CHAPTER 10A

Summary and future perspectives

J.L. Kuiper
This thesis describes the results of clinical studies conducted among EGFR-mutated NSCLC-patients and NSCLC-patients who developed resistance to first-generation EGFR-TKIs. The first part reports on diagnostic and predictive markers, and the second part focuses on treatment. Here, the results and clinical implications are summarized and future perspectives are discussed.

SUMMARY

Part 1: Diagnostic and predictive markers in EGFR-mutated NSCLC

Chapter 2 describes the results of a retrospective study of Dutch NSCLC-patients with an EGFR-mutation. We evaluated prevalence, clinical characteristics, and outcome on EGFR-TKI treatment according to type of EGFR-mutation, i.e. classic EGFR-mutations, EGFR exon 20 insertion and other uncommon EGFR-mutations. The proportion of exon 20 insertions and uncommon EGFR-mutations among Dutch EGFR-mutated NSCLC-patients was in accordance with previously published results. Outcome on EGFR-TKI treatment was poor in patients with an EGFR exon 20 insertion. For patients with an uncommon EGFR-mutation outcome was inferior compared to patients with a classic EGFR-mutation, but varied widely among the different types of EGFR-mutations.

In chapter 3 we evaluated 66 EGFR-mutated NSCLC-patients who were (sequentially) rebiopsied after they had progressed on EGFR-TKI treatment. The T790M mutation was detected in 52% of the patients at first rebiopsy following EGFR-TKI treatment. Interestingly, in 37% of the patients who were sequentially rebiopsied, T790M-status of subsequent rebiopsies was not consistent with the first rebiopsy result after EGFR-TKI treatment; some patients who were T790M-positive at first post-TKI biopsy became T790M-negative in later rebiopsies and vice versa. Therefore, we conclude that T790M-status is not steady over time in an individual patient.

In chapter 4a we describe the use of an innovative method of PET-imaging in an EGFR-mutated NSCLC-patient prior to and after EGFR-TKI treatment. Uptake of [11C]erlotinib had been heterogeneous after EGFR-TKI treatment. We concluded that innovative diagnostic imaging like these [11C]erlotinib PET scans could play a role in the detection of intratumour heterogeneity in the future, to ultimately guide treatment.

In chapter 4b we describe an EGFR-mutated NSCLC-patient in whom a rare type of histological transformation was detected after development of acquired resistance to EGFR-TKI treatment; transformation from adenocarcinoma to squamous cell carcinoma. This type of histological transformation had previously not been reported. We hypothesize that the same selection-hypothesis applies to this type of histological transformation as to transformation from adenocarcinoma to SCLC.
Chapter 5 describes the results of the use of the serum biomarker VeriStrat, a test based on a signature of eight protein or peptide features identified by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS), in a phase II trial of advanced-stage NSCLC-patients who were treated with erlotinib and sorafenib. The two groups that were categorized by VeriStrat serum samples (VeriStrat Good and VeriStrat Poor), differed significantly in terms of overall survival and progression-free survival. Therefore, we concluded that VeriStrat might have the potential to predict response to treatment with erlotinib and sorafenib in treatment-naïve NSCLC-patients.

Part 2: Treatment of EGFR-mutated NSCLC with acquired EGFR-TKI resistance

Chapter 6 reviews some of the challenges in the current era of treatment of EGFR-mutated NSCLC-patients; response evaluation, the role of rebiopsy, EGFR-TKI resistance mechanisms and treatment strategies after acquired EGFR-TKI resistance.

In chapter 7 a multi-institutional cohort of 356 EGFR-mutated NSCLC-patients was evaluated for diagnosis of leptomeningeal metastasis (LM), and treatment and survival after diagnosis of LM. Thirty-two (9.0%) patients were diagnosed with LM and median survival was 3.1 months. This poor survival was comparable to existing data on median survival of EGFR-wild type (WT) NSCLC-patients with LM (1). Nevertheless, 43.8% and 18.8% of the patients were still alive six and twelve months respectively after the diagnosis of LM. Only performance status at time of diagnosis of LM was associated with prognosis.

