Chemotherapy in patients with lung cancer and interstitial lung disease

Georgia Gomatou[1], Evangelos Bouros[1], Argyrios Tzouvelekis[1], Demosthenes Bouros[1]

[1]First Academic Department of Pneumonology, Interstitial Lung Diseases Unit, Hospital for Diseases of the Chest, "Sotiria", Medical School, National and Kapodistrian University of Athens, Athens, Greece

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Correspondence to:
Prof. Demosthenes Bouros MD, PhD, FERS, FAPSR, FCCP; First Academic Department of Pneumonology, Interstitial Lung Diseases Unit, Hospital for Diseases of the Chest, "Sotiria", Medical School, National and Kapodistrian University of Athens, Athens, Greece; 152 Messogion Ave., Athens 11527, Greece
E-mail: debouros@med.uoa.gr
debouros@gmail.com

Interstitial lung disease (ILD) is frequently associated with lung cancer.[1,2] Idiopathic pulmonary fibrosis (IPF) has been identified as an independent risk factor for the development of lung cancer and shares several pathogenic commonalities with tumorigenesis[3]. Patients with lung cancer and concomitant ILD have been excluded from the majority of clinical trials of chemotherapeutic regimens, considering the increased risk of acute exacerbations (AE) of preexisting ILD[4,5]. Thus, there is no consensus statement with regards to therapeutic approach of this specific subgroup of patients.

The past few years have seen the advent of novel discoveries in the pathogenesis of lung cancer leading to personalized medicine therapeutic approaches[6]. Current standard of treatment for advanced NSCLC consists of a doublet regimen of a platinum and a third generation agent. Molecular targeted therapies for tumors with driver mutations –EGFR mutation and ALK and ROS1 rearrangement- and immune checkpoint inhibitors for tumors with high expression of PD-L1 represent alternative options in specific subsets of patients[7]. Doublet regimen of platinum plus etoposide or platinum plus irinotecan represents the first-line standard of treatment for small cell lung cancer (SCLC)[8].

In light of the rapidly increasing incidence of concomitant ILD-LC and the emergence of the novel chemotherapeutic agents physicians have focused on addressing the following dilemmas: **1)** Can we establish an **optimal regimen** for ILD-LC patients which is both efficacious and safe. **2)** Can we identify a **reliable biomarker** to predict treatment response and disease progression on an individual basis? **3)** Can we expect that delineation of **common pathogenetic pathways between IPF and lung cancer** will open new therapeutic revenues potentially through **drug repurposing**?

Regarding **cytotoxic chemotherapy,** a recent meta-analysis demonstrated that a **platinum-based doublet** presents with an acceptable efficacy profile as first-line therapy in ILD-NSCLC patients given that response rate, progression-free survival and overall survival are comparable to those of patients with NSCLC without ILD[9]. Currently, **carboplatin in combination with paclitaxel** represents the gold-standard of safety and efficacy in patients with IPF and NSCLC. Carboplatin plus nanoparticle-albumin-bound-paclitaxel has also shown both safety and efficacy in a small cohort of ILD-NSCLC patients[10]. The incidence of ILD-AE following first-line chemotherapy is highly variable mainly due to the lack of definitive diagnostic criteria

for AE[11-14]. The aforementioned meta-analysis estimated that **incidence of AE** after first-line chemotherapy was **8.47%.** Limited data on **second-line treatment** with docetaxel[15] or pemetrexed[16] as monotherapy have shown increased risk for ILD-AE. With regards to **SCLC,** existing data suggests that **standard treatment** with **platinum plus etoposide/irinotecan** is relatively efficacious and safe in ILD-SCLC patients[17-19].

Data on the efficacy and safety of **molecular-targeted therapies** in ILD-NSCLC patients is still scarce and controversial. Gefitinib has been associated with ILD-AE[20,21] and thus **EGFR-TKIs** are generally avoided in ILD-NSCLC patients. It's also noteworthy that frequency of EGFR mutations is significantly lower in patients with ILD-NSCLC compared to non-ILD-NSCLC patients[22]. Choi et al (2014) reported poor outcomes when EGFR-TKIs were used as second-line therapy in ILD-NSCLC patients, of whom the majority did not harbor a mutation of EGFR. Authors suggested that the use of EGFR-TKI should be restricted to those patients harboring specific EGFR mutations[23]. Regarding safety and efficacy of **ALK inhibitors** as well as **immune checkpoint inhibitors** data is limited and deserves further investigation[24]. **Molecular profiling** of this subset of NSCLC could be very useful for the application of personalized medicine approaches with minimal side-effects and optimal efficacy[25].

