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(Article begins on next page)

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**Transient asymptomatic pulmonary opacities (TAPO) and interstitial lung disease (ILD) in *EGFR*-mutated NSCLC treated with osimertinib**

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**Abstract**

**Introduction**: Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI) approved as first-line therapy for advanced *EGFR*-mutated NSCLC. Some osimertinib-related interstitial lung diseases (ILDs) were shown to be transient and were called 'transient asymptomatic pulmonary opacities (TAPOs): clinically benign pulmonary opacities that resolve despite continued osimertinib treatment and are not associated with the clinical manifestations of typical TKI-associated ILDs.

**Materials and Methods:** In this multicentric study, we retrospectively analyzed 92 *EGFR*-mutated NSCLC patients treated with osimertinib. Computed tomography exams were reviewed by two radiologists and TAPOs were classified according to radiologic pattern. We also analyzed associations between TAPOs and patients' clinical variables and compared clinical outcomes (time to treatment failure, TTF, and overall survival, OS) for TAPO-positive and TAPO-negative groups.

**Results**: TAPOs were found in 18/92 patients (19.6%), with a median follow-up of 114 weeks. Median onset time was 16 weeks (range 6-80), and a median duration time was of 14 weeks (range 8-37). The most common radiological pattern was focal ground glass opacity (54.5%). We did not find any individual clinical variable significantly associated with the onset of TAPOs nor significant difference in clinical outcomes between TAPO-positive and TAPO-negative groups.

**Conclusions**: TAPOs are benign pulmonary findings observed in patients treated with osimertinib. TAPOs variability in terms of CT features can hinder the differential diagnosis with either osimertinib-related mild ILD or tumor progression. However, since TAPOs are asymptomatic per se, it could be reasonable to continue therapy and verify the resolution of the CT findings at follow-up in selected cases.

**Keywords**: *EGFR*-mutated non-small cell lung cancer; osimertinib; TAPO; interstitial lung disease.

## 1. Introduction

*Epidermal growth factor receptor* (*EGFR*) mutations characterize a subset of non-small cell lung cancer (NSCLC) patients with a distinct pattern of clinico-pathological characteristics and therapeutic options, with a frequency that ranges from 15% to 40-50% in Western and Eastern countries, respectively [1,2].

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI) that is highly selective for *EGFR* activating mutations and for T790M mutation in patients with *EGFR*-positive NSCLC [3].

Currently, osimertinib is the only approved third-generation EGFR-TKI for T790M-positive patients progressed on first- or second-generation EGFR-TKIs [4,5]. Furthermore, it has been recently approved as first-line therapy for advanced *EGFR*-mutated NSCLC [5], considering the benefit in progression-free survival (PFS) and overall survival (OS) compared to gefitinib or erlotinib [6,7].

EGFR TKI-related adverse events usually involve either the digestive tract (e.g. diarrhea, hepatotoxicity) or the skin (e.g. rash, paronychia) [8]. Pulmonary adverse events are less common, with an incidence of 0-5-7%, as reported in recent clinical trials [9,10]. In particular, TKI-associated interstitial lung disease (ILD) is of particular importance as it may trigger drug discontinuation. Osimertinib-related ILDs were variably reported in 4-6.8% of patients [4,6,11].

Nevertheless, some osimertinib-related ILDs were shown to be transient and were called 'transient asymptomatic pulmonary opacities (TAPOs)'. Indeed, TAPOs are defined as clinically benign pulmonary ground-glass opacities that resolve in a variable time despite continued osimertinib treatment and are not associated with the clinical manifestations of typical TKI-associated ILDs [12]. A TAPO classification was subsequently proposed on the basis of radiological pattern, as follows: COP-like pattern (e.g. multifocal areas of opacification or nodules with subpleural or peribronchial distribution) type; simple eosinophilic-like pneumonia (e.g. transient and migratory areas of consolidation with peripheral eosinophilia) type and nodular type [13].

Given the broader clinical use of osimertinib as the new standard of care in the first-line treatment of advanced *EGFR*-mutated NSCLC as well as its potential future indication in resected disease [14], ILDs and TAPOs represent a relevant aspect in clinical practice.

Moreover, TAPO could be a diagnostic challenge especially in the "COVID era", as COVID-19 pneumonia is typically characterized by ground glass opacities [15] that could resemble TAPOs in osimertinib treated patients.

