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1 Drug description

Generic/Brand name: Gefitinib/Iressa®

Developer/Company: Astra Zeneca

Description: Gefitinib belongs to the group of tyrosine kinase inhibitors (TKIs). One mechanism of action is the inhibition of tyrosine kinases (TK) involved in the downstream signalling of the epidermal growth factor receptor (EGFR) [1]. These enzymes are expressed on the cell surface and are responsible for the growth and proliferation of normal as well as of tumour cells. Activating mutations of the EGFR TK domain within cancer cells can be partially held accountable for tumour growth, blockage of apoptosis and an increased likelihood of metastasis [2].

gefitinib is a tyrosine kinase inhibitor

Several clinical characteristics have been identified which predict response to gefitinib treatment. These are female gender, non-smokers, patients of Asian ethnicity and individuals with bronchoalveolar adenocarcinomas [3-7]. Within this group activating EGFR mutations are also more likely to be found [4, 7], hence, these characteristics might be used to select a population with an increased frequency of mutation rates which range in unselected Caucasian populations from 12% - 17% [8, 9] where gefitinib treatment might be more effective.

The recommended way of administration is one 250 mg tablet Iressa® daily, taken orally. No clear recommendations on treatment duration were found, hence, it was assumed that treatment should continue as long as disease does not progress or as long as toxicity remains acceptable.

1 tablet per day administered orally

2 Indication

Gefitinib is indicated as first-line therapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR TK.

as first-line therapy for locally advanced or metastatic NSCLC

3 Current regulatory status

The EMEA granted market authorization for gefinitib for the treatment of adult patients with locally advanced or metastatic NSCLC with activating mutations of EGFR TK in June 2009 [2].

EMEA: market authorization in June 2009

In the US, the FDA had approved gefitinib in 2003 but limited the indication in 2005 to monotherapy for the continued treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from gefitinib [10].

FDA: approved since 2003, limited indication in 2005

4 Burden of disease

NSCLC is leading type of cancer worldwide

NSCLC is one of the leading types of cancer and causes of cancer deaths worldwide [11]. Its primary risk factors are first- and second-hand smoke exposition [12]. Men are still more often affected by NSCLC than women, with the majority of patients being diagnosed at an age ≥ 65 years [13]. On average, patients are aged 71 years at the time of diagnosis of NSCLC.

primarily men aged >65 years with history of smoking affected

3,400 people died of lung cancer in 2007

estimates of people with activating EGFR mutations in Austria: 435

About 3,400 people died of lung cancer and, overall, nearly 4,000 new cases of lung cancer were diagnosed in Austria in 2007 [14]. As NSCLC accounts for about 85% of all lung cancer cases [12, 15] of which 85% [16] can be expected to present with advanced disease, results in an estimated 2,900 persons with advanced NSCLC per year. Applying estimates of an average frequency of activating EGFR mutations (within an unselected population about 15%) to these numbers would give about 435 individuals with activating EGFR mutations and so, patients potentially eligible for treatment with Iressa®.

staging depends on size, location, invasion of tissue, presence of metastasis

Depending on certain tumour characteristics, for example tumour size, location and invasion of the surrounding tissue, presence of metastasis in the lymph nodes or distant metastasis, the tumour node metastasis (TNM) system is used for the staging of the disease. Locally advanced and metastasised NSCLC corresponds to TNM stage IIIB and IV, respectively. In addition to this staging, the histological subtype of the tumour and the patients' performance status, as well co-morbidities are taken into account in order to develop a treatment regimen. Wherever possible, therapy should be individualized based on results of molecular (e.g. EGFR status) and other tumour characteristics [6].

prognostic factors: early-stage disease, good performance status, female gender, no significant weight loss and biomarkers

Prognostic factors are early-stage disease at diagnosis, good performance status according to the Eastern Cooperative Oncology Group (ECOG PS 0 - 2), female gender and no significant weight loss [12]. Other prognostic and predictive factors for lung cancer response are, again, biomarkers like EGFR expression and mutational state, the occurrence of downstream signal transduction pathway modifications (K-Ras mutation) and others [12].

5-year survival rate ranges from 3.7% - 54.2%

In 2005, the 1-year survival rate for patients with cancer of the lung and bronchus of all stages was 44.4% in the US [13]. The 5-year survival rate in NSCLC depends on both tumour stage and patient's age at diagnosis and is 17.2% for all stages of NSCLC. The 5-year survival rate for localized NSCLC is 54.2%, for regional 25.2%, for distant 3.7% and for unstaged 8.5%. In individuals aged under 45 years it is 25.7% and decreases to 15.1% in patients > 65 years of age [13]. Median overall survival for patients with stage IIIB disease is about 10 months, for patients with stage IV it is 6 months [17] and disease progression after first-line chemotherapy can be expected within 3 to 6 months after the initiation of therapy [15].

