BRIEF REPORT

A Brief Report of Transformation From NSCLC to SCLC: Molecular and Therapeutic Characteristics

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ABSTRACT

Introduction: Histologic transformation from NSCLC to SCLC is a mechanism of resistance in EGFR-mutant tumors but is also occasionally observed in nonmutated NSCLC.

Methods: We performed a multicenter retrospective collection of cases presenting between 2005 and 2017. The objectives were to analyze survival data and to define epidemiologic, clinical, treatment and histomolecular characteristics at both the time of diagnosis of NSCLC and of SCLC.

Results: Forty-eight EGFR-mutant NSCLC and 13 non–EGFR-mutant cases were registered. Most EGFR-mutant tumors retained the same EGFR mutation after transformation. The median time to SCLC transformation was shorter in the EGFR-mutant group than in non-EFGR mutants (16 months versus 26 months ($p = 0.01$)). Both tumors were responsive to platinum etoposide regimens (45% partial response for the EGFR-mutant group versus 40% for non-EFGR mutants). The median overall survival rates were 28 months in the EGFR-mutant group versus 37 months in the non–EFGR-mutant group, respectively. After transformation, the median overall survival was 9 months in the non–EGFR-mutant group versus 10 months in the EGFR-mutant group.

Conclusions: Transformation into SCLC seems to occur more quickly in EGFR mutated tumors; however, once the tumor is transformed its survival and response to treatment seems comparable to that of classical SCLC.

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Introduction

Phenotypic transformation to SCLC is a resistance mechanism in EGFR-mutant tumours.[1,2] Less frequently, SCLC is diagnosed in patients without EGFR mutations and little is known about the characteristics of these patients. The diagnosis of this transformation in non–EGFR-mutated NSCLC is rare and this might be partly explained by the limited use of repeat biopsy in clinical routine. In these cases most pathologists consider that the emergence of a subclone in a combined tumor explains the transformation.

In the original description of transformation and in clinical cases there are anecdotal descriptions of sensitivity to platinum etoposide chemotherapy.

In the current study, we describe and compare the characteristics of SCLC arising from EGFR-mutant or non–EGFR-mutant NSCLC.

Materials and Methods

We performed a retrospective collection of cases seen between 2005 and 2017. Thirty-one Italian and French centers participated. Consecutive stage III or IV NSCLC patients, with or without an initial EGFR mutation and with secondary transformation to SCLC, were included. Patients with a previous history of SCLC or neuroendocrine tumor of the lung were excluded, as well as patients with combined SCLC/NSCLC on the initial pathology sample.

The primary objective of this study was to analyze survival data after transformation. The secondary objectives included epidemiologic, histomolecular, and treatment characteristics at both the time of diagnosis of NSCLC and SCLC. Histopathologic slides were centralized for revision.

No patients were lost to follow-up until July 26, 2017. Overall survival (OS) was the time from the initial diagnosis to death and survival after SCLC transformation was from the repeat-biopsy to death.

Results

Sixty-one cases of SCLC transformation were registered. Forty-eight in EGFR-mutant NSCLCs and 13 in non–EGFR-mutant NSCLC groups were included. Epidemiologic, clinical, histologic, and molecular characteristics are shown in Tables 1 and 2. Tobacco use and histology were significantly different between the two groups, whereas the other characteristics were mostly comparable.

The median time to transformation was 16 months (interquartile range [IQR] 25%–75%: 11 to 27 months) in the EGFR-mutant group and 26 months (IQR: 23 to 36 months) in the other ($p = 0.01$). The first treatment line in the EGFR-mutant patients was an EGFR tyrosine

Table 1. Patients' Characteristics

	All (N = 61)	EGFR Mutant (n = 48)	Non-EGFR Mutant (n = 13)	Chi Square Test or Wilcoxon
Age, y (IQR)	62 (52-70)	61 (51-72)	62 (56-64)	0.70
Female	39 (64)	33 (69)	6 (46)	0.19 (Fisher)
PS (MD = 2)				0.86
0	27 (46)	21 (46)	6 (46)	
1-2	32 (54)	25 (54)	7 (54)	
Tobacco smoking (MD = 3)				0.03
Active	5 (9)	3 (7)	2 (15)	
Former	22 (38)	14 (31)	8 (62)	
Never	31 (53)	28 (62)	3 (23)	
Pack/year (MD = 7)				
≤20	7 (35)	6 (46)	1 (14)	
>20	13 (65)	7 (54)	6 (86)	
Stage IV/III	53 (87)/8 (13)	43 (90)/5 (10)	10 (77)/3 (23)	0.35 (Fisher)
Histology				0.02 (Fisher)
Adenocarcinoma	55 (90)	45 (94)	10 (77)	
Squamous	3 (5)	0	3 (23)	
NOS	3 (5)	3 (6)	0	
Median number of lines of treatment before transformation (range)	2 (1-3)	2 (1-2)	2 (1-3)	0.33

Data are expressed as the median (IQR: 25%-75%) for continuous variables and as n (%) for categorical variables.
MD, missing data; NOS, not otherwise specified; IQR, interquartile range.

