ARTIGO DE REVISÃO

Epidermal growth factor receptor inhibitors in non-small cell lung cancer: current status and future perspectives

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SUMMARY

Two classes of epidermal growth factor receptor (EGFR) inhibitors are currently available for clinical use: tyrosine-kinase inhibitors (TKIs) and monoclonal antibodies. The introduction of pharmacological agents that are able to inhibit EGFR represents an important step in the management of patients with advanced non-small cell lung cancer (NSCLC), the leading cause of cancer death worldwide. The use of EGFR inhibitors has not only led to meaningful therapeutic gains for patients, but has also expanded our knowledge about the disease itself, as it is now recognized that activating mutations of EGFR play a pathogenetic role in NSCLC, especially in adenocarcinoma, patients who never smoked or former light smokers, females, and Asian individuals. Patients with NSCLC and one or more of these features are more likely to harbor tumors with EGFR mutations, and hence to respond to TKIs, than individuals without these features. Currently, TKIs are considered by many as the treatment of first choice in both the first- and second-line treatment of patients with clinical or molecular predictors of therapeutic benefit, and chemotherapy is a second option in these cases, especially when activating mutations of EGFR are present. Moreover, TKIs and anti-EGFR antibodies may be used in other settings, and their therapeutic role in NSCLC is clearly expanding. However, despite an initially successful treatment course, patients with advanced NSCLC eventually develop resistance to TKIs; and novel agents that hold promise for the future include irreversible EGFR inhibitors with activity against resistance-conferring EGFR mutations.

Keywords: Receptor, epidermal growth factor; lung neoplasms; mutation; oncogenes.

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RESUMO

Inibidores do receptor do fator de crescimento epidérmico no câncer de pulmão em células não pequenas: estado atual e perspectivas futuras

Duas classes de inibidores do receptor do fator de crescimento epidérmico (EGFR) estão atualmente disponíveis para uso clínico: inibidores de tirosina-quinase (TKI) e anticorpos monoclonais. A introdução de agentes farmacológicos capazes de bloquear o EGFR representa um passo importante no manejo de pacientes com câncer de pulmão de células não pequenas (CPCNP) avançado, principal causa de morte por câncer no mundo. Além dos benefícios clínicos significativos obtidos com os inibidores de EGFR, o uso desses agentes proporcionou um maior conhecimento sobre a doença, sendo agora reconhecido que mutações ativadoras de EGFR desempenham um papel patogênico importante no CPCNP, especialmente em adenocarcinomas, indivíduos não fumantes, mulheres e asiáticos. Indivíduos com CPCNP e uma ou mais dessas características são mais propensos a apresentar tumores com mutações de EGFR e, portanto, a responder aos TKIs do que pacientes sem essas características. Atualmente, os TKIs são considerados por muitos como a estratégia terapêutica de escolha na primeira e segunda linhas de tratamento de pacientes com fatores clínicos ou moleculares preditivos de benefício terapêutico, com a quimioterapia sendo vista como a segunda opção nesses casos, especialmente na presença de mutações ativadoras de EGFR. Além disso, TKIs e anticorpos anti-EGFR podem ser usados em outras situações, e seu papel no CPCNP está em clara expansão. No entanto, apesar de um curso de tratamento inicialmente bem-sucedido, pacientes com CPCNP avançado eventualmente desenvolvem resistência aos TKIs. Novos agentes promissores incluem inibidores irremissíveis de EGFR com ativação contra formas mutantes de EGFR que conferem resistência.

Unitermos: Receptor do fator de crescimento epidérmico; mutação; oncogenes; neoplasias pulmonares.

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INTRODUCTION
Non-small cell lung cancer (NSCLC), which currently represents nearly 85% of primary malignant lung tumors, is the leading cause of cancer deaths worldwide. Despite the potential benefits of improved diagnostic modalities, approximately 50% of patients with NSCLC present with advanced, incurable disease. For such patients, treatment is performed with a palliative intent, and prognosis is still poor. Cytotoxic chemotherapy, although able to improve the overall survival (OS) of patients with advanced NSCLC, seems to have reached a plateau of efficacy nearly a decade ago. In recent phase III trials among patients with advanced NSCLC, the median OS has typically ranged from only eight to 12 months. Therefore, new treatment modalities have been thoroughly investigated in recent years, usually based on advances in our understanding of tumor biology. Given the role of the epidermal growth factor receptor (EGFR) in the pathogenesis of NSCLC, inhibitors of this receptor have received the greatest attention, and have indeed been found to provide therapeutic benefits for certain patients. This review summarizes the current knowledge regarding the role of EGFR inhibitors in the treatment of patients with advanced NSCLC.

