Challenges of the phase I drug development in non-small cell lung cancer

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Abstract: In this article, the challenges and strategies of phase 1 drug development for lung cancer are discussed. These include the use of precise dose determinations via statistical modelling, the improved selection of patients based on genetic or molecular biomarkers, relevant pharmacokinetic and pharmacodynamic analyses, and the early evaluation of efficacy. The application of molecular tumor profiling for individualizing therapy is increasingly seen in phase I trials. Finally, the implication of a shift towards multi-institutional trials and centralized study management are discussed.

Keywords: Lung cancer; phase 1 development; molecular profiling

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Introduction

Both targeted therapy and immunotherapy have a significant progress in past decade in non-small cell lung cancer (NSCLC). Osimertinib, the third-generation epidermal growth factor receptor (EGFR) tyrosine kinas inhibitor (TKI), is effective in EGFR-mutant NSCLC patients who had been treated with the prior-generation EGFR TKIs (e.g., gefitinib, erlotinib) and whose tumors harbor the EGFR T790M mutation as the acquired resistance (1). Osimertinib also outperforms gefitinib or erlotinib in the first-line setting (2). In ALK fusion-positive NSCLC, the second-generation ALK inhibitors are better than crizotinib in the first-line setting (3, 4). Lorlatinib, the third-generation ALK inhibitor, is useful after resistance to other ALK inhibitors (5). Immunotherapy has fundamentally changed the treatment landscape for many patients with NSCLC. An anti-programmed death receptor-1 (PD-1) and its ligand (PD-L1) antibody alone [e.g., pembrolizumab (6)] or in combination [e.g., pembrolizumab (7, 8), atezolizumab (9)] with chemotherapy is now the preferred first-line option in patients with non-genomic driven NSCLC. Many targeted therapies (Table 1) and immunotherapies are currently in clinical development in NSCLC.

The success of the recent targeted therapy [e.g., osimertinib (10)] and immunotherapy [e.g., pembrolizumab (11)] makes some people believe that the classical concepts of oncology phase I trials, e.g., dose-limiting toxicity (DLT), maximum tolerated dose (MTD), dose-response/toxicity relationship, pharmacodynamics (PD), pharmacokinetics (PK), are no longer relevant. For example, there was neither DLT nor MTD in the first-in-human phase I trial of osimertinib. Dose-response relationship was also not demonstrated among the five doses (20, 40, 80, 160, and 240 mg/day) being tested (10). As for immunotherapy, there was no DLT in the first-in-human phase I trial of pembrolizumab. The study only reached the maximum administered dose but not MTD. Preliminary antitumor response was quickly observed in malignant melanoma and NSCLC. This phase I trial was then seamlessly transitioned to multiple expansion cohorts to define the efficacy and the optimal dose/schedule (11).

Do we have to abandon the “classical” concepts (e.g., MTD, DLT, PD, PK) to conduct phase I trials of new targeted or immunotherapies in NSCLC? In this review, I will discuss several important dimensions to argue against giving up the
"classical" concepts of oncology phase I trials in NSCLC.

Defining the dose-limiting or treatment-related toxicities in the phase I trials

In the current era of NSCLC drug development, people who believe that DLT is no longer relevant usually use osimertinib as an example. Osimertinib is a drug designed and engineered driven by strong preclinical rationale, e.g., EGFR T790M mutation as the major acquired resistance to the prior-generation EGFR TKIs. Osimertinib is an inhibitor against EGFR exon 19 deletion/L858R mutation and against EGFR T790M mutation, but not against EGFR wild type (12). This design theoretically creates a wide therapeutic window. Therefore, there was neither DLT nor maximum tolerated dose (MTD) of osimertinib in the first-in-human phase I trial. The preliminary antitumor responses were observed across all five dose levels (20, 40, 80, 160, and 240 mg/day) tested (10).