Chapter 8 describes treatment with high-dose, weekly erlotinib in EGFR-mutated NSCLC-patients. In chapter 8a we describe two EGFR-mutated NSCLC-patients with acquired resistance to EGFR-TKI treatment, who developed LM. Both patients were treated with this ‘pulsatile’ treatment regimen of high-dose, weekly erlotinib and obtained an intracerebral response that was radiologically confirmed. Interestingly, one of these patients had a remarkable response of intrathoracic lesions as well, whereas recent chemotherapy had resulted in stable disease at best. From this finding, we hypothesized that pulsatile erlotinib could be a treatment option for EGFR-mutated NSCLC-patients who acquired resistance to EGFR-TKI in standard dose. Therefore, we evaluated this hypothesis (i.e., pulsatile EGFR-TKI treatment in NSCLC-patients with acquired resistance to EGFR-TKIs) in a prospective phase II trial that is described in chapter 8b. Eleven EGFR-mutated NSCLC-patients with acquired resistance to standard-dose EGFR-TKI treatment were included and treated with pulsatile erlotinib. The objective response rate was 9.1% and progression-free survival was 1.6 months. This was insufficient to proceed to the next phase of the trial and the study was discontinued prematurely. Toxicity of pulsatile erlotinib was acceptable in this study. From the results of this study, it can be concluded that pulsatile erlotinib is not an effective treatment option in EGFR-mutated NSCLC-patients with acquired resistance to EGFR-TKIs in standard-dose.
In chapter 9 we describe 38 advanced-stage NSCLC-patients with acquired resistance to first-generation EGFR-TKIs, who were subsequently treated with afatinib. Irrespective of T790M-status, median PFS was 2.7 months and ORR was 18.4%. There was no difference in outcome between patients who were T790M-positive or T790M-negative prior to treatment with afatinib. We concluded that T790M-status is not associated with clinical outcome after treatment with afatinib.
The results of the studies described in this thesis have several implications for clinical practice, which are further discussed below.

Tumours are dynamic and molecular evolution may occur following targeted treatment (2). Analysis of the tumour tissue following resistance and prior to the next treatment may unveil the (molecular) composition and guide best selection for therapy. Following our observations, we recommend rebiopsy after every line of treatment for EGFR-mutated NSCLC, whenever possible. We demonstrated that T790M-status may alter throughout the course of the disease (chapter 3). Since T790M-status has implications for therapeutic decision-making, especially for the third-generation EGFR-TKIs that are discussed later, it is important to be informed about molecular tumour characteristics once resistance has been acquired. Moreover, other mechanisms of resistance, such as transformation to SCLC or to squamous cell carcinoma (chapter 4b), can be detected and may guide therapeutic decision-making.

Patients with uncommon EGFR-mutations represent a heterogeneous group, considering prognosis and EGFR-TKI sensitivity that varies widely among different types of uncommon EGFR-mutations (chapter 2). Therefore, treatment of patients with non-classic EGFR-mutations is complicated and treatment should be based on the type of EGFR-mutation. Consequently, we recommend that treatment of patients with non-classic EGFR-mutations (i.e., both uncommon EGFR-mutations and patients with exon 20 insertions) should not only be discussed multidisciplinary, but preferably also with a tertiary referral centre. Patients with EGFR exon 20 insertions (except for the EGFR exon 20 insertion A763_Y764insFQEA (3)) should not be treated with first-generation EGFR-TKIs, since outcome on these agents is poor.

A substantial part of EGFR-mutated NSCLC-patients may develop leptomeningeal metastases (chapter 7). In general, prognosis of these patients is poor, but some will have a prolonged survival. For now, the sole prognostic factor for survival in EGFR-mutated NSCLC-patients with leptomeningeal metastases is performance status.

High-dose erlotinib did not improve prognosis in EGFR-mutated NSCLC-patients, neither in EGFR-mutated NSCLC-patients with leptomeningeal metastases nor in patients with acquired resistance to standard-dose EGFR-TKIs (chapter 7 and 8b). Therefore, although we demonstrated that toxicity of high-dose erlotinib is acceptable, there is no evidence-based rationale to treat EGFR-mutated NSCLC-patients with high-dose erlotinib.

Clinical results of afatinib in the setting of acquired resistance to first-generation EGFR-TKIs were disappointing, irrespective of T790M-status (chapter 9). Therefore, the role of afatinib mono-treatment in the setting of acquired resistance to first-line, first-generation EGFR-TKIs is limited.
FUTURE PERSPECTIVES

Clinical experience with first-generation EGFR-TKIs has led to recognition of different patterns of progressive disease, with potential different treatment approaches. Gandara et al described three different groups of patients with acquired resistance to EGFR-TKIs: CNS sanctuary progressive disease, oligo-progressive disease and systemic progressive disease (4). Some data have shown that the former two groups (CNS sanctuary progressive disease and oligo-progressive disease) can be treated locally, for example with surgery, stereotactic ablative radiation (SABR) or radiofrequency ablation (RFA), with or without continuation of EGFR-TKI treatment (5, 6). Both NCCN and ESMO guidelines have incorporated these approaches in their guidelines, albeit on a low level of evidence (7, 8). Several trials are currently open and will hopefully generate more and high-quality prospective data (9, 10).

Pre-clinical and translational investigation has led to an improved understanding of the biology of NSCLC driven by \(\text{EGFR}\)-mutations as an oncogene. From this, more rationally developed agents and combination strategies have been developed for patients with progression from the third category (systemic progressive disease).

