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Clinical question: What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC?

Guideline contents > What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC?

**Information on authorship and revision**

**Guidelines commissioned by**

Australian Government Cancer Australia

**Last modified:**
2 December 2016 16:04:50

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Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of this section of this guideline is based on the evidence in support of the new practice paradigm of treatment for stage IV NSCLC by selection, either by histology, clinical (patient) phenotype or by molecular tumour target.

Selection by histology

Stanfield et al conducted a systematic review of prospective, randomised controlled trials (RCTs) to examine whether histology had a treatment modifying effect (TME) on the efficacy outcomes (OS and PFS) of chemotherapeutic agents in patients with advanced NSCLC. A total of 17 systematic reviews, five individual patient data (IPD) meta-analyses, and 165 potentially relevant primary studies were identified for full review. Four of the five IPD meta-analyses investigated TME of histology and one did not, but none found a significant TME by histology. One hundred and twenty two (74%) of the 165 primary publications retrieved for full review did not report data in a way in which the TME of histology could be determined. Data from three pemetrexed RCTs, comparing (i) second-line pemetrexed versus docetaxel, (ii) first-line pemetrexed and cisplatin versus gemcitabine and cisplatin, and (iii) switch maintenance pemetrexed versus placebo, showed a statistically significant TME by histology for OS and PFS.

A fourth RCT comparing pemetrexed and carboplatin versus gemcitabine and carboplatin found no significant association between histology and OS. Patients with non-SCC appear to gain the greatest benefit from treatment with pemetrexed, whilst patients with SCC appear to have poorer OS when pemetrexed is compared with other active treatments, and similar OS when compared with placebo. A reproducible pattern of TME effect by histology was not seen clearly with other chemotherapeutic agents.

Histology has also been shown to be a predictor for toxicity with the anti-VEGF Mab, bevacizumab, with higher incidence of pulmonary haemorrhage observed in SCC. Is histology also associated with a treatment modifying effect with bevacizumab? Sandler et al, in a post hoc analysis of their pivotal phase III RCT of first-line...
Clinical question: What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC? A carboplatin/paclitaxel (PC) +/- bevacizumab (PCB) study in 878 carefully selected patients with non-SCC, reported their findings by histologic subgroups. The largest histologic subgroup in the study was adenocarcinoma (68.8% of patients), whilst not-otherwise specified represented 18.9% of patients. For adenocarcinoma, median OS was 10.3 months for PC treatment (n= 302) and 14.2 months for PCB (n = 300), HR 0.69 (95%CI: 0.58–0.83). Sample sizes for other specific histologic subtypes were considered too small for meaningful comparisons.

The TME of histology in predicting benefit from pemetrexed, the observation of greater toxicity with bevacizumab and possibly other anti-VEGF therapies in SCC, and the finding of activating EGFR gene mutations (EGFR GMTs and other mutations) in adenocarcinomas has led to a great clinical need for diagnostic accuracy in the sub-classification of NSCLC on diagnostic specimens. Consequently, the International Association for the Study of Lung Cancer (IASLC) undertook a systematic literature review of the adenocarcinoma histologic classification. In their review, Travis et al describe a revised classification system for diagnosing and reporting NSCLC with guidance for small biopsies, cytology and resected specimens, to enable classifying NSCLC primarily into adenocarcinoma or SCC due to the therapeutic implications of this distinction.

**Selection by clinical phenotype**

The early single arm and RCTs evaluating the first generation EGFR TKIs gefitinib and erlotinib identified that benefit from EGFR TKIs appeared to be greatest in certain NSCLC patient sub-populations: never smokers with adenocarcinoma, and especially, but not exclusively, in women, and Asian background.