5 Current treatment

Treatment options for patients with advanced disease (TNM IIIB, IV) are

platinum based chemotherapy is standard of care,

- platinum based chemotherapy: modern regimens are mostly based on a platinum compound (cisplatin, carboplatin) in addition to one or two out of numerous other substances (e.g. vinorelbine, paclitaxel, docetaxel, gemcitabine, irinotecan) but for none of these combinations superiority has been established unequivocally.

other chemotherapy regimens without platinum compound

- other chemotherapy regimens: due to the toxicity of platinum based regimens, other drug combinations can be used (gemcitabine + docetaxel/paclitaxel/vinorelbine/pemtrexed, paclitaxel + vinorelbine)

single agent only for elderly,

- single agent chemotherapy as first-line treatment is generally used for elderly patients or for those with worse PS

radiation therapy

- radiation therapy

others: targeted drugs

- targeted therapies: EGFR inhibitors (erlotinib), monoclonale antibodies (bevacizumab, cetuximab)

combined modality approach

- a combined modality approach [6].

6 Evidence

three phase III trials, plenty of other study designs

Three phase III trials [8, 18, 19] and several other studies, including phase II trials, were identified. All phase III trials showed similar results in overall survival (OS) for patients treated with either gefitinib or chemotherapy. In patients with activating EGFR mutations, favourable results for progression-free survival (PFS) were found in two of these studies [8, 18]. Quality of life (QoL) was an outcome measure in two trials and demonstrated better results for the gefitinib group. Adverse events occurred less frequent in the Iressa® groups than in the chemotherapy groups.

The phase II studies varied in terms of study population and interventions. Accordingly, differences in outcomes were observed with OS ranging from 3.7 months to 17.5 months and PFS between 3.2 months to 9.2 months. Severe side effects were generally rare but interstitial lung disease, a major complication believed to be associated with gefitinib, was observed in up to 7.5% of the study population.

Two retrospective analyses which included only patients with EGFR mutations were found. Both demonstrated prolonged PFS for the gefitinib group, but results on OS differed.

6.1 Efficacy and safety - phase III studies

Reference	IPASS trial, published [8]	NEJ002, unpublished, abstract available [18]	first-SIGNAL study, unpublished, conference presentation available [19, 20]
Sponsor	Astra Zeneca		Astra Zeneca
Country	China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, Thailand	Japan	Korea
Design	phase III, open-label, multicenter, randomized controlled trial	multicenter phase III	randomized phase III
Participants characteristics	I 609 pts: median age 57 yrs, range 24-84 yrs; 79.5% women, 93.8% never smoker C 608 pts: median age 57 yrs, range 25-84 yrs; 79.1% women, 93.6% never smoker EGFR status determined in 437 pts out of which 59.7% had EGFR mutations overall; I=132 pts, C=129 pts	I 98 pts: median age 63 years, 63% women, 97% stage IV, 90% adenocarcinoma C 100 pts: median age 63 years, 64% female, 75% stage IV, 96% adenocarcinoma	I 159 pts vs C 150 pts, 89% women EGFR status determined in 96 pts (31.1%) out of which 42 pts were EGFR mutation positive
Treatments	I(ntervention): gefitinib 250 mg daily, administered orally C(ontrol): first-line chemotherapy with paclitaxel (day 1: 200 mg/m² body surface area) + carboplatin (dose calculated to produce area under concentration time curve of 5.0-6.0/ml/min iv. once every 3 weeks up to 6 cycles) treatment continued until disease progression, unacceptable side effects occurred, or completion of 6 chemotherapy cycles, I group was allowed to cross-over to C group if tumour progressed	I(ntervention): gefitinib 250 mg daily C(ontrol): carboplatin AUC[1] 6 + paclitaxel 200mg/m² in 21 day cycles	I(ntervention): gefitinib 250 mg daily, administered orally q 3 weeks C(ontrol): 1250mg/m² gemcitabine (d 1 and d8) + 80mg/m² cisplatin (d 1) q 3 weeks x 9 cycles post-study use of EGFR TKIs in 81% of patients in chemotherapy group
In-/exclusion criteria	previously untreated patients in East Asia, NSCLC stage IIIB or IV, non smokers (<100 cigarettes in their lifetime) or light smokers (≤10 pack-years, or quit smoking ≥ 15 yrs before), ECOG PS 0 to 2,	previously untreated with sensitive EGFR mutations, ECOG PS 0-1	previously untreated, never-smokers, adenocarcinoma, ECOG PS 0-2, stage IIIB or IV,
Follow-up	median: 5.6 months	interim analysis	
Outcomes	Primary: progression-free survival (PFS) Secondary: overall survival (OS), objective response rate (ORR), quality of life (QoL), adverse events	Primary: progression-free survival (PFS) Secondary: overall survival (OS), response rate, quality of life (QoL), adverse events	overall survival (OS), progression-free survival (PFS), objective response rate (ORR), quality of life (QoL), adverse events
Key results	Primary: - median PFS: I 5.7 months vs C 5.8 months - 12-month rates of PFS: I 24.9% vs C 6.7%	Primary: PFS I 10.4 months vs C 5.5 months, HR = 0.357, p<0.001	Median OS: I 21.3 months vs C 23.3 months; HR=1.003 (95%CI 0.749 to 1.343, p= 0.428)

