Anti-cancer therapy with EGFR inhibitors: factors of prognostic and predictive significance

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Key words: EGFR, tyrosine kinase inhibitor, non-small cell lung cancer

introduction

The epidermal growth factor receptor (EGFR) pathway plays an important role in development and progression of many human malignancies, including non-small cell lung cancer (NSCLC). Several new molecules inhibiting this critical biological pathway have been synthesized and tested in clinical trials, including small tyrosine-kinase inhibitors (TKIs), such as gefitinib and erlotinib, and monoclonal antibodies, such as cetuximab. To this regard, emerging data suggest that patients with the highest chance of responding to TKIs should be selected on the basis of clinical and, most of all, biological characteristics. In fact, recent studies showed that NSCLC patients with increased EGFR gene copy number or with activating mutations of the EGFR catalytic domain which also present Akt activation or HER2 gene gain, have a better outcome than patients without these features. Interestingly, new predictors of response in tumors other than NSCLC are also being progressively highlighted. Although biological markers of sensitivity may differ for each form of malignancy, they invariably depend on the degree of activation of the EGFR pathway and on the importance that EGFR signalling holds as oncogenic determinant of a specific type of cancer. Prospective trials are warranted to validate criteria for selection of patient selection for EGFR-inhibitors.

The Epidermal Growth Factor Receptor (EGFR) family is a group of four receptors including EGFR (Erb-B1), HER2/neu (Erb-B2), HER3 (Erb-B3) and HER4 (Erb-B4) [1]. The rationale for developing drugs targeting the EGFR is based on the evidence that this receptor, commonly expressed primarily in non-malignant cells of epithelial origin, is implicated in proliferation and survival of a number of tumors in which its over-expression appears to be related to poor prognosis and resistance to chemo- and/or radiotherapy [2]. So far, several drugs interfering with the EGFR have been synthesized. Among these, small molecules tyrosine kinase inhibitors (TKIs), such as gefitinib (Iressa) and erlotinib (Tarceva), or cetuximab (Erbitux), a monoclonal antibody directed against the extracellular domain of the EGFR, have been tested in preclinical and clinical models, especially in non-small cell lung cancer (NSCLC).

tyrosine kinase inhibitors and NSCLC

Gefitinib and erlotinib inhibit the TK activity of EGFR by reversibly competing with adenosine triphosphate (ATP) at the ATP-binding site within the EGFR protein.

In phase II trials of unselected patients with heavily pretreated advanced NSCLC, gefitinib and erlotinib yielded a 10% to 20% of responses while a symptomatic improvement was reported in about 40% of patients [3–5]. Disappointingly, in large phase III trials of chemo-naı̂ve advanced NSCLC patients it was observed that the combination of TKIs with chemotherapy was not able to confer a survival advantage over standard chemotherapy alone [6–9]. More recently in two large phase III trials (BR21 and ISEL), evaluating the efficacy of erlotinib or gefitinib as second or third line therapy, it was demonstrated a statistically significant survival advantage over placebo only for erlotinib [10, 11].

Due to these results, TKIs are currently being administered to patients as second or third line therapy after failure of a standard platinum based chemotherapy, but the observation that only a small group of patients with predefined clinical and/or biological characteristics obtains the highest benefits suggests that patients’ selection is critical for TKIs sensitivity.

Retrospective analyses of phase II trials showed that Asian origin, female gender, adenocarcinoma histology and never smoking history were significantly associated with response to TKIs [3–5, 12, 13]. Recent findings clearly indicate that among clinical characteristics associated with sensitivity to TKIs, smoking history is the most important. In the TRIBUTE trial [9], median survival was significantly longer in never smokers treated with erlotinib than in never smokers treated with placebo. Similarly, in the BR21 and ISEL trials, it was shown that never smokers treated respectively with erlotinib or gefitinib had a significantly longer survival when compared to never smokers treated with placebo, with no survival difference.
in smokers irrespectively of the treatment [10, 11]. The increased sensitivity of never smokers suggests that TKIs could represent a valid alternative to standard chemotherapy in never smokers, and prospective phase III trials should compare standard chemotherapy with TKIs in this subgroup of patients.

