REVIEW ARTICLE

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A Benefit-Risk Assessment of Erlotinib in Non-Small-Cell Lung Cancer and Pancreatic Cancer

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Contents

Abstract

Non-small-cell lung cancer (NSCLC) and pancreatic cancer represent two major causes of cancer-related morbidity and mortality worldwide. Conventional cytotoxic agents seem to have reached a therapeutic plateau in the last decade but prognosis remains dismal for both tumour types.

Recent advances in molecular biology have allowed the development of novel molecular agents that target specific pathways implicated in the process of neoplastic transformation. Epidermal growth factor receptor (EGFR) represents an appealing therapeutic target in both malignancies and a number of EGFR-targeting agents have recently been approved for the first- or second-line treatment of locally advanced, recurrent or metastatic disease.

Erlotinib, an orally administered EGFR tyrosine kinase inhibitor has recently received approval by both the US FDA and the European Medicines

Agency (EMA) for the treatment of advanced NSCLC after chemotherapy failure and in combination with gemcitabine for the treatment of advanced pancreatic cancer, on the basis of large, randomized, phase III trials that demonstrated survival benefit over standard therapy or best supportive care. Erlotinib toxicity, as reported in these trials, seems to be modest, with the most prevalent adverse events being fatigue, acneiform rash and diarrhoea. However, recent pharmacovigilance reports, as well as sporadic case reports from the literature, raise concern of some serious adverse events, including pulmonary toxicity, sepsis and some rare cases of treatment-related deaths.

In the current review, we present an evidence-based summary of the benefits and risks associated with erlotinib treatment in both advanced NSCLC and pancreatic cancer. Evidence for survival benefit in each of the drug's indications is provided, and treatment-related risks and costs are discussed. Finally, synthetic evaluation of the benefit-risk equilibrium is attempted, in order to help clinicians put this drug into perspective.

Lung cancer remains the most common and most lethal human malignancy, accounting for approximately 1.1 million deaths annually worldwide.[1] Histologically, almost all types of lung cancer are of epithelial origin and include two main subtypes: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), which account for 15% and 85% of all cases diagnosed in the US annually, respectively.[2] Despite incremental improvements in lung cancer therapeutics, including radical surgical resection, radiotherapy and platinum-based chemotherapy, overall prognosis remains dismal, with overall 5-year survival rates of about 15% in the US.[3]

Pancreatic cancer is the fourth leading cause of cancer death, with an estimated 43 000 new cases and 37 000 deaths reported in 2010 in the US.[4] The cytotoxic antimetabolite gemcitabine became the standard treatment for advanced disease 10 years ago, after showing superiority over fluorouracil, and no other agent has been shown to improve survival when compared with gemcitabine.[5]

1. Molecular Targeted Therapy

Systemic cancer treatment seems to be entering a new and exciting era, characterized by a more 'sophisticated' selection of therapeutic targets, leading to the development of more 'intelligent', carefully selected drugs, specifically aimed at those targets. This approach is referred to as molecular targeted therapy, which, by definition, includes every specific treatment strategy directed against well defined molecular targets considered to be involved in the process of neoplastic transformation. Consequently, every pharmaceutical molecule aiming at a well defined molecular target implicated in the process of carcinogenesis may be considered as a molecular targeted agent (MTA).[6]

Erlotinib (Tarceva®; Genentech, South San Francisco, CA, USA) is a new MTA currently indicated in the treatment of advanced NSCLC and pancreatic cancer.[5,6] Despite its proven clinical efficacy in these indications, cases of serious adverse events, including rare cases of toxic death that may be associated with the drug, have been consistently reported.[5,6-9] Given the fact that erlotinib is currently in wide clinical use and that a plethora of clinical protocols are evaluating the drug's activity against numerous other types of human malignancies, there is increasing concern from the scientific community for its expanding use.