[1] AUC = area under curve

[2] FACT-L = functional assessment of cancer therapy, lung

[3] TOI= trial outcome index

	- HR (for progression or death) = 0.74 (95% CI 0.65 to 0.85, p<0.001) - EGFR positive subgroup analysis: HR (progression) = 0.48 (95% CI 0.36 to 0.64, p<0.001) - EGFR negative subgroup analysis: HR (progression) = 2.85 (95% CI 2.05 to 3.98, p<0.001) Secondary: OS: median survival: I 18.6 months vs C 17.3 months HR (for death in I group)= 0.91 (95%CI 0.76 to 1.10) EGFR positive subgroup analysis: HR = 0.78 (95% CI 0.50 to 1.20) EGFR negative subgroup analysis: HR= 1.38 (95% CI 0.92 to 2.09) - ORR: I 43% vs C 32.2%, OR=1.59 (95% CI 1.25 to 2.01, p<0.001) - EGFR positive subgroup analysis: ORR: I 71.2% vs C 47.3% (p<0.001) - EGFR negative subgroup analysis: I 1.1% vs C 23.5% (p=0.001) QoL: FACT-L[2] questionnaire OR=1.34 (95% CI 1.06 to 1.69, p=0.01) EGFR positive subgroup FACT-L QoL improvement rate: 70.2% vs 44.5%, p<0.0001 EGFR negative subgroup FACT-L QoL improvement rate: 14.6% vs 36.3%, p=0.0021 TOI[3]: OR= 1.78, (95%CI 1.4 to 2.26, p<0.001)	Secondary: OS I 28.0 months vs C 23.6 months, p=0.353 response rate: I 74.5% vs 29.0%, p<0.001	EGFR positive: I 30.6 months vs C 26.5 months, HR= 0.82 (95%CI 0.35 to 1.92, p= 0.65) EGFR negative: I 18.4 months vs 23.3 months, HR=1.2 (95%CI 0.57 to 2.52, p= 0.63) Median PFS: I 6.1 months vs C 6.6 months; HR= 0.813 (95%CI 0.641 to 1.031, p=0.044) EGFR positive: I 8.4 months vs C 6.7 months, HR= 0.61 (95%CI 0.31 to 1.22, p= 0.08) EGFR negative: I 2.1 months vs 6.4 months, HR=1.5 (95%CI 0.88 to 2.62, p= 0.07) Objective response: OR[4] = 1.39 (95%CI 0.89 to 2.17, p=0.15), DCR[5]= 0.54 (95%CI 0.32 to 0.9, p=0.02) ORR[6]: EGFR positive: I 84.6% vs C 37.5%, OR= 9.17 (95%CI 2.11 to 39.85, p= 0.002) EGFR negative: I 25.9% vs C 51.9% , OR= 0.33 (95%CI 0.10 to 1.02, p=0.05) DCR: EGFR positive: I 88.5% vs C 100%, p= 0.28 EGFR negative: I 40.7% vs C 81.5%, OR= 0.16 (95%CI 0.05 to 0.54, p=0.002) QoL: more favourable outcomes for I group for global health status, role functioning, social functioning
Adverse effects (AEs)	overall grade 3/4 AEs: I 28.7 vs C 61.0% discontinuation due to AEs: I 6.9% vs C 13.6% Deaths associated with AEs: I 3.8% vs C 2.7% Serious AE, including death: I 16.3% vs C 15.6% AEs leading to hospitalization: I 13.8% vs C 13.1% ILD[7] events all grades/grade 3,4 ,5 : I 2.6% vs C 1.4%/I 1.3% vs C 0.2%	neutropenia grade 4: I 1% vs C 33%, grade 3-4 liver dysfunction I 25% vs C 1% grade 3 neuropathy 0% vs 5%, p<0.01	more favourable outcomes for I group for appetite loss, peripheral neuropathy, alopecia grade 5 ILD: I 2 pts
Commentary	EGFR mutation was a robust predictor of improved PFS with gefitinib, indicating that patients in whom an EGFR mutation has been identified will benefit most from first-line therapy with gefitinib.	gefitinib as the first-line treatment for advanced NSCLC harbouring EGFR mutations significantly improves PFS with favourable toxicity profiles against chemotherapy, thus should be considered as new standard treatment for sensitive EGFR mutation-positive NSCLC pts	EGFR mutation status strong predictive marker for overall response and PFS with gefitinib, unprecedented survival outcome along with high ORR and better toxicity profile, gefitinib might be reasonable first-line therapy for never-smoker lung adenocarcinoma pts