PATHOGENETIC ROLE OF EGFR IN NSCLC
EGFR is a member of a family of closely-related membrane receptors with intrinsic tyrosine-kinase activity. The generic structure of the four known members of the human epidermal receptor (HER) family is shown in Figure 1. Upon ligand binding to the extracellular portion of EGFR, receptor dimerization with another EGFR molecule or with another member of this family (namely, HER-2, HER-3, or HER-4) leads to autophosphorylation of the intracellular tyrosine-kinase domain of the receptor, which serves as a docking site to a series of adaptor molecules and kinases that are able to transduce the signal downstream towards the nucleus. EGFR is overexpressed in the majority of lung tumors and is correlated with poor prognosis, thus providing the rationale for the development of novel agents that target this receptor.

EGFR INHIBITORS: CHEMICAL CLASSES AND MODE OF ACTION
At least theoretically, the activity of EGFR may be inhibited at different molecular levels, including the EGFR gene, its messenger RNA, and the receptor protein itself. To date, only receptor-targeting strategies have reached advanced phases of clinical development. Two classes of EGFR inhibitors are currently available for clinical use in many countries: tyrosine-kinase inhibitors (TKIs) and monoclonal antibodies. Both classes of agents exert antitumor activity, but their mode of administration and mechanism of action are different, with potential implications for clinical efficacy.

Erlotinib and gefitinib are the TKIs currently approved in some countries for the treatment of advanced NSCLC. They are orally administered, quinazoline-derived adenosine triphosphate (ATP) analogs that work by reversibly inhibiting the binding of ATP to the intracellular tyrosine-kinase domain of EGFR (Figure 1). As a result, downstream signaling by this receptor is reversibly blocked. Cetuximab is an intravenously administered monoclonal antibody that binds to the extracellular portion of EGFR, potentially blocking downstream signals from the receptor. Binding of cetuximab leads to receptor endocytosis and degradation; in addition, cetuximab and other monoclonal antibodies may lead to antibody-dependent cell-mediated cytotoxicity and tumor eradication through immunological mechanisms.

CLINICAL DEVELOPMENT OF TKIs
HISTORICAL DEVELOPMENT AND THE ROLE OF EGFR MUTATIONS
Following extensive pre-clinical testing and phase I trials, both currently available TKIs provided encouraging results in phase II trials. In those trials, erlotinib and gefitinib were used as single agents after the failure of conventional chemotherapy. Although the dose of 150 mg per day was established early in the development of erlotinib, gefitinib was used at two dose levels (250 mg and 500 mg) in some of its phase II and phase III trials. The most common adverse events resulting from the use of erlotinib and gefitinib are acneiform rash (most frequently involving the face and trunk) and diarrhea. Other adverse events are infrequent and seldom lead to treatment discontinuations.

Given the pre-clinical evidence for synergism between TKIs and chemotherapy, a generation of phase III trials was launched in an attempt to evaluate whether the addition of TKIs to first-line chemotherapy would improve treatment results. Unfortunately, four phase III trials involving a total of over 4,000 patients provided negative results in progression-free survival (PFS) and OS. In spite of the negative results from phase III trials, it soon became clear that the use of TKIs in clinical practice benefited some patients in a preferential manner. Those conflicting observations appeared puzzling at the time and were explained only when the role of somatic EGFR mutations became evident.
We now know that acquired mutations in the portion of the EGFR gene (exons 18 to 24) encoding the tyrosine-kinase domain of the receptor confer sensitivity to TKIs. Such mutations, also called activating mutations, have been found in 15% to 40% of cases in various published studies.

Overall, activating EGFR mutations are more frequent in females, Asian individuals, and non-smokers. Interestingly, these same features had been associated with an increased sensitivity to erlotinib and gefitinib in clinical trials, and the discovery of the correlation between their presence and EGFR mutations provided the missing link at the time. Likewise, patients with adenocarcinoma as the histological subtype of NSCLC also appeared to derive more benefit from TKIs, and the demonstration that EGFR mutations are more common in individuals with adenocarcinoma eventually explained that observation. Of note, adenocarcinoma is currently the most frequent histological type of NSCLC in most studies, having thus surpassed squamous tumors.