In the current review, we aimed to report all the available data on the benefits and risks of this agent in the treatment of advanced NSCLC and pancreatic cancer. For this purpose, we provide an overview of the benefits of erlotinib treatment in relation to the seriousness of these diseases, and a summary of reported adverse drug events, and we attempt a synthesis of the benefit-versus-risk assessment, which would help clinicians put this agent into perspective.

2. Search Methodology

We performed a computerized literature search using the following search terms: 'erlotinib' AND ('non small-cell lung cancer' OR 'pancreatic') AND ('benefit' OR 'adverse drug reaction' OR 'toxicity'). The search was performed using OvidWeb (Ovid Technologies Inc., New York, NY, USA) in four databases: MEDLINE, EMBASE, Scopus and Google™ Scholar (including Cochrane Database), with results limited to human studies and the English or French language. Performing this search on 14 February 2010, we obtained 351 entries. The majority of these results were 'false positive'; in most cases they evaluated erlotinib in preclinical models, did not report on the clinical benefit and toxicity of the drug, or reviewed/commented on results from other studies. Data were thus manually and independently reviewed by the two authors in order to limit risks of selection bias, and we obtained 55 clinical studies reporting safety and/or efficacy data on the use of erlotinib in NSCLC or pancreatic cancer. During this process, we identified several editorials and reviews on related subjects. The manual verification of bibliographies from these literature reviews uncovered 13 additional clinical trials related to erlotinib treatment in both settings. The relevant papers were reviewed and summarized, and the studies were categorized according to the disease indication (NSCLC, pancreatic cancer) and the line of treatment (adjuvant, second-line monotherapy, first-line monotherapy, in combination with chemotherapy and in the maintenance setting).

3. Erlotinib

3.1 Mechanism of Action

Recent advances in molecular biology have elucidated the role of proliferative signals in the acquisition of a malignant phenotype by the respiratory epithelial cell. This signalling cascade can be segregated into three distinct but interlocking phases. The upstream phase consists of the interaction of growth factors or ligands and the associated membrane receptors through the complementary extracellular binding domain. This leads to receptor homo- or heterodimerization and subsequent conformational changes that trigger the activation of the protein kinase activity located in the intracellular domain. These enzymes catalyse the covalent attachment of phosphate groups to amino acids (serine, threonine or tyrosine) of cytoplasmic proteins resulting in activation or inactivation, thus facilitating the transduction of the signal from the cell membrane to the nucleus.[7]

Epidermal growth factor receptor (EGFR; ErbB1) is a member of the family of tyrosine kinase (TK) receptors called ERBB, which also includes ErbB2 (also known as HER2/neu), ErbB3 (HER3) and ErbB4 (HER4). EGFR is a transmembrane glycoprotein that consists of an intracellular domain with TK activity, a transmembrane lipophilic domain and an extracellular portion that is responsible for the binding of ligands (e.g. epidermal growth factor). EGFR is encoded by a gene located on the short arm of chromosome 7 and, specifically, in the 7p12.1–12.3 region consisting of 26 exons. Exons 1–14 code for the extracellular portion, exon 15 for the transmembrane and exons 16–20 for the intracellular domains of the receptor.[10]

EGFR is expressed in a number of solid tumours, including colorectal cancer, head and neck cancer and lung cancer.[10] EGFR and HER2 are overexpressed in approximately 70% and 30% of NSCLC cases, respectively, but they are rarely expressed in SCLC.[11] The crucial role of the EGFR pathway in NSCLC tumorigenesis renders it an appealing target for the development of targeted anticancer agents. The two main categories of MTAs against EGFR are (a) monoclonal antibodies (MoAbs) against the receptor and (b) TK inhibitors (TKIs). Abnormal TK activity may result from receptor overexpression, increased ligand availability or constitutive activation of the enzyme through mutation in the gene sequences of the receptor itself.[11]

