The Impact of Use Serum Carcinoembryonic Antigen and Beta 2-microglobulin in Monitoring Bronchogenic Carcinoma Therapy

Halla Ragab[1], Nabila Abd El Maksoud[1] and Tarek Essam[2]

[1]Biochemistry Department, Genetic Engineering and Biotechnology Division, National Research Center, Dokki, Giza, Egypt, [2]Surgical Department, National Cancer Institute, Faculty of Medicine, Cairo University, Egypt

ABSTRACT

Bronchogenic carcinoma is a disease of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis. Bronchogenic carcinoma, the most common cause of cancer-related death in men and the second most common in women (after breast cancer), it is responsible for 1.3 million deaths worldwide annually. The aim of this current study is to evaluate the prognostic properties and discriminative values of serum carcinoembryonic antigen (CEA) and beta2-microglobulin ($\beta2$ M) in different stages of bronchogenic carcinoma. Its feasibility usage an easy and cheap marker especially in developing countries and their use instead an invasive biopsy to avoid its risk factors for improving the accuracy of diagnosing and screening of bronchogenic carcinoma. In addition, we aim to detect and monitor the response to the therapy. This prospective study performed on eighty patients with bronchogenic carcinoma before receiving any treatment. Their age ranged from 30-65 years with a mean of 55.6 ± 11 years. The patients 78 followed up three weeks and six months after receiving treatment. Besides 40 healthy sex and age, matching individuals were also included as control. Their age ranged from 25-67 years with a mean of 49.7 ± 10.1 years. Quantitative measurements of CEA and $\beta2$M in serum performed with commercially available Enzyme Immunoassay Kit. Upper limit of normal levels for serum CEA and $\beta2$ M were 5 ng/ml and 3 mg/L, respectively. The data revealed that both the CEA and $\beta2$ M were increased in bronchogenic carcinoma patients when compared to control. CEA values showed a significant elevation in patients have + ve pleural effusion and in metastasis more than in –ve ones. CEA have been increased significantly in non small lung cancer in stage IV than in stage III. The serum levels of CEA significantly decreased in cases responding to the treatment. $\beta2$ M levels were decreased significantly in + ve pleural effusion than in –ve one.

We concluded that pretreatment and post treatment measurement of serum CEA concentrations yields valuable information for follow up and detecting patients at high risk of poor survival. The combination of CEA and $\beta2$M determination proved to be most useful in cases of non small lung carcinoma and for follow up of cases serial determination of the CEA is recommended with each course of treatment to help in predicting patient's response and monitoring the disease.

Key Words: Bronchogenic carcinoma, CEA, beta 2-microglobulin ($\beta2$ M), tumor marker.

Corresponding Author: Halla M. Ragab
E-mail: hmragab@yahoo.com

INTRODUCTION

Bronchogenic carcinoma (lung cancer) is the most common malignancy in the world and about 80% of them are non-small cell lung cancer (NSCLC) *(Samet, 1993)*. Over 90% of these new cases will die because of the disease *(Jemal et al., 2003)*. Bronchogenic carcinoma, the most common cause of cancer-related death in men and the second most common in women (after breast cancer), it is responsible for 1.3 million deaths worldwide annually *(WHO 2006)*. The latter figure may be an underestimation due to the lack of reliable statistics in many countries. Bronchogenic carcinoma may be seen on chest radiograph and Computed Tomography (CTscan). The diagnosis confirmed with a biopsy. This usually performed via bronchoscopy or CT-guided biopsy. Treatment and prognosis depend upon the histological type of cancer, the stage (degree of spread) and the patient's performance status. Possible treatments

include surgery, chemotherapy and radiotherapy. With treatment, the five-year survival rate is 14 % *(Minna and Schiller, 2007)*. Bronchogenic carcinoma classified into four major cell types by histology: Small cell lung cancer (SCLC); lung adenocarcinoma (LADC); squamous cell lung cancer (SQCLC); and large cell lung cancer (LCLC) *(WHO, 1982)*; the last three types being grouped together as non small cell lung cancer (NSCLC). Other known types of lung cancer not represented in this study. Differentiation between SCLC and NSCLC is very important for prognostic and therapeutic reasons, due to their different behaviour *(Ihde and Minna, 1991 and Sandler and Buzaid, 1992)*. This distinction is important, because the treatment varies; non-small cell lung carcinoma (NSCLC) is sometimes treated with surgery, while small cell lung carcinoma (SCLC) usually responds better to chemotherapy and radiation. In

addition to histology, an alternative diagnostic methodology may be useful, especially if the system based on simple laboratory tests, performed on serum. Until now, by using single tumor markers, it was not possible to classify lung cancer as SCLC or NSCLC.

