Treatment optimization in patients with non-small cell lung cancer

Chapter 7

IMPACT

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In this chapter of the thesis, the most important findings of our work, the potential scientific impact of our research, and the relevance for patients, physicians and society are discussed. At the end, the dissemination of our work is addressed.

Aims and conclusion of this thesis

In this thesis we have evaluated several options that can be applied to optimise the systemic anti-cancer treatment of patients with non-small cell lung cancer (NSCLC). This was done by focusing on three different areas. First, we validated three analytical methods which can be used to quantify drug concentrations of nine tyrosine kinase inhibitors (TKIs). Secondly, multiple retrospective observational studies were performed. Two studies focused on treatment outcomes (effectiveness and safety) with osimertinib in clinical practice using data from electronic health records. Another two studies were done to evaluate to what extent patients included in clinical trials are a good representation of the general population with lung cancer. And thirdly, we evaluated the effect of cobicistat as booster of the osimertinib exposure in patients with NSCLC. This strategy could potentially be used to improve treatment effectiveness, such as progression-free survival (PFS) or overall survival (OS) on one hand but might also reduce the costs associated with osimertinib treatment on the other hand. We will discuss the results, and scientific/societal impact individually for each topic.

Therapeutic drug monitoring (TDM)

Three different analytical methods were developed and validated [2 - 4], which can be used to quantify the plasma drug concentration of nine TKIs. TKIs are drugs that are used to treat patients with advanced or metastatic NSCLC, or as adjuvant treatment, and acts on a specific target. The reason for developing the different analytical methods was twofold. Firstly, it can be used to evaluate the potential role for TDM in the treatment of patients with NSCLC, searching for a minimum effective concentration or a maximum level to avoid severe toxicity. Secondly, the quantification of drug concentrations enables evaluating intervention research opportunities, such as the osimertinib boosting proof-of-concept clinical trial, which is presented in this thesis. All analytical methods complied with the guideline of the European Medicines Agency (EMA) and can therefore be used in clinical practice to quantify drug concentrations in human plasma. However, limited stability of osimertinib at room temperature was found, especially in human serum and plasma (heparin) and we recommend performing sample preparation for osimertinib samples on dry ice, to ensure accurate quantification [2]. Similar instability was not seen for any other TKI, which were all stable in whole blood and EDTA plasma for at least 24 hours at room temperature [3, 4].

For some TKIs (crizotinib and alectinib) clinical target concentrations in plasma are proposed [5], but for most TKIs the potential role that TDM can play is not fully elucidated.

Based on our results [6], combined with previously published work, no concrete osimertinib target plasma trough concentration during steady state ($C_{min,SS}$) could be found that predicts treatment outcomes (progression-free or overall survival). Future research should focus on further elucidating the potential role of TDM in the treatment with osimertinib, as well as other TKIs that are frequently used in patients with NSCLC. This applies to TKIs that are already approved and reimbursed, but also for TKIs that are nearing market introduction. Ideally, a collaboration of multiple Dutch centres in which TKI care is performed would be preferred to ensure the inclusion of a large(r) number of patients for measuring plasma trough concentrations. For this thesis, we have collaborated with some centres in the Netherlands, and future efforts should focus to build on this.

Real-world data

During the development of new systemic anti-cancer treatment options, randomised (placebo) controlled trials (RCTs) are generally large international multicentre studies that are prospectively performed to establish the efficacy and safety of a new drug. RCTs have a strict set of in- and exclusion criteria. This results in a patient population that is homogeneous, and therefore is well fitted to precisely establish the treatment outcomes for the new drug compared to the standard treatment (at that time). However, extrapolation of treatment results to subsets of the population in clinical practice is sometimes hampered, as the clinical trial population is not representative of the patient population that is treated with the drug in the real world. Retrospective observational studies, which evaluate the effectiveness and safety outcomes of patients treated in clinical practice, can be used to complement data from RCTs. We performed a study evaluating the treatment outcomes (PFS, OS, objective response rate [ORR], disease control rate [DCR], and safety) for NSCLC patients that were regularly treated with osimertinib, with a special focus on age, body mass index (BMI) and $C_{min,SS}$ [6]. Herein, we found that PFS was worse in patients with a low BMI (<20 kg/m^2) and patients with a high $C_{min,SS}$, while age did not significantly influence PFS. Furthermore, female patients and patients with the exon 19 deletion as primary epidermal growth factor receptor (*EGFR*) mutation experienced significantly better PFS, while a trend for better PFS was seen in patients with *TP53* wild type. The second study with data from electronic health records focused on bone specific treatment outcomes of osimertinib users. This study concluded that bone metastases are frequently occurring in patients treated with osimertinib and can be accompanied by serious skeletal events (SREs). The use of bone targeting agents (BTAs), which can be used to prevent SREs, is relatively limited in patients with NSCLC [7]. A broader use of BTAs could decrease the number of SREs, and subsequently improve the quality of life of NSCLC patients treated with osimertinib. While survival of patients with lung cancer was previously limited, the development of treatment options during the last decades have improved survival considerably, especially in patients with EGFR mutated NSCLC. In this subgroup of patients, survival rate approaches the survival seen in patients with advanced/metastatic breast cancer or prostate cancer, where BTAs are prescribed more frequently. The results from these two observational studies can be used by treating physicians to make treatment