3.2 Current Indications

Erlotinib is an oral drug administered at a daily 150 mg dosage until disease progression or unacceptable toxicity occurs. With an accumulating

experience of more than 4 years of clinical use and more than 50 000 patients having received the drug, erlotinib is currently implemented in everyday clinical practice, and its efficacy as well as its toxicity profile are well documented.[12] There is an increasing amount of data outlining the role of EGFR mutations in predicting the benefit of EGFR TKI treatment in NSCLC. Numerous studies have shown that lung cancers harbouring EGFR activating mutations are remarkably sensitive to erlotinib and gefitinib.[13-15] EGFR gene amplification also appears to be associated with improved survival outcomes, whereas no clear association has been found between EGFR overexpression and response to EGFR TKIs. V-Ki-ras2 Kirsten rat sarcoma viral oncogene (KRAS) and EGFR mutations are mutually exclusive in NSCLC. Patients harbouring mutations of KRAS seem to be resistant to EGFR TKI therapy.[14]

Gefitinib (Iressa®; AstraZeneca, Wilmington, DE, USA) was recently approved in the first-line setting of EGFR-mutant NSCLC. The IPASS (Iressa Pan-Asia Study) study, an open-label, phase III trial, showed that gefitinib significantly improved progression-free survival (PFS) versus a platinum-based doublet in patients harbouring EGFR mutations.[13] Gefitinib had already been the first agent to receive both US FDA and European Medicines Agency (EMA) approval in November 2004 and October 2005, respectively, for the treatment of chemotherapy-resistant patients with advanced NSCLC.[6]

4. Benefit Assessment of Erlotinib in Non-Small-Cell Lung Cancer (NSCLC)

4.1 Erlotinib as Monotherapy in Second-Line Treatment

Erlotinib has dose-dependent pharmacokinetics and daily dosing does not result in drug accumulation. A dosage of 150 mg/day was determined to be the maximum tolerated dose at which biologically relevant plasma levels were achieved and this was the dosage that was recommended for phase II trials.[16] After the encouraging results of phase II studies using erlotinib as salvage treatment in advanced NSCLC,[17] the drug was evaluated in a large, randomized, phase III trial as second- and third-line treatment of NSCLC. In the hallmark BR.21 trial conducted by the National Cancer Institute of Canada Clinical Trials Collaborative Group,[6] 731 patients with stage IIIB or IV NSCLC were randomized to receive erlotinib or placebo. Patients in the experimental arm had a response rate of 8.9% compared with <1% in the placebo group ($p < 0.001$); median PFS was 2.2 months and 1.8 months (hazard ratio [HR] 0.61, adjusted for stratification categories; $p < 0.001$) and median overall survival (OS) was 6.7 months and 4.7 months (HR 0.70; $p < 0.001$), in the erlotinib and placebo arms, respectively.[6] Despite the modest absolute gain in OS (2 months), the study demonstrated a 30% reduction in the risk of death in this heavily pre-treated group of patients. On the basis of these results, erlotinib received both FDA and EMA approval in November 2004 and October 2005, respectively, for the treatment of chemotherapy-resistant patients with advanced NSCLC.

4.2 Erlotinib in First-Line Treatment

Based on the positive results achieved with EGFR-TKIs in the second- and third-line therapy settings, these agents were studied as first-line therapy in advanced NSCLC. It was noticed that in all erlotinib studies, patients with certain characteristics (never or light smokers, female patients, Asian descent, adenocarcinoma histology) had high response rates to treatment.[18] Moreover, it became apparent that the efficacy of EGFR-TKIs in these patients could be, at least partially, attributed to the presence of EGFR activating mutations.[19] There are ongoing first-line trials of erlotinib monotherapy in previously untreated patients, such as the phase III EURTAC (European Randomized Trial of Tarceva vs Chemotherapy) trial, that plans to compare outcomes with erlotinib monotherapy versus those with chemotherapy in chemotherapy-naive patients harbouring EGFR mutations.[20,21]

A combination strategy with cytotoxic chemotherapy was pursued in the first-line treatment setting with no success. The TALENT (Tarceva

