

SYSTEMIC THERAPY FOR NON-SMALL CELL LUNG CANCER IN 2011

Multiple options linked to improved survival and quality of life

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The last 2 decades have seen a movement from relative nihilism about the role of systemic therapy for non-small cell lung cancer (NSCLC) to support based on high-quality evidence for the use of chemotherapy in the adjuvant setting^{1,2}, as well as first³⁻⁵ and subsequent lines of therapy for advanced disease.⁶⁻⁹ Data have emerged to promote the use of maintenance therapy following first-line chemotherapy.¹⁰⁻¹¹ Targeted agents have been incorporated into treatment algorithms for advanced NSCLC,¹²⁻¹⁴ and an understanding of the molecular phenotypes of NSCLC is being used to guide treatment selection.¹⁵⁻¹⁷ This article provides an overview of the current status of therapy for NSCLC.

ADJUVANT CHEMOTHERAPY

Prior to 2004, routine use of postoperative adjuvant systemic therapy was not recommended. Many trials published since then^{1,2,18} demonstrate about a 10% improvement in overall survival (OS) for completely resected stage II and III NSCLC patients receiving adjuvant cisplatin-vinorelbine chemotherapy.¹⁹ Retrospective subgroup analyses of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) BR.10 and Cancer and Leukemia Group B (CALGB) 9633 trials also support improved survival from adjuvant chemotherapy for patients with larger, Stage IB tumours (≥ 4 cm).^{20,21} Adjuvant chemotherapy is now the standard of care for patients with resected Stage IB ≥ 4 cm, II and IIIA NSCLC.

FIRST-LINE CHEMOTHERAPY

We have known for some time that chemotherapy results in modest survival improvements for patients with advanced NSCLC.²² Gemcitabine, vinorelbine, paclitaxel or docetaxel combined with a platinum agent are all similarly effective and result in gains in median survival of 3 to 4 months.^{3,5} Typically, chemotherapy would not be continued

beyond 4 to 6 cycles. Recent data have shown the importance of histologic subtypes in the selection of chemotherapeutic drugs.^{4,23} For patients with non-squamous histology, regimens containing pemetrexed may offer small OS improvements compared to other regimens. However, recent evolution of the NSCLC treatment paradigm means that no one first-line treatment option is clearly superior.

MAINTENANCE THERAPY

Recent data have challenged the theory on duration of therapy. Several trials have shown improved survival for patients switching to pemetrexed or erlotinib immediately following 4 cycles of first-line chemotherapy.^{10,24} Questions exist about the design of these trials and whether the benefit is limited to subgroups of patients with stable disease following first-line therapy. Nevertheless, maintenance therapy is now a consideration for patients completing first-line chemotherapy.

TREATMENT BEYOND PROGRESSION

Data from a number of randomized trials indicate that second- and third-line treatments improve survival of NSCLC patients.⁶⁻⁹ Trials initially demonstrated that docetaxel increased median survival by 2 to 3 months.⁸ These gains were associated with quality of life improvements.²⁵ Subsequently, pemetrexed was shown to be noninferior to docetaxel.⁷ A retrospective analysis also showed non-squamous histology was predictive of improved survival for patients treated with pemetrexed.²³ More recently, molecular-targeted agents have also shown benefit for this patient group. Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, improves survival and quality of life as second- or third-line therapy in patients not eligible for further chemotherapy.^{9,26}

Questions continue about the appropriate



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sequence of therapy following progression on first-line therapy. Two trials, INTEREST (IRESSA NSCLC Trial Evaluating Response and Survival against Taxotere),²⁷ which compared second-line docetaxel vs gefitinib, and TITAN (Tarceva in Treatment of Advanced NSCLC,²⁸ evaluating pemetrexed vs erlotinib, showed similar progression-free survival (PFS) and OS for second-line chemotherapy or second-line EGFR therapy. These data suggest that the sequence of second- and third-line therapy is probably less important than maximizing the number of patients who receive both lines.

INTEGRATING TARGETED THERAPIES INTO SYSTEMIC TREATMENT

Many molecular targets have been identified that appear important in NSCLC cell growth and proliferation. To date, the most promising approach has been the inhibition of angiogenesis. Bevacizumab, a monoclonal antibody against circulating vascular endothelial growth factor (VEGF), is the only agent approved for NSCLC. The Eastern Cooperative Oncology Group (ECOG) 4599 trial evaluated the addition of bevacizumab to carboplatin-paclitaxel chemotherapy.¹³ Results showed increased objective response rates (ORR) and PFS, translating to a 2-month OS improvement. A second trial, AVAIL (Avastin in Lung), studied bevacizumab in combination with cisplatin and gemcitabine,^{12,29} but was not able to demonstrate any improvement in OS. Nevertheless, bevacizumab is incorporated in first-line treatment algorithms for advanced NSCLC. Toxicity concerns limit this to good-performance status patients with non-squamous histology, no brain metastases, no history of hemoptysis and no history of venous thromboembolic or bleeding disorders.

Several trials have assessed the addition of cetuximab, a monoclonal antibody against EGFR, in combination with chemotherapy.^{14,30} FLEX (First-Line Erbitux in Lung Cancer) showed a small OS improvement, with increased toxicity.¹⁴ Cetuximab does not have regulatory approval for NSCLC and has had limited impact on treatment. To date, approaches targeting the insulin-like growth factor receptor (IGFR) have not improved survival.³¹

MOLECULAR-GUIDED THERAPY

The discovery of activating mutations of the EGFR gene has changed the paradigm that all NSCLC

patients should be treated in the same manner.^{32,33} The presence of an exon 19 deletion or an L858R point mutation of exon 21 is predictive of a high likelihood of response to EGFR tyrosine kinase inhibitors. Multiple randomized trials have now demonstrated large improvements in PFS for EGFR mutation-positive patients receiving first-line gefitinib or erlotinib in comparison to platinum-based doublets.^{15,16,34} Additionally, EGFR wild-type patients appear to suffer harm from first-line EGFR therapy.¹⁵ Testing for the presence of an EGFR mutation should be routinely performed in patients with advanced NSCLC.

More recently, a new molecular subset of NSCLC has been defined based on a translocation of the echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) genes.³⁵ The presence of such translocations appears to predict benefit from crizotinib, an ALK inhibitor.¹⁷ Comparative trials against first- and second-line chemotherapy options are ongoing, as is research to further characterize the molecular phenotypes of lung adenocarcinomas.

BALANCING BENEFITS AND RISKS

Multiple options now exist for the systemic treatment of NSCLC. Benefits are modest but linked to both improved survival and quality of life. The challenge for clinicians treating patients with NSCLC remains to balance the expected benefits against toxicities and patient preference.

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