decisions or inform patients in clinical practice more precisely, as previous reported correlations were confirmed in our study, and new, potentially predictive, parameters were found. In the first study we observed decreased PFS in patients with a high $C_{min,SS}$, which does not align with the general consensus (lower exposure – worse outcomes). We hypothesized that underlying processes could be responsible for this effect. One such process could be cachexia, which is characterized by weight loss, increased inflammation, and lower liver (and intestinal) enzyme CYP3A-activity. All those factors may influence the body distribution of osimertinib and its $C_{min,SS}$. Unfortunately, parameters to measure cachexia were not included in our analyses, and therefore, could be the topic of further research.

In addition to studies using electronic health records, we also performed two studies with data from large databases [8, 9]. As mentioned previously, the RCT population is often not a good representation of the total target population in clinical practice. We evaluated the potential eligibility of patients diagnosed with lung cancer in clinical practice for large RCTs in Clinical Practice Research Datalink (CPRD) GOLD [8]. Subsequently, a similar study was performed in a more recently launched database (CPRD Aurum), and results from both studies were compared [9]. Both CPRD GOLD and CPRD Aurum are two British, primary care databases, that can be used for medical research. We concluded that a considerable proportion of patients diagnosed with lung cancer in clinical practice would have been ineligible for RCT participation. Our research adds to previously published studies that RCT and clinical practice populations differ substantially. As a consequence, previous research has also shown that treatment outcomes in clinical practice are lower than the efficacy seen in RCTs [10]. Recognition of the differences between the RCT and clinical practice population and potential implications for expected treatment outcomes is crucial for treating physicians. Future research could focus on further elucidating the efficacy-effectiveness gap of recently emerged immunotherapy or targeted therapy used in patients with NSCLC. This could be further improved by linking CPRD-databases to cancer specific databases in the United Kingdom (cancer registry, systemic anti-cancer treatment dataset). This will enable us to more precisely identify patients that may benefit from a specific treatment, since disease status, histology of the primary tumour, and driver mutation data are better categorized.

Pharmacokinetic treatment enhancement

The use of boosting agents is widely applied in other disease areas, (i.e., patients with acquired immune deficiency syndrome), however, in cancer patients, it has been scarcely reported. In our study, we evaluated the boosting capacity of cobicistat in patients that were regularly treated with osimertinib. We demonstrated that osimertinib exposure can be boosted with cobicistat, a strong CYP3A4 inhibitor. The mean increase in osimertinib exposure was 60%, with a range from 19% - 192% [11]. Boosting the exposure to osimertinib, by the addition of cobicistat, could hypothetically be used in different patient subgroups. Firstly, it can be applied in patients that would benefit from higher intratumoral or intracranial exposure to osimertinib. While a target concentration has

not been established for osimertinib, it could be hypothesized that increased exposure to osimertinib could potentially benefit patients with brain metastases. An increased total exposure to osimertinib, as well as the effect of cobicistat on transporter enzymes in the blood brain barrier, may increase the exposure to osimertinib in the central nervous system (CNS). This could potentially lead to a better control of existing metastases or prevent the growth of new intracranial metastases. Another study has indirectly shown benefit of increasing the systemic osimertinib exposure, by doubling the daily osimertinib dose, in patients with CNS-metastases who experienced progression [12]. As a much more affordable alternative, the addition of cobicistat might also increase intratumoral and/or osimertinib brain exposure, thereby possibly increasing the effectiveness of osimertinib [13]. Further studies may evaluate if the addition of cobicistat leads to improved CNS control with osimertinib.

Another possible application of cobicistat is reducing the high costs associated with the treatment of osimertinib. An approach in which a lower average daily dose of osimertinib is used, which is supplemented by the boosting effect of cobicistat, could result in a considerable cost saving. As of now, the effect of cobicistat is only evaluated in patients with low exposure to osimertinib, while the effect of cobicistat in patients with higher exposure to osimertinib is unknown. Hypothetically, lower CYP3A4 activity could be the potential reason for higher exposure to osimertinib in those patients, within the whole population of NSCLC patients that is regularly treated with osimertinib. Subsequently, if the CYP3A4 activity is lower in patients with a higher osimertinib exposure, the effect of cobicistat on osimertinib exposure could be diminished. A future study should focus on evaluating the effect of cobicistat in all patients treated with osimertinib, in combination with further elucidating a potential cost-saving approach using cobicistat. However, simply lowering the daily dose of osimertinib will not lead to cost savings, as 40 and 80 milligram Tablets of osimertinib are priced similarly. A study in which the weekly cumulative dose of osimertinib is lowered, and supplemented with the co-treatment with cobicistat, could be performed in the future. In addition to further elucidating an approach to improve osimertinib effectiveness, as well as cost-efficiency, other targeted agents could be selected for which a similar approach would potentially yield benefit (therapeutic or financial). Drugs that are primarily metabolized by CYP3A4 and are still patented, which is often accompanied with high drug prices, may be selected for future boosting studies.