[4] OR= odds ratio

[5] DCR= disease control rate (complete remission + partial remission + stable disease)

[6] ORR= objective response rate (complete remission + partial remission)

[7] ILD = interstitial lung disease

untreated patients randomized to either gefitinib or platinum based chemotherapy

Previously untreated patients suffering from NSCLC were randomized to either gefitinib treatment or to a platinum based chemotherapy with the main objective of showing the non-inferiority of gefitinib in comparison to standard chemotherapy. The population included consisted mainly of women (overall 80%) of Asian origin, patients with good performance status and never smokers (94%), factors all known to impact positively on the treatment with EGFR TKIs [8]. Nevertheless, EGFR mutation status was not a prerequisite for inclusion, leading to determination of EGFR status in 35.9% of patients. Out of these 437 samples, 261 (60%) had a confirmed positive EGFR mutation status, resulting in 132 EGFR mutation positive patients treated with gefitinib and 129 individuals treated with chemotherapy.

study population: mainly women of Asian origin, never smokers, good PS

no difference in OS, improved outcomes especially for subgroups based on EGFR status

more treatment related deaths and interstitial lung disease in gefitinib group but overall more adverse events in chemotherapy group

For the gefitinib group, favourable results for PFS were found, especially if a planned subgroup analysis according to EGFR mutational status was performed but, as mentioned above, these subgroups were considerably small. Similarly, QoL showed also superior results for the gefitinib group, foremost, if mutational status was taken into account. On the other hand, no benefit in terms of OS was demonstrated - but follow-up is still ongoing. Despite higher overall frequencies of adverse events of grade 3 or 4 in the chemotherapy group, serious adverse events, such as deaths associated with treatment occurred slightly more often after the administration of gefitinib. Interstitial lung disease was seen nearly twice as often in the intervention group than in the chemotherapy group.

two further phase III trials showed no difference in OS

results for PFS differed

A further phase III trial conducted in Japan (only abstract available) compared patients with confirmed EGFR mutations treated with either gefitinib or carboplatin + paclitaxel [18]. Similar to the trial mentioned above, OS was not statistically different in between the groups, but PFS showed a difference of 4.9 months in favour of the gefitinib group. Regarding side effects, neutropenia and neuropathy occurred less frequent, liver dysfunctions more often in the Iressa® group.

study populations: Asian origin, more females, in one study only never-smokers

On the 13th conference on lung cancer, *Lee et al.* [19] presented results of the "first-SIGNAL" study – a randomized phase III trial assessing first-line therapy with gefitinib in comparison to gemcitabine + cisplatin. The study population comprised 309 never-smokers suffering from adenocarcinoma and with an ECOG PS 0-2. EGFR status was determined in 96 patients of whom 42 had activating EGFR mutations. OS did not differ even if a subgroup analysis according to EGFR status was performed. Median PFS showed overall better outcomes for the gefitinib group, results which were not repeated when only patients with activating EGFR mutations were taken into account. According to the presentation, gefitinib was superior to standard chemotherapy in terms of QoL related measures and in a number of selected adverse events.

6.2 Efficacy and safety - further studies

Several phase II trials were identified which evaluated first-line gefitinib for the treatment of advanced or metastasised NSCLC.

