Crizotinib

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

ATC codes: L01ED01

Indication	Other specified malignant neoplasms of bronchus or lung ICD11 code: 2C25.Y
INN	Crizotinib
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid:** 200 mg ; 250 mg
EML status history	Application rejected in 2017 (TRS 1006)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Crizotinib
DrugBank	Crizotinib

Expert Committee recommendation

The Expert Committee noted that presentation of the evidence in the application was unsatisfactory: the application did not follow the standard template, and some important elements of the evaluation were missing or inadequately addressed. Applications in general would benefit from greater focus on the benefits and harms associated with the medicines that are to be evaluated. Extensive search of available evidence is preferable to selective inclusion of some studies. Data from trials and reviews should be summarized in the application, and transparent descriptions of the limitations of the evidence should be provided. Applications should provide the key information to allow evaluation of the merits of medicines proposed for the EML relative to those already listed. Information should be quantified, in forms that facilitate the assessment of benefits and harms. The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options, across treatment lines. The working group should support WHO in establishing some guiding principles in relation to the potential inclusion of second-line treatments, clarifying what constitutes a clinically relevant therapeutic effect – and one that is sufficient for a cancer medicine to be granted the status of essential medicine. The Committee considered that epidermal growth factor receptor tyrosine kinase inhibitors and the anaplastic lymphoma kinase inhibitor may be a valid treatment option for use in patients with non-small cell lung cancer. Erlotinib, gefitinib and afatinib are associated with a more favourable tolerability profile and comparable efficacy to cytotoxic chemotherapy, and crizotinib has been associated with greater efficacy in terms of progression-free and overall survival compared with chemotherapy. However, the need to screen patients to determine suitability for treatment must be taken into account by health

systems. The availability, affordability and quality of diagnostic screening of patients for epidermal growth factor receptor mutations and anaplastic lymphoma kinase gene rearrangements will be an important factor requiring consideration by the working group in prioritizing cancer therapies for future EML applications. The Expert Committee therefore recommended that erlotinib, gefitinib, afatinib and crizotinib should not be added to the EML at this time, but should be reconsidered as part of a high-quality review considering a wider spectrum of options in non-small cell lung cancer at its next meeting.

Background

The application requested addition of the tyrosine kinase inhibitor erlotinib to the Complementary List of the EML, with a square box as the representative of the pharmaceutical class, with gefitinib and afatinib available as alternatives, for the treatment of non-small cell lung cancer (NSCLC) in patients with activating mutations of epidermal growth factor receptor. The application also requested addition of the anaplastic lymphoma kinase (ALK) inhibitor crizotinib to the Complementary List of the EML as first-line treatment for NSCLC in patients with ALK gene rearrangements. A comprehensive review of NSCLC medicines was conducted in 2015. The Expert Committee endorsed etoposide, carboplatin and paclitaxel (already included on the Complementary List) and recommended the addition of vinorelbine, gemcitabine and cisplatin to the Complementary List for this indication. At that time, the Committee did not recommend addition of the TKIs gefitinib and erlotinib to the Complementary List, acknowledging that, while individual patients with a drugsensitive epidermal growth factor receptor (EGFR) mutation may derive a substantial extension of life, the average increase in progression-free survival was modest (3–4 months). The Committee also considered that substantial infrastructure would be required to establish routine and reliable molecular testing for EGFR mutations in NSCLC. The Committee considered it was neither practical nor cost effective to establish molecular testing, and the use of TKIs as essential medicines for this disease could therefore not be supported. Afatinib and crizotinib were not proposed for inclusion by applicants nor recommended by the Expert Committee.

