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CASE REPORTS

Long-term survivors of advanced and metastatic lung cancer

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Abstract: The overall prognosis in patients with advanced and metastatic lung cancer is poor, however a subset of these patients has durable survival and they are called long-term survivors (LS). The definition of LS varies in published series from 18 months to 5 years. Few studies have focused on them. We report six cases of LS patients: three cases of non-small-cell lung cancer (stage IIIB and stage IV), two cases of small cell lung cancer, and a case of composite carcinoma (small cell carcinoma and squamous carcinoma), all having a survival of five years or more. Our patients show clinical and evolutionary similarities with LS in the literature regarding the prognostic factors associated with prolonged survival performance status and good response to first-line chemotherapy.

Keywords: lung-cancer, stage III and IV, prognosis, chemotherapy, survivors

Abbreviations

BMI: Body Mass Index
CD51: Cell Differentiation antigen 51
COPD: Chronic Obstructive Pulmonary Disease
CT: Computed tomography
CYFRA 21-1: Cytokeratin 19 Fragments 21-1
EGFR: Epidermal Growth Factor Receptor
Gm-CSF: Granulocyte-macrophage Colony Stimulating Factor
GOLD: Global Initiative for Chronic Obstructive Lung Disease
KRAS: K RAt Sarcoma oncogene
LC: Lung Cancer
LS: long-term Survivors
NSCLC: Non-Small Cell Lung Carcinoma
PS: Performance Status
SCLC: Small Cell Lung Carcinoma
TKI: Thyrosin Kinase Inhibitors

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1 Introduction

Lung cancers are frequent cancers with poor prognosis[1,2]. They are the leading cause of cancer-related mortality in men worldwide and represent therefore a major problem health[3]. However in clinical practice, very heterogeneous outcomes are observed between patients with locally advanced or metastatic non-small cell (NSCLC) and small cell carcinoma (SCLC)[4–6]. In fact, some patients will have prompt progression of the disease in spite of adequate treatments, on the contrary others will present a prolonged survival and will be called long-term survivors (LS). LS definition varies in published series, survival is greater than or equal to 18, 24, 30 months or 5 years[7–12]. Devoted studies are several. We report cases of 6 LS patients: 3 with NSCLC (IIIB and IV stages), one localized SCLC, one advanced SCLC and a case of composite carcinoma (SCLC and squamous cell carcinoma) who had all 5-year or more survival and we propose to review some literature data analyzing this topic.

2 Cases series

Table 1 shows the clinical features of all patients.

2.1 Case 1

A 52-year-old man, 90 packet-year smoker with a medical history of pulmonary tuberculosis 30 years ago, presented to us with isolated low abundance hemoptysis. Physical examination showed no abnormalities and performance status (PS) was normal (PS = 0). Chest

Table 1. Clinical features of all patients

Patient	Age/ Gender	Smoking status	Symptoms	TNM stage	Histological subtype	PS	First-line treatment	Outcomes	Second-line treatment	survival	Death
Case 1	52/Male	90 pack/year	Hemoptysis	IIIB T4N2M0	Adenocarcinoma	0	platinum and gemcitabine chemotherapy 3cycles	Almost complete regression	No	7 years	No
Case 2	46/Male	28 pack/year	Chronic cough & fever	IIIB T4N2M0	Squamous cell cancer	0	platinum and gemcitabine chemotherapy 3cycles+ radiotherapy	Almost total regression	No	6 years	No
Case 3	60/Male	no	Hemoptysis	Limited T4N2M0	small cell lung carcinoma (SCLC)	0	Platinium and etoposid chemotherapy 6 cycles + thoracic radiotherapy+ brain radiotherapy	Total regression	Yes : endoxan + adriamycin + etoposid	5 years	Yes
Case 4	45/Male	25 pack/year	Hemoptysis	Limited T4N2M0	SCLC+ Squamous cell cancer	0	Platinium and etoposid chemotherapy 6 cycles + thoracic radiotherapy	Total regression	No	6 years	No
Case 5	62/Male	100 pack/year	Dyspnea chronic cough	T4N2M1b	Squamous cell cancer	0	Concomitant platin-based-radio-chemotherapy+ Gemcitabine and Cicsplatin 3 cycles then Gemcitabine and carboplatin 3 cycles	Partiel regression then stability	Yes	8 years	No
Case 6	70/Male	80 pack/year	Hemoptysis	Extensive T4N2M1b	SCLC	0	Cisplatin and etoposid chemotherapy 6 cycles	Partiel regression then stability	No	5years	No

