Erlotinib

Essential medicine status

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

ATC codes: L01EB02

Indication	Other specified malignant neoplasms of bronchus or lung ICD11 code: 2C75.Y
INN	Erlotinib
Medicine type	Chemical agent
List type	Complementary
Formulations	Oral > Solid: 100 mg ; 150 mg
EML status history	Application rejected in 2017 (TRS 1006) Added in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	gefitinib (ATC codes: L01EB01) afatinib (ATC codes: L01EB03)
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Cancer
Wikipedia	Erlotinib
DrugBank	Erlotinib

Expert Committee recommendation

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of the tyrosine kinase inhibitors afatinib, erlotinib and gefitinib. The Committee noted that afatinib, erlotinib and gefitinib were all scored as 4/5 on the ESMO-MCBS v1.1 for this indication. The Expert Committee recommended the addition of erlotinib with a square box to the complementary list of the EML for first-line treatment of EGFR mutation-positive advanced non-small cell lung cancer. Afatinib and gefitinib should be considered as therapeutically equivalent alternatives. The Committee noted that these medicines are associated with relevant survival benefits for patients, acceptable toxicity and improvements in quality of life compared to chemotherapy. The Committee also noted that since these medicines were considered for inclusion on the EML in 2015, generic versions of these medicines are more widely available, as are quality-assured diagnostic molecular tests for EGFR mutations.

Background

The application requested the addition of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) to the complementary list of the EML for first-line treatment of EGFR mutation positive, non-small cell lung cancer. EGFR TKIs have been considered and rejected for inclusion on the EML on two previous occasions in 2015 and 2017. In each case, the Expert Committee acknowledged that individual patients with a drug-sensitive EGFR mutation may derive benefit from TKI therapy, which has been associated with similar efficacy and more favourable tolerability compared to cytotoxic chemotherapy. However, the requirements to screen patients for suitability for treatment must be taken into account by health systems (1, 2). Cytotoxic chemotherapy

currently included on the EML for treatment of non-small cell lung cancer (NSCLC) includes carboplatin, cisplatin, etoposide, gemcitabine, paclitaxel and vinorelbine.

Public health relevance

Lung cancer is the most commonly diagnosed cancer globally, and the leading cause of cancer death, with estimated 2 million new cases and 1.7 related deaths in 2018. The economic impact of lung cancer has been estimated at around US$ 8 billion in lost productivity in the BRICS countries (Brazil, Russia, India, China and South Africa) (3). Moreover, in the absence of wide coverage of effective screening programmes on a global scale, lung cancer diagnoses occur in advanced stage in more than 60% of cases, with highly regional variability (4, 5). The mutational pattern of NSCLC varies across the different regions, with a higher prevalence in Asia Pacific (up to 76% of patients) and the lowest registered in Oceania (12%). Africa, Europe and North America registered the same rate of EGFR-mutated NSCLC, at around 20% (6–8). Non-squamous NSCLC has been linked to gene mutations in EGFR. This disease, given its incidence, comprises a high burden and leads to a high mortality. However, with advances in cancer gene-directed treatment, the outcome of the disease has improved. The response rate doubled as compared to chemotherapy, the progression free survival (PFS) doubled and the median survival time increased to nearly three years if patients receive both the targeted medicines and chemotherapy together (the median survival time for patient receiving chemotherapy only is approximately 10 months, in historical series).

Benefits

The application reported the findings and recommendations for EGFR-mutated NSCLC from the 2018 European Society For Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow up of metastatic nonsmall cell lung cancer (9). The ESMO guidelines state that EGFR-TKIs are the standard of care for first-line treatment for advanced EGFR-mutated NSCLC (level of evidence: I; grade of recommendation: A). EGFR mutation as an oncogenic target has proven predictive power in NSCLC from multiple Phase III trials of EGFR-TKIs versus platinum-based chemotherapy (10–15). The improvement in objective response rate (ORR) and progression free survival (PFS) is consistent across all age groups, genders, smoking status and performance status. However, none of the above studies demonstrated an overall survival benefit for a EGFR-TKI over platinum-based chemotherapy, likely due to the high level of crossover (16). The use of EGFR-TKI as first-line therapy has been associated with a greater benefit than as second-line treatment after chemotherapy for PFS (12.9 months vs 9.0 months (HR 0.78, 95%CI 0.61 to 0.98. p=0.034)), ORR (67.8% and 55.6%, respectively, p=0.001). Overall survival in patients receiving first-line TKI followed by second-line chemotherapy was longer than in patients receiving TKI second-line after chemotherapy (30.7 months vs 27.2 months (HR 0.69, 95%CI 0.50 to 0.94, p=0.02) (17). Evidence supports the continuation of EGFR-TKI treatment beyond radiological progression in patients who are clinically stable (18). EGFR-TKI use in combination with local radiation therapy in patients with oligoprogressive disease, has also been shown to be associated with significantly longer PFS (19). The IMPRESS trial tested the continuation of gefitinib plus chemotherapy with placebo plus chemotherapy in patients with EGFR mutation-positive advanced NSCLC with progression after first-line gefitinib (20). The trial failed to show a benefit of the continuation strategy of the EGFR-TKI as add-on strategy; the continuation of gefitinib plus cisplatin and pemetrexed was detrimental to OS when compared with placebo plus cisplatin and pemetrexed (hazard ratio [HR] 1.44, 95%CI 1.07 to 1.94; p=0.016; median OS, 13.4 v 19.5 months). Therefore, continuous use of EGFR-TKI in combination with chemotherapy is not recommended. The NEJ009 trial evaluated the efficacy of a combination of gefitinib and carboplatin/pemetrexed in untreated advanced NSCLC patients with EGFR mutations (21). Carboplatin/pemetrexed/gefitinib demonstrated better PFS (mPFS: 20.9 vs 11.2 months, HR 0.49, 95%CI 0.39 to 0.62) and OS (mOS: 52.2 vs 38.8 months, HR 0.69, 95%CI 0.52 to 0.92) compared with gefitinib monotherapy in advanced EGFR mutated NSCLC, representing a first-line therapy option. The choice between first- (gefitinib or erlotinib, (reversible)) and second-generation (afatinib, (irreversible)) EGFR-TKIs was investigated in two randomized studies. The Phase IIB LUX-Lung 7 trial compared afatinib with gefitinib (22). The study reported similar tumour ORR and a modest nonclinically meaningful difference in PFS (mPFS 11.0 vs 10.9 months; HR 0.73, 95%CI 0.57 to 0.95, p=0.0165). OS was not statistically different (23). There was no difference in OS in patients with EGFR exon 19 mutation, contrary to earlier claims of benefit in this sub-group from the pooled analysis of LUX-Lung 3 and LUX-Lung 6 studies (24). ARCHER 1050 is a randomized Phase III study that compared dacomitinib (a second-generation EGFR-TKI) with gefitinib in stage IV EGFRmutated lung cancer patients without central nervous system (CNS) metastasis (25, 26). The study showed an improved PFS in the dacomitinib arm (mPFS 14.7 vs 9.2 months; HR 0.59, 95%CI 0.47 to 0.74, p<0.0001). The mOS was 34.1 months with dacomitinib vs 26.8 months with gefitinib (HR 0.76, 95%CI 0.58 to 0.993, p<0.04).