To this end, the identification of a **reliable prognosticator** to stratify patients at high risk for exacerbation following chemotherapy represents a major challenge. Small studies have identified **smoking status**[10], **elevated CRP**[11] and **decreased baseline FVC% predicted**[26] as independent risk factors for disease AE. **Usual interstitial pneumonia (UIP) pattern on pre-treatment chest CT** has been also shown to be associated with increased risk of ILD-AE[13].

IPF and lung cancer are two disease paradigms that share many epidemiologic and pathogenetic commonalities. **Nintedanib, an FDA-approved agent for the treatment of IPF,** has been originally identified as anticancer drug in combination with docetaxel as second-line treatment for NSCLC. This evidence has raised the attention on exploiting the existing data of oncology research to IPF therapeutics. In particular, dysfunctional activity of the **signal transduction pathway PI3/AKT** is involved in both IPF and cancer pathogenesis and inhibition of PI3K which is currently being explored as anticancer treatment has also been suggested as a novel option in IPF therapeutics[27]. **Epigenetic modifications** have been involved in both fibrogenesis and tumorigenesis and thus targeting the epigenome may hold therapeutic promise for both disease entities[28,29]. Finally, in the case of patients with concomitant IPF-NSCLC it's interesting to examine whether **a combination of anti-fibrotic and anti-cancer drugs could present with synergistic action.** A preclinical study demonstrated that **pirfenidone in combination with cisplatin** led to increased cell death of NSCLC cells and cancer-associated fibroblasts[30]. In addition, **perioperative treatment with pirfenidone** of IPF-LC patients has been associated with fewer AE after lung cancer operation[31]. Currently, a new, prospective, randomized study has been designed in order to compare **nintedanib, combined with carboplatin plus nab-paclitaxel** to carboplatin plus nab-paclitaxel alone in IPF-NSCLC patients[32].

In conclusion, patients with ILD and lung cancer present with **increased risk for chemotherapy-induced ILD-AE.** To this end, physicians should apply the Hippocratic premise **"first do no harm".** Unfortunately, there is major lack of knowledge with regards to safety and efficacy profiles of the majority of conventional chemotherapeutic regimens as well as the novel immune-checkpoint inhibitors. Both disease paradigms present with considerable pathogenetic and phenotypic heterogeneity and thus randomized controlled clinical trials involving highly characterized enrolled patients are extremely difficult and challenging. The application of high-throughput screening strategies may help clinicians to stratify patients based on their risk profile and apply precision medicine approaches that will maximize therapeutic benefits and reduce chemotherapy-induced cytotoxicity.

REFERENCES

1. Raghu G, Nyberg F, Morgan G. The epidemiology of interstitial lung disease and its association with lung cancer. Br J Cancer 2004; 91:Suppl 2:S3-10.
2. Archontogeorgis K, Steiropoulos P, Tzouvelekis A, Nena E, Bouros D. Lung cancer and interstitial lung diseases: a systematic review. Pulm Med 2012;2012:315918.
3. Vancheri C. Common pathways in idiopathic pulmonary fibrosis and cancer. Eur Respir Rev 2013;22:265-72.
4. Tzouvelekis A, Spagnolo P, Bonella F, et al. Patients with IPF and lung cancer: diagnosis and management. Lancet Respir Med 2017; pii: S2213-2600(17)30478-2.
5. Karampitsakos T, Tzilas V, Tringidou R, et al. Lung cancer in patients with idiopathic pulmonary fibrosis. Pulm Pharmacol Ther 2017; 45:1-10.
6. Li T, Kung HJ, Mack PC, Gandara DR. Genotyping and genomic