One randomized phase II study compared chemo-naïve patients with poor PS which were treated with best supportive care either in combination with gefitinib (100 patients) or with placebo (101 patients) [21]. Neither PFS nor OS (median OS 3.7 months for gefitinib group vs 2.8 months for placebo group) nor QoL showed statistically significant improvements for the intervention group. An analysis in patients with EGFR FISH- positive (fluorescent in situ hybridization) tumours, however, demonstrated more favourable outcomes in terms of PFS for the gefitinib group (HR=0.29, 95% CI 0.11 to 0.73) but this group consisted of only 32 patients.

several phase II studies with different study populations

Two studies concentrated on patients with EGFR mutations [9, 22]. Sample size was 16 in a trial conducted in Japan [9], and 31, mainly non Asians, in another study [22]. Both trials included more women and a high proportion of never smokers (38% and 46%). Median PFS was 8.9 to 9.2 months and objective response rates were observed in 58% to 81% with the majority being partial responses. *Sequist et al.* calculated a projected median OS of 17.5 months. An objective response was achieved in 12 patients (2 complete responses, 10 partial responses) [9] and 17 patients (1 complete response, 16 partial responses) [22].

Five further phase II trials assessing first-line gefitinib were found [23-27]. Sample size varied from 34 patients [27] to 70 patients [24]. Median OS differed substantially. The shortest OS was 6.3 months in a study which included mainly individuals with history of smoking, poor ECOG PS and with a median age of 75 years [24]. The longest OS of 14.1 months was found in a study conducted in Japan [27]. Median age was 64 years and patients had good PS. In the other studies, OS ranged from 9.6 months, evaluated in an older population (median age 75 years) which had received chemotherapy with docetaxel additionally to gefitinib [23], to 11.5 months [25]. Results of median PFS fluctuated from 3.2 months [26] to 6.9 months [23].

PFS from 3.2 to 9.2 months, OS from 6.3 months to 17.5 months

QoL was assessed in three studies [21, 25, 27]. One trial found, depending on the instrument used for evaluation, improvements in 15% to 41% of patients, but the majority of patients remained stable [25]. The study by *Suzuki et al.* [27] observed no changes in global health status, but significant improvements in insomnia, appetite loss and gastrointestinal side-effects, whereas the last study did not find improved outcomes for the intervention group [21].

differing results for QoL

Regarding side-effects, the vast majority were mild or moderate and included rash (up to 55%) or diarrhoea (51%) [21, 26]. More severe adverse events of grade 3 occurred in up to 17%, consisting of fatigue [24, 27], hepatotoxicity [9, 27], haematological side effects [23, 25], or rash [27]. Grade 4 events were relatively rare and comprised deep vein thrombosis or pulmonary embolus in about 3% [24] and grade 4 anaemia in up to 6% [9, 23]. Reports on interstitial lung disease, a serious complication related to gefitinib treatment [6], were found in four studies and occurred in up to 7.5% of all patients [9, 22, 23, 26]. Three studies did not observe any pulmonary toxicities [21, 25, 27] in patients treated with gefitinib. Treatment discontinuation because of drug related toxicity was reported in only two studies [9, 22].

most side-effects mild or moderate

grade 3 or 4 included hepatotixicity, rash, haematological side effects

interstitial lung disease, a serious complication related to gefitinib occurred in up to 7.5%

A pooled analysis of five reports, comprising 101 patients with EGFR mutation, found a median PFS of 7.7 to 12.9 months. OS had just been reached in one of the trials included and was 15.4 months [3]. Two of the reports evaluated first-line gefitinib and the remaining ones assessed a mixed population treated with gefitinib first-line therapy or after exposure to chemotherapy.

other study designs...

Morita et al. performed a combined survival analysis of seven phase II trials incorporating results from 148 patients with EGFR mutations which had received gefitinib either as first-line therapy (87 patients) or after chemotherapy (61 patients) [4]. At a median follow-up time of 20.7 months, median PFS was 9.7 months (95% CI 8.2 to 11.1 months) and median OS was 24.3 months (95% CI 19.8 to 28.2 months). Good ECOG PS (0, 1) and no prior chemotherapy were significantly associated with improved results for PFS and OS. When the first-line gefitinib group was compared to those patients who had previously received systemic chemotherapy, PFS was significantly extended for the first-line group, whereas no differences were found for OS.

A retrospective analysis compared 51 chemonaïve never smokers treated with gefitinib and gemcitabine-carboplatin to a historical cohort of 29 never smokers treated with gemitabine-carboplatin alone [28]. Adding gefitinib to the chemotherapy resulted in an improved PFS (adjusted HR=0.19, 95% CI 0.0105 to 0.351, $p<0.001$) and median OS increased from 14.1 months in the chemotherapy only group to 20.5 months ($p=0.05$).

7 Estimated costs

cost estimates for one package gefitinib € 2,463 - € 3,601

Cost estimates for one package containing 30 tablets 250 mg Iressa® range between € 2,463 [29] and € 3,601 [30]. It remains unclear whether the majority of costs will be in addition to or instead of other forms of therapy by reasons that the EMEA approval does not clearly state whether gefitinib should be used as monotherapy or in combination with chemotherapy. Nevertheless, at the moment clinical practice is in clear favour of monotherapy.