Although drugs interfering with EGFR are generally well tolerated, cutaneous toxicity and diarrhoea are observed in the majority of treated patients. Development of rash has been associated with sensitivity to erlotinib [5] and cetuximab [14]. The role of rash as a marker of sensitivity to gefitinib is more controversial as some trials show a correlation between rash and response [15, 16] while others do not [5]. Escalation of gefitinib to a dosage that causes skin toxicity in order to improve clinical outcome in patients with low grade or no rash after initial exposure to gefitinib, is a fascinating hypothesis [17], and this strategy deserves further evaluation.

Although clinical factors, especially smoking history, could be useful for patients selection, the fact that in the BR21 trial the improved survival after erlotinib was observed in all clinical subgroups being as large in males as in females and in squamous cell carcinomas as in adenocarcinomas suggests that patients’ selection should be performed on the basis of biological characteristics (Table 1). In fact, clinical features associated with sensitivity to EGFR-inhibitors are important only because they reflect a particular biological aspect of the disease.

In 2004, it was shown that mutations in the TK domain of EGFR were associated with sensitivity of NSCLC to gefitinib or erlotinib [18–20]. These mutations were found to be significantly related to asian ethnicity, female gender, adenocarcinoma histology, and never smoking history [18–20]. Importantly, tumors with these mutations generally do not present K-ras mutations typically occurring in smokers, and significantly associated with primary resistance to TKIs [21]. The fact that EGFR and K-ras mutations are mutually exclusive, suggests a different pathogenic mechanism in smokers from never smoker patients [22].

Although initial reports of a responders-enriched population found that EGFR gene mutations were present in nearly all responders [18–20], recent studies demonstrated that there is a significant fraction of patients with EGFR mutations refractory to the therapy [23–25]. Importantly, EGFR mutations are virtually absent in patients with stable disease [23], and in the BR-21 study it was demonstrated that disease stabilization contributed to the overall survival advantage seen with erlotinib [10].

Moreover, although survival analyses of retrospective series showed a significant association of EGFR gene mutations and improved survival of TKIs treated patients, association with survival was not significant in subgroup analyses of large phase II-III trials (Table 2). Emerging data suggest that patients with EGFR gene mutations have a better prognosis than individuals with EGFR wild-type regardless of the treatment [26, 27]. Therefore, it is not possible to exclude that patients with EGFR gene mutations have a survival advantage because the prognosis of their disease is particularly favourable.

Data regarding the prognostic role of EGFR expression on immunohistochemistry (IHC) are not conclusive. Although association of EGFR expression with survival is still somewhat controversial, patients with high EGFR copy number by

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<th>Study</th>
<th>Evaluated (n)</th>
<th>EGFR mutation (%)</th>
<th>Association with survival</th>
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<tr>
<td>Ideal 1 &amp; 2</td>
<td>78</td>
<td>18.0</td>
<td>Not significant</td>
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<tr>
<td>Intact 1 &amp; 2</td>
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<td>Tribute</td>
<td>228</td>
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<td>Not significant</td>
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<tr>
<td>BR 21</td>
<td>177</td>
<td>23.0</td>
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partner of EGFR for the heterodimerization process, simultaneous presence of both receptors may indicate a higher potential of tumor proliferation. Moreover, a preclinical report showed that, although gefitinib selectively inhibits EGFR activity, tumors with synchronous over-expression of EGFR and HER2 are particularly sensitive to the drug [34]. Recently, we evaluated HER2 status by FISH in a cohort of 102 NSCLC patients treated with gefitinib and previously evaluated for EGFR status by FISH, IHC and DNA sequencing observing that patients with an increased HER2 gene copy number at FISH who were also EGFR positive (either at IHC or FISH) had better response rate, disease control rate, time to progression, and survival [32]. These results support the use of HER2 FISH analysis as a complementary test for selection of patients for TKIs therapy and therapeutic strategies directed against both EGFR and HER2 deserve further evaluation in lung cancer.

