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Phase I clinical trials in patients with advanced non-small cell lung cancer treated within a Drug Development Unit: What have we learnt?

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ABSTRACT

Objectives: Despite advances in novel drug development for patients with advanced non-small cell lung cancer (NSCLC), there are still only a limited number of approved treatments. We therefore evaluated the clinical outcomes of patients with advanced NSCLC referred to a dedicated phase I clinical trials unit assessed baseline clinical factors associated with successful enrollment onto phase I trials.

Material and methods: We conducted a retrospective study involving patients with advanced NSCLC referred to the Drug Development Unit at the RMH between January 2005 and December 2013.

Results: 257 patients with advanced NSCLC were referred for consideration of phase I trials, of which only 89 (35%) patients successfully commenced phase I trials. The commonest reasons for not entering study included poor ECOG performance status and rapid disease progression. A multivariate analysis identified that ECOG performance status (0–1) and RMH prognostic score (0–1) were associated with successful enrollment onto phase I trials ($p < 0.001$).

Single agent therapies included novel agents against the phosphatidylinositol-3 kinase pathway, insulin growth factor-1 receptor and pan-HER family tyrosine kinases. These trial therapies were well tolerated and mainly associated with grade 1–2 adverse events, with a minority experiencing grade 3 toxicities. Nine (10%) patients, 4 with known *EGFR* or *KRAS* mutations, achieved RECIST partial responses. Median time to progression was 2.6 months and median overall survival was 8.1 months for patients enrolled.

Conclusions: Phase I trial therapies were generally well tolerated with potential antitumor benefit for patients with advanced NSCLC. Early referral to drug development units at time of disease progression should be considered to enhance the odds of patient participation in these studies.

1. Introduction

Lung cancer is the main cause of cancer mortality worldwide and has a five-year survival rate of less than 15% [1,2]. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers and is histologically classified into adenocarcinoma and squamous cell carcinoma, which account for 50% and 30% of NSCLC, respectively. NSCLC is a molecularly heterogeneous disease and may harbor different putative driver aberrations [3,4]. The landscape of therapeutic options for patients diagnosed with advanced NSCLC has changed dramatically over the past decade, especially with recent advances in the development of immunotherapies and next generation molecularly targeted agents [5–9]. Novel immune checkpoint inhibitors have demonstrated longer overall survival (OS) and better toxicity profiles compared to platinum-based chemotherapy in patients whose tumors have ≥ 50% PD-L1 expression in the first-line setting, and to docetaxel in patients with advanced NSCLC who had progressed during or after platinum-based chemotherapy [5–7,10,11]. Phase III trials have demonstrated that first

Abbreviations: ALK, Anaplastic Lymphoma Kinase; DDU, Drug Development Unit; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EPR, electronic patient record; HDAC, histone deacetylase; IGF-1R, insulin growth factor-1 receptor; LDH, lactate dehydrogenase; NSCLC, non-small cell lung cancer; OS, overall survival; PARP, poly(ADP-ribose) polymerase inhibitor; PI3K, phosphatidylinositol-3 kinase; PFS, progression-free survival; PR, partial response; RMH, poyal Marsden Hospital; SD, stable disease; TKI, tyrosine kinase inhibitor; TTP, time to progression

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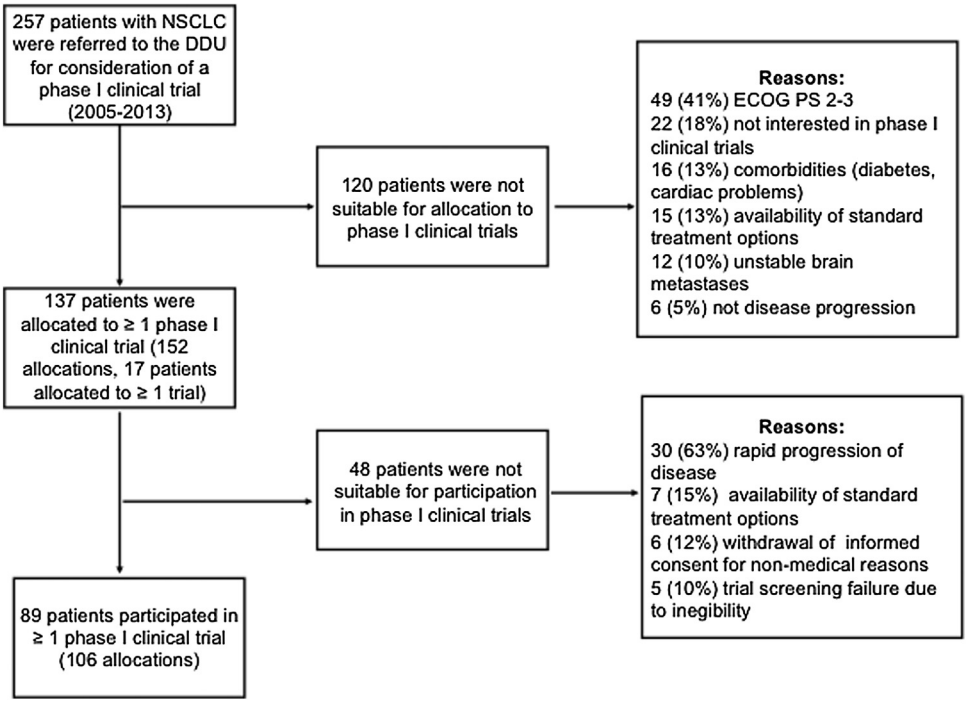