**Second- or third-line treatment with TKIs**

In parallel with the first-line studies, randomized trials continued to investigate TKIs as single-agents in second- or third-line therapy. Two phase III trials compared a TKI with placebo in patients with advanced disease previously treated with conventional chemotherapy. Erlotinib was evaluated as second- or third-line therapy in patients with tumor-node-metastasis stage IIIB or IV NSCLC who had received one or two prior chemotherapy regimens, which were platinum-based in 93% of the cases. A total of 731 patients were randomized in a 2:1 ratio to receive either erlotinib or placebo. The median OS was 6.7 months with erlotinib and 4.7 months with placebo, translating into a relative reduction in the risk of death by 30% (p < 0.001). Gefitinib was assessed as second- or third-line treatment in a similar population of 1,692 patients who were randomized in a 2:1 ratio to receive either TKI at the dose of 250 mg per day or placebo. There was no significant difference in OS between the two groups (median of 5.6 versus 5.1 months; p = 0.087), but preplanned subgroup analyses showed significantly longer survival in the gefitinib group than in the placebo group for never-smokers and for patients of Asian origin. Gefitinib was also compared with chemotherapy in the treatment of patients whose disease had progressed after platinum-based regimens; in that setting, gefitinib was found to be non-inferior to single-agent docetaxel in the largest phase III trial published to date in advanced NSCLC (n = 1,466).

**First-line treatment with TKIs**

The recognition of the predictive role of patient features and EGFR mutations led to the design of a second generation of first-line studies in which patients were selected on the basis of clinical or molecular features. Phase II trials of gefitinib as a single agent among such patients readily demonstrated encouraging results, with response rates typically ranging from 30% to 75%. Moreover, the response rates ranged from 55% to 75% when patients were selected for the presence of EGFR mutations. Those results paved the way for phase III trials of gefitinib versus chemotherapy in patients selected for clinical or molecular features.

In the first study, Asian patients with adenocarcinoma who were non-smokers or former light smokers (defined as having stopped smoking at least 15 years prior and having a total of ≤ 10 pack-years of smoking) were randomized to receive gefitinib (250 mg/day) or carboplatin plus paclitaxel. 437 of the 1217 patients were tested for the presence of EGFR mutations. The primary objective of assessing the non-inferiority of gefitinib with respect to PFS was met; in addition, superiority of the TKI was demonstrated in the intention-to-treat population (26% relative risk reduction; p < 0.001) and in the subgroup of 261 patients with EGFR mutations (52% relative risk reduction; p < 0.001). On the other hand, the PFS was significantly longer among patients treated with chemotherapy when EGFR mutations were absent, thus confirming the predictive role of these mutations. In the second study, patients with metastatic NSCLC and EGFR mutations were randomized to receive gefitinib or carboplatin plus paclitaxel. In a planned interim analysis of the first 200 patients, the PFS was significantly longer in the gefitinib group than in the chemotherapy group (64% relative risk reduction; p < 0.001), resulting in early termination of the study. Other study endpoints, such as response rate and OS, also favored the group treated with gefitinib.

**Maintenance treatment with TKIs**

The concept of maintenance treatment has recently gained greater acceptance in advanced NSCLC, despite the fact that improvements in OS have remained elusive in some studies. A phase III trial among patients with stage IIIIB or IV NSCLC whose disease had not progressed after four cycles of platinum-based first-line chemotherapy showed that erlotinib significantly prolonged the PFS and OS, with relative risk reductions of 29% and 19%, respectively. In a second phase III trial, published thus far only in abstract form, maintenance treatment with erlotinib and bevacizumab (the anti-vascular endothelial growth factor (VEGF) antibody) was found to prolong the PFS, in comparison with single-agent bevacizumab, in advanced NSCLC; however, this combined regimen is still considered experimental.