Akt is an anti-apoptotic protein whose phosphorylation status, which reflects the activation of the EGFR downstream pathway through the phosphatidylinositol 3-kinase/Akt (PI3K/Akt) cascade, has been recently found to be a negative prognostic factor in NSCLC [35]. Due to its involvement in EGFR signalling, also p-Akt has undergone initial investigation as a potential molecular marker of tumor responsiveness to gefitinib. In a recently published study, conducted in 103 NSCLCs, we observed that p-Akt positive patients had a significantly higher response rate, disease control rate, and time to progression than p-Akt negative [36]. Consistent with these findings is a recent research demonstrating that Akt is constitutively activated in gefitinib sensitive cell line H3255, and treatment with gefitinib completely inhibited the Akt [37]. The general conclusion seems to be that high sensitivity to gefitinib in NSCLC is strongly dependent on Akt activation when the EGFR pathway is active, thus p-Akt status assessed by IHC is another complementary test for patients candidate to EGFR-inhibitors.

tyrosine kinase inhibitors and gliomas

In malignant gliomas, unlike NSCLC, the relationship between EGFR copy number and sensitivity to TKIs is controversial [38–40]. Furthermore, the 10–20% of sensitivity to EGFR-inhibitors cannot be accounted to EGFR mutations of the TK domain as they are a very rare event in this tumor [41]. On the contrary there is little doubt that the most common form of mutated EGFR in gliomas is the EGFR variant III (EGFRvIII) [42]. Recently it was postulated that this variant of EGFR, that as a result of a genomic deletion in the extracellular domain promotes cellular proliferation and survival through aberrant and constitutional activation of the PI3K/Akt signalling pathway, might be associated to responsiveness of glioblastomas to TKIs [40]. Interestingly, in this study molecular analyses performed in 26 glioblastomas showed that tumors co-expressing EGFRvIII and PTEN, a tumor suppressor gene of the PI3K/Akt downstream pathway, had the highest likelihood of response to TKIs. These findings suggest again that also in malignant gliomas the identification of tumors whose mechanism of survival depends on EGFR signalling is essential for selecting patients for EGFR-inhibitors.

cetuximab and colorectal cancer

In the BOND study, in patients with metastatic colorectal cancer, the combination of cetuximab, a human-murine anti-EGFR IgG1 monoclonal antibody, and irinotecan significantly improved response rates and median time to progression over single agent cetuximab in patients progressing during or within 3 months after an irinotecan-containing chemotherapy [43]. This led to cetuximab approval for use in colorectal cancer tumours expressing EGFR assessed by IHC in combination with irinotecan in irinotecan-refractory patients, and as a single therapy in patients intolerant to irinotecan. Although the FDA approval states that cetuximab should be administered only to patients with EGFR-positive tumours, recent data suggest that EGFR detection by IHC has little or no predictive value of response to cetuximab. As reported by Chung et al., cetuximab has also shown activity in colorectal tumours that are negative for EGFR by IHC [44]. Moreover in the BOND study, the efficacy of cetuximab was not related to levels of EGFR expression. More recently it was observed that increased EGFR copy number detected by FISH is associated with response to the anti-EGFR monoclonal antibodies cetuximab or panitumumab [45]. EGFR mutations are rare in colorectal cancer: in the Moroni et al. study, only one out of 31 patients had a somatic mutation of the EGFR catalytic domain, and that occurred in a non-responding patient. A preclinical study found also that EGFR mutant NSCLC cell lines are sensitive to gefitinib to a greater extent than cetuximab, suggesting that mutations of the EGFR TK domain are not predictive of sensitivity to cetuximab [46].

conclusion

Novel targeted therapies are raising new hopes for cancer patients. EGFR-inhibitors have led to impressive and durable responses in a small fraction of patients with NSCLC. Nevertheless the role of EGFR-inhibitors is constantly widening. However, regardless of the tumors where they are used, only patients with predefined molecular alterations show to benefit from therapy with EGFR-inhibitors, suggesting that these agents should not be given to all patients irrespectively of their clinical and/or biological characteristics, but their use should be limited to individuals presenting the molecular target of the therapy and in whom this target is crucial for cancer cell survival.

references