A tumor marker is a substance found in the blood, urine, or body tissues that can be elevated in cancer, among other tissue types. There are many different tumor markers, each indicative of a particular disease process. An elevated level of a tumor marker can indicate cancer; however, there can also be other causes of the elevation. Tumor markers can be produced directly by the tumor or by non-tumor cells as a response to the presence of a tumor. Serum tumor markers are not only significant to the researcher in developing theories concerning the biology of tumors but also to the clinician in treating patients with cancer (Pamies and Crawford, 1996). In oncology practice, serum tumor markers may be helpful in the diagnosis, pathologic classifications and evaluation of the stage of disease and prognosis. When measured serially after the diagnosis of cancer is established they may aid in assessing the response to treatment, monitoring the spontaneous course of the illness and watching for tumor recurrences (Coombes and Powels, 1982). Bronchogenic carcinoma does not make exception to this rule and the expression of serum biomarkers in this particular tumor is various and abundant. Lung tumor markers fall into several categories including oncofetal proteins, structural proteins, enzymes, cell membrane components, secreted peptides, hormones and other tumor-associated antigens. Among them cytokeratin-derived molecules, neuroendocrine markers and CEA are probably the most used and helpful (Ferrigno et al., 1994 and Buccheri, 1999). Many adenocarcinomas are known to have high serum levels of CEA (Szklarz and Gawlikowski, 1989 and Niklinski et al., 1991). In bronchogenic carcinoma, carcinoembryonic antigen (CEA) remains one of the most used tumor markers and represents a heterogeneous group of oncofetal glycoprotein antigens, which circulate in high concentrations in patients with certain malignances. A long-standing experience with CEA, have found that it is helpful in a variety of clinical situations and complementary to the use of cytokeratins, other valuable serum markers (Buccheri and Ferrigno, 2001). However, other uses of CEA that have not been investigated so far. A potentially useful one is the prediction of surgical failure in patients apparently cured by tumor removal.

β2-Microglobulin (β2M), a well-known housekeeping gene, is a 12-kDa nonglycosylated polypeptide composed of 100 amino acids. β2M is synthesized by all nucleated cells and forms complexes with the heavy chain of MHC class I (Masaki et al., 1999). MHC class I, or HLA antigen plays an important role in tumor immunity. Beta 2-microglobulin is present in small amounts in serum, CSF and urine of normal people and to a much greater degree in the urine and plasma of patients with tubular proteinaemia, renal failure, or kidney transplants. β2M an interesting and underutilized metabolite, can be used in assessing renal function, particularly in kidney-transplant recipients and in patients suspected of having renal tubule-interstitial disease. It also can serve as a nonspecific but relatively sensitive marker of various neoplastic, inflammatory and infectious conditions. Early hopes that it would be a useful serum test for malignancy have not been fulfilled (Chen et al., 1996). More reports that are recent have suggested a role for β2M as a prognostic marker in Human Immunodeficiency Virus (HIV) infection, infectious mononucleosis, cytomegalovirus and influenza A. (Bethea and Forman, 1990).

β2 -Microglobulin identified as an apoptosis-inducing factor in various kinds of tumors and it enhances antibody induced MHC complex-apoptosis in the T-cell leukemia cell line (Delgado et al., 2007). Serum β2-microglobulin established as a marker of disease activity in several advanced malignant conditions, autoimmune conditions, chronic granulomatous, lymphoproliferative disorders and infections. β2 M has an important role in prognosis assessment and disease monitoring. β2 M protein expression by normal and cancer cells and its clinical usefulness has been the subject of investigation for long time. Increased synthesis and release of β2 M occur in several malignant diseases as indicated by an elevated serum or urine β2 M concentration (Mey-Tal et al., 1997). In addition, the level of β2 M is one of the most important independent prognostic factors and survival predictors in some tumors (Dargemont et al., 1989 and Mátrai et al., 2007).

The aim of this study was to assess the clinical significance of the tumor markers CEA and β2 microglobulin in sera of patients with bronchogenic carcinoma. Study their diagnostic utility, the predicting ability of these tumor markers with respect to histological types and pathological stages that will also assessed to attain the useful markers that aid in the staging predicting prognosis and monitoring the response to therapy.

PATIENTS AND METHODS

The studied population consisted of 80 patients with bronchogenic carcinoma who were admitted to the Surgical Department, National Cancer Institute, Faculty of Medicine, Cairo University. All patients were subjected to standard evaluation included medical history, clinical examination, blood chemistry, chest x- ray, CT scan whenever needed, pathologic examination and immunohistochemistry has been done for all patients. The diagnosis confirmed primarily by bronchogenic biopsy and lavage. Thoracocentesis and pleural fluid cytology done for cases that presented with pleural effusion. Lymph node biopsy was the method of pathologic diagnosis whenever lymphadenopathy encountered. A biopsy from metastatic lesion was done for diagnosis. Exfoliative cytology of the sputum performed routinely for all patients who had productive cough. Tumors staged according to the TNM classification (Sobin and Wittekinal, 1997) and graded using criteria recommended by the World Health Organization (WHO, 1982).

