Her2-neu: a target in lung cancer?

In addition to the steady flow of new cytotoxic drugs for lung cancer during the last decade, the elegant concept of targeted agents has in recent years become a source of optimism and pitfalls. Among all the targets, Her2-neu is a typical example of how preclinical data can be translated into clinical progress.

Her2-neu in breast cancer: the ideal model

Erb-B2 (Her2-neu) is a 185 kDa glycoprotein with tyrosine kinase activity. This protein is a member of the ErbB receptor family that also includes ErbB1 (EGFr), ErbB3 and ErbB4. The implication of Her2-neu in mammary carcinogenesis has been shown in vitro [1] and in vivo [2]. Since then, most of the studies focusing on ErbB2 have been carried out in breast cancer. In this model, it has been shown that ErbB2 overexpression was associated with poor prognosis in some subsets of patients [3, 4] and with tamoxifen resistance [5]. Since ErbB2 overexpression was involved in mammary carcinogenesis, the idea has emerged that its inhibition could lead to tumor regression. Monoclonal anti-ErbB2 antibodies have been developed in this setting. Preclinical studies that tested anti-Her2-neu antibodies have shown that (i) injection of monoclonal anti-Her2neu antibodies induce tumor regressions in mice and (ii) the anti-Her2neu antibody induces tumor cell growth inhibition in vitro. Following these data, a humanized monoclonal antibody directed against Her2-neu (trastuzumab) has been tested in clinical trials. The pivotal trial was published in the New England Journal of Medicine in 2001 [6]. This randomized trial compared anthracycline- or taxane-based chemotherapy versus the same chemotherapy plus trastuzumab. The results showed that the addition of trastuzumab increased response rates (50% versus 34%), time to progression (7.4 versus 4.6 months) and overall survival (25 versus 20 months). Some technical and logistical considerations must be put forward. This trial included patients presenting weak to moderate Her2-neu overexpression (coded as 2+) and more than moderate Her2-neu overexpression (3+) in >10% of tumor cells while 70–80% of tumors were coded 3+. This restriction allowed the recruitment of 469 patients during a 2-year period. Encouraged by these exciting data, investigators have looked at potential indications of trastuzumab in other cancers, including non-small-cell lung cancer (NSCLC).

Her2-neu in lung cancer: is the mammalian model adequate in bronchial tumors?

Some studies have shown that a small subset of NSCLC overexpress Her2-neu. Nevertheless, the exact percentage of Her2-neu overexpression in NSCLC is difficult to assess since papers report overexpression rates ranging from 4% to 27% [7, 8]. This heterogeneity is mainly due to differences in the methods used to assess Her2-neu expression. Although Her2-neu overexpression is limited to a small subset of patients with NSCLC, there are at least three reasons that support the evaluation of the efficacy of trastuzumab in this disease. First, NSCLC cell lines that overexpress Her2-neu are sensitive to trastuzumab exposure in vitro [9]. Second, Her2-neu overexpression is involved in cisplatinum resistance [10]. It could therefore be speculated that the addition of trastuzumab to cisplatin-based chemotherapy could circumvent this resistance. Third, it is not clear whether the bioactivity related to complement- and cell-mediated cytotoxicity is similar in NSCLC and breast cancer. All these arguments have rendered interesting the evaluation of trastuzumab in NSCLC although only a small fraction of these patients overexpress Her2-neu.

In this issue, Gatzmeier et al. [11] report the first randomized trial evaluating trastuzumab in NSCLC. This phase II randomized trial compares gemcitabine plus cisplatin with the same chemotherapy plus trastuzumab in 103 patients with stage IIIB-IV NSCLC that overexpress Her2-neu. Her2-neu overexpression included tumors scored 2+ and 3+ according to the Herceptest. This group reports two important findings: (i) of 619 patients screened for Her2 expression using a clinically approved diagnosis test, only 103 (17%) were coded 2+/3+ and only five (1.1%) were reported to be 3+; (ii) the addition of trastuzumab to cisplatin-based chemotherapy did not improve any efficacy end point. Two questions have emerged from this negative trial. (i) Should we follow the breast cancer model to evaluate trastuzumab in NSCLC? (ii) Why do so many trials using a targeted therapy fail to show any efficacy in NSCLC while the concept works in other tumor models?

The development of trastuzumab could be considered in two different ways by either following the breast cancer model, or developing trastuzumab according to lung cancer specificities. In the first case, investigators could use the model provided by breast cancer, and use trastuzumab only in patients presenting Her2 overexpression only in patients presenting Her2 overexpression coded 3+, or 2+ plus FISH+. The concept is to inhibit the oncogenic activity of Her2-neu. Preliminary results suggest that trastuzumab could be efficient in this subset of patients since five of six NSCLC patients with Her2 overexpression coded 3+ or FISH+ presented a tumor response in the study by Gatzmeier et al. [11]. Nevertheless, a trial based on this rationale would need to screen around 15 000 patients for Her2 overexpression in order to include 200 patients in the trial!

The second possible way to develop trastuzumab in NSCLC should take into account the specificities of NSCLC. Indeed, at least two important findings have been reported in this field. First, Her2 overexpression is probably not involved directly in lung carcinogenesis, but cooperates with ErbB1 [12] and ErbB3 [13].
Indeed, it has been suggested that the malignant transformation of lung epithelial cells induced by ErbB2 requires a functional EGFr [12], and that ErbB2 overexpression actually works as a coactivator of ErbB1 in this model. The second particularity of NSCLC compared with breast cancer is the use of cisplatinum-based chemotherapy as first-line treatment. This suggests that a cisplatinum sensitizer could improve survival in stage IV NSCLC patients. Several papers have reported that ErbB2 and ErbB1 mediate at least partially the cisplatinum resistance [10, 14]. Interestingly, the inhibition of these tyrosine kinases circumvents the platinum resistance in cell lines. Once again, ErbB2 cooperates with ErbB1. Considering these data, it might be suggested to re-evaluate anti-ErbB2 therapy in association with anti-ErbB1 treatment. This association might be developed in two settings of patients. First, in combination with cisplatinum-based chemotherapy—this combination could be evaluated in patients with Her2-neu 2+ and 3+, and compared with a cisplatinum-based chemotherapy alone. Second, the association might be compared with ErbB1 inhibitors alone. These two trials would be based on the hypothesis that ErbB2 and ErbB1 cooperate together.

In conclusion, although the last few years have seen the successful emergence of targeted therapies in breast cancer [8], gastrointestinal stromal tumours (GISTs) [15] and lymphoma [16], the results of these new therapies have been quite disappointing in the front line treatment of lung cancer [11, 17, 18]. Two explanations can be put forward for this: (i) the target is just an ‘accidental’ event, not involved in the carcinogenesis; (ii) the target is involved in carcinogenesis or drug resistance, but as a co-activator. The best illustration for the first explanation is provided by the disappointing results provided by the use of Gleevec in small-cell lung cancer [18]. Encouraged by overexpression of CD117 in small-cell lung cancer, c-kit inhibitors have been tested in this setting, but have failed to show any efficacy. This was probably due to the fact that CD117 overexpression is probably not directly involved in the carcinogenesis of lung cancer, and is perhaps an additional oncogenic event. In that case, the target was probably not relevant. The use of Her2-neu inhibitors could illustrate the second explanation. Indeed, as previously discussed, Her2-neu cooperates with EGFr to induce cell transformation in lung carcinogenesis, and to mediate cisplatinum resistance. Since the couple of proteins constituted by ErbB1 and ErbB2 are so complementary, it could be speculated that the concomitant inhibition of the two proteins could lead to clinical benefit in NSCLC.

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References