In this multicentric retrospective study, we evaluated the incidence, the radiologic features, and the clinical implications of TAPOs and ILDs in a large cohort of patients treated with osimertinib for advanced *EGFR*-mutated NSCLC.

## 2. Materials and Methods

### *2.1 Study Population*

Patients with *EGFR*-mutated NSCLC treated with osimertinib at the Oncology Departments of the University Hospitals of Parma and Bologna between October 2015 and July 2020 were retrospectively enrolled. Inclusion criteria were as follows: patients treated with osimertinib for advanced *EGFR*-mutated NSCLC; availability of one chest computed tomography (CT) timepoint before osimertinib treatment beginning; availability of two chest CT timepoint after osimertinib beginning treatment or availability of one chest CT timepoint after osimertinib treatment beginning with no new pulmonary findings; availability of patients' clinical data (e.g. toxicity- or infection-related symptoms, administration of steroids, antibiotics or radiotherapy etc.) and outcome. The presence of any synchronous cancer was considered an exclusion criterion. Patients usually underwent a routine CT scan every 3 months; closer timepoints were performed in case of clinical suspicions for ILD or infection. This retrospective study was approved by the Institutional Review Board of both Hospitals.

### *2.2 CT Analysis*

CT scans were independently reviewed by a young radiologist and an expert thoracic radiologist . Individual CT scans were scored in random order with the observers were

blinded to any clinical and timepoint information. Technical standard for CT examination was as follows: slices thickness ≤ 2 mm, slice increment ≤ 2 mm, high-spatial resolution kernel and smooth kernel, lung window and mediastinal window.

The presence and the distribution of individual CT patterns such as ground-glass opacities, consolidation, nodules, reticular were recorded [16]. After reaching the consensus upon any disagreement, the reviewers were informed about the CT timepoint data. TAPO were classified as those CT abnormalities that underwent spontaneous resolution in one of the subsequent CT timepoints .

*2.3 Clinical integration*

Clinical data were compared to the visual scoring of the CT scans. In particular, the CT findings were integrated to the following clinical data: infection/toxicity symptoms onset, drug suspension/resumption, lung irradiation, antibiotics/steroid administration. Only if the new findings spontaneously resolved in one of the subsequent CT timepoints, without drug discontinuation, infection/toxicity symptoms appearance or lung radiotherapy administration, they were considered as a TAPO. The study cohort was grouped according to history of either TAPO or ILD as follows: patients with onset of TAPOs (TAPO-positive); patients without onset of TAPOs (TAPO-negative); and patients with onset of ILD.

*2.4 Statistical Analysis*

Median follow-up was calculated with reverse Kaplan Meyer method. Patients with onset of TAPOs and patients without onset of TAPOs groups were compared by Kaplan-Meier method and log rank test. Associations between TAPO and individual clinical variables were evaluated using univariate logistic regression analysis. Multivariate model was set to include all variables with $p < 0.20$. All p values were 2-sided, and values less than 0.05 were considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program version 25.0 (IBM, Armonk, NY).

## 3. Results

### *3.1 Patients' Characteristics*

Patients' characteristics are summarized in Table 1. The study cohort included a total of 92 patients. Sixty were men (65.2%); overall, median age was 67 years (mean 65, range 38-88); 35 patients (38%) had smoking history, for two patients (2.2%) smoking history was unknown. Almost all patients (91/92, 98.9%) had non-squamous NSCLC. 72/92 patients (78.2%) had exon 19 deletion: 18 patients (19.5%) had L858R mutation; one patient had L861Q mutation and one patient G719X mutation. 82 patients (89.1%) underwent previous TKIs therapies and all of them had a T790M *EGFR* secondary mutation. Eastern Cooperative Group Performance Status (ECOG-PS) was 0 for 42 patients (45.6%), 1 for 44 patients (47.8%), 2 for 6 patients (6.5%).

At time of data analysis, 35/92 (38%) patients were still under treatment with osimertinib, and 46/92 (50%) were still alive. Median follow-up was 114 weeks (95% CI 77.6 – 156.7), with a median of three CT timepoints after beginning of treatment (mean 4.4, range 1-14). A total of 407 chest CT timepoints were evaluated.