Patients divided into two groups:
Group (A): Eighty patients before receiving any treatment. They were 72 males and 8 females. Their age ranged from 30-65 years with a mean of 55.6 ± 11 years. 66 of those patients were smokers. The patients 78

have been followed up three weeks and six months after receiving treatment (two patients have been died).

Group (B): Fourty healthy normal controls selected to match the patients in, age, gender, smoking status and absence of any non-malignant pulmonary disorders. They were 25 males and 15 females, their age ranged from 25-67 years with a mean of 49.7 ± 10.1 years.

Exclusion Criteria:
Any patients with history of liver disease or suffering from any hepatic problem or renal disorder, recent history of cardiovascular disease or diabetes were excluded from the study.

Specimen Collection:
After obtaining informed verbal consent, ten-ml fasting blood samples collected in dry clean plastic tubes from both controls and patients. The blood were allowed to clot and sera were separated by centrifugation for 10 min at 3000 r.p.m, divided into several aliquots and stored at $-80°C$ until assayed. Samples confirmed to be collected without hemolysis.

Laboratory Investigation:
Sera from controls and patients subjected to the following investigations:

1. Complete blood picture.
2. Liver function tests including:
    Serum bilirubin level measured by using the commercially available kit from Bio-Merieux Company, France *(Berry et al., 1983)*.
    ALT, AST and alkaline phosphatase measured by using the method recommended by the committee on enzymes of the Scandinavian Society for Clinical Chemistry and Clinical physiology, 1974. The test performed using commercially available kit from Boehringer-Mannhiem Company, Germany.
3. Kidney function tests including:
    Urea using commercially available kit from Randox, Laboratories Ltd., USA *(Husdan and Rapoport, 1968)*.
    Creatinine measurement by using Jaffe reaction *(Fawcett and Scotto, 1960)*.
4. Quantitative determination of CEA was performed with commercially available Enzyme Immunoassay Kit (Bio Check, Inc. catalog number: BC-1011) *(Uotila et al., 1981)*.
5. Quantitative determination of β2 M was performed with commercially available Enzyme Immunoassay Kit (Quantizing IVD 2-Microglobulin EIA RandD Systems, Inc. Catalog Number DBM200) *(McCarthy et al., 1994)*.

Statistical Analysis:
The data processed and analyzed using the program (SPSS) statistical package for social sciences version II under windows XP. Descriptive statistics performed for categorical data using percents for quantitative data using the mean and standard deviation. Inter group comparisons conducted

using Pearson chi-square for categorical data. Quantitative variables were tested for normality and pooled T test was used for inter group comparisons involving such variables. The significance level preset at the 0.05 level *(Saunders and Trapp, 1994)*.

RESULTS

The clinical and biochemical data of the studied subjects showed in (Table 1) and (Figures 1,2). The study comprises 80 consecutive patients who were referred to the outpatient clinic of Surgical Department, National Cancer Institute, Faculty of Medicine, Cairo University, for treatment of histologically proven lung cancer. All patients investigated before and after received treatment and checked after three weeks and six months, during the follow up there was two cases died.

All patients have normal liver functions (bilirubin, AST and ALT) and kidney functions (urea and creatinine) before the initiation of therapy.

The cell typing of these bronchogenic carcinoma patients before treatment: Twenty four cases were of adenocarcinoma type, 20 patients with small cell carcinoma, 24 squamous cell carcinoma and 12 patients with large cell carcinoma. 46 patients out of 80 cases were poorly differentiated, 11 were moderately differentiated and 23 well differentiated. Thirty out of 80 cases had metastasis (20 bone metastasis, 8 liver and 2 both liver and bone metastasis). Twenty five patients out of 80 had pleural effusion and 37 out of 80 cases were positive for lymph nodes. Twenty nine patients out of 80 cases had high alkaline phosphatase.
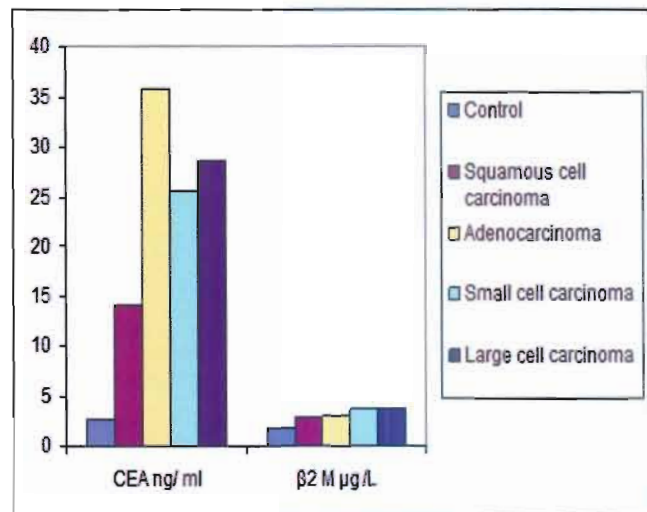

Figure 1: Serum levels of CEA and β2 M in different histological types in lung cancer patients.