6 months treatment between € 14,616 and € 21,606

It was assumed that treatment should continue as long as disease does not progress or as long as toxicity remains acceptable. In the phase III trial mentioned above [8], median duration of treatment was 6.4 months, hence assuming treatment lasting on average for 6 months, would result in € 14,616.- to € 21,606.-. However, by sparing patients the considerable side-effects associated with platinum-based chemotherapies, gains in QoL-related outcome measures as well as diminished expenses for in-patient treatment have to be taken into account.

8 Ongoing research

Two open phase III studies were identified on clinicaltrials.gov

2 further phase III trials assessing first-line gefitinib

NCT01017874, which is not yet recruiting, will compare first-line gefinitib alone or in combination with chemotherapy (pemetrexed/cisplatin) for the treatment of NSCLC in never- smoking patients with East Asian origins.

NCT00807066, a study conducted in Italy, has an estimated completion date in November 2011 and will compare patients with locally advanced or metastatic NSCLC treated with either first-line platinum based chemotherapy or first-line gefintinib.

Moreover, the final publications of the NEJ002 and first-SIGNAL are expected.

Plenty phase II trials were found additionally, assessing gefitinib for different indications such as maintenance therapy, in combination with hydroxochloroquine or with radiation therapy or for the treatment of carcinomatous meningitis in patients with NSCLC.

9 Commentary - English

EMEA market authorization in 2009

In June 2009, the EMEA granted market authorization for gefitinib for the treatment of advanced or metastatic NSCLC with activating mutations of EGFR TK. The decision for approval as first-line therapy was mainly based on the results of the IPASS study [8] which assessed first-line monotherapy with gefitinib in selected patients (mainly younger, women with Asian origin, non-smokers), where EGFR TKI treatment is the most effective. Within this highly selected population, OS did not differ between patients treated with gefitinib or standard chemotherapy - but follow-up is still ongoing. PFS, on the other hand, showed favourable results for the population treated with gefitinib (HR=0.74, 95% CI 0.65 to 0.85, $p<0.001$). Moreover, in a preplanned subset analyses, PFS and QoL scores were significantly improved in patients with activating EGFR mutations. Nevertheless, as a positive EGFR mutational status was determined in only 261 patients, this group was, overall, considerably small.

IPASS trial included mainly younger patients, females with Asian origins, non-smokers

similar results for OS, but improvements for PFS and QoL

Regarding adverse events, the gefitinib group experienced less often events of grade 3 or 4 than the chemotherapy group. Interstitial lung disorders were more common in the gefitinib group (2.6%) than in the chemotherapy group (1.4%) and slightly more deaths associated with adverse events occurred in the intervention group (I 3.8% vs C 2.7%). Overall however, treatment with gefitinib was better tolerated than chemotherapy, indicating that it should be used as monotherapy and not in combination with other chemotherapeutic agents.

less often severe adverse events in gefitinib group, but more often interstitial lung disorders

two other phase III trials

Two further phase III trials were found [19, 20]. Both trials were also conducted in an Asian setting, included more females than males and one study assessed gefitinib treatment only in never-smokers. These studies did not show any difference between gefitinib and chemotherapy in terms of OS. With regards to PFS, results differed. One of the trials evaluated Iressa® therapy in a study population with confirmed activating EGFR mutations and showed a difference of 4.9 months in favour of the EGFR-TKI group ($p<0.001$) [18]. The "first-SIGNAL" study on the other hand, did not confirm these results within a subgroup of 42 patients with activating EGFR mutations [19]. The adverse events mentioned, such as alopecia, neutropenia or neuropathy, occurred less often if gefitinib was administered, leaving liver dysfunction the only side-effect more common in this treatment arm. QoL related outcome measures were presented for the "first-SIGNAL" study, indicating benefits for gefitinib over chemotherapy.

study population: more females than males, Asian origin, never-smokers

no difference in OS, results for PFS differed

EMEA expressed concerns whether findings of Asian population can be extrapolated to Caucasian population post-marketing trial within a Caucasian population

Despite data indicating that patients with EGFR mutations might benefit eventually from gefitinib, studies assessing its value in a population representative for the majority of NSCLC patients in Europe are missing. Accordingly, EMEA's Committee for Medicinal Products for Human Use expressed concerns whether results stemming from an Asian population can be used to extrapolate efficacy of gefitinib to a Caucasian population. EMEA's Scientific Advisory Group concluded that because gefitinib shows "across all studies [...] a consistent pattern of activity in EGFR mutation status positive patients" [31] a confirmatory first-line study is not necessary, but a post-marketing prospective trial within a Caucasian population with confirmed EGFR mutations should be conducted. As a consequence, Astra Zeneca has agreed on developing, in accordance with the EMEA, an appropriate trial design [31].

