Professional Organisation Statement

Multiple Technology Appraisal:
Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175) [ID620]

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What is the expected place of the technology in current practice?

Background

Lung cancer is one of the most common cancers in the UK with over 41 thousand new cases being diagnosed each year. In 2010, there were 34,859 deaths from lung cancer, a statistic that demonstrates how very poor the prognosis is for these patients[1] (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/lung). Lung cancer is the most common cause of cancer mortality in the UK, accounting for more than a fifth of all cancer deaths and constitutes almost a quarter (24%) of all male deaths from cancer and is also the most common cause of cancer death in women (21%).
The majority of patients with non-small cell lung cancer (NSCLC) present with advanced disease and although treatment rates vary across the UK, an average of 55% of patients who have good performance status (PS 0-1) receive first line chemotherapy[2] (http://www.ic.nhs.uk/webfiles/Services/NCASP/audits) with approximately 25% of all patients undergoing systemic treatment. Palliative chemotherapy modestly improves in median survival from 6 months to 8-11 months compared to best supportive care alone [3] for patients with stage IV NSCLC.
NICE guidance on the diagnosis and treatment of lung cancer (CG121) suggests that patients of good performance status (PS 0-1) diagnosed with stage III or IV disease should be offered platinum doublet chemotherapy (cisplatin or carboplatin plus one of the third generation drugs {docetaxel, gemcitabine, paclitaxel or vinorelbine}) in addition to supportive care.
More recently pemetrexed has been shown to improve outcomes for patients with NSCLC other than those with predominantly squamous cell histology[4,5]. The guidance goes on to recommend that patients who have progressed following initial chemotherapy should be considered for 2nd line treatment with docetaxel or erlotinib. Pemetrexed, although licensed for the 2nd line treatment of non-squamous NSCLC has not received NICE approval (TA 124, August 2007). Approximately 25% of patients who are treated with 1st line chemotherapy go on to receive 2nd line treatment in the UK.

Gefitinib is an oral tyrosine kinase inhibitor (TKI) which is licenced for the treatment of the sub-group of NSCLC patients in whom an epidermal growth factor receptor (EGFR) activating mutation is present and has received NICE approval for the 1st line treatment in this setting (TA 192, July 2010). In the UK, it is not licensed for the treatment of unselected patients with NSCLC and consequently, the use of gefitinib is confined to the 1st line treatment of patients with activating EGFR mutations.
Erlotinib is also an oral EGFR TKI, which is licensed for the treatment of the sub-group of NSCLC patients in whom an EGFR activating mutation is present, and has received NICE approval for this indication (TA 258, June 2012). In addition, it is licensed and NICE approved for the 2nd line treatment of unselected patients with NSCLC, as an alternative to docetaxel (TA162, November 2008).

Clinical Practice

In UK clinical practice gefitinib is not used in the area of interest for this appraisal, i.e. treating non-small cell lung cancer that has progressed following prior chemotherapy, but erlotinib is widely used for 2nd line treatment, whereas docetaxel treatment is reseved for the fittest patients. There are a number of reasons why erlotinib is used in preference to docetaxel in the majority of patients:

1. Erlotinib has a significantly different and more tolerable side effect profile compared to docetaxel: the majority of patients experience rash and diarrhoea, but there is less nausea, vomitting, lethargy, alopecia, arthralgia and neutropaenia
2. In clinical practice, admission rates for neutropaenic sepsis and treatment complications are 25-50% with docetaxel compared to <5% with erlotinib
3. Erlotinib is an oral therapy which has little impact on chemotherapy service delivery, whereas docetaxel is a 3 weekly intravenous treatment
4. There is evidence for patient preference for oral therapy

Clinical Evidence

EGFR plays an important role in the development and progression of NSCLC and in 10-15% of patients with non-squamous NSCLC activating mutations within the receptor can be identified. However, the NLCA data[2] shows that 30% of patients with NSCLC do not have an adequate tissue diagnosis and 1-5% of samples sent for EGFR mutation analysis fail due to insufficient or poor quality DNA, consequently, in a significant proportion of patients, the EGFR staus is unknown.