The value of CEA in sera of patients ranged between 2.2- 66.46 ng/ ml with a mean value of 22.89 ± 3.22 ng/ ml. Using 5 ng/ ml the upper normal level of CEA as a cut off point for diagnostic sensitivity. The sensitivity of CEA (85%) in small cell lung cancer patients, the mean value of CEA of the limited disease was 26.44 ± 9.62 ng/ ml and for extensive disease 22.20 ± 8.32 ng/ ml. In non small cell the mean value for stage III was 21.03 ± 4.29 ng/ ml and for stage IV was

29.02 ± 7.05 ng/ ml. Metastases were detected in 30 patients and the mean values of CEA were 25.21 ± 5.49 ng/ ml and 20.18 ± 2.98 ng/ ml in patients without metastases. In smoking patients the mean value of CEA was 22.24 ± 2.89 n/ ml while in non-smoking was 22.98 ± 7.89 ng/ ml. According to the histological cell type, CEA increased in 16 out of 20 patients with SCLC (82 %), 22 out of 24 with adenocarcinoma (92%), in 10 out of 12 with large cell (84%) and in 20 out of 24 with squamous cell carcinoma (84%).

The value of β2-microglobulin in sera of patients ranged between 1- 7.6 µg /L with a mean value of 3.5 ± 0.273 µg /L.

Using 3 µg /L the upper normal level of β2 M as a cut off point for diagnostic sensitivity. The sensitivity of β2 M was 44 of 80 patients (55 %). In small cell lung cancer patients the mean value of β2 M of the limited disease was 2.97 ± 0.64 µg /L and for extensive disease 3.26 ± 0.36 µg/L. In non-small cell the mean value for stage III was 3.12 ± 0.38 µg /L and for stage IV was 2.88 ± 0.36 µg /L. β2 M were 3.67 ± 0.36 and 2.87 ± 0.32 µg /L in patients with metastases and without metastases respectively. In smoking patients the mean value of β2 M was 3.51 ± 0.26 µg /L while in non smoking was 3.12 ± 0.69 µg /L.

Table 1: The clinical and biochemical data of the studied subjects, the data expressed as mean ± SD.

| Clinicopathological parameters	No	CEA (ng/ ml)	β2 M (µg /L)
Controls	40	2.7 ± 1.66	1.7 ± 1.21
patients	80	22.89 ± 3.22	3.5 ± 0.273
Age range (years)		30-65	30-65
Age mean (years)		55.6	55.6
Smoking	66	22.24 ± 2.89	3.51 ± 0.26
Non smoking	14	22.98 ± 7.89	3.12 ± 0.69
Squamous cell carcinoma	24	14.09 ± 2.68	2.82 ±0.39
Adenocarcinoma	24	35.86 ± 9.48	2.98 ± 0.49
Small cell carcinoma	20	25.66 ± 6.64	3.65 ± 0.45
Large cell carcinoma	12	28.61 ± 9.09	3.72 ± 0.91
Pre treatment	80	22.89 ± 3.22	3.48 ± 0.42
3 weeks Post treatment	80	18.22 ± 2.93	3.49 ± 0.39
6 months Post treatment	78	9.46 ± 3.40	4.02 ± 0.52
Responding to treatment	40	8.88 ± 3.20	6.08 ± 0.36
Non Responding to treatment	38	22.64 ±6.10	2.43 ± 0.42
Metastasis	30	25.21 ±5.49	3.67 ± 0.36
No- metastasis	50	20.18 ±2.98	2.87 ± 0.32
Poorly differentiated	46	21.58 ± 4.98	3.11 ± 0.30
Moderately diff.	11	25.21 ± 16.11	3.81 ± 1.71
Well differentiated	23	22.82 ± 8.51	4.11 ± 0.81
Limited small cell	12	26.44 ± 9.62	2.97 ± 0.64
Extensive small cell	8	22.20 ±8.32	3.26 ± 0.36
Non small cell Stage III	38	21.03 ±4.29	3.12 ± 0.38
Non small cell Stage IV	22	29.02 ±7.05	2.88 ±0.36
+ ve Pleural effusions	25	26.13±23.95	2.88 ± 0.36
- ve Pleural effusions	55	12.09±19.04	4.33 ± 0.45
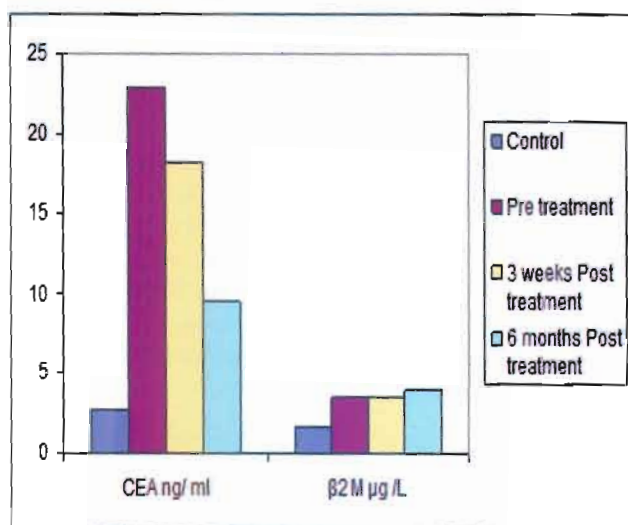
Figure 2: Serum levels of CEA and β2 M in pre and post treatment in lung cancer patients.