The OS probabilities at 30 months were 56.2% and 46.3% with dacomitinib and gefitinib, respectively.

Harms

The toxicity profile of EGFR-TKIs is generally clinically manageable, with 6% of toxicity-related treatment discontinuation reported in one pooled analysis (27, 28). The use of EGFR-TKI was favoured over chemotherapy in quality of life (QoL) analyses, reporting a longer time to clinical deterioration and maintained overall QoL (29–31). For afatinib, an extensive investigation of patient-reported symptoms and health-related QoL benefits have been reported, showing that afatinib delayed the time to deterioration for cough (HR 0.60, 95%CI 0.41 to 0.87; p=0.007) and dyspnoea (HR 0.68, 95%CI 0.50 to 0.93; p=0.015), with more patients on afatinib (64%) versus chemotherapy (50%) experiencing improvements in dyspnoea scores (p=0.010), the cardinal symptom for lung cancer patients (32). For erlotinib, a secondary analysis from the OPTIMAL (CTONG-0802) Phase III clinical trial, showed that patients receiving erlotinib experienced clinically relevant improvements in QoL compared with the chemotherapy group, across different scales to assess general outcome and lung-specific subscales (33). Data for gefitinib are still consistent with the findings for the other two EGFR-TKIs: time to deterioration in physical and life well-being favoured gefitinib over chemotherapy (HR of time to deterioration, 0.34, 95%CI 0.23 to 0.50; p<0.0001 and HR 0.43, 95%CI 0.28 to 0.65; p<0.0001, respectively) (29).

Cost / cost effectiveness

A cost-effectiveness analysis performed by the Institute for Clinical and Economic Review showed that the use of each of the first-line EGFR-TKI regimens resulted in a 0.84 life-year gain in survival relative to chemotherapy. Quality-adjusted life-years (QALYs) gained versus chemotherapy were also very similar, ranging from 0.60 for gefitinib to 0.62 for afatinib and erlotinib. Incremental costs versus chemotherapy were lower for gefitinib (approximately US$ 66 000) than for the other EGFR-TKIs, as a function of a shorter duration of time spent in the progression-free state (and a consequently shorter duration of treatment). Cost-effectiveness estimates were similar across the EGFR-TKIs, ranging from approximately US$ 110 000 to US$ 150 000 per QALY gained (34). In another cost-effectiveness analysis, two different strategies were compared: the 'EGFR testing strategy', in which EGFR mutation testing was performed before treatment and patients with EGFR mutations received gefitinib while those without mutations received standard chemotherapy, to the 'notesting strategy,' in which genetic testing was not conducted and all patients were treated with standard chemotherapy. The authors concluded that the combination use of gefitinib and EGFR testing can be considered a cost-effective first-line therapy compared to chemotherapy such as carboplatin-paclitaxel for the treatment for NSCLC in Japan (35). Technology appraisal guidance issued by National Institute for Health and Care Excellence (NICE) for first-line EGFR-TKIs gefitinib, erlotinib and afatinib state that these medicines are recommended treatment options people with locally advanced or metastatic EGFR mutation-positive NSCLC if the manufacturers provide the drugs at agreed fixed or discounted prices (36–38).

WHO guidelines

None available.

Availability

Originator brands of afatinib, erlotinib and gefitinib are manufactured by Boehringer Ingelheim, Roche and AstraZeneca, respectively. Generic brands are becoming available.

Other considerations

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of EGFR TKIs on the EML, stating that there is sufficient evidence that these medicines are equivalent or superior to existing listed medicines, based on updated meta-analysis and real-world data, particularly in middle-income countries. Based on the results of the LUX-Lung 3 study (14, 32), afatinib received a score of 4 on the ESMO-Magnitude of Clinical Benefit Scale (MCBS, v1.1) for first-line use in metastatic EGFR+ NSCLC (39). Based on the results of the OPTIMAL (40) and EURTAC (13) studies, erlotinib received a score of 4 on the ESMO-MCBS v1.1 for use in metastatic EGFR+ NSCLC (39). Based on the results of the IPASS study (10, 41), gefitinib received a score of 4 on the ESMO-MCBS v1.1 for first-line use in metastatic EGFR+ NSCLC (39).

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