Table 2. Different Types of EGFR Mutations

	Mutation at the Time of Initial Diagnosis		
n = 48	exon 19, n = 36	L858R, n = 10	exon 18 or 20, n = 2
	Mutation at the time of SCLC transformation		
No molecular analyses	6/36 (17%)	3/10 (30%)	1/2 (50%)
Molecular analyses performed	30/36 (83%)	7/10 (70%)	1/2 (50%)
Exon 19	24 (80%)[a]	0	0
L858R	1 (3%)	6 (86%)	0
Exon 18 or 20	0	0	1 (100%)
No mutation	5 (17%)	1 (14%)	0

Data are expressed as the median (interquartile range 25%–75%) for continuous variables and as *n* (%) for categorical variables.
[a]Associated with a second mutation in exon 20.

kinase inhibitor (TKI) in 38 patients and doublet chemotherapy (n=10). The last line of treatment before transformation was a TKI in 39 cases (81%) of the EGFR-mutant group and in three patients (23%) of the non–EGFR-mutant group.

Forty-two patients (88%) were treated and received at least one line of treatment after transformation in the EGFR-mutant group (median number 1, IQR: 1 to 2) (Supplemental Table A); six patients had only supportive care. The most frequent chemotherapy regimen was a combination of etoposide and platinum. In the non–EGFR-mutant group, 11 of 13 (85%) patients received at least one line of treatment (median number 2, IQR: 1 to 2), and this was also a combination of platinum and etoposide. The response characteristics are shown in Figure 1.

Molecular analyses after SCLC transformation were performed on 38 cases (79%) in the EGFR-mutant group, whereas no molecular analyses were performed in the other group. Thirty-two SCLC cases (84%) kept the same mutation as the one observed initially (Table 2). In three cases, initially mutated on EGFR exon 19, the transformation into SCLC was associated with PI3K mutation and MNNG HOS transforming gene (c-MET) amplification (1 case), ALK fusion alone (1 case) and ALK fusion and EGFR exon 21 and 18 mutations (1 case). One case initially mutated on EGFR exon 19 displayed both exon 19 and exon 20 T790M after transformation.

Supplementary Tables B and C summarize the final results of the histologic revision (initial diagnosis 22 cases, SCLC transformation 33 cases). When considering patients without histologic revision there was no difference in the clinical profile and survival characteristics with those with pathologic confirmation. This last point suggests that all patients were sufficiently similar to be included in the descriptive analyses of this cohort.