Lung Cancer Investigation) and TRIBUTE (Tarceva Responses in Conjunction with Paclitaxel and Carboplatin) trials were two large, phase III trials that evaluated whether adding erlotinib to a platinum-based doublet (gemcitabine/cisplatin in the TALENT trial) or (carboplatin/paclitaxel in the TRIBUTE trial) in the first-line setting could result in survival benefit.[22,23] In the TRIBUTE study, more than 1000 patients with untreated, advanced stage IIIB/IV NSCLC were enrolled.[23] Median OS for patients who received a combination of chemotherapy with erlotinib was 10.6 months versus 10.5 months for the chemotherapy arm (HR 0.99; 95% CI 0.86, 1.16; $p = 0.95$) and objective response (OR) rates were similar in both arms (21.5% vs 19.3%, respectively; $p = 0.36$). Also, in the TALENT trial, there was no statistically significant difference in any clinical outcome, with a median OS of 301 versus 309 days, respectively.[23] There was, however, a beneficial effect found in a subset analysis of patients with EGFR mutant tumours who continued to receive erlotinib after completion of the regimen of erlotinib and chemotherapy combination.[23] An ongoing, randomized, phase II trial by the Cancer and Leukemia Group B (CALGB) will evaluate erlotinib versus erlotinib plus carboplatin and paclitaxel in never or light smokers with adenocarcinoma (CALGB-30406; NCT00126581).[24]

4.3 Erlotininb as Maintenance Therapy

The SATURN trial (Sequential Tarceva in Unresectable NSCLC)[25] was a randomized, phase III trial that assessed the clinical benefit of erlotinib as maintenance therapy in non-progressing patients after completion of four cycles of first-line, platinum-based doublet therapy. The observation that prolonged therapy with erlotinib delayed disease progression in the TALENT trial provided the justification for the evaluation of erlotinib in the maintenance setting. 889 of 1949 patients with advanced NSCLC remained progression-free at the completion of four cycles of first-line chemotherapy (the choice of chemotherapy regimen was at the investigator's discretion). These non-progressing patients were randomly assigned to receive erlotinib or placebo. Treatment was continued until the development of intolerable toxicity or disease progression. Patients in the erlotinib arm had better outcomes in terms of response rate (12% vs 5%), PFS (12 vs 11.1 weeks; HR 0.71; 95% CI 0.62, 0.82; $p < 0.0001$) and OS (12 vs 11 months; HR 0.81; 95% CI 0.70, 0.95; $p = 0.0088$). Biomarker and subset analysis showed that the benefit of maintenance therapy with erlotinib extends across ethnic groups, tumour histologies and smoking status.[25]

The ATLAS (Avastin and Tarceva in Lung with NSCLC) study[26] tried to build on the survival advantage achieved in the frontline Eastern Cooperative Oncology Group (ECOG) E4599 trial, where the addition of bevacizumab to frontline chemotherapy followed by bevacizumab maintenance therapy offered significant survival benefit.[23] The ATLAS study enrolled 1160 patients who received platinum-based doublet chemotherapy along with bevacizumab as first-line treatment. After completion of four cycles of chemotherapy, 768 non-progressing patients were randomized in a 1 : 1 fashion to receive bevacizumab alone or in combination with erlotinib. With a median PFS of 4.76 versus 3.75 months (HR 0.722; CI 0.592, 0.881; $p < 0.0012$) in favour of the erlotinib plus bevacizumab arm, the study met its primary objective. In the updated report, no survival benefit was reported for the combination arm but the study was perhaps underpowered to detect a significant difference in OS.[26] Based on the results of the SATURN and ATLAS studies, the use of erlotinib as maintenance therapy is becoming a treatment option for patients with good performance status (PS) who respond to first-line chemotherapy.