Public health relevance

According to GLOBOCAN, lung cancer has been the most common cancer globally for several decades; estimated worldwide incidence in 2012 was 23.1 per 100 000 (agestandardized rate (ASR)) (12.9% of all cancers) (1). Of the 1.8 million new cases in 2012, 58% occurred in less-developed regions; ASR incidence rates were highest in central and eastern Europe (53.5 per 100 000) and in eastern Asia (50.4 per 100 000) and were 25% higher for men than for women (205 and 165 per 100 000 respectively). GLOBOCAN estimated the global mortality ASR in 2012 to be 19.7 per 100 000. Lung cancer had the second highest absolute incidence globally after breast cancer, and was the leading cause of death from malignant disease in 93 countries, accounting for one fifth of the total global burden of disability-adjusted life years from cancer. The most common form of the disease is NSCLC, which accounts for 85–90% of all lung cancers (2, 3). Most patients with NSCLC present with advanced stage disease – stage IV in particular – and half of all patients treated initially for potentially curable early-stage disease will experience recurrences with metastatic disease (4). Patients with stage IV disease are never curable, and chemotherapy, targeted therapy and radiation can only extend survival and palliate symptoms. Although NSCLC is generally regarded as a disease of the elderly, a third of cases are diagnosed in patients under 65 years of age (4). Platinum-based doublet chemotherapy is the standard first-line treatment for patients with advanced (stage IV) disease.

Benefits

Where high-quality molecular diagnostics and targeted therapies are available, patients with activating mutations of EGFR may benefit from treatment with TKIs (erlotinib, gefitinib and afatinib). EGFR-sensitizing mutations (defined as in-frame deletions in exon 19 and L858R substitution in exon 21), are found in 10% of Caucasians with NSCLC and up to 50% of Asian patients (5). ALK gene rearrangements are found in 3–7% of NSCLC (6–9). The incidence of mutation rates is still unknown in most parts of the world. Patients with driver oncogenes who have not previously received a targeted therapy may be treated with EGFR-TKIs or crizotinib as salvage therapy (10). The application did not summarize the evidence and conclusions were not supported by a valid review process.