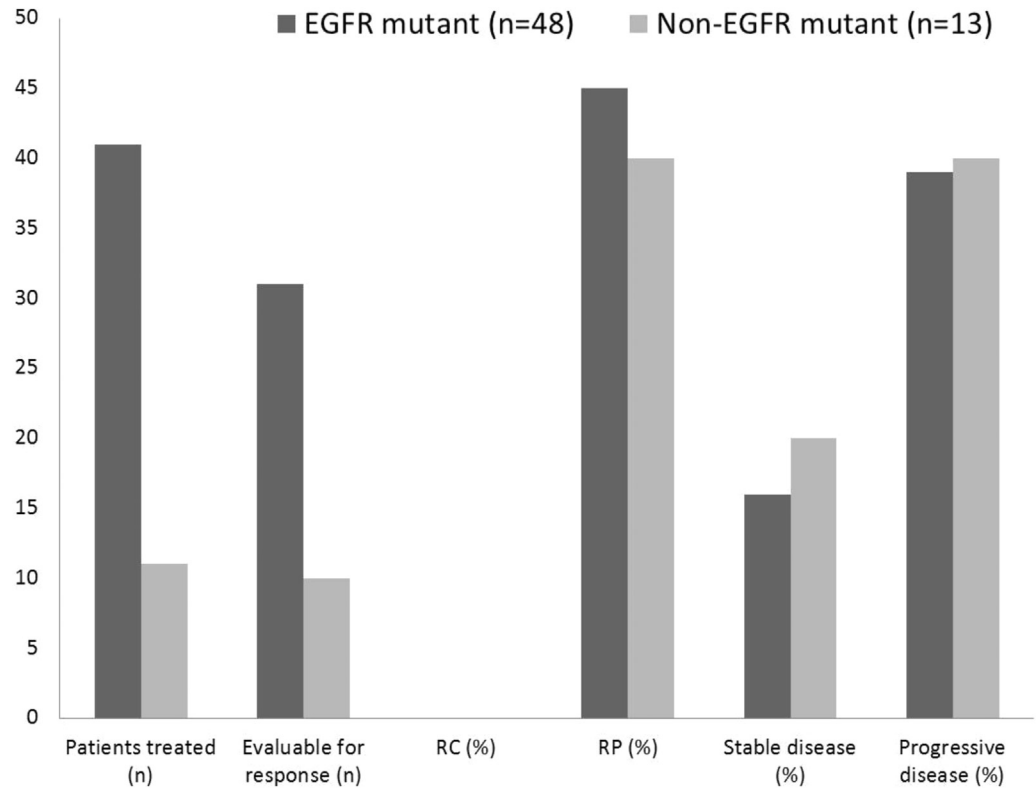
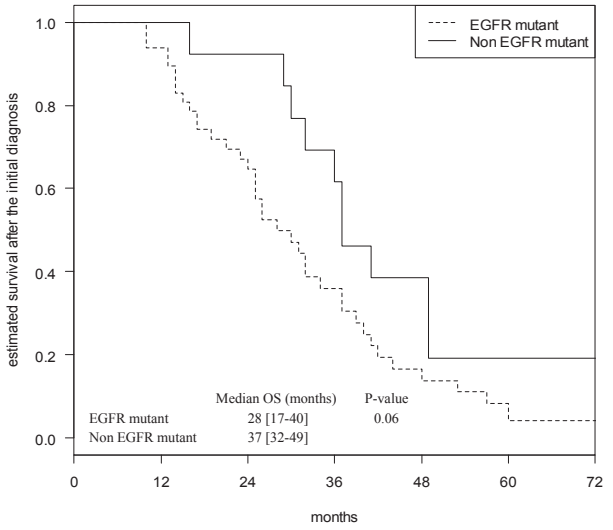


Figure 1. Number of patients treated and number of patients evaluable for response and response characteristics. There was no statistical difference in the type of response between the two groups.

In the EGFR-mutant group, the median OS times were 28 months (IQR: 17 to 40 months) after the initial diagnosis and 9 months (IQR: 3 to 13 months) after transformation. In the non–EGFR-mutant group, the median OS times were 37 months (IQR: 32 to 49) after the initial diagnosis and 10 months (IQR: 6 to 15 months) after transformation (Figs. 2 and 3). OS from the initial diagnosis tended to be worse in the mutated EGFR group compared to the non–EGFR-mutant group ($p = 0.06$); however, OS from the time of transformation into SCLC was comparable ($p = 0.56$).

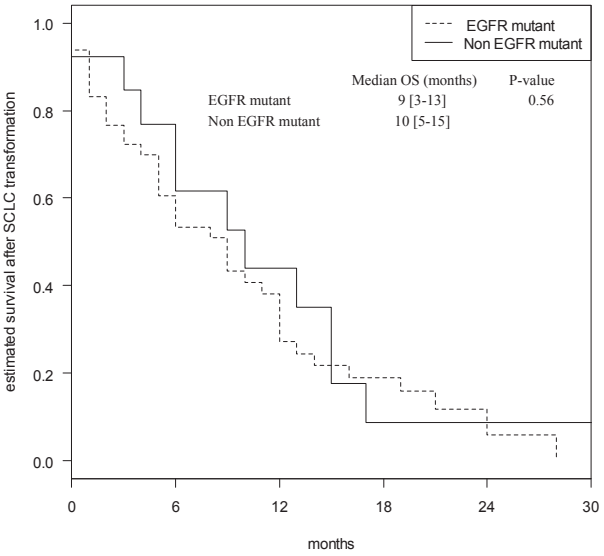
Discussion

Among the different mechanisms of resistance to EGFR TKI, most of the cases are associated with the occurrence of the T790M mutation or c-MET amplification. In 4% to 14% of EGFR-mutants, histologic transformation to SCLC occurs. The transformation might be explained either by a phenotypic switch from NSCLC to SCLC or a combination of SCLC and adenocarcinoma that may be present at baseline, with SCLC becoming the main component after treatment.[3] Recently, Lee et al.[4] used whole-genome sequencing in nine tumors to detect genetic predictors of small-cell transformation. In the initial adenocarcinoma as well as in the transformed SCLC, Rb and p53 were inactivated, suggesting that SCLC transformation is likely to be a clonal evolution event in adenocarcinoma cells that relies on the complete inactivation of these two genes.



