Second-line options for EGFR- and Alk-unmutated lung cancers

Therapeutic decisionmaking in the molecular era

by Normand Blais, MD, MSc

ABSTRACT

Current treatment based algorithms for NSCLC are often derived from studies that were conducted prior to the extensive wealth of knowledge that was gained by subtyping lung cancer into distinct molecular entities. New studies are now helping to refine strategies for second-line approaches in EGFR-mutated, Alk-rearranged, as well as in EGFR/Alk-unmutated tumours. This review will focus on treatment decisions after the failure of first-line therapy, considering both patient selection and patient preferences. Selected studies that have specifically looked at second-line therapy in EGFR-negative patients will be reviewed and placed into the current context of therapeutic decisions in the molecular era.

INTRODUCTION

Second-line therapy for non-small cell lung cancer (NSCLC) was shown to be beneficial in the late 1990s, and second and third line therapy is now standard of care in most eligible patients with NSCLC. Docetaxel was the first agent to show benefit in this setting. Shepherd et al.1 showed a significant prolongation of overall survival from 4.6 months with placebo to 7.5 months with docetaxel 75 mg/m² (p=0.47). Fosella et al.2 showed improvement in one-year survival rates with docetaxel (32%) compared to either vinorelbine or ifosfamide (19%, p=0.025). In 2005, the BR.21 study3 demonstrated that erlotinib could further extend overall survival in the second- to third-line setting from 4.7 months in the placebo group to 6.7 months in those receiving erlotinib (p<0.001). Additionally, Hanna et al.4 demonstrated the therapeutic equivalence of pemetrexed to docetaxel in the second-line setting. Since the publication of this study, 3 important subgroup analyses have demonstrated the limited efficacy of pemetrexed for squamous cancer populations, and pemetrexed use has since been restricted to non-squamous histologies.5 Although many randomized studies have been conducted since the publication of these most studies with novel agents or drug combinations, monotherapy with docetaxel, pemetrexed (non-squamous histology only) or erlotinib remains the standard approach. In tumours with squamous histology, cisplatin+gemcitabine proved superior to cisplatin+pemetrexed. These results have led to variable uptake of the cisplatin+pemetrexed regimen for patients with non-squamous tumours. Reasons for variation include: variable coverage of pemetrexed in this setting by Canadian provinces; the belief by some oncologists that switch maintenance therapy with pemetrexed is a better strategy in non-progressing patients; and the desire by some oncologists to reserve pemetrexed as a second-line option.

In 2014, the standard treatment of unmutated squamous cell carcinoma of the lung is thus usually a platinum doublet including gemcitabine, vinorelbine or paclitaxel. As an added option for these patients, erlotinib can be used as a switch maintenance option based on results of the SATURN trial.7 For non-squamous histology tumours, patients can receive these same doublets with the added option of using pemetrexed upfront. Maintenance options for non-squamous tumours include switch maintenance with erlotinib based on the SATURN data,7,8 switch maintenance with pemetrexed based on the JMEN study,9 or continuation maintenance with pemetrexed based on the PARAMOUNT trial.9 Differences in the uptake of switch maintenance include patient preferences (see below), variable interpretation of study results based on limitations in the study design of the JMEN and the SATURN trials, and provincial variations in coverage for these treatments. That said, the concept of

FIRST-LINE AND MAINTENANCE THERAPIES

Based on poor public coverage of bevacizumab in Canada, standard options for first-line chemotherapy for EGFR- and ALK-unmutated lung cancers include either cisplatin or carboplatin in combination with gemcitabine, vinorelbine or paclitaxel. In 2008, a randomized study of cisplatin+gemcitabine vs cisplatin+pemetrexed showed a statistically significant and clinically meaningful improved overall survival for patients with non-squamous histologies in the cisplatin+pemetrexed arm.6 The cisplatin+pemetrexed combination requires only half the number of visits to the chemotherapy suite and has lower toxicity than cisplatin+gemcitabine. In tumours with squamous histology, cisplatin+gemcitabine proved superior to cisplatin+pemetrexed. These results have led to variable uptake of the cisplatin+pemetrexed regimen for patients with non-squamous tumours. Reasons for variation include: variable coverage of pemetrexed in this setting by Canadian provinces; the belief by some oncologists that switch maintenance therapy with pemetrexed is a better strategy in non-progressing patients; and the desire by some oncologists to reserve pemetrexed as a second-line option.

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continuation maintenance with pemetrexed has gained marked approval in the lung cancer community despite the fact that funding is still a major limitation in many provinces.

**IMPACT ON SECOND-LINE OPTIONS**

This growing list of first-line and maintenance options results in some confusion when deciding on second-line approaches. The usual practice consists of using agents that were not used previously in an individual patient, except in rare cases where a rechallenge is offered. Patients showing substantial response to an agent and benefiting from a chemotherapy-free interval of more than 12 months are best suited for rechallenge.