challenges in determination of EGFR status: acquisition of tumour tissue, mutational status might depend on where tissue was derived from, acquired drug resistance

Another issue which has been discussed repeatedly is the method for detecting EGFR mutations [8, 9, 28]. In addition to the absence of standardized methods, challenges include the acquisition of enough tumour tissue for analysis which might be particularly difficult in patients with advanced disease whom are not candidates for surgery [28]. Moreover, mutational status might differ depending on where the tissue has been derived from (i.e. primary tumour vs metastatic lesions) [6] and mutations, possibly leading to an acquired drug resistance against EGFR TKIs, may even occur during therapy. With the possibility of an acquired drug resistance, regular monitoring of the cancer's genotype might become necessary [6, 32]. These resulting uncertainties impact not only on the potential clinical benefit but also on the financial burden as determination of EGFR status prior to and even during EGFR TKI treatment, would increase costs further. It is also debatable whether current study findings justify repeated biopsies in critically ill patients. On the other hand, gains in QoL can be expected by sparing patients considerable toxicities associated with platinum-based chemotherapies.

gefitinib offers advantages but final clinical benefit difficult to judge

Undoubtedly, the oral application of gefitinib in an outpatient setting and, in general, less severe side-effects in comparison to chemotherapy offer advantages. Nevertheless, a number of issues surrounding first-line gefitinib therapy for NSCLC still remain unresolved, making it difficult to conclusively judge its potential clinical benefit. However, this drug might prove quite effective if used in patients identified by more refined molecular targeting.

10 Commentary – German

EMEA Marktzulassung 2009

Die EMEA erteilte im Juni 2009 für Gefitinib die Marktzulassung für die Behandlung von erwachsenen PatientInnen mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden Mutationen der EGFR TK.

Die Entscheidung für die Zulassung als Erstlinientherapie basierte im Wesentlichen auf den Ergebnissen der IPASS Studie [8], welche die Erstlinienmonotherapie mit Iressa® in einer ausgewählten Studienpopulation (jüngere PatientInnen, Frauen von asiatischer Herkunft, Nichtraucher), in der Therapien mit EGFR TKIs sehr wirksam sind, untersucht hatte. In dieser hoch selektierten PatientInnengruppe, zeigte sich in Bezug auf Gesamtüberleben kein Unterschied zwischen Iressa® und Standardchemotherapie - das Follow-up ist allerdings noch nicht abgeschlossen. Das progressionsfreie Überleben (PFS) hingegen, zeigte bessere Ergebnisse für die Gefitinib-Gruppe als für die Chemotherapiegruppe (HR=0,74; 95% CI 0,65 bis 0,85, p<0,001). In einer geplanten Subgruppenanalyse in Patienten mit EGFR Mutationen wurde ebenfalls eine statistisch signifikante Verbesserung von sowohl PFS, als auch der Lebensqualität gefunden. Nichtsdestotrotz soll erwähnt werden, dass EGFR aktivierende Mutationen in insgesamt nur 261 PatientInnen nachgewiesen wurden und diese Subgruppe daher relativ klein war.

IPASS Studie hauptsächlich Frauen asiatischer Herkunft, jüngere PatientInnen, Nichtraucher

Gesamtüberleben gleich, bessere Resultate für PFS und Lebensqualität vor allem für PatientInnen mit aktivierenden EGFR Mutationen

In Bezug auf unerwünschte Nebenwirkungen von Grad 3 und Grad 4 wurden diese seltener in der Gefitinib-Gruppe als in der Chemotherapiegruppe beobachtet. Interstitielle Lungenerkrankungen (I 2,6% vs C 1,4%) als auch Therapieassoziierte Todesfälle (I 3,8% vs C 2,7%) traten jedoch häufiger unter Therapie mit Iressa® auf. Insgesamt war Gefitinib aber besser verträglich als Chemotherapie, sodass die Iressa® Monotherapie mit eher angezeigt scheint, als eine Kombinationstherapie.