Dissemination of our knowledge

To share the results of our studies with other researchers and healthcare professionals, we have published (most of) the articles in scientific journals and are in the process of publishing the ones that are not published yet. Furthermore, we have presented the results of our study at international conferences (European Lung Cancer Congress 2022, European Society for Medical Oncology 2022, International Society for Pharmacoepidemiology 2020) and at scientific meetings in the Netherlands and our own hospital. Lastly, the results are

also published at the website of the Netherlands Organisation for Health Research and Development, which have subsidized our work.

REFERENCES

[1] Kang JS and Lee MH. Overview of therapeutic drug monitoring. Korean J Intern Med. 2009 Mar;24(1):1-10.

[2] van Veelen A, van Geel R, de Beer Y, Dingemans AM, Stolk L, ter Heine R, *et al.* Validation of an analytical methodusing HPLC-MS/MS to quantify osimertinib in human plasma and supplementary stability results. BiomedChromatogr. 2020 Apr;34(4):e4771.

[3] van Veelen A, van Geel R, Schoufs R, de Beer Y, Stolk LM, Hendriks LEL, *et al.* Development and validation of anHPLC-MS/MS method to simultaneously quantify alectinib, crizotinib, eerlotinib, gefitinib and osimertinib inhuman plasma samples, using one assay run. Biomed Chromatogr. 2021 Dec;35(12):e5224.

[4] Gullikers J, van Veelen A, Sinkiewicz E, de Beer Y, Tjan – Heijnen VCG, Hendriks LEL, *et al.* Development andvalidation of an HPLC-MS/MS method to quantify six newly registered TKIs for the treatment of non-small celllung cancer. In preparation.

[5] Groenland SL, Geel DR, Janssen JM, de Vries N, Rosing H, Beijnen JH, *et al.* Exposure-response analyses ofanaplastic lymphoma kinase inhibitors crizotinib and alectinib in non-small cell lung cancer patients. ClinPharmacol Ther. 2021 Feb;109(2):394-402.

[6] van Veelen A, Veerman GDM, Verschueren M, Gulikers J, Brouns AJWM, Dursun S, Tjan – Heijnen VCG, *et al.* Real-world data of osimertinib for the treatment of patients with metastatic epidermal growth factor receptor non-small cell lung cancer, with a focus on age, body mass index and plasma trough levels. In submission.

[7] Brouns AJWM, van Veelen A, Veerman M, Steendam C, Dursun S, van der Leest C, *et al.* Efficacy of osimertinib onprevention of bone metastases and skeletal related events in patients with epidermal growth factor receptormutated non-small cell lung cancer. In preparation.

[8] van Veelen A, Abtahi S, Souverein P, Driessen JHM, Klungel OH, Dingemans AC, *et al.* Characteristics of patientswith lung cancer in clinical practice and their potential eligibility for clinical trials evaluating tyrosine kinaseinhibitors or immune checkpoint inhibitors. Cancer Epidemiol. 2022 Jun;78:102149.

[9] Gulikers J, van Veelen A, Driessen JHM, Souverein P, Tjan – Heijnen VCG, Hendriks LEL, *et al.* Comparison ofcharacteristics of patients with lung cancer in UK primary care databases; Clinical Practice Research DatalinkAurum and GOLD. In preparation.

[10] Cramer – van der Welle CM, Peters BJM, Schramel FMNH, Klungel OH, Groen HJM, van de Garde EMW, *et al.*Systemic evaluation of the efficacy-effectiveness gap of systemic treatments in metastatic nonsmall cell lungcancer. Eur Respir J. 2018 Dec 20;52(6):1801100.

[11] van Veelen A, Gulikers J, Hendriks LEL, Dursun S, Ippel J, Smit EF, *et al.* Pharmacokinetic boosting of osimertinibwith cobicistat in patients with non-small cell lung cancer: the OSIBOOST trial. Lung Cancer. 2022 Sep;171:97-102.

[12] Piper-Vallillo AJ, Rotow JK, Aredo JV, Shaverdashvili K, Luo J, Carlisle JW, *et al.* High-dose osimertinib for CNSprogression in EGFR+ NSCLC: a multi-institutional experience. JTO Clin Res Rep. 2022 Apr 21;3(6):100328.

[13] van Eijk M, Boosman RJ, Schinkel AH, Huitema ADR and Beijnen JH. Cytochrome P450 3A4, 3A5, and 2C8expression in breast, prostate, lung, endometrial, and ovarian tumors: relevance for resistance to taxanes. CancerChemother Pharmacol. 2019 Sep;84(3):487-499.