**Patient and physician preference**

Perceptions and beliefs vary widely about the best course of action following the conclusion of first-line therapy for lung cancer. Canadian oncologists usually have discussions about maintenance therapy with patients at some point during first-line treatment, though physician perception and its importance in the eventual selection of maintenance therapy are poorly documented. Peeters et al studied 30 patients with NSCLC for whom maintenance therapy was recommended. He found that most patients had a positive attitude towards maintenance therapy and, when informed that therapy provided an incremental benefit in overall survival of 6, 3 and 1 month(s), respectively, 83%, 67% and 43% of patients considered it worthwhile. Preference for maintenance therapy decreased as the number of first-line treatment cycles increased.

Similar studies have not been conducted to evaluate patient preference for and attitudes toward second-line therapies, though patients faced with documented progressive disease are usually more eager to start a second active therapy. This becomes even more acute in the setting of progressive and symptomatic disease. Although lung cancer can sometimes be associated with slow growth kinetics, most patients develop rapidly progressive disease after the failure of first-line chemotherapy. This is well documented by the demonstration of radiologic or clinical progression in roughly 70% of patients within the first 12 weeks of inclusion in the placebo arm of the switch maintenance studies, and in 60% of patients in the PARAMOUNT continuation maintenance trial. The timing of second-line treatment will be determined by physician and patient beliefs about impending failure, the acceptability of treatment to the patient, and the intensity of radiologic and clinical followup available to patients who are on no treatment following the completion of first-line therapy, or are on maintenance treatment.

The acceptability of second-line therapies is influenced by the patient’s performance status, the presence of comorbidities and the patient’s experience during first-line therapy. In this regard, cumulative toxicity from platinum containing regimens may affect patients’ performance status and render them less willing to undergo further therapy. As randomized trials have not shown significant additional benefit from more than 4 cycles of a platinum-containing regimen in first-line therapy, limiting the number of cycles may reduce chemotherapy-related toxicity and lead to broader acceptance of either maintenance or second-line options.

**Toxicity of second-line therapy**

The commonly discussed options in the second-line setting are docetaxel, pemetrexed and erlotinib. These options are associated with very different toxicity profiles (Table 1). Alopecia, nail growth disturbance, myalgias, arthralgias, neurotoxicity, severe neutropenia and, more uncommonly, febrile neutropenia are associated with docetaxel. Asthenia and a low rate of hematologic toxicity are associated with pemetrexed. Rash, dry skin, pruritus and diarrhea are associated with erlotinib. Erlotinib has the added advantage of being administered orally. These different features have an impact on patient preference and often determine the final selection of the agent used, especially when clinical efficacy is perceived to be similar.

**SECOND-LINE THERAPY IN THE MOLECULAR ERA**

Trials conducted in the early 2000s did not differentiate patients with recurrent NSCLC by mutation status and would have included a large proportion of patients with EGFR mutations and ALK rearrangements. The contemporary approach to second-line therapy is based on knowledge of a patient’s mutation status and the appropriate agents are selected accordingly.

**Unmutated NSCLC**

In the setting of known EGFR/Alk negativity, 3 recent randomized trials have documented that progression-free survival (PFS) is inferior and that overall survival (OS) may be inferior with EGFR-TKIs compared to chemotherapy. The phase III TAILOR trial randomised patients with EGFR wild-type NSCLC to either docetaxel or erlotinib as second-line treatment. This study included 222 patients and showed that median OS was 8.2 months with docetaxel versus 5.4 months with erlotinib (adjusted HR=0.73; p=0.05). PFS was 2.9 months with docetaxel versus 2.4 months with erlotinib (adjusted HR=0.71; p=0.02). The phase III DELTA trial randomized patients with wild-type EGFR NSCLC to either placebo or erlotinib. PFS was 2.9 months with erlotinib versus 2.4 months with placebo (adjusted HR=0.71; p=0.02). These results are consistent with those from the PARAMOUNT continuation maintenance trial.
or mutant EGFR tumours to erlotinib or docetaxel as second- or third-line therapy. Median OS was 9.2 months with docetaxel and 9.0 months with erlotinib (HR=0.98; p=0.914) and median PFS was 2.9 months with docetaxel and 1.3 months with erlotinib (HR=0.69; p=0.013).

A phase II randomized trial, CTONG 080617, compared pemetrexed versus gefitinib as second-line therapy in 157 patients with non-squamous wild-type EGFR tumours. Median PFS was superior with pemetrexed (4.8 months) than gefitinib (1.6 months) with a hazard ratio of 0.54 (p<0.001). OS trended with superiority with pemetrexed (12.4 months) vs gefitinib (9.6 months), with a hazard ratio of 0.72 (p=0.077).

The PROSE study tested the ability of the VeriStrat assay to distinguish patients who would be better treated with chemotherapy or erlotinib as second-line therapy. The VeriStrat assay is a serum test that classifies patients as VS-G (VeriStrat-Good) or VS-P (VeriStrat-Poor) based on 8 mass spectral peaks. The PROSE phase III study randomized 285 patients with NSCLC to erlotinib or chemotherapy (pemetrexed or docetaxel) as second-line treatment. Trial participants were stratified based on VeriStrat results. Some 70% were classified as VS-G and 30% as VS-P. The analysis in the EGFR-negative and -unknown patients in the PROSE trial was recently presented at the World Lung Cancer Conference in Sydney.18 Patients in the VS-P group did better on chemotherapy, with a PFS of 2.8 vs 1.7 months on erlotinib (p=0.03) and OS of 6.4 vs 3.0 months (p=0.01). The VS-G group receiving chemotherapy also had better PFS (5.0 vs 2.4 months, p=0.01) although OS was not apparently different (10.5 vs 10.4 months). These new results tend to suggest that second-line treatment that includes chemotherapy may lead to superior outcomes in the setting of wild-type NSCLC.

