small-cell lung cancer (NSCLC) patients have measurable disease like pleural effusions, diffuse nodules, tumors with poorly defined margins; thus complicating the possibility of evaluating objective responses. Serum markers are useful for such cases where the clinical picture does not match the topographic measurements. The use of serum markers as predictors of response to treatment have been clearly established in advanced prostate (prostate specific antigen (PSA) and ovarian cancer (CA 125) and these markers are used routinely in clinical practice to monitor the effects of therapy [6].

The carcinoembryonic antigen (CEA) is an important tumor marker for malignant tumors including NSCLC. High serum CEA levels have been identified as a prognostic factor in both resected (7-14)and metastatic NSCLC (15,16). The role of CEA as a predictive marker of response to chemotherapy have not been widely evaluated. So far only few prospective studies published in literature. The aim of the present study is to assess the role of CEA as predictive and prognostic marker of response to chemotherapy in advanced NSCLC.

2. Aims and Objectives

Aim

To determine the role of serum carcinoembryonic antigen (CEA) in advanced Non small cell lung cancer (NSCLC) as a predictive and prognostic marker of response to treatment.

Objectives

1) To assess sensitivity and specificity of the changes in CEA levels and their relationship to response to chemotherapy.
2) To assess the association between CEA levels and progression free survival.

3. Materials and Methods

Patients of advanced NSCLC attending Sri Venkateswara Institute of Medical Sciences, a tertiary care center in Andhra Pradesh from South India between May 2017 to May 2018 were included in the study.

Inclusion criteria

1) Histologically confirmed NSCLC
2) Stage III and IV
3) Base line CEA level > 10ng/ml
4) Patients ECOG PS ≤ 2

Exclusion criteria

1) Base line CEA level < 10ng/ml
2) Dual malignancy which express CEA
3) Patients ECOG PS ≥ 3
4) Patients not willing to participate in this study

4. Study Design

A prospective observational study to evaluate the utility of serum CEA in unresectable and metastatic NSCLC. Newly diagnosed histologically confirmed Non small cell lung cancer patients with baseline serum CEA level > 10ng/ml patients will be recruited. Demographic data, medical history, and physical examination will be performed before study entry. Height, weight, vital signs, Eastern Cooperative Oncology Group Performance status (ECOG PS) and vital signs will be assessed at every medical visit. CEA levels will be measured at study entry before starting chemotherapy and after 3 cycles of chemotherapy. Patients will be followed until progression, death or last medical visit. Tumor assessment by computed tomography will be made at baseline and three cycles after chemotherapy using the established RECIST 1.1 criteria. Peripheral blood samples will be obtained at base line day 1 before chemotherapy and after three cycles of chemotherapy. Patient will be treated according to standard treatment guidelines. All recruited subjects will be followed up at every subsequent 3 – 4 weeks for a minimum period of 6 months. Progression free survival is defined as the time period from date of beginning of treatment to date of progressive disease by confirmed imaging or last follow up.

CEA determination and analysis:

Peripheral blood samples will be obtained on day 1 before CT and after two CT cycles. Measurement will be performed at the Clinical biochemistry laboratory of the SVIMS using ELISA method.

Statistics analysis:

Data was recorded on a pre designed proforma using Microsoft excel spread sheet. The collected data was analysed with SPSS software version 23. Continuous variables were calculated as arithmetic means, medians and standard deviations. Categorical variables were expressed as proportions with 95% confidence intervals. Sensitivity and specificity was calculated for the CEA levels and response was measured by CT. The association between CEA levels with overall response was calculated with Chi square test. Receiver operating characteristics (ROC) curve analysis to determine the best cut off value for CEA levels to achieve a 80% specificity was undertaken. PFS was analysed with the Kaplan Meier method and sub groups were compared with the log rank test. P value <0.05 was considered significant**.**

5. Results

A total of 168 patients with the diagnosis of advanced NSCLC were screened for CEA levels before the start of CT. 105 patients with an abnormal baseline CEA level (>10 ng/mL) with ECOG PS ≤ 2 were prospectively recruited and 79 patients finally included in the analysis.