profiling of non small-cell lung cancer: implications for current and future therapies. J Clin Oncol 2013;31:1039-49.
7. Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage iv non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35:3484-515.
8. Stahel R, Thatcher N, Früh M, et al; Panel members. 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010: small-cell lung cancer. Ann Oncol 2011;22:1973-80.
9. Chen YJ, Chen LX, Han MX, Zhang TS, Zhou ZR, Zhong DS. The efficacy and safety of chemotherapy in patients with non-small cell lung cancer and interstitial lung disease: A PRISMA-Compliant Bayesian Meta-Analysis and Systematic Review. Medicine (Baltimore). 2015;94:e1451
10. Niwa H, Nakahara Y, Yokoba M, Mitsufuji H, Sasaki J, Masuda N. Safety and efficacy of carboplatin plus nab-paclitaxel for treating advanced non-small-cell lung cancer with interstitial lung disease. Mol Clin Oncol 2017;7:604-8.
11. Isobe K, Hata Y, Sakamoto S, Takai Y, Shibuya K, Homma S. Clinical characteristics of acute respiratory deterioration in pulmonary fibrosis associated with lung cancer following anti-cancer therapy. Respirology 2010;15:88-92.
12. Minegishi Y, Takenaka K, Mizutani H, et al. Exacerbation of idiopathic interstitial pneumonias associated with lung cancer therapy. Intern Med 2009;48:665-72.
13. Minegishi Y, Sudoh J, Kuribayasi H, et al. The safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced non-small cell lung cancer with idiopathic interstitial pneumonias. Lung Cancer 2011;71:70-4.
14. Kenmotsu H, Naito T, Kimura M, et al. The risk of cytotoxic chemotherapy-related exacerbation of interstitial lung disease with lung cancer. J Thorac Oncol 2011;6:1242-6.
15. Watanabe N, Niho S, Kirita K, et al. Second-line docetaxel for patients with platinum-refractory advanced non-small cell lung cancer and interstitial pneumonia. Cancer Chemother Pharmacol 2015;76:69-74.
16. Kato M, Shukuya T, Takahashi F, et al. Pemetrexed for advanced non-small cell lung cancer patients with interstitial lung disease. BMC Cancer 2014;14:508.
17. Minegishi Y, Kuribayashi H, Kitamura K, et al. The feasibility study of Carboplatin plus Etoposide for advanced small cell lung cancer with idiopathic interstitial pneumonias. J Thorac Oncol 2011;6:801-7.
18. Togashi Y, Masago K, Handa T, et al. Prognostic significance of preexisting interstitial lung disease in Japanese patients with small-cell lung cancer. Clin Lung Cancer 2012;13:304-11.
19. Watanabe N, Taniguchi H, Kondoh Y, et al. Chemotherapy for extensive-stage small-cell lung cancer with idiopathic pulmonary fibrosis. Int J Clin Oncol 2014;19:260-5.
20. Kudoh S, Kato H, Nishiwaki Y, et al; Japan Thoracic Radiology Group, Jiang H, Itoh Y, Armour A, Watkins C, Higenbottam T, Nyberg F. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. Am J Respir Crit Care Med 2008;177:1348-57.
21. Naito Y, Tsuchiya S, Ishihara S, et al. Impact of preexisting pulmonary fibrosis detected on chest radiograph and CT on the development of gefitinib-related interstitial lung disease. Am J Clin Oncol 2008;31:340-4.
22. Kojima Y, Okudela K, Matsumura M, et al. The pathological features of idiopathic interstitial pneumonia-associated pulmonary adenocarcinomas. Histopathology 2017;70:568-78.
23. Choi MK, Hong JY, Chang W, et al. Safety and efficacy of gemcitabine or pemetrexed in combination with a platinum in patients with non-small-cell lung cancer and prior interstitial lung disease. Cancer Chemother Pharmacol 2014;73:1217-25.
24. Delaunay M, Cadranel J, Lusque A, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. Eur Respir J 2017; 50(2):1700050. doi: 10.1183/13993003.00050-2017.
25. Guyard A, Danel C, Théou-Anton N, et al. Morphologic and molecular study of lung cancers associated with idiopathic pulmonary fibrosis and other pulmonary fibroses. Respir Res 2017;18:120.
26. Enomoto Y, Inui N, Kato T, et al. Low forced vital capacity predicts cytotoxic chemotherapy-associated acute exacerbation of interstitial lung disease in patients with lung cancer. Lung Cancer 2016;96:63-7.
27. Mercer PF, Woodcock HV, Eley JD, et al. Exploration of a potent PI3 kinase/mTOR inhibitor as a novel anti-fibrotic agent in IPF. Thorax 2016;71:701-11.
28. Antoniou KM, Tomassetti S, Tsitoura E, Vancheri C. Idiopathic pulmonary fibrosis and lung cancer: a clinical and pathogenesis update. Curr Opin Pulm Med 2015;21:626-33.
29. Comer BS, Ba M, Singer CA, Gerthoffer WT. Epigenetic targets for novel therapies of lung diseases. Pharmacol Ther 2015;147:91-110.
30. Mediavilla-Varela M, Boateng K, Noyes D, Antonia SJ. The anti-fibrotic agent pirfenidone synergizes with cisplatin in killing tumor cells and cancer-associated fibroblasts. BMC Cancer 2016;16:176.
31. Iwata T, Yoshida S, Fujiwara T, et al. Effect of perioperative pirfenidone treatment in lung cancer patients with idiopathic pulmonary fibrosis. Ann Thorac Surg 2016;102:1905-10.
32. Otsubo K, Kishimoto J, Kenmotsu H, et al. Treatment rationale and design for J-SONIC: A randomized study of carboplatin plus nab-paclitaxel with or without nintedanib for advanced non-small-cell lung cancer with idiopathic pulmonary fibrosis. Clin Lung Cancer 2018; 19:e5-e9.