One of these is the third-generation EGFR-TKI osimertinib (AZD9291, Tagrisso, Astra Zeneca). A phase I study that evaluated osimertinib in \(\text{EGFR}\)-mutated NSCLC-patients with acquired resistance to first- and second-generation EGFR-TKIs with and without T790M-mutation, showed a response rate of 51% and 21%, respectively (11). Reported side effects are diarrhoea, rash and nausea, but interestingly, toxicity is relatively mild since the wild-type EGFR is spared (11). In November 2015, the FDA granted accelerated proof for osimertinib and one month later osimertinib received the marketing authorization for treatment of NSCLC-patients with a T790M-mutation in the Netherlands (12). Currently, osimertinib is extensively being investigated (13), both in treatment-naïve patients (14) as in previously-treated patients (15). Although resistance to osimertinib has already been described (16-20), it certainly is a promising new player in the field of \(\text{EGFR}\)-mutated NSCLC-patients that could potentially improve prognosis of \(\text{EGFR}\)-mutated NSCLC-patients.

After being named ‘breakthrough of the year’ in 2013 by Science (21), immunotherapy is rapidly evolving in the treatment of NSCLC, as in other fields of oncology. Recently, nivolumab (an anti-PD-1 monoclonal antibody) was approved for squamous cell lung cancer (22) and recent evidence shows similar effectiveness in non-squamous histology (23). No molecular characteristics that predict for response to immunotherapy have been identified (yet). However, a recent study demonstrated that only 3.6% of \(\text{EGFR}\)-mutant or ALK-positive patients responded to PD-1/PD-L1 inhibitors, versus 23.3% of EGFR wild-type or ALK-negative/unknown patients (24). As of today, there is no rationale to treat \(\text{EGFR}\)-mutated NSCLC-patients with immunotherapy, outside clinical trials.
In 10 – 20% of EGFR-mutated NSCLC-patients who acquired resistance to EGFR-TKIs, MET amplification is detected in tumour tissue obtained at progression (25). So far, studies evaluating MET-inhibitors, such as tivantinib, showed inconclusive results (26). However, most of these trials were conducted in molecularly unselected patients and their clinical effectiveness in EGFR-mutated NSCLC-patients with acquired resistance to EGFR-TKIs remains unknown. Therefore, results from the GEOMETRY duo-1 study, that evaluates the cMET inhibitor capmatinib with or without erlotinib versus platinum plus pemetrexed in EGFR-mutated, cMET-amplified NSCLC with acquired resistance to prior EGFR-TKI treatment are eagerly awaited (27).

Another target in tumour cells that acquired resistance to EGFR-TKIs is the HER2-receptor. Several lines of evidence suggest that HER2 signalling contributes to EGFR-TKI resistance in EGFR-mutated patients. In cell lines, it was demonstrated that acquired resistance to cetuximab (an EGFR directed antibody) is mediated by activation of ErbB-2 signalling (28). This acquired resistance to cetuximab could be restored by inhibition of HER2. Also, another preclinical study identified HER2 amplification in 12% of TKI-resistant cell lines (29). Subsequently, in an in vivo study HER2-amplification was detected in 13% of NSCLC-patients with acquired TKI-resistance (30). Hence, we initiated a phase II trial to evaluate EGFR-mutated NSCLC-patients who express HER2-amplification in their tumour cells after progression on EGFR-TKIs, that is currently recruiting (31).

Ideally, subsequent treatment is based on the molecular characteristics of the tumour cells at that time. Currently, invasive biopsies are necessary to obtain tumour tissue to be able to identify these characteristics. However, some patients may not be amenable to re-biopsy due to comorbidity. Another subject of intensive on-going investigation is the field of circulating tumour cells or circulating derivatives of tumour cells; so-called ‘liquid biopsies’ (32, 33). In recent years techniques for detecting and analysing these circulating tumour cells, tumour-educated platelets or circulating cell-free DNA were improved. Theoretically, this has the potential to diagnose or monitor cancer with a blood-based- or urine-sample, thereby directing treatment and monitoring resistance, ultimately guiding the timing and choice of subsequent treatment (34). Recently, important developments in the field of liquid biopsies have been made for the detection of T790M in EGFR-mutated NSCLC-patients (35). When further clinically validated and utility proven, liquid biopsy could likely benefit cancer patients in defined settings as supplement, or eventually substitute, to standard biopsies and for subsequent serial monitoring of biomarker status after treatment and/or clinical progression.

Altogether, the field of EGFR-mutated NSCLC-patients with acquired resistance to first-line EGFR-TKIs is evolving rapidly. Improved diagnostic procedures will hopefully lead to better identification of molecular characteristics of the tumour after acquisition of resistance. Also, the therapeutic landscape is changing, with rationally developed third-generation agents entering the clinic. Further investigation on optimal use and sequence of first-,
and third-generation EGFR-TKIs is mandatory. It is hoped that these recent diagnostic and therapeutic developments will improve prognosis for patients with \textit{EGFR}-mutated NSCLC, thereby someday changing this fatal disease into a chronic one.
REFERENCE LIST