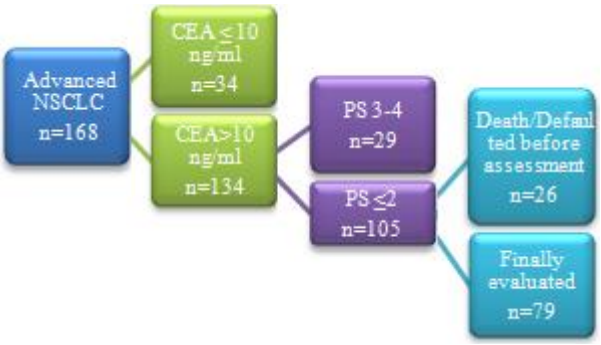


Figure 1: Consort flow diagram

Out of 79 patients, Fifty two (66%) were men and twenty seven (46%) were women. The mean age of our study cohort was 54.4 (± 10.2) yrs.

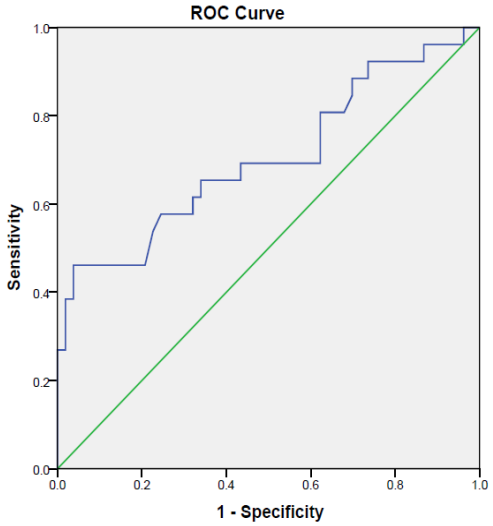
Table 1: Baseline patient and tumor characteristics

n=79		mean±SD	Patients n (%)
Age (years)		54.4 (± 10.2)	
Gender	Male Female		52 (66%) 27 (46%)
Smoking History	Positive Negative		43 (54%) 36 (46%)
ECOG	1 2		47 (67%) 32 (33%)
Clinical stage	III		7 (9%)
Histology	IV Adeno carcinoma Squamous cell		72 (91%) 68 (86%) 11 (14%)
Baseline CEA(ng/ml)		492.6(±362)	
Treatment	Platinum based CT TKIs		49 (72%) 30 (28%)
Tumor response evaluation	Complete/partial Stable disease Progressive disease		51(76%) 7(9%) 21(15%)

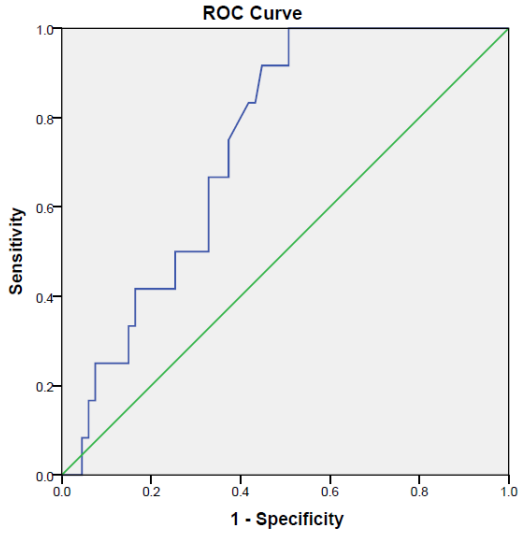
Forty three were smokers (54%) and thirty six (46%) were non smokers. Adenocarcinoma was the most common histological subtype found, being present in 68 patients (86%). Out of 79 patients with elevated CEA levels, 72% (n=56) received a platinum-based chemotherapy, while 28% (n=23) received a TKIs. Objective response (complete plus partial response, OR), stable disease (SD) and progressive disease (PD) were 76, 9 and 15% respectively. Patients with OR had a CEA level reduction of 76.7% (95% CI 80.4-68.9); while patients with SD and PD had an increase of 9.4% (95% CI 1.5 to 17.3) and 87.5% (95% CI 60.9 to 114), respectively ($p < 0.001$).