**Clinical development of cetuximab**

Following extensive pre-clinical and phase I testing in various settings, a series of phase II trials of cetuximab in combination with platinum-based chemotherapy...
suggested a role for this approach in the first-line treatment of advanced NSCLC49,50. When used as a single agent, the most important adverse events associated with cetuximab are acneiform rash, allergic reactions, and hypomagnesemia. Two phase III trials of cetuximab in advanced NSCLC have been reported to date51,52. In the FLEX trial, 1,125 patients with advanced NSCLC and positive EGFR expression by immunohistochemistry were randomized to cisplatin-based chemotherapy alone or combined with cetuximab51. Patients given chemotherapy plus cetuximab had a median OS of 11.3 months, compared with 10.1 months for those given chemotherapy alone (relative risk reduction of 13%; p = 0.044). There was no preferential benefit in subgroups of patients defined by various demographic or clinical features. Of note, the addition of cetuximab had no effect on time to tumor progression, a secondary endpoint in the study. In the second phase III trial, the addition of cetuximab to carboplatin-based chemotherapy led to a significant improvement of response rate, but not of PFS, the primary endpoint of the study51. Taken together, these results are less impressive than those seen with single-agent TKIs as first-line therapy for patients selected on the basis of clinical or molecular features44. However, cetuximab has been approved in some countries based on the FLEX trial.

Resistance to TKIs and perspectives for the future

After the discovery of activating mutations, it soon became apparent that mutations in the tyrosine-kinase domain of EGFR were also associated with resistance to TKIs53. These somatic mutations represent a mechanism of acquired resistance, as they have been found in tumors that were previously sensitive to reversible EGFR inhibition by erlotinib or gefitinib. Thus, despite an initial response to TKIs, patients with NSCLC harboring these mutations often manifest the acquired resistance within 6 to 12 months of therapy44. As reported by Pao et al., molecular analysis in patients with acquired resistance to gefitinib or erlotinib often discloses a secondary mutation in exon 20 of EGFR, which leads to substitution of methionine for threonine at position 790 (T790M) in the kinase domain55. Thus, T790M is considered the gatekeeper residue, an important determinant of inhibitor specificity within the ATP-binding domain of EGFR. Substitution of threonine at this residue with the bulky methionine may cause resistance by steric interference with binding of TKIs55,55. However, further research on this mutation has led to the suggestion that it causes resistance by increasing the affinity for ATP56. Since these reports were first published, several studies have shown that the T790M mutation is often present before the patient starts therapy57, which suggests that it may confer a survival advantage during TKI treatment.

Based on this knowledge, new inhibitors of EGFR have been developed in the attempt to overcome such resistance58. Thus, irreversible inhibitors of EGFR, such as afatinib59,60, have been developed and are presently undergoing clinical trials. In addition, combined inhibitors of EGFR and other membrane receptors, such as the vascular endothelial growth factor receptor (VEGF)61, hold promise for the future. On the other hand, it appears that the commercially available combined inhibitor of EGFR and HER-2 does not display clinically relevant activity in NSCLC62. Also, several other anti-EGFR antibodies, including panitumumab, matuzumab, and nimotuzumab, have been developed and may theoretically be useful in the treatment of NSCLC63. At present, however, only cetuximab has undergone clinical development to the point of being approved in some countries51.

There are other possible mechanisms of resistance to EGFR inhibitors. Met is a receptor protein that is mutated or overexpressed in many cancers, and is typically associated with a worse prognosis, including in NSCLC. Importantly, Met has been identified as one of the mechanisms of resistance to EGFR TKIs over the last few years, and it appears to be involved both in primary resistance (i.e., from the very start of EGFR TKI therapy), and in acquired resistance after an initial response46,65. Furthermore, Met appears to be involved in resistance to cetuximab as well66.

Conclusions

The introduction of EGFR inhibitors represented an important step in the management of patients with advanced NSCLC, both in terms of therapeutic gains and of the knowledge that resulted from the study of mutations that confer sensitivity and resistance to TKIs. These agents have altered the overall approach to advanced NSCLC, particularly in cases of adenocarcinoma and tumors not associated with smoking. Currently, TKIs are considered by many as the first choice in the first- or second-line treatment of patients with clinical or molecular predictors of therapeutic benefit, with chemotherapy being seen as a second option in these cases67. However, despite an initially successful course of treatment, patients with advanced NSCLC eventually develop resistance to TKIs, and novel agents are clearly needed. Moreover, ongoing studies are assessing the role of TKIs in other settings, such as an adjuvant treatment of early-stage NSCLC.

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