DISCUSSION

Bronchogenic carcinoma is a disease of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, which is the invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are carcinomas of the lung, derived from epithelial cells. The most common symptoms are shortness of breath, coughing (including coughing up blood) and weight loss *(Minna and Schiller, 2007)*. The main types of lung cancer are small cell lung carcinoma and non-small cell lung carcinoma. The most common cause of lung cancer is long-term exposure to tobacco smoke *(Merck Manual, 2007)*. The occurrence of bronchogenic carcinoma in nonsmokers, who account for as many as 15% of cases, is often attributed to a combination of genetic factors, radon gas, asbestos and air pollution, including secondhand smoke. *(Thun et al., 2007)*.

Tumor markers classified in two groups: Cancer-specific markers and tissue-specific markers. An example of a cancer-specific marker, CEA, or carcinoembryonic antigen, is a blood-borne protein, first noted to be produced by tumors of the gastrointestinal system. Further investigation showed that it produced by the occasional lung and breast cancer cases and probably it is the most widely studied marker in bronchogenic carcinoma. CEA relationship to extent of the disease and possibly its use in monitoring response to therapy is being increasingly appreciated *(Koepke, 2006)*.

Our results showed that CEA was elevated in 82% of small cell lung cancer, 92% of adenocarcinoma, in 84% of large cell carcinoma and 84% in squamous cell carcinoma. These values are greater than that obtained in *1988* by *Krischke et al.* who have been detected elevated serum CEA levels in about 35% of patients with small cell lung cancer; 23% with limited stage disease and 50% with extensive stage disease. Other investigator had shown similar pattern, serum CEA levels reported to be elevated in 29% to 45% of non-small lung cancer *(Asao et al., 1989 and Walop et al., 1990)* and usually it correlates with the extent of the disease and levels generally go parallel with the antitumor response. A number of reports have suggested that this marker may have some value

for staging and in the monitoring of patients with lung cancer. In the present study, the sensitivity of CEA in 68 of 80 patients was (85 %) which was in agreement with the data obtained by *(Pauwels and Straeten, 1975* and *Buccheri, 1996, 1999)*, who noticed that the level of CEA significantly increases in sera of patients with bronchogenic carcinoma (lung cancer). Our data showed increased incidence of elevated CEA in adenocarcinoma in 92 % of patients. While in patients with SCLC, it was elevated in 82 % versus 84 % in NSCLC group, by which we proved the limited value of its use in differentiation between SCLC and NSCLC.

In the present study, we found significantly higher CEA levels in the bronchogenic carcinoma group before treatment than in the control group. The two studied groups (patients and control groups) carefully matched for age, sex and smoking habits. It reported that these variables might influence the levels of tumor markers, especially for CEA *(Vincent et al., 1979)*. Differences according to the histological types detected in CEA. Although some statistical differences between certain histological types found, the levels of CEA are not specific to one histological type and they are not useful in distinguishing one from another. Except for adenocarcinoma, this showed the highest value and significantly increased than other histological types. Our results were in agreement with that obtained by *Buccheri* and *Ferrigno* in *2003*, who found an increase in the levels of CEA in bronchogenic carcinoma in all histological types but more in adenocarcinoma.

As regards TNM stage of cancer, our results for CEA showed a significant relation between tumor marker levels and TNM stage. These results are in accordance with several authors *(N.H.I., 1981, American Joint Committee on Cancer, 1988 and Buccheri G., 1999)* who suggest that there seems to be a correlation between the serum level of CEA antigen, the stage of the disease and the therapeutic response, nevertheless, a stage identification that was in agreement with our findings. CEA was highly significant increased in NSCL stage IV (29.02 ± 7.05 ng/ ml) more than NSCL stage III (21.03 ± 4.29 ng/ ml). The patients who were responding to the treatment the CEA levels were significantly decreased in response to chemotherapy (8.88 ± 3.20 ng/ ml) compared to the increase in the progression of the disease in the non responding patients (22.64 ± 6.10 ng/ ml). Our data are in agreement with that obtained by *Buccheri* and his colleague in *1986*, who concluded that the sequential CEA measurements appears to be of value in monitoring the response to treatment. Although the TNM classification includes tumors of any size with invasion of the visceral pleura, several studies have failed to establish visceral pleura invasion as a significant prognostic factor for NSCLC *(Padilla et al., 1997, The Japan Lung Cancer Society, 1999 and Rena et al., 2002)*.