4.4 Combination Strategies for Improved Efficacy of Erlotinib

Simultaneous blockade of the EGFR with the combined use of a receptor targeting monoclonal antibody and an EGFR TKI was thought to result in total pathway blockade and improved efficacy. The vascular endothelial growth factor (VEGF) and EGFR pathways are important in NSCLC and there is strong rationale for their

combined therapeutic targeting. Additionally, there is documented crosstalk among these pathways as VEGF is known to become downregulated by EGFR inhibition through hypoxia-inducible factor 1α-dependent and -independent mechanisms.[27] The combination of bevacizumab plus erlotinib may prove to be a viable second-line alternative to chemotherapy or erlotinib monotherapy in patients with NSCLC.[28] The benefits of the combination may be further enhanced by selecting for patients who are likely to respond to this therapy. The erlotinib and bevacizumab combination displayed very encouraging activity in a randomized phase II trial in patients with previously treated NSCLC, although the outcome of a large, randomized, phase III trial (Beta trial) was less promising.[29,30]

5. Risk Assessment of Erlotinib in NSCLC

Since early phase II clinical trials, it became evident that erlotinib exhibited a toxicity profile that resembled that of other TKIs used in targeted treatment of solid tumours.[14] The main reported adverse events included fatigue (65–83%), acneiform rash of the face, trunk and proximal surfaces of the extremities (58–76%), anorexia (55–73%), nausea (36–48%), vomiting (18–29%), stomatitis (16–27%) and diarrhoea (44–66%).[6,16,22,23,25,26]

It soon became apparent that a considerable number of treated patients develop dermatological adverse events, such as acneiform eruption, xerosis and eczema. Quality of life is thus negatively affected.[9] Acneiform rash, in particular, is generally localized on the upper torso, face and neck, occurs after approximately 1 week of treatment and reaches a maximum intensity after 2–3 weeks.[12] Data from phase I dose-escalation trials indicate that the rash is dose-dependent.[16] The positive correlation between the development of rash and OR to treatment and/or survival, which has been shown in both gefitinib and erlotinib clinical trials, makes the prevalence of dermatological reactions a potential surrogate marker for anti-EGFR drug efficacy.[31] This finding has also been confirmed in the subgroup analysis of the TRIBUTE and TALENT phase III trials.[22,23]

In the BR.21 study, which included pre-treated patients, erlotinib administration was associated with severe (≥ grade 3 according to the National Cancer Institute common toxicity criteria) rash or diarrhoea in 9% and 6% of patients, respectively, leading to dose reduction in 12% and 5% of patients in the experimental arm, respectively.[6] Pneumonitis with pulmonary infiltrates or pulmonary fibrosis occurred in six patients who received erlotinib, and one death from pneumonitis was recorded, as was recorded in the control arm also.[6] In the TALENT trial, based on previously untreated patients, the combination of erlotinib with chemotherapy was associated with a small increase in serious adverse events and, more importantly, in treatment-related deaths.[22] An unexpected finding was the increased incidence of renal failure in patients receiving erlotinib plus chemotherapy as compared to the group receiving chemotherapy alone (5% vs <1%). It was attributed to the inadequate hydration after erlotinib-induced diarrhoea, thus exacerbating the already known renal toxicity of cisplatin.[22] Both the TALENT and TRIBUTE trials reported a higher rate of deaths in the erlotinib arm compared with the placebo arm (e.g. 163 and 125 deaths in the erlotinib and placebo arms, respectively, in the TRIBUTE trial), regardless of whether death was related to NSCLC progression or toxicity.[22,23] Nevertheless, life-threatening toxicity, such as interstitial lung disease (ILD), was rarely observed in both trials (e.g. 1.0% vs 0.2% for the erlotinib and placebo arms, respectively, in the TRIBUTE study).[22,23]

In the SATURN trial,[25] rash and diarrhoea of any grade occurred in 60% and 20% of patients, respectively, but severe toxicity (grade 3 or 4) was observed in 9% and 2%, respectively, and led to dose modification or interruption in 16% of the study population. However, preliminary results did not attribute any deaths to erlotinib toxicity.[25] In the ATLAS study, on the other hand, the combination of two targeted agents (bevacizumab and erlotinib) after completion of chemotherapy was associated with serious (grade 3–5) adverse events in 44.1% of patients in the experimental arm that were possibly related to erlotinib, including eight deaths because of