For this reason, evidence has been complemented by the Secretariat. Erlotinib, gefitinib, afatinib A Cochrane systematic review assessed the effectiveness of single-agent or combination EGFR therapies used in the first-line treatment of people with locally advanced or metastatic EGFR mutation-positive NSCLC compared with other cytotoxic chemotherapy agents, used alone or in combination, or best supportive care (11). Nineteen trials were included, involving 2317 patients, of whom 1700 were of Asian origin. The review reports that "overall survival (OS) data showed inconsistent results between the included trials that compared EGFR-targeted treatments against cytotoxic chemotherapy or placebo". When erlotinib was compared with platinum-based chemotherapy, the overall treatment effect indicated no significant difference in OS between the groups, with a hazard ratio (HR) of 0.95 (3 studies; 95% confidence interval (CI) 0.75–1.22). For progression-free survival (PFS), however, erlotinib showed a statistically significant benefit compared with cytotoxic chemotherapy (4 studies; HR 0.30; 95% CI 0.24–0.38). One small trial (FASTACT 2) did report statistically significant OS (HR 0.48; 95% CI 0.27– 0.85) and PFS (HR 0.25; 95% CI 0.16–0.39) gains for participants treated with erlotinib plus cytotoxic chemotherapy compared with cytotoxic chemotherapy alone, while another trial showed no meaningful differences between erlotinib and vinorelbine (OS HR 2.16; 95% CI 0.58–8.10). It was not possible to combine all single estimates of the effect sizes in an overall estimate. Four trials compared gefitinib with platinum-based chemotherapy. Trial results did not show statistical differences for OS (1 trial, gefitinib vs gemcitabine plus cisplatin: HR 1.04, 95% CI 0.50–2.20; gefitinib vs carboplatin and paclitaxel: two trials, HR 0.95, 95% CI 0.77– 1.18; gefitinib vs docetaxel plus cisplatin: one trial, HR 1.25, 95% CI 0.88–1.78). Four studies provided data for PFS. Trials showed statistically significant differences in time before the cancer progressed between gefitinib and platinum-based chemotherapy, to a large extent in some cases (gefitinib vs gemcitabine plus cisplatin: HR 0.54, 95% CI 0.27–1.10; gefitinib vs paclitaxel plus carboplatin: two trials, HR 0.39, 95% CI 0.32–0.48; gefitinib vs docetaxel plus cisplatin: one trial, HR 0.49, 95% CI 0.34–0.71). When gefitinib was added to platinum-based chemotherapy and compared with platinumbased chemotherapy (two studies), results were not significantly different for either OS (HR 1.77 95% CI 0.50–6.23) or PFS (HR 0.55; 95% CI 0.19–1.60). Afatinib (n = 709) showed a statistically significant PFS benefit when compared with chemotherapy in a pooled analysis of two trials (HR 0.42; 95% CI 0.34–0.53). Results for OS were immature. Indirect comparisons showed that the three EGFR-TKIs have similar efficacy but may differ within class in terms of toxicities (12, 13). However, indirect comparisons might not be appropriate because of the different enrolled populations across the included trials. Crizotinib For patients with ALK gene rearrangements, second-line crizotinib has been associated with improvements in PFS when compared with pemetrexed or docetaxel (7.7 months in the crizotinib group and 3.0 months in the chemotherapy group: HR 0.49; 95% CI 0.37– 0.64). However, OS showed no significant improvement with crizotinib compared with chemotherapy (HR 1.02; 95% CI 0.68–1.54; P = 0.54) (14). Among patients givenIn crizotinib for first-line treatment, compared with pemetrexed in combination with cisplatin or carboplatin, there was a significantly longer PFS (median 10.9 months vs 7.0 months; HR 0.45; 95% CI 0.35–0.60) but no significant improvement in OS (median overall survival was not reached in either group; HR, 0.82; 95% CI 0.54–1.26) (15). Data are still too immature to allow firm conclusions to be reached. Selective cross-over from the control arm to the intervention arm might dilute the benefits associated with crizotinib, making inferences about effectiveness difficult, even when the total number of events required for the final analysis of OS is reached. Evidence from one observational study (10) showed that crizotinib was associated with improvement in OS compared with chemotherapy: 1-year OS was 70% (95% CI 50–83%) for the crizotinib-treated group versus 44% (95% CI 23–64%) for the crizotinib-naive group; 2-year OS was 55% (95% CI 33–72%) versus 12% (95% CI 2–30%) (HR 0·36; 95% CI 0.17– 0.75). This was a small study and should be interpreted with caution. More than a third of the crizotinib group had received multiple lines of therapy, suggesting a potentially more indolent disease course. Nearly a third of the control patients were screened for ALK with the intention of enrolling in a trial but were subsequently deemed ineligible. Patient selection and indication biases could therefore have contributed to a systematic imbalance that favoured improved survival in the crizotinib group and worse survival in the control group.

Harms

Both EGFR-TKIs and the ALK inhibitor are well tolerated by many patients. Agents have similar toxicity profiles, although the incidence of toxicity depends on the drug. Diarrhoea and skin rash are the most common grade 3 and

4 adverse events, but their incidence is highly variable (11). Rarely, more severe gastrointestinal toxicity, including perforation, can occur, particularly with erlotinib (16). All agents may also cause hepatic toxicity and increased hepatic transaminases. Hepatic failure and hepatorenal syndrome have been reported in patients treated with erlotinib, although the incidence is low. The common side-effects of crizotinib are diarrhoea, oedema, vision changes and elevation in aminotransferase levels. Cytotoxic chemotherapy was associated with greater grade 3/4 myelosuppression, fatigue and anorexia.

Cost / cost effectiveness

The contributors to the applications suggested that price adjustments are imminent that will make the cost of the three TKIs comparable in the near future. However, no data were provided on costs, cost comparisons or cost analyses. EGFR-TKIs and the ALK inhibitor are more expensive than standard chemotherapies. However, as they are oral medicines, administration is simple compared with that of, for example, docetaxel, which should be administered in a specialized health care unit.

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