### *3.2 TAPO: Features and Radiological Patterns*

TAPOs were observed in 18/92 patients (19.6%). Additionally, 2/18 (11.1%) and 1/18 (5.5%) patients showed two and three TAPOs, respectively. The median time interval between the starting of osimertinib and the development of TAPO was 16 weeks (range 6-80). TAPOs persisted for a mean time of 15 weeks (median 14, range 8-37). Longitudinal behavior for individual patients with TAPO is shown Figure 1.

The dominant CT patterns in TAPO were as follows (Figure 2): 12/22 (54.5%) focal ground glass opacities (involving one pulmonary segment in one lung), of which 10/12 (83.3%) subpleural unilateral ground glass opacities and 2/12 (16.6%) central unilateral ground glass opacities; 3/22 (13.6%) diffuse ground-glass opacities (involving more than one pulmonary segment in both lungs); 3/22 (13.6%) nodular opacities (defined as solid nodules with or without ground-glass halo) and 4/22 (18.2%) focal consolidations (involving one pulmonary segment in one lung). In subjects who developed multiple

TAPOs, the CT pattern of the follow-up TAPO was similar to the CT pattern of the baseline TAPO.

Representative cases of pulmonary findings occurred during follow-up, initially considered as suspected for TAPOs but not confirmed are shown in Supplementary Figure 1.

*3.3 Osimertinib-related ILD*

Four of 92 patients (4.3%) reported onset of pulmonary findings characterized by an OP pattern, NSIP-OP pattern, focal and diffuse peripheral ground-glass opacities, respectively, in association with onset of cough, dyspnea and hypoxia. Unlike findings consistent with TAPOs, these did not resolve spontaneously: combined osimertinib withdrawal and short term (two-four weeks) steroid treatment led to a substantial clinico-radiological improvement (Supplementary Figure 2).

*3.4 OS, TTF and TAPO predictive factors*

Time to treatment failure (TTF) and OS in both TAPO-positive and TAPO-negative group are shown in Figure 3. TTF was not significantly different between the two groups (97.2 versus 69.7 weeks, $p = 0.260$). Likewise, OS was similar between TAPO group and TAPO free group (128 versus 97 weeks, $p = 0.262$).

No variable (sex, smoking history, type of *EGFR* activating mutation, prior exposure to EGFR-TKI and disease response to osimertinib) was significantly associated with the development of TAPO at univariate logistic regression analysis (Table 2). As none of the variable resulted correlated with TAPO with $p < 0.20$, no multivariate analysis was performed.

## 4. Discussion

This study evaluated the frequency and the clinico-radiological features of both TAPOs and osimertinib-related ILDs in a retrospective cohort of advanced *EGFR*-mutated patients treated with osimertinib.

Prior studies reported symptomatic ILD in 0-5.7% of subjects undergoing TKI therapy. In this regard, ILD is a rare adverse complication that usually implies treatment discontinuation, with a potential prognostic impact [9,10]. In keeping with prior studies, we reported osimertinib-related symptomatic ILD in 4.3% of the study patients.

Given the relevance of clinical results of osimertinib, it is mandatory to have a correct clinical and radiological diagnosis of ILD, in order to discontinue the drug only when really necessary.

In concordance with previous studies [12,13], we detected TAPOs in 19.6% of patients treated with osimertinib; patients' and TAPOs characteristics comparison across previous studies are reported in Table 3. More than half (54.5%) of these TAPOs were characterized by focal ground-glass opacities, while 13.6% of them were characterized by bilateral patchy ground-glass opacities, raising issues of differential diagnosis with ILD.

A predominant nodular pattern was observed in 13.6% of TAPOs. In this regard, differential diagnosis with disease progression may be problematic, and short-term follow-up CT scan is required for confirming the transience of these opacities.

The nature and etiology of TAPOs have not yet been clarified. The variability of the TAPO-related CT patterns (e.g. diffuse abnormalities) makes any interpretation even more ambiguous. Nevertheless, some authors have suggested that TAPO may arise from a low-grade ILD [17]. Of note, in our study, we adopted a TAPO classification based on basic HRCT pattern of presentation, differently from the previous report from Lee at al. [13].

In our cohort of patients, TAPOs were not associated with any clinical outcome, patients' (e.g. sex, smoking history), or tumor characteristics (e.g. type of *EGFR* activating mutation, prior exposure to EGFR-TKI). TAPO-positive group did not show statistically significant differences as compared to the TAPO-negative group, both in terms of TTF (97.2 versus 69.7 weeks, $p = 0.260$) and OS (128 versus 97 weeks, $p = 0.262$). However, a trend towards a better TTF and OS has been observed in TAPO-positive compared to TAPO-negative group. Nonetheless, we speculate that numerically higher values of OS and TTF in the TAPO group are due to the increased likelihood for transient findings in patients treated for a higher number of weeks and with higher number of CT follow-up.