The ROC curve analysis for the changes in CEA levels in responsive patients had an area under the curve (AUC) of 0.803 (95% CI 0.67 to 0.93; Figure 13). Sensitivity and specificity were 85.4 and 86% ($p < 0.003$) respectively for a CEA level reduction of 28% or greater (Figure 2). Patients that achieved a decrease in CEA levels ≥28% presented an overall response in 76% of cases, stable disease in 13% and progression in 11%, while patients who did not attain a reduction ≥28% had an overall response of 14%, stable disease of 20% and progression of 66%.(figure 3)

The AUC in progressive disease was 0.840 (95% CI 0.72 to 0.95;fig 14), with a sensitivity and specificity of 86.7 and 87.2%, respectively, for a CEA level increase of 28% from baseline. The median follow up time was of 8.72 ± 3.97 months.PFS was longer in patients with ≥28% reduction in CEA ($p < 0.026$). Reduction of CEA was not predictive of OS.



AUC of 0.803 (95% CI 0.67 to 0.93).
Figure 2: ROC curve for CEA levels and overall response



AUC of 0.840 (95% CI 0.72 to 0.95).
Figure 3: ROC curve for CEA levels and progressive disease

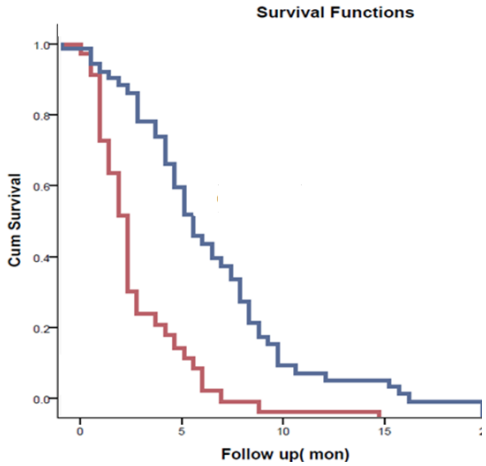


Figure 4: Kaplan Meier curve comparing PFS in patients with a ≥ 28% reduction of CEA levels

Patients with ≥ 28% reduction of CEA levels had better PFS which was statistically significant ($p<0.016$)

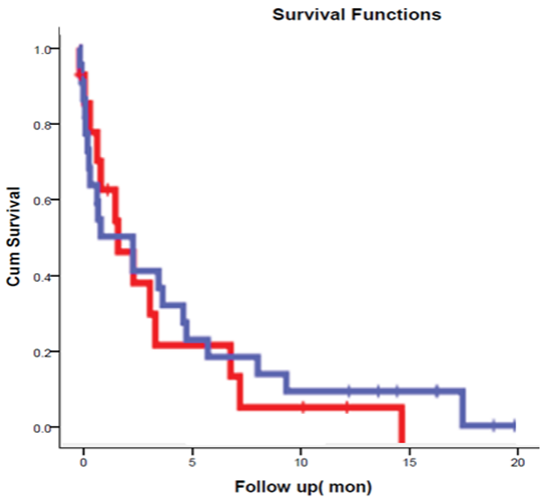


Figure 5: Kaplan Meier curve comparing PFS in responders vs stable/progressive disease

No difference in PFS was observed between responders and patients with stable/progressive disease.

6. Discussion

CEA is a member of the immunoglobulin super family, it serves as a cell adhesion molecule and may also play a role in innate immunity[18]. It is a glycoprotein product of the gene CEACAM-5.

CEA is often over expressed in many malignant neoplasms including lung cancer (NSCLC) and is readily detected in serum samples making it a valuable tool for the follow up and prognosis of patients.

Among 79 patients in the study majority were males (66%), smokers (54%), adenocarcinoma histology (86%), stage IV disease (91%) and treated with platinum based chemotherapy (71%); which were consistent with other studies done by Arrieta et al[16] and Ardizzoni et al [15].

The mean age in the our study was 54.4 (± 10.2) yrs.

Studies by Arrieta et al and Ardizzoni et al assessed role of serum CEA in advanced NSCLC after 2 cycles of chemotherapy. Xu et al and Okamoto et al assessed the clinical value of serum CEA in prediction of EGFR TKI therapy. In presented study we assessed role of CEA in advanced NSCLC after 3 cycles of chemotherapy.

