Systemic treatment of non-small-cell lung cancer

Rohit Lal, Deborah Enting, Hartmut Kristeleit

Medical Oncology, Guy's Hospital, King's Health Partners, London, United Kingdom

The development of new therapies and predictive biomarkers has increased the complexity of treating non-small-cell lung cancer (NSCLC). We review the indications and rationale for systemic treatments in the context of recent advances.

Pre-operative chemotherapy

Pre-operative or induction chemotherapy for early-stage NSCLC may downstage tumours to facilitate complete resection. The term neo-adjuvant chemotherapy is incorrect as Gilligan and colleagues updated a systematic review to show no improvement in overall survival (OS) [1,2].

Adjuvant chemotherapy

Survival benefit from chemotherapy, post-operatively, varied with stage. There was no interaction between chemotherapy effect and sex, age, histology, type of surgery, radiotherapy and total cisplatin dose. Adjuvant chemotherapy for stage 1A was not recommended [3]. For stage 1B, the confidence interval did not support the hazard ratio favouring adjuvant chemotherapy [4].

Cisplatin-based doublet chemotherapy was recommended for resected stage II NSCLC based on the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis [5]. Two trials (FRE-IALT [6] and ANITA [7]) reported OS benefit with adjuvant chemotherapy in stage IIIA, occult N2, disease, with good performance status patients benefiting the most. A retrospective analysis of JBR.10 [8] of adjuvant cisplatin/vinorelbine, patients over 65 years were found to benefit from prolonged OS with no difference in serious adverse events whilst receiving less treatment. Both IALT and JBR.10 reported contrasting long-term survival data. The IALT Bio study indicated that ERCC1-negative tumours derived a greater benefit from cisplatin than ERCC1-positive tumours [9].

Radical chemo-radiotherapy

Concomitant platinum-based chemo-radiotherapy may improve survival of patients with locally advanced NSCLC [10]. Van Meerbeeck and colleagues reported 579 patients with pathologically-proven stage IIIA-N2 NSCLC [11]. All patients received three cycles of platinum-based induction chemotherapy and clinical responders were then randomised to surgery or radiotherapy. In the surgical arm, six patients died compared with one in the radiotherapy arm. Median survival, five-year OS and progression-free survival (PFS) were similar between both arms and chemo-radiotherapy is recommended for these patients.

Advanced stage

Epidermal growth factor receptor (*EGFR*) mutant lung cancer is a clinically relevant subset of lung adenocarcinoma. Activating mutations have a high response rate to EGFR tyrosine-kinase inhibitors (TKIs). The Iressa Pan-Asia Study (IPASS) showed a significant improvement in PFS among patients with *EGFR* mutations or clinically relevant features [12] compared with first-line carboplatin/paclitaxel. Anti-EGFR antibody treatment with cetuximab had shown modest survival benefit in combination with platinum-based chemotherapy [13] in unselected patients.

Anti-vascular endothelial growth factor therapy with bevacizumab has shown modest survival benefit when combined with chemotherapy first-line [14]. The risk of significant pulmonary haemorrhage precluded its use in squamous cell cancers. The elderly experienced increased toxicity and death [15].

Platinum-based combination chemotherapy for advanced-stage NSCLC is associated with survival benefit. Third-generation/platinum combinations have similar outcomes [16].

Histology was a predictive factor for pemetrexed efficacy. Scagliotti and colleagues showed significant treatment-by-histology interaction for pemetrexed, indicating superior OS and PFS for cisplatin/pemetrexed

combinations compared with cisplatin/gemcitabine in patients with non-squamous histology [17].

Maintenance therapy

The Southwest Oncology Group 0023 trial demonstrated a detrimental effect of gefitinib as maintenance therapy in unselected patients [18]. Maintenance treatment with pemetrexed or erlotinib was associated with OS benefit. Pemetrexed was given as switch maintenance after carboplatin/paclitaxel, but subsequently became standard first-line treatment [19]. At the time of accrual to the SATURN study, second-line erlotinib was not standard [20].

Second-line therapy

Docetaxel was the first agent to show OS and clinical benefit. Pemetrexed showed non-inferior efficacy to docetaxel and fewer serious adverse events [21]. Erlotinib or gefitinib should be used for patients with activating *EGFR* mutations who have not received an EGFR TKI first-line. Erlotinib is marginally beneficial in unselected relapsed patients.

Future treatments

K-Ras mutation may reduce the benefit of adjuvant chemotherapy [22] and was resistant to EGFR inhibition [23] in advanced disease. Addition of EGFR inhibitor to chemotherapy reduced the efficacy, other than with carboplatin/paclitaxel [24].

Conflict of interest statement

R. Lal has received an unrestricted educational grant from Eli-Lilly. H. Kristeleit and D. Enting have no conflict of interest to disclose.

References

1 Burdett SS, Stewart LA, Rydzewska L. Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *Cochrane Database Syst Rev* 2007;(3): CD006157.

2 Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet* 2007;**369**(9577):1929–37.

3 Crino L, Weder W, Van Meerbeeck J, Felip E; on behalf of the ESMO Guidelines Working Group. *Ann Oncol* 2010;**21**(Suppl 5):v103–15.

4 Pisters KMW, Evans WK, Azzoli CG, et al. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I–IIIA resectable non-small-cell lung cancer guidelines. *J Clin Oncol* 2007;**25**:5506–18.

5 Pignon J-P, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE collaborative group. *J Clin Oncol* 2008;**26**:3552–9.

6 Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;**350**(4):351–60.

7 Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006;**7**(9):719–27.

8 Pepe C, Hasan B, Winton TL, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. *J Clin Oncol* 2007;**25**(12):1553–61.

9 Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med* 2006;**355**:983–91.

10 Aupérin A, Le Péchoux C, Pignon JP, et al. Concomitant radiochemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;**17**(3): 473–83.

11 van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;**99**(6):442–50.

12 Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**:947–57.

13 Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet* 2009 May 2;**373**(9674):1525–31.

14 Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;**355**:2542–50.

15 Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non-small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. *J Clin Oncol* 2008;**26**:60–5.

16 Scagliotti GV, De Marinis F, Rinaldi M, et al.; Italian Lung Cancer Project. Phase III randomized trial comparing three-platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 2002;**20**:4285–91.

17 Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist* 2009;**14**:253–63.

18 Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol* 2008;**26**:2450–6.

19 Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;**374**:1432–40.

20 Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet* 2010;**11**:521–9.

21 Hanna N, Shephard FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;**22**:1589–97.

22 Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;**352**:2589–97.

23 Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. *PLoS Med* 2005;**2**:e17.

24 Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005;**23**:5900–9.