Hong Kong J Radiol. 2022;25:170-1 | https://doi.org/10.12809/hkjr22seped

EDITORIAL

First-line Treatment Options for Non-small Cell Lung Cancer

CK Law

Honorary Consultant in Clinical Oncology, Hong Kong Sanatorium & Hospital, Hong Kong

Lung cancer is the number one cancer in incidence and mortality in Hong Kong,[1] and non-small cell lung carcinoma (NSCLC) accounts for 94% of all lung cancers with known histopathology. Among staged cases, 22% are early (stage I and II), 17% are intermediate (stage III), and 61% are advanced (stage IV) NSCLC. Surgery is the standard upfront treatment for early-stage NSCLC, whereas the treatment for intermediate- or advanced-stage NSCLC falls mainly under the auspices of clinical and medical oncologists. For stage III NSCLC, surgery may be added after neoadjuvant systemic treatment for resectable cases and radiotherapy is usually administered concurrently with systemic treatment for unresectable cases. For stage IV NSCLC, systemic treatment is the main theme, targeted therapy is applied whenever the tumour undergoes actionable mutation, and immunotherapy and/or chemotherapy is used for the remaining cases.

In this issue of the *Hong Kong Journal of Radiology*, two local retrospective studies report on an intravenous chemotherapy regimen for concurrent use with radiotherapy for unresectable stage III NSCLC, and a second-generation oral tyrosine kinase inhibitor (TKI) targeted therapy for metastatic cases of NSCLC.

Wong et al[2] report their 10-year experience of two of the commonly used chemotherapy drugs in concurrent chemoradiotherapy—paclitaxel and carboplatin—in an uncommon 3-weekly regimen instead of the usual weekly regimen. At the time commenced in 2007, the standard chemotherapy regimen for concurrent chemoradiotherapy in lung cancer was etoposide or vinblastine plus cisplatin, or weekly paclitaxel-carboplatin. In the early 2010s, pemetrexed was added and vinblastine was gradually phased out. Over the years, concurrent chemoradiotherapy has remained the standard of care for unresectable stage III NSCLC. Only one breakthrough study of the PACIFIC trial found that the addition of 1 year of immunotherapy using durvalumab improves overall survival for all unresectable stage III NSCLC except those with programmed death-ligand 1 <1%.[3] Thus, this timely study by Wong et al[2] serves as a useful reference for daily practice, boosting confidence in administering paclitaxel-carboplatin in a more flexible manner, potentially reducing overall workload in the public hospital setting. For tumours with actionable targets, recent and upcoming studies regarding the use of upfront TKIs may revolutionise future practice with the possibility of obviating the need for chemotherapy altogether.[4]

For stage IV, as over 50% of all patients locally got actionable mutation, targeted therapy should be the first choice. An example is the report by Chow et al[5] on their experience of using afatinib, a second-generation TKI, for stage IV NSCLC harbouring *EGFR* mutation. This study was initiated in 2015, shortly after reports that showed the superiority of afatinib over chemotherapy for the common *EGFR* mutation in metastatic lung cancer.[6,7] These studies showed that the effect on deletion 19 mutation was better than that on L858R mutation, and

Correspondence: *Dr CK Law, Department of Clinical Oncology, Hong Kong Sanatorium & Hospital, Hong Kong*
Email: chunkey.law@hksh.com

Contributors: The author contributed to the editorial, approved the final version for publication, and takes responsibility for its accuracy and integrity.

Conflicts of Interest: The author has disclosed no conflicts of interest.

Funding/Support: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

this finding was also observed by Chow et al.[5] A study published in 2016 confirmed that afatinib is superior to gefitinib on both common *EGFR* mutations, although the effect of on L858R mutation was slightly inferior.[8] Initial results of the 2018 FLAURA study showed the superiority of osimertinib over gefitinib or erlotinib in terms of progression-free and overall survival; however, results published in 2020 showed no benefit for Asian populations.[9] Most recently, the ARCHER-1050 trial showed more gain in overall survival for dacomitinib than for gefitinib, and the efficacy was more prominent in L858R than in deletion 19, although central nervous system metastases were excluded.[10]

For uncommon point mutations of *EGFR* such as G719X, L861Q and S768I, there is more data to substantiate the use of afatinib than for any other TKI. Although afatinib is relatively ineffective in exon 20 insertion, the pulse regimen of a single weekly dose of 280 mg seemed promising.[11] However, with the availability of monoclonal antibodies such as amivantamab, the use of TKIs will likely become less popular.

The existing literature suggests that for first-line systemic treatment for metastatic lung cancer harbouring common *EGFR* mutations and without central nervous system metastases, either of the two second-generation TKIs should be the treatment of choice, with dacomitinib specifically favoured in L858R. This is supported by local results from Chow et al.[5] However, the use of first-generation TKIs is losing favour because of inferior results compared with the second-generation TKIs. Moreover, the prevalence of T790M resistance mutation upon progression is similar for both generations of TKIs, and equally amenable to salvage with third-generation drugs. In contrast, for uncommon point mutations, afatinib remains the treatment option with the most robust supporting data. For patients with brain metastases on presentation, osimertinib is undoubtedly the best option for first-line systemic treatment.

In conclusion, these two retrospective local studies support the current literature on standard first-line treatments for NSCLC, including in Asian patients. Despite the fast-paced developments in systemic therapy for this disease, these results remain clinically relevant.

REFERENCES

1. Hospital Authority. Hong Kong Cancer Registry 2019. Available from: https://www3.ha.org.hk/cancereg/pdf/factsheet/2019/lung_2019.pdf. Accessed 6 Aug 2022.
2. Wong HC, Lim FM, Cheng AC. Three-week cycles of paclitaxel-carboplatin administered concurrently with radiotherapy for inoperable stage III non-small cell lung cancer: 10-year single-centre experience. Hong Kong J Radiol. 2022;25:172-83.
3. Paz-Ares L, Spira A, Raben D, Planchard D, Cho BC, Özgüroğlu M, et al. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. Ann Oncol. 2020;31:798-806.
4. Harris JP, Fujimoto DK, Nagasaka M, Ku E, Harada G, Keshava H, et al. Controversies in lung cancer: heterogeneity in treatment recommendations for stage III NSCLC according to disease burden and oncogenic driver alterations. Clin Lung Cancer. 2022;23:333-44.
5. Chow DY, So TH, Leung DK, Tse RP, Lau KS. First-line afatinib in epidermal growth factor receptor–mutant metastatic non-small cell lung cancer: a clinical retrospective study. Hong Kong J Radiol. 2022;25:184-91.
6. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31:3327-34.
7. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15:213-22.
8. Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol. 2017;28:270-7.
9. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med. 2020;382:41-50.
10. Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. J Clin Oncol. 2018;36:2244-50.
11. Costa DB, Jorge SE, Moran JP, Freed JA, Zerillo JA, Huberman MS, et al. Pulse afatinib for ERBB2 exon 30 insertion-mutated lung adenocarcinomas. J Thorac Oncol. 2016;11:918-23.