Other examples to demonstrate the irrelevance of DLTs are anti-PD-1/PD-L1 antibodies. There was only one patient [with thymoma (13)] experienced a DLT (myasthenia gravis) among first-in-human phase I trials of approved anti-PD-1 [nivolumab (14), pembrolizumab (11), cemiplimab (15)]/PD-L1 [atezolizumab (16), avelumab (13), durvalumab (17)]. We have to be careful in interpreting this result, as monoclonal antibodies with their antigen-antibody binding specificity traditionally rarely lead to off-target drug-related adverse events/off-target DLTs. There is no dose-response/toxicity relationship in monoclonal antibodies (18). Anti-PD-1/PD-L1 antibodies are the mainstay of immunotherapy in NSCLC nowadays. But this class of compounds will not be the only immunotherapy in NSCLC in the future. It is better to define immunotherapy in NSCLC into two categories, the biologics [approved: anti-PD-1/PD-L1 antibodies; in development: e.g., anti-lymphocyte-activation protein 3 (LAG3) antagonistic antibodies, anti-TIM3 antagonistic antibodies, anti-OX40 agonistic antibodies, anti-4-1BB agonistic antibodies, anti-glucocorticoid-induced TNFR family related gene (GITR) agonistic antibodies] and the small molecules [in development: e.g., colony stimulating factor 1 receptor (CSF1R) inhibitors, transforming growth factor (TGF)-beta inhibitors, A2aR inhibitors]. For antibodies, “treatment limiting” (sometimes beyond cycle 1) immune-related toxicities are more appropriate DLTs than ‘traditional’ DLTs (19), as some severe/life threatening immune-related adverse events (e.g., gastrointestinal, endocrine, hepatic, pulmonary) could occur late in the whole treatment course and doses of immunotherapy are often held rather than reduced when severe/life threatening adverse events do occur (20). On the contrary, dose limiting “immune-related” toxicities are still an important component to be clearly define for the small molecule immune modulators in the first-in-human phase I trials in NSCLC.

Defining the optimal biologic or immunology doses in the phase I trials

The assumption behind the MTD is that there is a dose-
response of dose-toxicity relationship. As previously mentioned, the dose-response relationship does not exist in anti-PD-1/PD-L1 antibodies (11,13-17). To push the dose of cancer immunotherapy to the highest tolerable (or administered) needs to reconsider. The optimal biologic or immunologic doses for targeted or immunotherapies, respectively, needs to be conceptualize and individualized target by target. Research in this area is highly encouraged.

**Pharmacodynamics is more critical than before in the phase I trials**

One of the notable examples is the phase I trials of the first-generation EGFR TKIs, gefitinib versus erlotinib. The recommended phase II dose of the first-in-human phase I trial of erlotinib is 150 mg daily, which is the MTD (21). The recommended phase II doses of 4 first-in-human phase I trials of gefitinib are 250 or 500 mg daily (22-25). The latter is the MTD and the former based on the minimal dose of normal skin (as surrogate tissue) EGFR and downstream signaling target inhibition (pharmacodynamics) (26). The 250 mg daily was chosen as the dose for the registration phase III trial after two randomized phase II trials showed equal efficacy but different toxicities in unselected NSCLC patients (27,28). This mostly explains why patients who take gefitinib usually experience less adverse events compared with those who take erlotinib (29).

The importance of pharmacodynamics in phase I trials in NSCLC has been well illustrated in the above examples. More and more phase I trials of targeted therapies and immunotherapies in NSCLC nowadays require serial (pre-treatment and on-treatment) not only surrogate tissues [e.g., normal skin for EGFR signaling, normal skin follicles for smoothened (SMO) signaling] but also tumor tissues. This is doable and does not confer too much additional risk to patients (30).

**The use of adaptive phase 1 protocol**

It is not uncommon to observe the preliminary antitumor activities in the phase I trials nowadays. The cohort expansion not only is a confirmatory stage of the recommended phase II dose (more adverse event and PK collection in more patients) but also serves other purposes such as evaluation of efficacy. The sample sizes of the cohort expansion should be justified with respect to their primary aim (dose-seeking based on DLTs, ineffectiveness, or target modulation) and include interim analyses to allow for early stopping.

**Conclusions**

I discuss the challenges in NSCLC phase I trials, such as more precise dose determinations using statistical modelling; improved selection of patients based on genetic or molecular biomarkers; pharmacokinetic and pharmacodynamic analyses; and the early evaluation of efficacy—in addition to safety. Accelerated approval pathways in major industrialized countries that can accelerate drug development require demonstration of efficacy in early phase trials. The application of molecular tumor profiling for matched therapy is increasingly seen in phase I trials. Finally, the shift towards multi-institutional trials and centralized study management results in consequent implications for institutions and investigators.

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**Footnote**

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