schwere NW seltener in Gefitinib-Gruppe

Zwei weitere Phase III Studien [18, 19], die ebenfalls in Asien durchgeführt worden waren, wobei in beiden Studien mehr Frauen als Männer und in einer nur Nichtraucher eingeschlossen worden waren [19], zeigten für Gefitinib und Chemotherapie keine Unterschiede hinsichtlich Gesamtüberleben. In Bezug auf PFS waren die Ergebnisse unterschiedlich: Eine Studie, welche Iressa® in einer Studienpopulation mit aktivierenden EGFR Mutationen bewertet hatte, fand eine Differenz von 4,9 Monaten zu Gunsten der mit EGFR-TKI behandelten Gruppe (p<0.001) [18]. Die „first-SIGNAL" Studie hingegen zeigte für diese PatientInnensubgruppe, welche allerdings nur aus 42 PatientInnen bestand, keinen Vorteil [19]. Unerwünschte Nebenwirkungen, wie etwa Alopezie, Neutropenie oder Neuropathie, waren seltener in der Gefitinibgruppe zu beobachten, lediglich Dysfunktionen der Leber traten häufiger auf. Auch für die Lebensqualität zeigten sich günstigere Ergebnisse für die mit Iressa® behandelte Gruppe [19].

weitere Phase III Studien

Studienpopulation: mehr Frauen als Männer, Nichtraucher, asiatischer Herkunft

kein Unterschied in Gesamtüberleben

Nichtsdestotrotz sind Studien ausständig, die den Wirksamkeitsnachweis für eine im europäischen Kontext relevante Population mit NSCLC erbringen. EMEAs Ausschuss für Humanarzneimittel äußerte Bedenken, ob die Ergebnisse einer asiatischen Studienpopulation auf eine kaukasische Bevölkerung umlegbar seien. Der wissenschaftliche Beirat der EMEA folgerte aber, dass für Gefitinib „aufgrund des durch alle Studien hinweg durchwegs einheitlichen Aktivitätsprofils in PatientInnen mit positiven EGFR Status" [31] keine bestätigende Erstlinienstudie mehr nötig sei. Allerdings sollte im Weiteren eine Anwendungsbeobachtungsstudie in einer klar definierten, kaukasischen PatientInnengruppe mit nachgewiesener EGFR Mutation durchgeführt werden [31]. Astra Zeneca, der Hersteller, erklärte sich einverstanden, unter Rücksprache mit der EMEA eine entsprechende Studie durchzuführen.

EMEA äußerte Bedenken, ob Studienergebnisse einer asiatischen Bevölkerung auf Kaukasier umlegbar sind

Anwendungsbeobachtungsstudie in kaukasischer Population geplant

Herausforderungen bei Bestimmung des EGFR Status: Gewinnung von Tumorgewebe, Metastasen und Primärtumor möglicherweise unterschiedlicher EGFR Status, erworbene Resistenz

Zusätzlich soll erwähnt werden, dass bisher kein einheitlicher Standard zur Bestimmung des EGFR Status existiert [8, 9, 28] und vor allem bei PatientInnen, die aufgrund eines fortgeschrittenen Stadiums der Erkrankung keine Kandidaten für ein operatives Vorgehen sind, es schwierig sein kann, ausreichend Tumorgewebe zur Bestimmung des EGFR Status zu gewinnen [28]. Zusätzlich wird diskutiert, dass je nach dem woher Gewebe gewonnen wurde (Primärtumor, Metastasen), der Mutationsstatus unterschiedlich sein kann [6]. Da es auch während einer EGFR TK Therapie zu einer erworbenen Resistenz gegen EGFR TKIs kommen kann, könnte ein regelmäßiges Monitoring des EGFR Status nötig sein [6, 32]. Die daraus resultierenden Unsicherheiten könnten nicht nur auf den potentiellen therapeutischen Nutzen von Gefitinib Auswirkungen haben, sondern auch auf die Kosten, da der EGFR Status *vor* Gefitinibtherapie und in weiterer Folge auch *während* der Therapie bestimmt werden müsste. Diskussionswürdig ist auch, ob die derzeitige Datenlage wiederholte Biopsien in schwerkranken PatientInnen rechtfertigen kann. Durch die Vermeidung von den mit Platinhältiger Chemotherapie verbundenen, schweren Nebenwirkungen kann aber auf der anderen Seite mit einer Verbesserung der Lebensqualität gerechnet werden.

Gefitinib bietet Vorteile, allerdings endgültige Einschätzung des therapeutischen Nutzens schwierig

Zweifellos bietet Gefitinib aufgrund der oralen, ambulanten Einnahme und der, im Vergleich zu Chemotherapie, selteneren schwerwiegenden Nebenwirkungen Vorteile. Allerdings sind noch etliche Fragen offen, die eine endgültige Einschätzung des therapeutischen Nutzens von Gefitinib für die Erstlinientherapie bei NSCLC erschweren. Die Substanz bietet aber durchaus das Potential, eine effektive Therapieoption in molekular noch besser zu charakterisierenden Patientenkollektiven zu werden.

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