radiography showed right speculated hilar opacity. At bronchoscopy, an endobronchial mass obstructed completely the upper right lobe. Biopsy and cytology confirmed adenocarcinoma. Chest and abdomen Computed Tomography (CT) found a right upper lobe mass invading the mediastinum with lateral tracheal lymphadenopathy without distant metastasis. The tumor stage proved to be IIIB (T4N2M0). Three cycles of chemotherapy were conducted in previous delays associating platinum and gemcitabine at a dose of 75 mg/m^2 and 1250 mg/m^2. However the third cycle was complicated by a vagal attack with heart arrhythmia and low ejection fraction on transthoracic echocardiogram (45%). The checkup after 3 cycles showed an almost complete regression of the endobronchial mass in both bronchoscopy and chest CT. Considering complete response and heart toxicity, chemotherapy was discontinued. The patient is free of disease 8 years after chemotherapy.

2.2 Case 2

A 46-year-old man, active smoker (28 packs/year) who complained of 4-week history of cough and fever. His examination and PS were normal. Radiography showed a basal left speculated opacity. Fiberoptic bronchoscopy showed left lower lobe infiltration and an endobranchial mass obstructing the left basal pyramid.

Biopsy revealed well differentiated squamous cell carcinoma. Computed body tomography showed a tumor mass of the lower left lobe associated with subcarinal lymph nodes. We classified the tumor on stage IIIB (T4N2M0). He was treated by 6 cycles of chemotherapy based on platinium and gemcitabine followed by radiotherapy at the dose of 60 Gy. Endoscopic control noted complete regression of the basal pyramid endobranchial mass and imaging showed the persistence of basal peribronchial thickening. Therefore follow-up was decided. Seven years after, no recurrences of the disease have been noted.

2.3 Case 3

A 60-year-old man, nonsmoker, with a history of asthma was admitted in our department. He has been suffering from repetitive hemoptysis for about a month. His physical and general condition were normal (PS = 0)

Chest radiography noted a tumor mass of the right pulmonary hilum. Bronchoscopic examination revealed an almost complete occlusion of the right upper lobe with an endobronchial tumor whose biopsy had confirmed the diagnosis of small-cell cancer. Staging showed a mediastinal pulmonary mass measuring $50\times45\times45$ mm invading the right pulmonary artery associated with sub carinal lymph nodes and no distant metastases. So it's a limited SCLC. Thus the patient underwent 6 cycles of chemotherapy including etoposide and platinum every 3 weeks with concomitant mediastinal pulmonary radiotherapy at the dose of 60 Gy. Then a prophylactic brain radiotherapy was performed. Check-up tomography and bronchoscopy after radio-chemotherapy showed total regression of the tumor. Since then, the patient has had regular scans at the rhythm of 3 to 6 months. 3 years later, progression of the tumor has occured. Bronchoscopy noted reappearance of the upper right lobe mass and at tomography a trilobar massively necrotic mediastinal pulmonary complex with downstream lung collapse, associated to right lateral tracheal adenomegaly, right great abundance pleural effusion and costal and iliac lytic lesions. Considering preserved general state (PS = 0), the patient received 3 cycles of second line of chemotherapy including endoxan, adriamycin, etoposide and cisplatin. After the end of the chemotherapy the patient was lost for 7 months and then consulted again in a chart of profound deterioration of the general state (PS at 4), he died in few days in a table of respiratory failure . The overall survival for this patient was 5 years.