Deeper knowledge of the TAPO nature and etiology and its possible clinical implications is largely needed. The approval of osimertinib as adjuvant therapy for radically resected *EGFR*-mutated NSCLC [14,18] would lead to a further increase in the number of patients treated with osimertinib, and a better characterization of TAPOs would be of great importance for the proper management of these events.

Moreover, TAPOs existence is a noteworthy knowledge for the radiologist in the "COVID era", since they represent a differential diagnosis for COVID-19 pneumonia, especially when they occur as ground-glass opacities. Indeed, TAPOs must be taken into consideration in patients treated with osimertinib given the low specificity of CT in COVID-19 pneumonia diagnosis [19].

## 5. Conclusions

TAPOs are benign pulmonary findings observed with non-negligible frequency in patients treated with osimertinib. TAPO's variability in terms of CT features can hinder the differential diagnosis with either osimertinib-related mild ILD or tumor progression. However, since TAPOs are asymptomatic *per se*, it could be reasonable to continue therapy and verify the resolution of the CT findings at follow-up in selected cases. More studies would be helpful to further characterize these findings, also in light of osimertinib approval as adjuvant therapy after surgical resection.

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**Ethics approval and consent to participate:** All patients provided written, informed consent to treatment with osimertinib. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was approved by the respective local ethical committees on human experimentation of each

institution, after previous approval by the coordinating center (Comitato Etico Area Vasta Emilia Nord, Protocol n.0027752, 17/07/2020).

**Authors' contributions:** All authors contributed to the publication according to the ICMJE guidelines for the authorship (study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision). All authors read and approved the submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study). Each author has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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**Table/Figure legends:**

**Table 1:** Clinical characteristics of patients. * Five patients reduced osimertinib dose due to non-pulmonary toxicity.

**Table 2:** Associations between TAPOs and individual clinical variables.

**Table 3:** Characteristic of TAPOs in our study compared to previous reports.

**Figure 1:** Timing of TAPO development pattern for each patient. TAPOs were observed in 18 patients; two patients showed a second TAPO during the follow-up and one patient showed three TAPOs; a total of 22 TAPOs were identified.

**Figure 2.** TAPO representative cases. (A-C) Patient n. 5 reported a focal ground glass opacity with subpleural localization in left upper lobe at 8 weeks, resolved at 31 weeks. (D-F) Patient n. 54 showed diffuse bilateral ground-glass opacities with reticulation involving middle lobe, lingula and apical segments of lower lobes, occurred at 14 weeks and spontaneously resolved at 27 weeks. (G-I) Patient n. 57 reported a consolidation after 25 weeks (J-L) In patient n.71, after 23 weeks, occurred a nodular opacity with ground-glass halo in the left upper lobe and then spontaneously disappeared at 43 weeks.

**Figure 3.** Time to treatment failure (TTF) and overall survival (OS) compared for TAPO-positive and TAPO-negative groups.

**Supplementary Figure 1:** ILD representative cases. (A-C) Patient n.7 developed ILD with OP pattern at 11 weeks; clinico-radiological improvement was observed following Osimertinib withdrawal and steroid treatment for two weeks. (D-F) Patient n. 21 developed focal ground glass opacity in right upper lobe at 7 weeks; she suspended the drug and received steroids for 3 weeks, with resolution of the symptoms and pulmonary opacities. (G-I) Patient n.44 reported ILD with NSIP-OP pattern at 8 weeks; clinico-radiological improvement was observed following osimertinib withdrawal and steroids administration (4 weeks).

**Supplementary Figure 2:** Representative cases of new pulmonary findings not related to TAPO nor ILD. (A-C) in patient n. 70 a new nodule occurred in right upper lobe but it enlarged in subsequent examination, and other lesions in the same lobe occurred, due to progression of disease. (D-E) in patient n.63 a wide ground-glass opacity occurred in left

upper lobe, but in consequence to lung radiotherapy. (F-H) in patient n.71 a pre-existing lesion in right lower lobe suddenly enlarged and then shrank in the following timepoint, in consequence to a stereotactic radiotherapy.