European Journal of Cancer Care **WILEY**

Chemotherapy and Tyrosine Kinase Inhibitors in the last month of life in patients with metastatic lung cancer: A patient file study in the Netherlands

Adinda Mieras[1,2,3] [ID] | Annemarie Becker-Commissaris[1,3] | H. Roeline W. Pasman[2,3] |
Anne-Marie M. C. Dingemans[4] | Edith V. Kok[5] | Robin Cornelissen[6] | Wouter Jacobs[7] |
Jan Willem van den Berg[8] | Alle Welling[9,10] | Brigitte A. H. A. Bogaarts[11] |
Lemke Pronk[12] | Bregje D. Onwuteaka-Philipsen[2,3]

[1]Department of Pulmonary Diseases, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[2]Department of Public and Occupational Health, Amsterdam Public Health Research Institute, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[3]Expertise Center for Palliative Care, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[4]Department of Pulmonary Diseases, Maastricht University Medical Center+, Maastricht, The Netherlands

[5]Department of Pulmonary Diseases, Streekziekenhuis Koning Beatrix, Winterswijk, The Netherlands

[6]Department of Pulmonary Diseases, Erasmus MC, Cancer Institute, Rotterdam, The Netherlands

[7]Department of Pulmonary Diseases, Martini Ziekenhuis, Groningen, The Netherlands

[8]Department of Pulmonary Diseases, ISALA, Zwolle, The Netherlands

[9]Department of Pulmonary Diseases, Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands

[10]Department of Pulmonary Diseases, Noordwest Ziekenhuisgroep Den Helder, Den Helder, The Netherlands

[11]Department of Pulmonary Diseases, VieCuri Medical Center, Venlo, The Netherlands

[12]Department of Pulmonary Diseases, Flevoziekenhuis, Almere, The Netherlands

Correspondence
Adinda Mieras, Department of Pulmonary Diseases, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam, The Netherlands.
Email: a.mieras@amsterdamumc.nl

Funding information
KWF Kankerbestrijding, Grant/Award Number: 2002946

Abstract

Objective: Chemotherapy in the last month of life for patients with metastatic lung cancer is often considered as aggressive end-of-life care. Targeted therapy with Tyrosine Kinase Inhibitors (TKIs) is a relatively new treatment of which not much is known yet about use in the last month of life. We examined what percentage of patients received chemotherapy or TKIs in the last month of life in the Netherlands.

Methods: Patient files were drawn from 10 hospitals across the Netherlands. Patients had to meet the following eligibility criteria: metastatic lung cancer; died between June 1, 2013 and July 31, 2015.

Results: From the included 1,322 patients, 39% received no treatment for metastatic lung cancer, 52% received chemotherapy and 9% received TKIs. A total of 232 patients (18%) received treatment in the last month of life (11% chemotherapy, 7% TKIs). From the patients who received chemotherapy, 145 (21%) received this in the last month of life and 79 (11%) started this treatment in the last month of life. TKIs

were given and started more often in the last month of life: from the patients who received TKIs, 87 (72%) received this treatment in the last month of life and 15 (12%) started this treatment in the last month of life.

Conclusion: A substantial percentage of patient received and even started chemotherapy or TKIs in the last month of life. For chemotherapy, this might be seen as aggressive care. TKIs are said to have less side effects, do not lead to many hospital visits and due to the rapid response, are considered good palliation. However, it is not known, yet possible that, when patients still receiving treatment until shortly before death, this might influence preparing for death in a negative way.