Unselected NSCLC populations – Studies of EGFR TKI compared to placebo

Two large phase III randomised placebo controlled clinical trials established the role of EGFR TKI's in the treatment of NSCLC after failure of chemotherapy: Shepherd and colleagues[6] randomised 731 unselected patients to receive erlotinib (n=488) or placebo (n=243). Overall survival was improved from 4.7 to 6.7 months (HR 0.7; CI 0.58-0.85; p,0.001) with erlotinib and was accompanied by benefit in quality of life measures despite treatment associated toxicities (commonly rash and diarrhoea). Subgroup analysis according to sex, histology, smoking status and ethnic origin demonstrated that all clinical subgroups derived benefit from treatment and, of interest, a subsequent presentation of 157 male smokers (current or ex) with squamous cell carcinoma from the study showed similar improvements in outcomes with a median survival time of 3.4 versus 5.5 months (HR 0.66; CI 0.47-0.92, p=0.016)[7]. A further study reported by Thatcher, et al[8] examined the role of gefitinib versus placebo in 1692 patients with previously treated NSCLC. Although overall survival was not statistically significant at 5.6 versus 5.1 months (HR 0.89, CI 0.77-1.02), there was a clear indication of activity, demonstrated by a response rate in the gefitinib arm of 8.0% compared to 1.3% with placebo.
In both of these studies, patients were not selected on clinical characteristics associated with the presence of EGFR mutations, such as light or never smoking history, female sex, adenocarcinoma histology or ethnic origin and, although some of the overall survival benefit may have been related to patients within the populations who harboured EGFR mutations, there is evidence that clinical benefit is not isolated to patients with EGFR mutations.

Unselected NSCLC populations – Studies of EGFR TKI compared to chemotherapy

Earlier studies suggested that EGFR TKIs were efficacious but less toxic than chemotherapy in NSCLC and in order to investigate this hypothesis several studies have compared to chemotherapy following failure of chemotherapy.
The INTEREST study[9] was designed as a non-inferiority study and reported on 1433 patients who had received at least 1 platinum containing regimen. Patients were randomised to receive gefitinib (n=723) or docetaxel (n=710) and equivalence was confirmed with median survival times 7.6 versus 8.0 months respectively (HR 1.09, CI 0.905-1.150). Adverse event recording showed more rash (49% vs 10%, all grades) and diarrhoea (35% vs 25%, allgrades) with gefitinib, but more neutropaenia (5% vs 74%), aesthenia (25% vs 47%) and alopecia (3% vs 36%) with docetaxel. The findings of this study were replicated in a Japanese study of similar design (n=489)[10] which confirmed non-inferiority of overall survival and improved toxicity with grade 3 or 4 toxicty occuring on 40.6% of patients on gefitinib and 81.6% of patients on docetaxel.
Ciuleanu[11] and colleagues enrolled 424 patients who had progressed during or immediately after platinum doublet first line chemotherapy to receive either erlotinib (n=203) or chemotherapy (n=221, docetaxel or pemetrexed at investigators discretion). Results showed that median survival times were similar (5.3 versus 5.5 months, HR 0.96, CI 0.78-1.19, p=0.73, for erlotinib versus chemotherapy) and toxicity profiles varied according to treatment type as expected.
These studies were conducted at a time prior to routine EGFR mutation testing, in unselected patients and the conclusion drawn was that EGFR TKIs provide an alternative to chemotherapy in patients who have progressed following initial systemic treatment,

demonstrating similar efficacy to chemotherapy, but with a favourable side effect profile and less impact on outpatient chemotherapy services.