toxicity (2.2% of the patients in the experimental arm).[26] Among these deaths, there were two associated with acute cardiovascular events, one with severe infection, one with arterial thromboembolism and one with venous thromboembolism.[26] There were also three cases of pulmonary haemorrhage, two cases of gastrointestinal perforation, six cases of severe proteinuria and three cases of newly diagnosed cardiac heart failure, which were possibly related to bevacizumab. Finally, in the post-chemotherapy phase, significantly more cases of rash and diarrhoea were recorded in the combination arm than in the bevacizumab arm (10.4% and 9.3%, respectively). Two cases of renal failure and one case of hepatic failure were reported in the combination arm compared with none and one such case in the control arm, respectively.[26] The accumulating data from the above-mentioned clinical trials, along with reports from the literature[32] and pharmacovigilance reports[33] have drawn the attention of the scientific community to erlotinib benefit-risk assessments. Most recently, the TOPICAL (Tarceva Or Placebo In Clinically Advanced Lung cancer) trial, conducted by Lee et al.,[34] showed that erlotinib can safely be administered to elderly patients, even when PS is poor.

There has been an effort to evaluate therapeutic strategies and reach a consensus regarding the management of erlotinib toxicity. Simplified systems of describing dermatological toxicity and therapeutic algorithms have been proposed in order to assist clinicians. It seems that expert and proactive use of supportive measures is successful, allowing maintenance of dose intensity in most cases.[35]

6. Benefit Assessment of Erlotinib in Pancreatic Cancer

As already mentioned, the antimetabolite gemcitabine has been considered the standard treatment for locally advanced, recurrent or metastatic pancreatic cancer, since it was the only cytotoxic drug to demonstrate survival benefit over fluorouracil.[36] A number of randomized, phase III clinical trials involving newer cytotoxic[37-41] or biological agents[42,43] followed but did not show any survival improvement when compared with gemcitabine monotherapy. In the year 2000, emerging preclinical studies showed that blocking EGFR TK-mediated signalling decreased the growth and metastatic propensity of human pancreatic tumour xenografts[44] and improved the antineoplastic activity of gemcitabine.[45] Early clinical data revealed modest clinical activity of erlotinib in advanced pancreatic cancer and a toxicity profile similar to the one reported in patients with NSCLC. In a recently published, landmark, randomized, phase III trial, 569 patients with previously untreated, unresectable, locally advanced or metastatic pancreatic cancer were randomized to receive gemcitabine (1000 mg/m^2/week for 7 of 8 weeks) in combination with placebo or with erlotinib 100 mg daily continuously, although a small cohort of patients received a higher dosage of 150 mg daily.[5] The study demonstrated that the combination of gemcitabine with erlotinib resulted in a small but statistically significant increase in median survival (6.24 vs 5.91 months, respectively) and in 1-year OS (23% vs 17%, respectively). Response rates and quality of life analysis gave similar results for both study arms. Despite the fact the absolute survival benefit was modest, this study was the first to show a statistically significant benefit with combination therapy over gemcitabine monotherapy (HR 0.82, 95% CI 0.69, 0.99; $p = 0.038$, adjusted for stratification factors) and, consequently, erlotinib became the first targeted therapy approved by the FDA for this indication in 2005.[5]

Erlotinib has also been investigated in combination with capecitabine in gemcitabine-refractory advanced pancreatic cancer;[46] 30 patients were administered capecitabine 1000 mg/m^2 twice daily for 14 of 21 days, and erlotinib 150 mg daily. Given that the study reported an overall response rate of 10% and a median survival of 6.5 months, it was concluded that this combination may represent an appropriate treatment in cases where gemcitabine is ineffective or inappropriate.[46]

The next step was a comparison between the two combinations of erlotinib with either gemcitabine or capecitabine. In a randomized, phase III clinical trial, 281 treatment-naive patients were randomly assigned between capecitabine