Time (months)	0	12	24	36	48	60	72
N at risk	61	57	40	22	10	4	2
EGFR mutant	48	44	28	13	6	2	0
Non EGFR mutant	13	13	12	9	4	2	2

Figure 2. Overall survival from initial diagnosis OS, overall survival.



Time (months)	0	6	12	18	24	30
N at risk	61	35	19	7	3	1
EGFR mutant	48	25	14	6	2	0
Non EGFR mutant	13	10	5	1	1	1

Figure 3. Overall survival from SCLC transformation OS, overall survival.

Furthermore, combined SCLC and non–EGFR-mutant NSCLC are described in the WHO classification of lung tumors and transformation to SCLC rarely occurs in non–EGFR-mutant NSCLC treated by chemotherapy.[2] In the current series of patients, 48 cases came from tumors with mutated EGFR and 13 from nonmutated NSCLC. We hypothesize that the latter cases might reflect the behavior of genuine classical SCLC. Indeed, these tumors occur mostly in current or former heavy smokers. In contrast, most of the EGFR-mutant tumors came from former or never smokers. The transformation has been confirmed by a histologic revision, and in those cases that were not SCLC, other neuroendocrine variants such as large cell neuroendocrine carcinoma or small and large cell carcinoma were observed. These neuroendocrine variants have been reported previously in other publications.[5]

Neither EGFR-mutant nor non–EGFR-mutant NSCLC displayed SCLC features in the primary biopsy specimen. However, one limitation was the small size of some biopsy samples. In agreement with previous reports, we observed identical EGFR mutations in both the primary tumor and the SCLC in the majority of the cases. One case had an exon 19 mutation and a T790M resistance mutation, indicating that more than one distinct mechanism of resistance to EGFR TKIs may be present within the

same tumor. These mutations were possibly present in the SCLC transformed cells or may also be present in a residual NSCLC subclone. One other case lost the EGFR mutation and presented an ALK fusion, most probably reflecting the coexistence of different subclones rather than an SCLC with an ALK fusion. Recently, transformation to SCLC of an NSCLC with an ALK fusion after treatment with alectinib has been described suggesting that although transformation into SCLC is rare, it is a common mechanism of resistance to TKI.[6]

The median time to SCLC transformation was significantly shorter in the EGFR-mutant group when compared to the non–EGFR-mutant group. This might reflect more aggressive behavior but may also be biased by the recommendations to rebiopsy EGFR mutant patients after a line of TKI, whereas this is not recommended in classical NSCLC.

In the published case reports of transformation to SCLC, patients were treated with etoposide-cisplatin combination and achieved tumor regression.[1]

Once transformation to SCLC has occurred, there is no significant difference in survival whether it occurs in patients with EGFR mutation or not. These survival data are comparable to those of the SCLC cohorts in the literature.[7] In contrast, survival from the initial diagnosis of NSCLC appears paradoxically lower in the mutated EGFR group, which suggests the transformation of a generally indolent disease into an aggressive disease.

The timing to SCLC transformation appears shorter than previously estimated and once SCLC is diagnosed the outcome is comparable to that of classical SCLC.

As with all research, this study has strengths and limitations. The strengths include the relatively large size of this cohort with cases collected in French and Italian thoracic oncology centers. The confidence in our results is strengthened by a significant number of cases confirmed by histologic revision and by the lack of difference in the clinical and survival profile between the cases confirmed by the revision and those that were not reviewed. Among the potential limitations, the retrospective and multicentric nature is clearly an obstacle to a uniform presentation of genomic results. This is an important limitation of this work. Furthermore, variations in sequencing techniques and in its depth from one center to another may also cause false-positives or false-negatives in the discovery of new mutations or the loss of known mutations. The fact that we could not assess the total number of lung cancer cases was also a limitation of this study.

Future studies must analyze the exome characteristics of paired tumor samples to characterize the molecular changes that contribute to transformation.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.08.2028.

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