EGFR wild type patients – EGFR TKI compared to chemotherapy

More recently there have been 2 randomised studies of EGFR TKI versus chemotherapy in EGFR wild type (negative) populations, however data from these studies has only been presented in abstract form, is not mature and should be interpreted with caution. The TAILOR study randomised 222 patients who had undergone genotyping to confirm EGFR wild type status, to receive either docetaxel (n=110) or erlotinib (n=109). The study was designed to detect a 30% difference in overall survival in favour of docetaxel and preliminary results, which were reported in a late breaking abstract at the ASCO annual meeting in 2012[12], demonstrated improved response rate (14% vs 2%, p=0.004) and progression free survival time (3.4 months vs 2.0 months, HR 0.69, CI 0.52-0.93) for docetaxel compared to gefitinib. Yang and colleagues[13] reported a phase II study of 157 patients with EGFR wild type non-squamous NSCLC who had received previous platinum doublet chemotherapy. Patients were randomised to receive pemetrexed (n=79) or gefitinib (n=81) and the primary end point was progression free survival (PFS). The study showed a benefit for chemotherapy with PFS 4.8 months in the pemetrexed arm versus 1.6 months in the gefitinib arm (HR 0.51, CI 0.36-0.76, p<0.001), disease control rate 61% vs 32%, although interestingly response rates were similar 13.3% vs 14.7%. It should be noted that all patients in this study were of good performance status (PS0-1) and were significantly younger (median 56 years) than the average NSCLC patient.
Neither of these studies have reported overall survival data as yet, but they fuel lively debate about the optimum treatment for EGFR wild type NSCLC patients. Clearly, further data is required in order to make robust conclusions.

NSCLC Treatment Guidelines

There are 3 internationally recognised guidelines for the treatment of NSCLC which offer advice on second line systemic therapy:

1. American Society of Clinical Oncology (ASCO) guidelines[14] state docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line, platinum-based therapy.
2. European Society of Medical Oncology (ESMO) clinical practice guidelines[15] recommend second line treatment for PS 0-2 NSCLC patients with pemetrexed (for non-squamous NSCLC) or docetaxel. It extends the recommendation for 2nd line treatment with erlotinib to patients of less good performace status (PS 0-3).
3. National Comprehensive Cancer Network (NCCN)[16] (USA) guidelines recommend second line treatment for PS 0-2 NSCLC patients with pemetrexed (for non-squamous NSCLC), docetaxel or erlotinib (or gefitinib in the countrries where it is licensed).

There is no restriction in any of these guidelines on the second line use of EGFR TKIs according to EGFR mutation analysis.

Where is the technology used?

The technologies are used in secondary care and administered through oncology out-patient clinics. Any change in guidelines which could result in increased use of chemotherapy would have an impact on treatment delivery in chemotherapy units.

The advantages and disadvantages of the technology

The main advantages of the technologies under appraisal are:

1. EGFR TKIs are oral treatment with more a tolerable toxicty profile than chemotherapy

2. EGFR TKIs exhibit a reduced incidence of grade 3/4 toxicity requiring hospital admission (with the associated costs) compared to chemotherapy
3. EGFR TKIs do not require growth factor support (needed in up to 50% of patients receiving docetaxel for secondary prophylaxis)
4. EGFR TKIs do not impact on chemotherapy unit service provision
5. EGFR TKIs provide a second line treatment option in patients for whom best supportive care would be the only option (2 month overall survival benefit demonstrated)

The main disadvantages of the technologies under appraisal are:

1. EGFR TKIs are associated with toxicity, mainly rash and diarrhoea, but these are manageble
2. In EGFR wild type patients who are fit enough to receive 2nd line chemotherapy, there **may** be a benefit of chemotherapy over EGFR TKIs, however there data is immature and there is no overall survival information to date

Implementation issues

The majority of patients who receive 2nd line treatment in the UK are treated with erlotinib. At present, some patients receiving erlotinib are assessed in nurse led clinics, but this method of follow up would not be appropriate for patients receiving docetaxel chemotherapy due to the high incidence and grade of toxicity. In addition, patients being treated with erlotinib are reviewed 4 weekly in clinic, but patients receiving docetaxel are reviewed 3 weekly. Both of these factors would add to the burden in medical oncology outpatient clinics if there was any change in guidance resulting in increased chemotherapy usage. Furthermore, there would be increased burden on chemotherapy administration services, pharmacy aseptic units, and in-patient services (due to the increased toxicity associated with chemotherapy).
Each provider of oncology services would need to assess locally the potential impact of any change in guidance for patients with NSCLC and consider how any increase in demand might be accomodated.

Equality

There is potential for a change in NICE guidance to disadvantage some groups of patients, e.g.there is a significant proportion of patients who are not fit enough to receive 2nd line chemotherapy, but currently benefit from treatment with 2nd line erlotinib.

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