(2000 mg/m^2/day for 14 days, once every 3 weeks) plus erlotinib (150 mg/day) and gemcitabine (1000 mg/m^2/week for 7 of 8 weeks) plus erlotinib at the same dosage.[47] Patients experiencing treatment failure were allowed to cross over to second-line treatment with the comparator cytostatic drug without erlotinib. The primary study endpoint was the time to treatment failure of second-line therapy. In the interim analysis of toxicity, both treatment combinations are feasible and clinical efficacy data are awaited.[47]

Preclinical studies have revealed a role for erlotinib as a potent radiosensitizing agent.[48] Thus, the feasibility of using the combination of erlotinib, gemcitabine, paclitaxel and concomitant radiotherapy followed by maintenance erlotinib therapy for locally advanced pancreatic cancer was the subject of a phase I trial conducted by Iannitti et al.[49] The maximum tolerated dosage of erlotinib during chemoradiation therapy was 50 mg daily due to dose-limiting diarrhoea. Given that this trial reported an encouraging partial response rate of 46% and median survival of 14 months, this treatment regimen merits further investigation.

7. Risk Assessment of Erlotinib in Pancreatic Cancer

Preliminary safety data of erlotinib in patients with advanced pancreatic cancer revealed a panel of adverse events similar to that seen in patients with advanced NSCLC. In the aforementioned study by Moore et al.,[5] patients receiving erlotinib and gemcitabine experienced a higher frequency of rash (72% vs 29%), diarrhoea (56% vs 41%), infection (43% vs 34%) and stomatitis (23% vs 14%) than patients receiving gemcitabine plus placebo, but these adverse events were generally mild (grade 1 or 2 in most cases). The incidence of other adverse events was similar in both arms. Six protocol-related deaths were recorded, all in the erlotinib plus gemcitabine arm. Two were attributed to treatment complications (interstitial pneumonitis and sepsis) and four were attributed to a combination of cancer and protocol treatment complications (interstitial pneumonitis, sepsis, cerebrovascular event and neutropenic sepsis).

It should be noted that a total of eight patients had an ILD-like syndrome, possibly related to therapy (seven of them were receiving gemcitabine plus erlotinib and one was receiving gemcitabine plus placebo).[5] Gemcitabine and EGFR are both known to cause an ILD-like syndrome in approximately 0.5–1.0% of patients and there is the possibility of a more than additive effect when these agents are combined.[50] Interestingly, the incidence reported in this study (2.4%) is higher than that observed in other trials with gemcitabine-erlotinib combinations.[22] The incidence of ILD in the aforementioned TALENT trial was <1% and no difference was seen between the treatment arms.[22]

The quality-of-life analysis conducted in the same trial in 376 assessable patients, showed that there was no significant difference between the arms in global quality of life or in the individual domains, with the exception of worse diarrhoea scores in the erlotinib plus gemcitabine arm ($p < 0.001$).[5]

8. Overall Benefit-Risk Assessment

8.1 NSCLC

The landmark BR.21 trial convincingly showed that erlotinib monotherapy in the second- or third-line treatment of advanced NSCLC offers a statistically significant OS benefit (median OS was 6.7 and 4.7 months in the erlotinib and placebo arms, respectively).[6] Despite the modest absolute gain in OS (2 months), the study was the first to demonstrate a 30% reduction in the risk of death in this heavily pre-treated group of patients. Moreover, erlotinib was generally well tolerated, with most adverse events being of mild to moderate severity. A large body of modelled pharmacoeconomic data suggest that second- or third-line erlotinib at a dosage of 150 mg/day is a cost-saving option when compared with treatment with the approved second-line intravenous chemotherapies of docetaxel and pemetrexed and their associated morbidity in patients with advanced NSCLC.[51] In patients who had received at least one prior chemotherapy regimen, erlotinib was predicted to be dominant (more effective and less costly) or cost saving (equally effective

and less costly) when compared with docetaxel or pemetrexed with regard to the cost per life-year gained in cost-effectiveness analyses.[51] Moreover, serious or life-threatening adverse events requiring prolonged hospitalization and specialized medical care are quite rare and thus the drug is considered a safe and cost-effective option.[52] However, these results may not be applicable outside North America since funding restrictions limit access to erlotinib in many countries. Moreover, differences in the type of model developed, the specific costs included, the health and insurance care programme of each country, or even the year of costing may influence analysis.[53]