2.4 Case 4

A 49-year-old man, with a 25 packs/year smoking history, presented with a symptomatology of low abundance isolated hemoptysis since a month. Physical examination and general status were normal (PS = 0). The chest X-ray showed a suspected right-sided lateral tracheal opacity. At bronchoscopy there was an extrinsic compression aspect. The baseline thoracic-abdominal-pelvic and brain scan showed a $6\times4\times7$ cm upper right lobe mass with wide contact with the mediastinum, associated with right paratracheal adenopathy. Thoracoscopic biopsy of the mass confirmed the diagnosis of composite carcinoma with a contingent of squamous cell carcinoma associated with a SCLC. Considering limited disease, the patient received 6 cycles of chemotherapy combining etoposide and platinium at the classical doses in association with concomitant radiotherapy at the dose of 60 Gy. Post-treatment imaging showed almost complete regression of the tumor process with post-radiation sequelae lesions. Until now after 7 years, the patient experienced no recurrence of the disease.

2.5 Case 5

A 62-year-old man with a history of peptic ulcer disease and COPD GOLD3 was found to have marked right-sided mediastinal widening associated to right mediastinal and lung opacity compressing the trachea on routine chest radiograph for COPD exacerbation. He had no unusual symptoms apart from common exercise dyspnea and chronic bronchitis. On examination, he had inspiratory wheezing and digital clubbing. His PS was normal. Bronchoscopy revealed extrinsic compression of the lower third of the trachea and a bronchial tumor obstructing the lumen of the right main bronchus. Transbronchial biopsy and bronchial cytology concluded the diagnosis of poorly differentiated non-microcellular carcinoma. Baseline imaging staging showed laterotracheal confluent tumour and lymph node mass with an endoluminal tissue mass protruding into the right main bronchus with paratracheal and subcarinal lymphadenopathies. Skeletal Scintigraphy revealed acromial and sacroiliac metastases corresponding to stage IV (T4N2M1b). Thus the patient underwent firstly decompressive radiotherapy then 11 cycles of concomitant platin-based radio-chemotherapy. Post-treatment imaging showed partial tumor regression and repeated bronchoscopy had the same aspect. Bronchial cytology revealed the persistence of tumor cells. Therefore a second reading of the transbronchial biopsy had been performed to make sure weather a second line of chemotherapy is required. This later confirms the diagnosis of non-keratinizing poorly differentiated squamous carcinoma. Then the patient had received 3 cycles of chemotherapy including Gemcitabine and Cisplatin at the classical doses. The following CT revealed more partial tu-

mor regression and post-radiation sequelae so 3 other cycles of Gemcitabine in association with Carboplatin were added. After that the patient developed tumor progression in both CT and bronchoscopy corresponding to a time to progression of 19 months. He subsequently underwent taxotere second-line monochemotherapy during 6 cycles. Since that a semestral follow-up imaging was decided in association to supportive care. In fact the patient received several doses of bisphosphonates with significant improvement of bone pain. Currently no progression of the tumor and the metastases has been noted after an overall period of 8 years.

2.6 Case 6

A 70-year-old COPD GOLD 3 man, presented with a history of multiple episodes of hemoptysis of 6 months duration. Physical examination showed no appear abnormalities. His general condition was normal (PS = 0). Chest X-ray showed a suspected hilar opacity. Flexible bronchoscopy revealed infiltrated mucosa of the lower third of the trachea, the carina and all the right bronchial tree. Biopsy was nondiagnostic and branchial cytology confirmed the diagnosis of small-cell cancer. A subsequent computed chest, abdominal and brain tomography displayed a proximal right mediastinal and pulmonary tumor infiltrating the carina associated with ipsilateral paratracheal lymphadenopathy and multiple scattered hypodense liver lesions. Thus the tumor was classified as an extensive stage. Therefore the patient underwent 3 cycles of chemotherapy combining cisplatin and etoposide at the classical doses. First check-up CT scan showed tumor progression and appearance of left adrenal and bone metastases. However the liver lesions turned to be in fact biliary cysts. Hence it was decided to complete 3 other cycles of the same chemotherapy. The fifth cycle was complicated by severe anemia and neutropenia requiring transfusion of red blood cell and Gm-CSF respectively. The second follow-up CT and bronchoscopy noted overall stability. Then a quarterly physical and radiological follow-up was preconized. Since that the patient was lost to follow-up for 4 years. Meanwhile he consults for a moderate COPD exacerbation. The check-up tomography showed still the same findings. Despite duration of 4 years treatment-free, our patient experienced no tumor recurrence after accurately 5 years from the SCLC diagnosis.