1 | INTRODUCTION

Palliative chemotherapy, immunotherapy and targeted therapy with Tyrosine Kinase Inhibitors (TKIs) are possible treatments for patients with metastatic cancer with the aim of relieving symptoms, temporary disease control and prolonging survival. However, it is difficult to balance the potential clinical benefit and potential harm due to side effects which may lead to a decreased quality of life (QOL) (Adam, Hug, & Bosshard, 2014; Prigerson et al., 2015; Wheatley-Price et al., 2014; Wright, Zhang, Keating, Weeks, & Prigerson, 2014). Moreover, timed discontinuation of these treatments may be essential for patients to prepare for their death (Adam et al., 2014). A recent study of Bekelman et al. (2016) showed that up to 12.7% of patients who died with cancer received chemotherapy in the last 30 days of life (Bekelman et al., 2016). In 2012, the American Society for Clinical Oncology (ASCO) recommended to avoid the use of chemotherapy at the end-of-life to improve patients' care (Schnipper et al., 2012). Mortality within 1 month after the last chemotherapy has been considered as an (negative) indicator of the quality of care (Earle et al., 2008, 2003; O'Brien et al., 2006).

In case of lung cancer, whether chemotherapy near the end of life is appropriate is frequently discussed (Yang et al., 2013). Metastatic lung cancer is an incurable disease associated with a high burden of symptoms, poor QOL and an estimated prognosis after the diagnosis of around 1 year (Jemal et al., 2011). According to national and international guidelines on lung cancer, patients with lung cancer can be treated with chemotherapy, immunotherapy (introduced in 2015) or TKIs. The availability of new anticancer agents (i.e. TKIs) has prolonged the timeline of medical treatment in metastatic cancer patients (Borghaei et al., 2015; Brahmer et al., 2015; Herbst et al., 2016; Maemondo et al., 2010; Mok et al., 2017; NSCLC Meta-Analyses Collaborative Group, 2008; Rosell et al., 2012; Santarpia et al., 2017; Schuler et al., 2016; Shaw et al., 2013). TKIs are oral drugs directed towards specific targetable protein driver mutations, such as EGFR and ALK mutations. Multiple clinical trials have shown that TKIs cause

less side effects compared with chemotherapy and are less burdensome in time and travelling for the patient compared to in-hospital treatments. Above that, TKIs are associated with a 5-year survival of more than 50% (Maemondo et al., 2010; Mok et al., 2017; Rosell et al., 2012; Santarpia et al., 2017; Schuler et al., 2016; Shaw et al., 2013). Therefore, the urgency to discontinue these drugs in the last month of life may be less obvious compared with chemotherapy. Moreover, due to the expected fast response of TKIs, starting these drugs in patients with a targetable driver mutation might be beneficial to their quality of life, especially in patients with a poor performance score.

Studies of Bekelman et al. (2016) and Yang et al. (2013) reported respectively that within different countries 5.7%–27.7% of patients who died with lung cancer were treated with palliative chemotherapy in the last month of life (Bekelman et al., 2016; Yang et al., 2013). Several studies attempt to identify the association between different patient characteristics and the use of palliative chemotherapy at the end of life. For instance, patients older than 75 years, women, unmarried patients, patients with a poor performance score and patients with comorbidities were less likely to receive palliative chemotherapy for metastatic lung cancer at the end of life (Adam et al., 2014; Choi et al., 2015; Earle et al., 2008; Kao, Shafiq, Vardy, & Adams, 2009). However, for TKIs less is known on how many patients who die of metastatic lung cancer were treated in the last month of life and which factors are associated with death within one month after the last treatment. A study among stage 3 and 4 lung cancer patients that started chemotherapy or TKIs as initial treatment showed that of patients who started chemotherapy 6.1% and of patients who started TKIs 8.6% died within 30 days after starting the initial treatment (Burgers & Damhuis, 2018). Although 30-day mortality after initial treatment is not immediately comparable to the percentage of deceased patients who received treatment in the last month of life, this shows that treatment with TKIs in the last month of life also occurs.

In light of the above, we studied what percentage of patients with metastatic lung cancer receive chemotherapy or TKIs and what percentage of patients receive this in the last month of life. We also

investigated which characteristics of patients, health care and oncologists are associated with receiving chemotherapy or TKIs in the last month of life.