A study done by Arrieta et al study shows patients who achieved an objective response had a reduction of CEA levels of 55.6% compared to its basal level, with an area under the ROC curve (AURC) of 0.945 and a sensitivity and specificity of 90.2 and 89.9%, respectively, for a CEA reduction of ≥14%. Patients that achieved a decrease in CEA levels ≥14% presented an overall response in 78% of cases, stable disease in 20.3% and progression in 1.7%, while patients that did not attain a reduction ≥14% had an overall response of 4.1%, stable disease of 63.6% and progression of 32.2% ($p < 0.001$). PFS was longer in patients with a ≥14% reduction in CEA. This study concluded that Patients who had ≥ 14% decrease in CEA levels had better overall response and prolonged PFS compared to those patients who did not attain a reduction ≥ 14%. Another study by Ardizzoni et al.[15] explored the value of CEA in advanced NSCLC patients receiving platinum based chemotherapy. They found that a reduction of ≥20% of CEA after 2 cycles of CT had accuracy for predicting response by ROC curve analysis of 0.65, with a sensitivity of 55% and a specificity of 75%. This study also concluded that Patients who had ≥ 20% decrease in CEA levels had better overall response and prolonged PFS compared to those patients who did not attain a reduction ≥ 20%. Xu et al. assessed the clinical value of CEA in prediction of EGFR TKI therapy response in advanced NSCLC patients. They found that a decrease of ≥32% from baseline was closely related to OR and a longer median survival time.

In present study best cut off limit for CEA reduction by ROC curve was 28%. Patients who achieved an objective response with an AURC of 0.803 and a sensitivity and specificity of 84.4% and 86%, respectively ($p<0.003$), for a CEA reduction of ≥28%.

In present study majority of patients received platinum based chemotherapy (71%) and TKI therapy in a small subset of patients.

ROC curve analysis for the changes in CEA levels in progressive disease showed AUC of 0.840 with a sensitivity and specificity of 86.7 and 87.2%, respectively, for a CEA level increase of 28% from baseline.

Patients who achieved a decrease in CEA levels ≥28% presented an overall response in 76% of cases, stable disease in 13% and progression in 11%, while patients who did not attain a reduction ≥28% had an overall response of 14%, stable disease of 20% and progression of 66% ($p < 0.006$). The median follow up time was of 8.72 ± 3.97 months.

In present study Patients with ≥28% reduction of CEA levels had better PFS which was statistically significant ($p<0.016$). PFS was longer in patients with a ≥28% reduction in CEA (7.1 vs 4.2 months). No difference in PFS was observed between responders and patients with stable/progressive disease ($p <0.076$).

In the present study demonstrated a significant association between the reduction of CEA and PFS but not OS, which is similar with previous studies.

Comparison with other studies: Table 2

Study	Arrieta et al n=180	Ardizzoni et al n=107	Xu et al n=75	Okamoto et al n=177	Our Study n=79
Disease Stage	Advanced NSCLC	Advanced NSCLC	Resectable Advanced NSCLC	Advanced NSCLCEGFR Mutant	Advanced NSCLC
Serum CEA cutoff limit	≥14%	≥20%	≥32%	≥10%	≥28%
Sensitivity	90.2%	55%	82.8%	88.9%	84.4%
Specificity	89.9%	75%	69.2%	77.2%	86%
Results	PFS ∞CEA reduction 8.7vs 5.1m	PFS ∞CEA reduction 13vs 8m	PFS ∞CEA reduction 9.5vs 6.7m	PFS ∞CEA reduction 6.4 vs 4.5m	PFS ∞CEA reduction 7.1 vs 4.2m

7. Conclusions

- Reduction of serum CEA levels ≥28% from baseline after three cycles of therapy in advanced NSCLC is associated with imageologically comparable response rates.
- An increase of serum CEA levels from baseline is associated with progression of the disease.
- Patients who demonstrated serum CEA levels ≥ 28% from baseline have better progression free survival.

We demonstrated the predictive value of measurement of CEA levels in NSCLC could be a part of the routine follow

up of advanced NSCLC patients who have increase levels of CEA (>10 mg/dl) at baseline.

8. Limitations

The drawback of the present study is small sample size. Further studies with a larger patient population might be necessary to validate these findings.

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