3 Discussion

Lung cancer (LC) is a cancer with a poor prognosis[1]. The 5-year survival rates for all stages are 12% for men and 16% for women in France[2]. In Tunisia, recent epidemiological data are alarming: North-Tunisia cancer registries show an increase in the incidence rate from 22.4/100,000 in 1994 to 30.8/100,000 in 2003[3]. Among lung tumors, NSCLC account for over 80% of cases. 70% of them are diagnosed in an already advanced or metastatic stage. The median survival for stages IIIB and IV undergoing chemotherapy ranged from 7.9 to 11.3 months and the 2-year survival rates from 11 to 21%[4,5]. SCLC is a very aggressive cancer characterized by rapid loco regional and distant progression. Median survival is 14-16 months for patients with limited SCLC and 8-11 months for those with extensive form[6]. However, patients are often different and have heterogeneous response to the different treatments. Some of them will have favorable outcome and prolonged survival and will be called long-term survivors, these latter are defined by a survival most often greater than 2 years. The identification of the prognostic factors of LC survival has been assessed in several studies[12–16]. These prognostic factors are various and may be distributed as follows: Clinical criteria (age, smoking, comorbidities, quality of life, PS, *etc*.), The TNM classification (stage, lymph nodes staging..), Histological criteria (adenocarcinoma, SCLC, *etc*.), Biological criteria (platelet count, hemoglobin, leukocytes, lactate desydrogenase (LDH), *etc*.), and Genetic criteria (EGFR mutations, KRAS, *etc*.).

Among these trials, a recent study of late-stage NSCLC identified 5 prognostic factors associated with limited survival: fatigue, anorexia, desaturation, hyponatremia, and hypoalbuminemia with a high probability of death within 2 weeks if at least 3 of these factors are present (with a sensitivity of 100% and a specificity of 75%)[16]. Few studies investigating LS patients' features in advanced stages have been reported. Some of them interest patients included in clinical trials and therefore responding from the start to specific selection criteria, others are monocentric or have concerned different stages of NSCLC including early stages[12]. The main studies that have focused on NSCLC are summarized in Table 2. These studies have highlighted 2 major prognostic factors associated with long-term survival (in multivariate analysis): PS and first-line chemotherapy response. Baseline PS before chemotherapy is the most important prognostic factor predicting prolonged survival[12–22]. The characteristics of our patients joined these results: their PS were at 0 and they had responded well to a first-line treatment. The particularity of patients 1 and 2 is the fact the tumor mass has almost completely disappeared after a single course of chemotherapy. In Dujon study, the response to first-line treatment multiplied by 3 the probability of being a LS[12]. This result

Table 2. Summary of studies on long-term survivors (LS) of advanced and metastatic lung cancer

Autours	Collection data date	Cases number	Trial	Studied stages	2 year LS N (%)	Factors associated with prolonged survival in multivariate analysis
Finkelstein DM, 1986	1979-1983	893	Yes	IIIB-IV	36 (4)	PS 0 Alumina level
Sculier JP, 1994	1980-1991	1052	Yes	All stages (60,5% IV)	65 (6,2)	Chemotherapy response Early stage
Moro D, 1997	1982-1991	1551	No	All stages (59,9% III-IV)	15 (2)	PS Stage III
Satoh H, 1998	1985-1996	195	No	III et IV	14 (7,2)	N0 N1 Stage III
Julien S, 2000	-	120	No	All stages (47,5% IV)	20 (16,6)	Chemotherapy response
Okamoto T, 2005	1990-1999	222	Non	IV	17 (7,7)	N0-N1 Surgery
Satoh H, 2007	1998-2007	109	No	IIIB-IV	14 (12,8)	PS 0 Gefitinib
Dujon C, 2009	2002-2006	169	No	IIIB-IV	23 (13,6)	PS 0-1 TKI response
Wang T, 2010	1986-2001	846	No	III-IV	56 (6,6%) (5-year survival)	Resecable N2 T3N0 Single distant metastatic site
Giroux E, 2012	-	245	No	IIIB-IV	39 (15,9%)	Surgery Maintenance chemotherapy PS 0-1 Tumor progression >3 months LDH level Number of chemothrapy lines
Van Damme V, 2013	March-August 2009	NP	No	IV	31	Chemotherapy response Number of chemothrapy lines
Chen YZ, 2014	1999-2013	206	No	IV	28(13,6%)	PS Chemotherapy response Chinese medicine treatment