Consequently, Mok et al, undertook a first-line RCT to compare gefitinib versus carboplatin/paclitaxel chemotherapy. They randomly assigned previously untreated patients in East Asia who had advanced pulmonary adenocarcinoma and who were nonsmokers or former light smokers to receive gefitinib (250 mg per day) or carboplatin/paclitaxel chemotherapy. The study met its primary objective of showing noninferiority of gefitinib and also showed its superiority, as compared with carboplatin–paclitaxel, with respect to PFS (HR 0.74; 95% CI 0.65 - 0.85; P<0.001). In the subgroup of 261 patients who were EGFR GMT + PFS was significantly longer with gefitinib than chemotherapy (HR 0.48; 95% CI 0.36 - 0.64; P<0.001), whereas in the subgroup of 176 patients who were negative for EGFR GMT, PFS was significantly longer among those who received chemotherapy than gefitinib (HR for progression or death with gefitinib 2.85; 95% CI,2.05 - 3.98; P<0.001). The most common adverse events in the gefitinib group were rash or acne (in 66.2% of patients) and diarrhea (46.6%).
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Selection by molecular testing of tumours

Several randomised controlled trials have been published with the first generation EGFR TKIs (gefitinib and erlotinib) in patients selected for treatment by the presence of an activating EGFR gene mutation.\[6\][7][8] All have compared first-line treatment with an EGFR TKI with standard chemotherapy on PFS. Similarly designed trials are in progress with newer generation EGFR targeting agents and inhibitors to other known driving molecular changes (eg. EML4-Alk gene fusion).

It is worth noting that this section on the evidence for treatment efficacy by molecular selection assumes that a validated method of molecular testing has been used, according to current best practice. It is acknowledged that more modern methods of gene sequencing/molecular profiling are likely to confer greater accuracy than early methods, some of which may have been used in these first generation clinical trials. A comprehensive review of the accuracy of the molecular methods used for the identification of EGFR gene mutation is being the scope of this guideline at this stage.

Bria et al has reported a literature-based meta-analysis undertaken to quantify the magnitude of benefit with upfront EGFR TKI in Asian patients with activating EGFR mutation (exon-19 deletions or exon-21 point mutations, (EGFR-GMT+))\[9\] They report findings from five RCTs involving 805 Asian patients, with results for efficacy in patients with activating EGFR mutations reported prospectively (three RCTs) or retrospectively (two RCTs).\[9\] Four trials evaluated the efficacy of gefitinib and one trial erlotinib, compared with a standard platinum based 3G chemotherapy regimen. EGFR TKI therapy significantly increased PFS (HR 0.45, 95% CI: 0.36–0.58, P < 0.0001), and overall RR (HR 2.08, 95% CI 1.75–2.46, P < 0.0001) over chemotherapy, with significantly lower neutropaenia.\[9\] The absolute difference in PFS was 26%, corresponding to three to four patients needed to treat for one to benefit, whilst the absolute difference in RR was 36.5%, which translating into two to three patients needed to treat for one to benefit.\[9\] No significant difference was observed in overall survival, thought largely to be due to treatment crossover with most patients initially treated with chemotherapy going on to receive EGFR TKIs at progression. The rate of exon-19 mutations, female gender, and nonsmoking status were identified as additional predictors of outcome in a meta-regression analysis.\[9\]

In a Caucasian population, Rosell et al, randomised 174 patients with advanced NSCLC and EGFR mutations (exon 19 deletion or L858R mutation in exon 21) to receive either first-line erlotinib 150 mg daily or a choice of a platinum based 3G doublet regimen. (cisplatin and gemcitabine or docetaxel).\[10\] The study met its primary endpoint of improved PFS at its pre-planned interim analysis, with median PFS in the erlotinib group of 9.7 months (95% CI 8.4–12.3), compared with 5.2 months (95% CI 4.5–5.8) in the standard chemotherapy group (HR 0.37, 95% CI 0.25–0.54; p<0.0001).\[10\] Response rate was also in favour of erlotinib (58% versus 15%).

These studies evaluating first line EGFR TKIs in EGFR GMT + patients, which demonstrate dramatic improvements in RR and PFS but not OS, have added to the debate regarding whether OS should remain the the most important therapeutic objective of first line studies in advanced NSCLC. As this guideline has demonstrated, there is evidence for improvement in PFS and OS beyond first line therapy with the use of first line maintenance, second line and even third line therapy. Survival post progression (SPP) on first line therapies has been evaluated in a systematic review by Hotta et al who reviewed 70 phase III trials initiated between 1988 and 2007 involving 38,721 patients with advanced NSCLC\[11\].
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This review also included studies evaluating molecularly targeted agents but did not report results according to each agent nor whether these studies were only conducted inpatients with an identified molecular target.