Nonetheless, improved outcomes from trials comparing erlotinib to placebo, such as the SATURN (in the maintenance setting) and BR.21 (in the second- to third-line setting) studies, demonstrate the usefulness of this agent in the salvage setting. It is thus usually perceived that both chemotherapy and erlotinib should ideally be offered to patients at some point in the management algorithm.

## INVESTIGATIONAL AGENTS

Research is increasingly focusing on molecular targets associated with subsets of lung cancer. Investigators are increasingly demonstrating the feasibility of targeting selected patients with specific inhibitors directed towards a lung cancer driver mutation. The identification of actionable mutations in adenocarcinoma is ever increasing, and these include ROS1 rearrangements, RET rearrangements, ARAF/BRAF mutations and HER2 mutations. Although squamous cell lung cancer is not associated with an approved targeted agent, promising targets include FGFR2 mutations and PIK3CA mutations.

Although few drug development programs currently target unselected EGFR/ALK-negative NSCLC, one outstanding exception is the emergence of agents targeting the PD-1/PD-L1 pathway. Inhibitors of PD-1, such as nivolumab, and inhibitors of PD-L1, such as BMS-936559 and MPDL-3280A, have shown consistent efficacy in relatively unselected patients with recurrent NSCLC.

Response rates in such patients vary between 10% and 23%,19-21 with no significant differences reported between squamous and adenocarcinoma histologies. Conversely, increasing responses have recently been described based on immunohistochemical expression of PD-L1 on either the tumour cell or peri-tumoural lymphocytic infiltrate. For example, in a phase I study of MPDL-3280A, responses were observed in 14% of the tumours without PD-L1 expression, in 31% with any PD-L1 expression, and in 83% with 3+ expression.21

Another important drug target is the tyrosine kinase receptor of the hepatocyte growth factor MET. Increased HGF/MET signaling is associated with acquired resistance to EGFR-targeted treatments. Studies were thus designed to study dual therapy with MET and EGFR inhibitors to try to overcome resistance to EGFR-TKI therapy. Studies targeting MET include a phase III trial in a broad population of patients with NSCLC22 and a randomized phase II trial of patients with NSCLC of any histology who had received 1 or 2 prior lines of systemic therapy23. Table 2 shows the overall and subgroup analyses of these trials. Although the overall results are apparently deceiving, further analysis of these studies shows that selected patients with overexpression of MET based on immunohistochemistry seem to derive benefit from MET-targeting agents, whereas the “MET-low” tumours are not advantaged. These findings have led to new studies addressing these agents in tumours that are prescreened and confirmed to be “MET-high.”

Although KRAS is one of the most commonly mutated oncoproteins in NSCLCs, targeting mutated KRAS tumours remains a challenge. Selumetinib is an inhibitor of MEK1 and MEK2, downstream mediators of KRAS activation. Considering preclinical synergistic activity of selumetinib with docetaxel, a randomized phase II study was recently completed testing this combination in previously-treated patients with KRAS mutated NSCLC.24 This study evaluated 43 patients in the selumetinib and docetaxel arm, and 40 patients in the placebo and docetaxel arm. Median OS was 9.4 months.
and 5.2 months (HR=0.80, p=0.21) in the combination and monotherapy arms, respectively. Likewise, PFS was 5.3 months and 2.1 months (HR=0.58, p=0.014), respectively.

A novel antiangiogenic agent, nintedanib, has been shown to improve results with chemotherapy in the second-line setting. Results of the LUME-Lung 1 trial presented at ASCO 2013 and ESMO 2013 showed an improvement in the overall study population, with NSCLC progressing after first-line therapy. An improvement in the PFS (3.5 months in the nintedanib plus docetaxel arm versus 2.7 months in the placebo plus docetaxel arm) was found for the overall study population (HR=0.85, p=0.007). Although OS failed to achieve statistical superiority for the entire study population, statistically significant results were achieved in the subgroup of patients with adenocarcinoma, with OS of 12.6 months (N+D) vs 10.3 (P+D) (HR=0.83, p=0.0359). Further studies are thus planned in adenocarcinoma patients. These results highlight once again the importance of personalized approaches in research.

CONCLUSIONS

Management of NSCLC no longer follows a one-size-fits-all approach. As EGFR mutation and Alk rearrangement information is commonly available at the time of second-line treatment decisions, new trials conducted in molecularly defined study populations become more relevant to modern treatment decisions. Current options include pemetrexed, docetaxel and erlotinib that are clinically used in a variable sequence based on efficacy, toxicity and personal preferences. New studies are further defining subsets of patients that may be treated more appropriately with targeted agents, underscoring the increasing importance of molecular pathology to support clinicians and their patients.

References