was also reported by Sculier: the response to chemotherapy multiplied survival by 2.2[13]. Recently, in the Van Damme prospective study, 34 LS patients were compared to 31 patients with a survival of less than 2 years, the response to chemotherapy was a predictor of long-term survival (p = 0.001)[22].

Thyrosin kinase inhibitors (TKI) are recent molecules in the treatment of advanced LC. This class was therefore not analyzed in older retrospective series in the literature. None of our patients received TKI due to its unavailability in our country. In Dujon trials, receiving a TKI appears as an independent survival factor, with a survival probability greater than 2 years multiplied by 1.9[12].

This report has also be observed in a recent Japanese study of 109 patients with advanced LC in which using gefitinib treatment was a survival prognostic factor in a multivariate analysis[14].

Prognostic SCLC factors are also various and are comparable to those in NSCLC. A recent Japanese study conducted on SCLC patients receiving third-line chemotherapy showed that prognostic factors before the start of third-line chemotherapy are: low level of LDH, high BMI (body mass index), normal hemoglobin level, a good response to second-line chemotherapy and progression delay after second-line chemotherapy[17]. Limited data are available about LS in SCLC. That's may be explained by: the prompt progression delay as well as acquisition of second-line or third-line resistance to chemotherapy, whose efficiency is debatable[18,19].

A Korean multicenter study published in 2014 retrospectively analyzed 295 patients with SCLC. Among them, 51 (17.3%) patients had a survival higher than 2 years with a mean of 42 months. Predictive factors of long-term survival were: PS 0-1, extent of the disease, and CYFRA 21-1 level[15]. Considering these factors, a prognostic index was elaborated to define four groups of patients with an average survival for each estimated to 22.7, 13.7, 8.5, and 3.2 months. In our study, SCLC patients' features were consistent with literature data. In fact they had a good PS at 0 and an early stage of the disease at presentation. In our patient with SCLC (patient 3) progression occurred 3 years after first-line treatment. This very long delay without any treatment is not frequently observed in SCLC. One case of SCLC with a 7-year survival after diagnosis was reported, this patient had received radiotherapy associated with several lines of chemotherapy and somatostatin analogues treatment[6].

The coexistence of SCLC and NSCLC has been reported in scarce cases[20,21]. Factors implicated in the development of this entity have not been well studied because of its rarity. Some authors have suggested its association with heavy smoking leading to p53 and KRAS gene mutations[21].

In a recent genetic study of 7 cases of patients with a composite tumor, 6 of them expressed CD51 and synaptophysin in the 2 tumor quotas. The authors concluded that there is a common tumor cell clone at the origin of these tumors that may explain the existence of genetic similarities[22].

Very limited data are available to evaluate composite tumors prognosis. We didn't find in literature trials analyzing this issue. For our patients with a composite carcinoma, the long survival could be explained by the limited quota of SCLC, its PS at 0 and the good response to first-line chemotherapy.

Comparing characteristics of our NSCLC to LS in literature, patients 1 and 2 had clinical and evolutionary similarities. In fact these latter were particular by complete response after only 3 cycles of first-line chemotherapy and with a 6-year follow-up without recurrence, the disease could be declared cured. For patient 5 who had a stage IV squamous cell cancer survival until now exceeds nearly 8 years. As for patient 3 with limited SCLC he is particular by long stability delay without progression during 3 years with any treatment.

4 Conclusion

All these data confirm that NSCLC advanced stages and SCLC LS exist and that thanks to the advent of novel therapies their number as well as survival duration are increasing.

In the next future, better identification of long-term survival factors based on clinical and genetic studies could better select this group and further improve survival.

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