In contrast to these studies, our study followed the definition of the UICC TNM system for staging NSCLC and found that visceral pleural invasion was a prognostic factor in bronchogenic carcinoma patients that in + ve pleural effusions the CEA level was (26.13 ± 23.95 ng/ ml) while in –ve one the level was (12.09 ± 19.04 ng/ ml). Also in metastasis, the levels of CEA showed more elevations than that obtained in that group without metastasis. Our results showed that the

CEA levels decreased but not significantly after three weeks of treatment. While the decrease was significant after six months and in the responding cases to treatment the decrease was highly significant. We have noticed that increased levels of CEA may be associated with poorer prognosis. 41% of patients showed partial remission (72% of them showed decrease in CEA levels) compared to 33% with stable disease (84% of them showed nearly plateau of CEA levels) and 26% did not show any response to therapy and categorized as progressive disease (88% of them showed increased CEA levels).

Regarding smoking, there was no significant difference between the CEA values in smoking and the non-smoking groups; this is in contrast to previously reported data by *Stevens* and *Mackay* in *1973,* who reported higher values in heavy smoker. This explained by the interaction of many variables as the stage and pathology in determining the value of the marker and thus minimizing the effect of smoking in raising the level of the marker.

β2-microglobulin is a low molecular weight protein that is a constituent of human histocompatibility antigens *(Chen et al., 1996)*. Elevated levels of serum β2M reported in many disorders such as renal disease, various malignant disorders, including lung cancer. In bronchogenic carcinoma, high serum levels found in 21-33% of the patients. The reason for raised levels is unknown. In several explanations, dominant hypothesis proposes that elevated levels of β2M may reflect an enhancement of immune system secondary to the malignant process *(Higuchi et al., 1986)*. The clinical usefulness of measuring serum β2M in lung cancer is controversial in the literature *(Hallgren et al., 1980)*. With respect to β2M, as harmony with literature, no significant differences in serum concentrations found between cancers patients sub-grouped according to the WHO classification. A strong correlation between the serum level of the markers and tumor stage appears likely, considering that it depends to great extent on tumor mass. However, serum β2M concentration might not be necessarily affected by total tumor mass but CEA seems to be so. CEA secreted from the lung cancer cells, as depending on the size of the primary tumor and existence of metastasis; Serum β2M is produced secondary to certain immunologic reactions against the underlying lung carcinoma *(Cha et al., 1986)*.

Our results showed that the sensitivity of β2M was 55% and it was elevated in 70% of patients with small cell lung cancer (SCLC), 42% in adenocarcinoma and 66% in large cell carcinoma and in 50 % of squamous cell carcinoma. Our results were in agreement with that obtained by *Evrin* and *Nilsson* in *1974* and also with that obtained by *Shuster et al. in 1976*, they found elevated levels of β2M in 33%, 40% of bronchogenic carcinoma respectively.

Our study demonstrates a relation between incidence of elevated β2M and histological cell type, the highest sensitivity was observed with SCLC (70%) followed by large, squamous and lastly adenocarcinoma. β2M did not show any significant difference in categorizing patients in according to stage or grade. In metastatic patients, β2M showed a significant elevation in 73% and the highest levels seen in liver metastases. β2M have been decreased

significantly in – ve pleural effusion patients than in + ve ones (4.33 ± 0.45, 2.88 ± 0.37 μg /L) respectively. When combined β2M and CEA, the sensitivity of detecting NSCLC increased to 97% and in adenocarcinoma and squamous cell carcinoma to 100%. Regarding β2M as a monitor to response 57% of patients showed a parallel elevation in β2M levels to the clinical detected response, while 43% did not express any elevation or decreasing while the patients were responding clinically. This proves the limited value of β2M in detecting response to therapy. In addition, the same results we have obtained in the progressive and in the stable disease.

CONCLUSION

In conclusion, evidence from this study reemphasizes the need of obtaining a routine CEA test in any potentially treated patient with bronchogenic carcinoma. This allows with very little cost the identification of a significant proportion of patients who are at high risk of developing an early tumor relapse. Of course, the number of subjects at risk being globally low, many patients will receive a useless but inexpensive blood test while few will obtain critical information. Computed tomography remains the gold standard for the preoperative evaluation of bronchogenic carcinoma. However, it may significantly underestimate the real extension of the tumor, giving no insight into the possible presence of micrometastases. This limitation shared by the preoperative pathologic staging, at least for the micrometastases growing out of the surgical field. The CEA test may correct such an underestimation and may help to decide the next steps.

The data showed that regarding serum β2M, there was no advantage over CEA in diagnosis and metastasis discrimination of bronchogenic carcinoma. β2 M was a marker of less importance but when combined its determination with CEA, it increases the sensitivity of the prediction.

REFERENCES

American Joint Committee on Cancer: Purposes and principles of staging. 1988. In Manual for Staging of Cancer, edited by O. H. Beahrs, D. E. Henson, R. V. P. Hutter and M. H. Myers. Philadelphia: JB Lippincott, pp. 3-10.