2 | METHODS

2.1 | Study design and population

We have conducted a retrospective patient file study in 10 hospitals across the Netherlands, 3 academic and 7 non-academic. We extracted demographic and clinical characteristics from medical files of patients who died of metastatic lung cancer. Medical files were selected based on diagnosis treatment combinations (DBC) codes (DBC 1303 = Non-Small Cell Lung Cancer [NSCLC], DBC 1304 = Small Cell Lung Cancer [SCLC]) or International Classification of Diseases (ICD) codes, Ninth and Tenth Revision (ICD9 and ICD10 for (N)SCLC). Out of this selection, patients were included if they were diagnosed with metastatic lung cancer and died between the 1st of June 2013 and the 31st of July 2015. We excluded patients when they were not treated for lung cancer in the investigated hospital (n = 123), when they were treated with an experimental drug for lung cancer (n = 6), or when the date of the end of treatment was not known (n = 18). A total of 1,322 patients were included in this study, ranging from 70 till 210 patients per hospital.

2.2 | Ethics, consent and permission

This study was approved by the medical ethical committee (METc) of the VU University Medical Centre in Amsterdam, the Netherlands. According to the committee, obtaining informed consent of the family of the patients was not required since this study is based on medical files of patients who already died and data are handled anonymously.

2.3 | Statistical methods

Statistical analyses were conducted using IBM SPSS statistics 22. Differences between the demographic characteristics of the study participants were tested with Analysis of Variance (ANOVA) for the continuous variable age and with the chi-square test for dichotomous and nominal variables. A p-value of ≤.05 denoted statistical significance. Generalised estimated equation (GEE) was used to attain understanding of the association between patient, health care and oncologist characteristics and the use of chemotherapy or TKIs in the last month of life. By using the 10 hospitals as a subject variable, GEE avoids the cluster effect present in the commonly used logistic regression models. The dependent variable was the use of chemotherapy or TKIs in the last month of life. This variable was dichotomized in: "use of medical treatment within 1 month before death (yes/no)." The independent variables were patient, health care and oncologist characteristics. Patient characteristics were sex (male/female), age (≤60, 61–70, ≥71), marital status (married/unmarried), comorbidity (yes/no), histology of the tumour (SCLC, NSCLC with targetable driver mutation [NSCLC+], NSCLC without targetable driver mutation [NSCLC–]) and performance status (ECOG [Eastern Cooperative Oncology Group] score 0, 1, 2, ≥3 or not known). When the performance status was described using the Karnofsky score, this was recoded into the ECOG score (90%–100% = 0, 70%–80% = 1, 50%–60% = 2, 30%–40% = 3, 10%–20% = 4). Healthcare characteristics were type of medical treatment for metastatic lung cancer (none/chemotherapy/TKIs), started medical treatment in the last month of life (yes/no), line of medical treatment (first, second, third and more) and hospital type (academic/non-academic). Oncologist characteristics were sex (male/female) and age (≤40, 41–50, ≥51).

Each statistically significant variable in the univariate GEE analyses (p < .10) was entered into a multivariate GEE model. The final model was derived using the backward selection method, with a p-value of <.05 as considered statistically significant. Results of the GEE analyses are presented as odds ratios (ORs) and associated 95% confidence intervals (CIs).

3 | RESULTS

3.1 | Patient characteristics

From the 1,322 patients with metastatic lung cancer, 509 patients (39%) did not receive chemotherapy or TKIs for metastatic lung cancer. The remaining 813 patients received a systemic treatment: 692 patients received chemotherapy (52%) and 121 patients received TKIs (9%). The three groups (no treatment, chemotherapy and TKIs) show a statistically significant difference on all characteristics: patients receiving no treatment had a higher age at death (70 ± 10 years) compared to patients receiving chemotherapy or TKIs (65 ± 9 and 64 ± 10 years respectively). Moreover, a higher prevalence of comorbidity was observed in patients receiving no treatment (81%) compared with patients receiving chemotherapy or TKIs (72% and 61% respectively). From the patients who received TKIs, 41 patients (34%) did not have a targetable driver mutation (NSCLC–). Only 23 patients with a targetable driver mutation (NSCLC+) (5%) received no treatment. Chemotherapy was mostly administered to patients in the first line (65%) while TKIs were mostly administered in the third line (41%). Lastly, compared to patients receiving chemotherapy or TKIs (65% and 51% respectively), patients receiving no treatment were found more often in a non-academic hospital (78%) (Table 1).

