

TRAIL apoptotic pathway-targeted therapies for NSCLC

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The global burden of lung cancer is a death every 4 seconds, round the clock, 365 days a year, with a global incidence estimated at 1,350,000 in 2002 (1). Lung cancers are classified into two major types: Small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC constitutes 75% of primary lung cancers and the prognosis for patients with NSCLC is poor. Less than 25% of new NSCLC cases present with local stage I or II disease treatable by surgical resection and chemotherapies; however, up to 50% of these stage I and II cases develop recurrence regardless of the treatments (2). The first-generation chemotherapy agents, doxorubicin, methotrexate and vincristine developed in the 1970s are essentially ineffective in treating NSCLC. Based on the experience with the second-generation agents (i.e., cisplatin, etoposide, mitomycin, vindesine, vinblastine) in the 1980s, cisplatin-based combination was recommended for the treatment of advanced NSCLC (3). With the third-generation agents (i.e., paclitaxel, docetaxel, gemcitabine, taxane) approved in the 1990s, cisplatin-based combination of the third-generation agents is used worldwide for the treatment of advanced NSCLC, despite the fact that the therapy only modestly improves patient survival (4). This grim reality demands better understanding of the molecular basis of NSCLC and requires innovative therapeutic strategies in order to achieve substantially improved treatment outcomes.

In the last decade, a new generation of target agents have been developed targeting cancer specific signaling pathways. Gefitinib (Iressa, AstraZeneca), for instance, is the first target agent to be approved for the treatment of patients with advanced NSCLC (5). Gefitinib is a small molecule that targets the mutated tyrosine-kinase domain of epidermal growth factor receptor (EGFR), which results

in substantial clinical responses in 10% to 18% patients with advanced NSCLC harboring *EGFR* mutations (6,7). Gefitinib, however, only improves patient survival for a few months and the cancer eventually starts growing due to the development of acquired resistance in part due to concurrent *EGFR* mutations (8), raising an issue of the cancer resistance to target agents. To improve the response, first-line gefitinib therapy was therefore suggested in a genotype-directed clinical approach to patients with advanced NSCLC that harbors *EGFR* mutations (9). The experience with gefitinib provides a tantalizing preview of what we hope will be a genotype-directed targeted therapy for the treatment of advanced NSCLC.

Recently, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL; also termed Apo2 ligand, Apo2L) has been emerging as a target agent for the treatment of NSCLC. TRAIL was identified in the middle 1900s (10,11) and soon recombinant human TRAIL (rhTRAIL) was generated and shown to be able to induce apoptosis in cancer cells and inhibit the growth of cancer xenografts, without causing damage to normal cells (12,13). Physiological studies further established the role of TRAIL in the innate and adaptive immunity against cancer and, therefore, TRAIL is considered as a natural cancer killer (14). Several lines of evidence in preclinical studies suggest that TRAIL could serve as a target agent in the treatment of advanced NSCLC, in particular in combination with chemotherapy: (I) TRAIL receptor 1 (TRAIL-R1; death receptor 4, DR4) and TRAIL-R2 (DR5) were detected in human NSCLC tissues (15); (II) rhTRAIL is capable of inducing apoptosis in NSCLC cell lines *in vitro* (16) and inhibiting NSCLC xenograft growth *in vivo* (13,17); and (III) combination of rhTRAIL with chemotherapy can overcome the TRAIL

resistance in NSCLC cells (18).

Based on the preclinical studies, clinical trials of rhTRAIL was launched and the first phase I trial of rhTRAIL (rhApo2L/TRAIL, dulanermin), co-developed by Amgen and Genentech, were released at the 2006 American Society of Clinical Oncology (ASCO) Annual Meeting, showing that the monotherapy of rhTRAIL was well-tolerated and associated with partial response in patients with advanced solid cancer (19). The phase Ib trial then revealed that the combination of rhTRAIL with paclitaxel, carboplatin, and bevacizumab (PCB) improved the progression-free survival of patients with advanced NSCLC (20). In contrast, however, the data from phase II trial of rhTRAIL was disappointings. Published in the November 2011 issue of *Journal of Clinical Oncology*, the phase II trial of 213 patients with advanced NSCLC revealed that the addition of PCB to rhTRAIL did not improve the progression-free survival of patients (21). While the factors such as small sample size and lack of control in the phase Ib may explain the difference between the phase Ib and II trials, the phase II trial in a large group of patients have indicated that advanced NSCLCs are resistant to the treatment of rhTRAIL.

TRAIL apoptotic pathway has also been targeted by its agonistic monoclonal antibody (Mab) against DR4 and DR5. At the 2002 American Association of Cancer Research (AACR) Annual Meeting, Human Genome Sciences reported for the first time the generation of a fully human agonistic MAb against DR4 (HGS-ETR1, mapatumumab) and DR5 (HGS-ETR2, lexatumumab). Phase I trials have successfully evaluated the safety and pharmacokinetics of HGS-ETR1, HGS-ERT2 and PRO95780 (drozitumab), a fully human DR5 MAb developed by Genentech (22-24). At the 2010 ASCO Annual Meeting, however, the results from two phase II trials in two large groups of patients revealed that the addition of PCB or PC (paclitaxel, carboplatin) to PRO95780 and HGS-ERT1 did not improve the response rates in patients with advanced cancer. Together with the phase II trial of rhTRAIL, these phase II trials of DR4 and DR5 MAb have demonstrated the resistance of advanced NSCLCs to the treatment of the TRAIL target agents.

In the last decade, a tremendous amount of preclinical and clinical efforts has led to the genesis of this new class of apoptosis target agents. Unfortunately, the data from phase II trials have also demonstrated the resistance of human cancers including NSCLC to the treatment of the TRAIL target agents. A number of molecular models of TRAIL resistance have been reported mainly from studies of cancer

cell lines, arranging from the genetic loss and mutation of TRAIL apoptotic elements to the overexpression of apoptosis inhibitory proteins and posttranslational modification of proteins (25). In contrast, however, a few studies have been carried out in patients' cancer tissues and the tissues-derived cell models such as cancer stem cells and the cell-derived xenografts. It is vital for us to understand the mechanisms of TRAIL resistance in patients' cancers and therefore develop the combination therapy that can overcome the resistance of TRAIL target agents for the effective clinical treatment of patients with advanced NSCLC.

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