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Comparison of clinical outcome after first-line platinum-based chemotherapy in different types of *KRAS* mutated advanced non-small-cell lung cancer

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ABSTRACT

Objectives: As suggested by in-vitro data, we hypothesize that subtypes of *KRAS* mutated non-small cell lung cancer (NSCLC) respond differently to chemotherapy regimens.
Methods: Patients with advanced NSCLC and known *KRAS* mutation, treated with first-line platinum-based chemotherapy, were retrieved from hospital databases. Primary objective: to investigate overall response rate (ORR), progression free survival (PFS) and overall survival (OS) between different types of platinum-based chemotherapy per type of KRAS mutation.
Results: 464 patients from 17 hospitals, treated between 2000 and 2013, were included. The majority of patients had stage IV disease (93%), had a history of smoking (98%) and known with an adenocarcinoma (91%). Most common types of *KRAS* mutation were G12C (46%), G12V (20%) and G12D (10%). Platinum was combined with pemetrexed ($n = 334$), taxanes ($n = 68$) or gemcitabine ($n = 62$). Patients treated with taxanes had a significant improved ORR (50%) compared to pemetrexed (21%) or gemcitabine (25%; $p < 0.01$). Patients treated with bevacizumab in addition to taxanes ($n = 38$) had the highest ORR (62%). The PFS was significantly improved in patients treated with taxanes compared to pemetrexed (HR = 0.72, $p = 0.02$), but not OS (HR = 0.87, $p = 0.41$). In patients with G12V, significantly improved ORR ($p < 0.01$) was observed for taxanes, but not PFS or OS. Patients with G12C or G12D mutation had comparable ORR, PFS and OS in all treatment groups.

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Conclusion: *KRAS* mutated NSCLC patients treated with taxane-based chemotherapy had best ORR. Response to chemotherapy regimens was different in types of *KRAS* mutation. Especially patients with G12V had better response to taxane treatment.

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1. Introduction

Personalized medicine has a major role in optimizing treatment and outcome of advanced cancers. Therapy focused on molecular characteristics has taken a substantial part in new treatment strategies for non-small cell lung cancer (NSCLC). Successful treatments have been developed for advanced NSCLC patients with an *EGFR* mutation or *ALK* translocation [1,2]. In non-squamous NSCLC, routine testing for these mutations is recommended as per guidelines when patients are no candidates for treatment with curative intent [3]. In the Netherlands, *KRAS* mutation is part of routine testing as a selection tool for EGFR mutation testing since both mutations are almost allways mutually exclusive [4]. *KRAS* mutation is observed in 20–30% of NSCLC patients, predominantly in patients with adenocarcinoma [5]. Its presence has an infamous reputation of quick progression and poor response to chemotherapy [6]. However, the current understanding is that *KRAS* mutated NSCLC patients have a similar response and survival compared to patients with *KRAS* wild type (wt) tumors [7–10]. Until now, no effective targeted therapy has been established and standard platinum-based doublet chemotherapy remains the recommended treatment option in this large group of patients.

Alternatively, optimizing treatment for NSCLC patients with a *KRAS* mutation might also be accomplished by selecting the best chemotherapy for these patients. A *KRAS* mutation occurs predominantly in codon 12, 13 or 61. Most common types of *KRAS* mutation are G12C, G12V, and G12D (http://www.mycancergenome.org). In-vitro data generated by Garassino et al. suggested differential sensitivity to chemotherapeutic agents across NSCLC cell lines harboring a G12C, G12V or G12D *KRAS* mutation [11]. They concluded that the G12C mutation was most sensitive to pemetrexed and paclitaxel, G12D was resistant to paclitaxel therapy and G12V was slightly less sensitive for pemetrexed. Exposure to gemcitabine resulted in a similar response in the 3 types of mutation. The aim of this multicenter, retrospective study was to investigate differences in overall response rate (ORR), progression free survival (PFS) and overall survival (OS) between subtypes of *KRAS* mutation in NSCLC patients treated with first-line commonly available platinum doublets.

2. Methods

2.1. Study subjects

We retrospectively selected all consecutive NSCLC patients with known *KRAS* mutation, treated with first-line platinum-based chemotherapy for metastatic disease and response evaluated by CT scan using RESIST criteria. Palliative radiotherapy during chemotherapy treatment was allowed. Exclusion criteria were: unknown mutational status; (concurrent) EGFR or ALK mutation; no documentation of response evaluation; adjuvant chemotherapy or chemoradiotherapy.

Patients were derived from databases from 17 hospitals in the Netherlands. All patients had access to the same standard of care treatment. Both regional and academic hospitals participated in this study. The following data were retrieved from the medical records: age, sex, smoking history, World Health Organization Performance Status (PS), histology, type of *KRAS* mutation, stage of disease, site of metastasis, chemotherapy combination, number of courses, response to treatment, type of second line treatment, number of lines of chemotherapy, date of diagnosis, date of start treatment, date of progression and date of death or date of last contact. The ethics committee of the VU University Medical Center Amsterdam approved this study.

2.2. KRAS *mutational screening*

From formalin-fixed paraffin-embedded tissue, tumor was macrodissected and DNA was extracted. Two methods were used for *KRAS* mutation analysis. In 16/17 hospitals, mutation analysis was performed using high resolution melting followed by polymerase chain reaction and sequencing of the *KRAS* exons 2 and 3. At one site mutation analysis was performed by Sanger sequencing only.

2.3. Statistical analysis

The primary objective was to evaluate differences in ORR, PFS and OS between different types of platinum-based chemotherapy per type of *KRAS* mutation. PFS was defined as time from start of first-line chemotherapy till objective disease progression or death; OS was defined as the time from start of treatment till death. The relation between categorical parameters was tested using Pearson's X^2-test or Fishers exact test for testing small cell sample sizes ($n \leq 5$). Kaplan–Meier curve was used to estimate the distribution of survival. Log-rank test was used to test difference in survival between subgroups. To estimate the hazard ratio (HR), cox regression analysis was used. The following variables were considered in a multivariate analysis: age, gender, performance score, histology, smoking history and stage of disease. *P*-Values <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

In total, data from 464 *KRAS* mutated patients with advanced NSCLC who received palliative platinum-based chemotherapy as first-line treatment were subtracted from databases of 17 hospitals. Patients were treated between 2000 and 2013, most patients (78%) between 2010 and 2013. Sixty patients in the present study were also part of a previously published study [10].

The patient characteristics are listed in Table 1. The mean age was 61 years (SD ± 9), a majority of patients had stage IV disease (93%), 98% of the patients had a history of smoking and 2% of patients had squamous cell carcinoma. Cisplatin ($n = 261$) or carboplatin ($n = 203$) was combined with pemetrexed ($n = 334$), taxane ($n = 68$) or gemcitabine ($n = 62$). In the taxane group, 38 patients received treatment with carboplatin/paclitaxel/bevacizumab (CPB). Codon 12 mutations were detected in 89% of the patients. G12C (46%) was the most common *KRAS* mutation followed by G12V (20%) and G12D (11%). Other codon 12 mutations were present in 12% of the patients. In 1 patient a double mutation was found: G12R + G12S.

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