Nonetheless, Hotta et al observed a stronger association between median survival time (MST) and SPP ($r^2 = 0.8917$) than MST and median PFS time ($r^2 = 0.2563$), finding that SPP and MPFS can account for 89% and 25% of the variation in MST, respectively[11]. This association between MST and SPP became closer over the years from 1988 to 2007, leading to the conclusion that a PFS advantage from first line treatment is unlikely to be associated with an OS advantage due to this increasing impact of SPP on OS, and that prolongation of SPP might impact on the ability for OS to assessing true efficacy from early-line chemotherapy in future clinical trials[11]. In simple terms, this review highlights the impact of cross over at the completion of initial study treatment to other active drug therapy. How does this relate to anti-EGFR TKIs? Assuming a majority of patients commenced in initial chemotherapy do get to cross over to anti-EGFR TKIs at progression then OS does not appear to be compromised for the population, as found in the Bria and Rosell studies[9][10]. However for an individual patient there is the potential risk that second line treatment may not occur. The study by Fidias et al of immediate versus delayed docetaxel in non progressing patients after first - line platinum based chemotherapy, demonstrated an attrition rate of 37% i.e. 58 of 156 patients allocated to receive docetaxel at progression did not end up getting treated, 43% (25/58) due to progressive disease[12]. Whilst this may not be the case for the less toxic EGFR TKIs, it would be unreasonable for any patient to miss out on receiving treatment that can result in such a large effect on RR and PFS.

Evidence summary and recommendations

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<tr>
<td>Histology (non-squamous cell carcinoma versus squamous cell carcinoma) is associated with a significant treatment modifying effect for patients treated with pemetrexed based chemotherapy, with superior survival effect of pemetrexed observed in non-squamous cell carcinoma histology and inferior survival effect observed in squamous cell carcinoma histology, compared with other standard regimens when pemetrexed is used first-line, as switch maintenance or as second-line treatment.</td>
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Evidence-based recommendation

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**Evidence-based recommendation**

Due to the therapeutic implications, it is important to classify the histologic subtype of NSCLC on diagnostic specimens as accurately as possible, particularly to enable accurate distinction between the key histologic subtypes: adenocarcinoma and squamous cell carcinoma.

Last reviewed December 2015

**Practice point**

Given the importance of accurate histologic diagnosis and the potential need to have sufficient tissue for subsequent molecular testing, it is important to obtain as much tissue as possible at initial diagnosis in patients suspected to have NSCLC.

A multidisciplinary team discussion may be required in order to decide on the most appropriate diagnostic method to obtain adequate tissue.

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**Evidence summary**

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<td>In Asian patients with advanced NSCLC and known common activating EGFR GMs (exon-19 deletions or exon-21 point mutations), first-line therapy with a first generation EGFR TKI (gefitinib or erlotinib) significantly prolongs progression free survival and increases overall response rate, compared with standard platinum-based chemotherapy.</td>
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<td>[9]</td>
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<td>In regards to progression free survival, first-line gefitinib is not inferior to carboplatin/paclitaxel chemotherapy in Asian patients, particularly females, with adenocarcinoma, who have never smoked.</td>
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**Evidence-based recommendation**

Patients with known activating gene mutations (exon-19 deletions or exon-21 point mutations) to EGFR should be treated with an EGFR TKI.

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<tr>
<td>Progression free survival is significantly longer among patients treated with initial chemotherapy, than those treated with gefitinib in patients known not to have EGFR mutations.</td>
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**Evidence-based recommendation**

Where EGFR mutation status is negative or unknown, patients should be treated with standard chemotherapy.

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Practice point

The evidence in support of large treatment benefits with first-line EGFR TKIs in response rate and progression free survival argues for consideration of obtaining adequate tumour tissue where possible, to enable molecular testing for the presence of activating EGFR gene mutations. This will enable clinicians to offer patients initial EGFR TKIs versus empirical therapy, bearing in mind that overall survival for EGFR+ patients does not appear to be compromised, as long they go on to receive EGFR TKIs after chemotherapy.

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