Fig. 1. Flow chart of advanced NSCLC patients participating in phase I clinical trials in the DDU at the RMH (2005–2013).

and second generation tyrosine kinase inhibitors (TKIs), such as erlotinib (Roche), gefitinib (AstraZeneca) and afatinib (Boehringer Ingelheim) in patients with epidermal growth factor receptor (EGFR) mutant NSCLC improve progression-free survival (PFS), but not OS when compared with platinum-based chemotherapy in the first and second-line settings [8,12–14]. Phase III studies performed in patients with Anaplastic Lymphoma Kinase (ALK) fusion rearrangements, which accounts for approximately 4% of NSCLC, when treated with crizotinib (Pfizer) have shown improvements in PFS compared with platinum chemotherapy [9,15].

Despite advances in the development of antitumor therapies, there are still only a limited number of approved lines of treatment available for patients with advanced NSCLC. Patients are typically considered for clinical trials within specialist lung cancer units upon the exhaustion of conventional treatment options. Such trials are often limited by protocol restrictions on patient eligibility and number of prior lines of treatments received. Patients who remain fit with acceptable organ function may then be referred to specialist drug development units for consideration of phase I trials of novel experimental therapies, including first-in-human studies. However, to the best of our best knowledge, there are currently no published data on the outcomes of patients with advanced NSCLC treated within the context of phase I clinical trials in dedicated drug development units, including treatment-related toxicities and antitumor activity. Such data will be important to establish the extent of benefit which may be anticipated from experimental phase I trials are *bona fide* antitumor treatment options for patients with advanced NSCLC.

A critical aspect of phase I trials is the selection of suitable patients, especially those with NSCLC who are at high risk of rapid clinical deterioration. Olmos and colleagues developed and validated the Royal Marsden Hospital (RMH) prognostic score – comprising serum albumin levels, number of metastatic sites and lactate dehydrogenase (LDH) levels – as a predictor of 90-day mortality to optimize the selection of appropriate patients for participation in phase I trials [16,17].

The main aim of this retrospective study was to evaluate the clinical outcomes of patients with advanced NSCLC referred to the Drug Development Phase I Unit at the Royal Marsden Hospital (RMH) for consideration of novel therapies, and to explore the outcomes of patients treated with molecularly targeted agents. The second aim was to identify baseline clinical factors associated with successful enrollment onto phase I clinical trials.

2. Material and methods

This retrospective study included patients with advanced NSCLC who were referred to the Drug Development Unit (DDU) at the Royal Marsden Hospital (RMH), London, United Kingdom, for consideration of phase I clinical trials from 1st January 2005 to 31st December 2013. This study was approved by the Royal Marsden Hospital Committee for Clinical Research.

Clinical parameters were collected from electronic patient records (EPR) during the patients' first visit to the DDU prior to starting a clinical trial, including: stage of cancer, sites of disease, histological subtype, mutation status, prior lines of antitumor therapy, Eastern Cooperative Oncology Group performance status (ECOG PS), full blood count, biochemistry, RMH prognostic score and genetic mutation status if known. The RMH prognostic score, which comprise serum albumin, number of metastatic disease and lactate dehydrogenase (LDH) levels, is a predictor of 90-day mortality used to optimize the selection of patients for phase I clinical trials. All patients enrolled on these clinical studies had provided their written informed consent for trial participation.

The primary endpoint of this study was to evaluate patient outcomes (treatment-related toxicities and antitumor activity) of patients with NSCLC who enrolled in at least one phase I trial. Toxicity data were collected as originally reported on EPR, i.e. graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 or 4.0 depending on the study. Antitumor response rates were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 or 1.1 depending on the study. Tumor responses were confirmed by a board-certified radiologist. OS data were obtained from EPR and when necessary, by contacting the patients' family physician.

The SPSS program version 20 was used for the statistical analysis. Univariate and multivariate binary Cox logistic regression was used to identify clinical factors associated with patients being enrolled onto phase I trials. OS was defined as the interval between the day of the first administered dose of clinical trial therapy and the date of death from