Asao, T., Yazawa, S., Nagamachi, Y., et al. 1989. Serum α(1→3)-L-fucosyltransferase, carcinoembryonic antigen and sialyl Lewis X-i antigen levels in lung cancer. Cancer **64**(12):2541--2545.

Bethea, M. and Forman, D. T. 1990. Beta 2-microglobulin: Its significance and clinical usefulness. Annals of Clinical and Laboratory Science **20**(3):163--168.

Buccheri, G. 1999. Tumor markers: Clinical meaning and use lung tumors. In Lung tumors: Fundamental biology and clinical management, edited by C. Brambilla and E. Brambilla. New York: Marcel Dekker, pp. 435--452.

Buccheri, G. F., Violante, B. and Sartoris, A. M. 1986. Clinical value of a multiple biomarker assay in patients with bronchogenic carcinoma. Cancer **57**(12):2389--2396.

Buccheri, G., Biggi, A., Ferrigno, D., et al. 1996. Anti-CEA immunoscintigraphy and computed tomographic scanning in the preoperative evaluation of mediastinal lymph nodes in lung cancer. Thorax 51(4):359--363.

Buccheri, G. and Ferrigno, D. 2001. Serum biomarkers facilitate the recognition of early-stage cancer and may guide the selection of surgical candidates: A study of carcinoembryonic antigen and tissue polypeptide antigen in patients with operable non-small cell lung cancer. Journal of Thoracic and Cardiovascular Surgery 122(5):891--899.

Buccheri, G. and Ferrigno, D. 2003. Identifying patients at risk of early postoperative recurrence of lung cancer: A new use of the old CEA test. Annals of Thoracic Surgery 75(3):973--980.

Cha, R. J., Chen, S. J., Xiao, C. Z., et al. 1986. Serum beta 2-microglobulin and carcinoembryonic antigen in patients with bronchogenic carcinoma. Chinese Journal of Oncology 8(5):342-344.

Chen, H. L., Gabrilovich, D., Tampé, R., et al. 1996. A functionally defective allele of TAP1 results in loss of MHC class I antigen presentation in a human lung cancer. Nature Genetics 13(2):210-213.

Coombes, R. C. and Powels, T. J. 1982. Tumour markers in the management of human cancer. In Topical Reviews in Radiotherapy and Oncology, edited by T. J. Deeley. Bristol: Wright PGS, pp. 39-52.

Dargemont, C., Dunon, D., Deugnier, M. A., et al. 1989. Thymotaxin, a chemotactic protein, is identical to β2-microglobulin. Science 246(4931):803--806.

Dawson-Saunders, B. and Trapp, R. G. 1994. Basic and clinical biostatistics.2nd ed. USA: Appleton and Lange Medical Books/ McGraw-Hill.

Delgado, J., Pratt, G., Phillips, N., et al. 2009. Beta2-microglobulin is a better predictor of treatment-free survival in patients with chronic lymphocytic leukaemia if adjusted according to glomerular filtration rate. British Journal of Haematology 145(6):801--805.

Evrin, P. E. and Nilsson, K. 1974. β2 Microglobulin production in vitro by human hematopoietic, mesenchymal and epithelial cells. Journal of Immunology 112(1):137--144.

Fawcett, J. K. and Scott, J. E. 1960. A rapid and precise method for the determination of urea. Journal of Clinical Pathology 13:156-159.

Ferrigno, D., Buccheri, G. and Biggi, A. 1994. Serum tumour markers in lung cancer: History, biology and clinical applications. European Respiratory Journal 7(1):186--197.

Hallgren, R., Nou, E. and Lundqvist, G. 1980. Serum beta 2-microglobulin in patients with bronchial carcinoma and controls. Cancer 45(4):780--785.

Higuchi, Y., Togawa, T., Moriya, H., et al. 1986. Clinical evaluation of serum beta 2-microglobulin in squamous cell carcinoma of the lung. Gan no Rinsho 32(15):1919--1924.

Husdan, H. and Rapoport, A. 1968. Estimation of creatinine by the Jaffe reaction. A comparison of three methods. Clinical Chemistry 14(3):222--238.

Ihde, D. C. and Minna, J. D. 1991. Non-small cell lung cancer part: I Biology, diagnosis and staging. Current Problems in Cancer 15(2):65--104.

Japan Lung Cancer Society. 1999. General rule for clinical and pathological record of lung cancer.5th ed. Tokyo: Kanehara: Japan Lung Cancer Society.

Jemal, A., Murray, T., Samuels, A., et al. 2003. Cancer statistics, 2003. CA Cancer Journal for Clinicians 53(1):5-26.

Keiding, R., Horder, M. and Gerhardt, W. 1974. Recommended methods for the determination of four enzymes in blood. Scandinavian Journal of Clinical and Laboratory Investigation 33(4):291--306.

Koepke, J. A. 1992. Molecular marker test standardization. Cancer 69(6 Suppl.):1578--1581.