Overall, results of the above studies were confirmed by two large, phase IV trials that studied safety data on erlotinib administration in advanced NSCLC. Reck et al.[54] reported that the incidence of erlotinib-related serious adverse events was 4% and dose reduction was necessary in 17% of patients. In the Mok et al.[55] trial, results were similar in Asian patients with advanced NSCLC receiving erlotinib. Both of these phase IV trials reached the conclusion that erlotinib is indeed effective and has a favourable safety profile.[54,55]

8.2 Pancreatic Cancer

Although erlotinib was the first pharmaceutical agent to exhibit a statistically significant OS benefit in combination therapy over gemcitabine monotherapy in advanced pancreatic cancer, the marginal absolute increase in median survival (6.24 vs 5.91 months for the erlotinib and placebo groups, respectively, or approximately 11 days), raised significant questions on the cost effectiveness of the drug for this indication.[5] A recent report[56] that commented on the results from the Moore et al.[5] trial, estimated the magnitude of the cost per quality-adjusted life-year (QALY) gained by adding erlotinib to gemcitabine by performing a *post hoc*, informal, cost-effectiveness analysis: oncology and pharmacy experts estimated drug and inpatient medical care costs (in 2007 $US) using the 2007 average US wholesale price and 2007 Medicare reimbursement rates.[56] The incremental cost-effectiveness ratio of adding erlotinib to gemcitabine was $US410 000 per year of life saved ($US7885 per week of life saved) and when adjusted for the quality-of-life impact of diarrhoea, the incremental cost-effectiveness ratio rose to $US430 000 (low impact of diarrhoea) and $US510 000 (high impact of diarrhoea) per QALY.[56] The authors concluded that these results are far above the commonly accepted cost-effectiveness threshold of $US50 000–100 000 per QALY and that the primary cost component is the cost of erlotinib. Overall, this analysis suggested that the clinical significance and value of erlotinib's small survival benefit may be limited. We need to wait for the final results of ongoing clinical trials, such as the Boeck et al.[47] study, in order to reach more definitive conclusions regarding benefits and risks of using erlotinib in pancreatic cancer.

9. Conclusions

In conclusion, in patients with advanced NSCLC, second- or third-line treatment with erlotinib seems to have a favourable safety profile with rare life-threatening toxicity and survival benefit, as has been proven in large heterogeneous phase IV study populations. However, no solid evidence of efficacy or cost effectiveness exists to date to justify the use of erlotinib as first-line treatment in combination with standard chemotherapy in the general population of advanced NSCLC.

Regarding advanced pancreatic cancer, while the primary endpoint in the PA.3 trial[5] reached levels of statistical significance, there was a marginal survival benefit afforded by erlotinib, important quality of life implications of treatment-related toxicity (especially diarrhoea) and lack of cost effectiveness. The use of erlotinib in advanced pancreatic cancer emphasizes the importance of further analyses of novel targeted therapies in order to better understand the value of potential treatment options.

Major efforts should be made to select patients who are more likely to benefit from erlotinib treatment or to combine it with another drug that increases clinical efficacy. Better selection of patients is becoming increasingly important in

almost all tumour types since novel therapeutic options have led to an increasing economic burden for healthcare systems and to more complex, toxic regimens that result in a significantly higher cost per life-year gained than is usually accepted.[56,57] The lack of correlation between EGFR expression rate (as determined by immunohistochemistry) and erlotinib activity emphasizes the necessity for future studies that will prospectively identify molecular markers predicting the likelihood of benefit from a targeted agent, as was the case with MoAbs against EGFR in advanced colorectal cancer.[58] This kind of approach would spare heavily pre-treated patients from unnecessary toxicity by an inactive drug and would focus on patients with predictive factors indicating benefit from TKI treatment. Such studies are currently underway and will lead to even more accurate erlotinib benefit-risk and cost-effectiveness assessments in the future.

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