Krischke, W., Niederle, N., Schutte, J., et al. 1988. Is there any clinical relevance of serial determinations of serum carcinoembryonic antigen in small cell lung cancer patients? Cancer 62(7):1348--1354.

Lung carcinoma: Tumors of the lungs. Merck Manual Professional Edition, Online edition, Retrieved on *2007--08--15*.

Mátrai, Z., Németh, J., Miklós, K., et al. 2009. Serum beta2-microglobulin measured by immunonephelometry: Expression patterns and reference intervals in healthy adults. Clinical Chemistry and Laboratory Medicine 47(5):585--589.

McCarthy, J. T., Williams, A. W. and Johnson, W. J. 1994. Serum beta 2-microglobulin concentration in dialysis patients: Importance of intrinsic renal function. Journal of Laboratory and Clinical Medicine 123(4):495--505.

Mey-Tal, S. V., Schechter, C. and Ehrlich, R. 1997. Synthesis and turnover of beta2-microglobulin in Ad12-transformed cells defective in assembly and transport of class I major histocompatibility complex molecules. Journal of Biological Chemistry 1997 Jan 3; 272(1):353--361.

Minna, J. D. and Schiller, J. H. 2008. Neoplasms of the Lung. In Harrison's Principles of Internal Medicine, edited by A. S. Fauci, et al. USA: McGraw-Hill Professional, pp. 551--562.

Mori, M., Terui, Y., Ikeda, M., et al. 1999. Beta(2)-microglobulin identified as an apoptosis-inducing factor and its characterization. Blood 94(8):2744--2753.

Niklinski, J., Furman, M., Palynyczko, Z., et al. 1991. Carcinoembryonic antigen, neuron-specific enolase and creatine kinase-BB as tumor markers for carcinoma of the lung. Neoplasma 38(6):645--651.

Padilla, J., Calvo, V., Penalver, J. C., et al. 1997. Surgical results and prognostic factors in early non-small cell lung cancer. Annals of Thoracic Surgery **63**(2):324--326.

Pamies, R. J. and Crawford, D. R. 1996. Tumor markers. An update. The Medical Clinics of North America **80**(1):185--199.

Pauwels, R. and Van-der-Straeten, M. 1975. Plasma levels of carcinoembryonic antigen in bronchial carcinoma and chronic bronchitis. Thorax **30**(5):560--562.

Perry, B. W., Doumas, B. T., Bayse, D. D., et al. 1983. A candidate reference method for determination of bilirubin in serum. Test for transferability. Clinical Chemistry **29**(2):297--301.

Rena, O., Oliaro, A., Cavallo, A., et al. 2002. Stage I non-small cell lung carcinoma: Really an early stage? European Journal of Cardio-Thoracic Surgery **21**(3):514--519.

Samet, J. M. 1993. The epidemiology of lung cancer. Chest **103**(1 Suppl):20S-29S.

Sandler, A. B. and Buzaid, A. C. 1992. Lung cancer: A review of current therapeutic modalities. Lung **170**(5):249--265.

Shuster, J., Gold, P. and Poulik, M. D. 1976. beta 2-microglogulin levels in cancerous and other disease states. Clinica Chimica Acta **67**(3):307--313.

Sobin, L. H. and Wittekind, C. 1998. UICC TNM classification of malignant tumors 5th ed. New York, NY: Wiley-Liss.

Stevens, D. P. and Mackay, I. R. 1973. Increased carcinoembryonic antigen in heavy cigarette smokers. Lancet **2**(7840):1238--1239.

Szklarz, E. and Gawlikowski, W. 1989. Antygen rakowoplodowy (cea) w surowicy krwi chorych na raka oskrzelopochodnego i wybranych chorobach ukladu oddechowego (Carcinoembryonic antigen (CEA) in the blood serum of patients with bronchogenic carcinoma and selected diseases of the respiratory tract). Pneumonologia Polska **57**(4):217--221.

The World Health Organization. 1982. The World Health Organization histological typing of lung tumours. American Journal of Clinical Pathology **77**(2):123--136.

Thun, M. J., Hannan, L. M., Adams-Campbell, L. L., et al. 2008. Lung cancer occurrence in never-smokers: An analysis of 13 cohorts and 22 cancer registry studies. PLoS Medicine **5**(9):e185.

Uotila, M., Ruoslahti, E. and Engvall, E. 1981. Two-site sandwich enzyme immunoassay with monoclonal antibodies to human alpha-fetoprotein. Journal of Immunological Methods **42**(1):11-15.

Vincent, R. G., Chu, T. M. and Lane, W. W. 1979. The value of Carcinoembryonic antigen in patients with carcinoma of the lung. Cancer **44**(2):685-691.

Walop, W., Chretien, M., Colman, N. C., et al. 1990. The use of biomarkers in the prediction of survival in patients with pulmonary carcinoma. Cancer **65**(9):2033--2046.

World Health Organization (WHO). Retrieved 2007-06-25. Cancer. http://www.who.int/mediacentre/factsheets/fs297/en/ World Health Organization.