3.2 | Percentage of patients receiving chemotherapy or TKIs in the last month of life

From all 1,322 patients with metastatic lung cancer, 232 patients (18%) received chemotherapy or TKIs in the last month of life: 145 patients (11%) received chemotherapy and 87 patients (7%) received TKIs in the last month of life (Figure 1a). From all the 692 patients

Variable	No treatment[a]	Chemotherapy	TKIs	p
	509 (39)	692 (52)	121 (9)	
Age—Years				
Mean ± SD	70 ± 10	65 ± 9	64 ± 10	**<.001**
Sex				
Male	313 (62)	422 (61)	56 (46)	
Female	196 (38)	270 (39)	65 (54)	**.006**
Marital status[b]				
Married	298 (71)	472 (78)	93 (85)	
Not married	123 (29)	136 (22)	17 (15)	**.003**
ECOG performance score start				
0	23 (4)	118 (17)	22 (18)	
1	57 (12)	181 (26)	33 (27)	
2	47 (10)	75 (10)	18 (15)	
≥3	65 (13)	33 (5)	9 (8)	
Not known	300 (61)	285 (42)	39 (32)	**<.001**
Comorbidity				
Yes	409 (81)	501 (72)	72 (61)	
No	99 (19)	191 (28)	47 (39)	**<.001**
Tumour histology				
SCLC	42 (9)	222 (32)	0 (0)	
NSCLC+	23 (5)	79 (11)	80 (66)	
NSCLC−	412 (86)	390 (56)	41 (34)	**<.001**
Line of treatment				
1st (490)		451 (65)	39 (33)	
2nd (185)		154 (22)	31 (26)	
≥ 3rd (134)	N.A.	85 (12)	49 (41)	**<.001**
Hospital type				
Academic	113 (22)	242 (35)	59 (49)	
Non-academic	396 (78)	450 (65)	62 (51)	**<.001**

Note: Bold values indicate a *p*-value <.05.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung cancer; N.A., not applicable; NSCLC, non-small cell lung cancer; NSCLC+, NSCLC with targetable driver mutation; NSCLC−, NSCLC without targetable driver mutation; TKIs, Tyrosine Kinase Inhibitors.

[a]No treatment is defined as receiving no chemotherapy or TKIs for metastatic lung cancer.

[b]>5% missing values: marital status (14%).

who received chemotherapy at any time for metastatic lung cancer, 21% received this medical treatment in the last month of life (Figure 1c). From all the 121 patients who received TKIs at any time for metastatic lung cancer, 72% received this medical treatment in the last month of life (Figure 1b). From the 145 patients who received chemotherapy in the last month of life, 72 patients (50%) only received one cycle (data not shown).

We also looked at the time between initiation of the treatment and death: from the 692 patients who received chemotherapy at any time for metastatic lung cancer, 79 patients (11%) died within one month after start of the chemotherapy. From the 121 patients who received TKIs at any time for metastatic lung cancer, 15 patients (12%) died within one month after start of TKIs. Of these 15 patients, 8 patients had NSCLC+ and 7 patients had NSCLC−. When treatment was given in the last month of life, this treatment was started in the last month of life in 54% in case of chemotherapy (n = 79) and in 17% in case of TKIs (n = 15).

3.3 | Association between the characteristics of the population and receiving chemotherapy or TKIs in the last month of life

In the multivariate model, most variables were not associated with receiving chemotherapy or TKIs in the last month of life, except for histology of the tumour and type of treatment: patients with NSCLC− had a 0.439 lower odds (p = .003) of receiving chemotherapy or TKIs

FIGURE 1 Percentages of patients receiving medical treatment

(a)

- Chemotherapy in the last month
- Chemotherapy not in the last mont
- TKIs in the last month
- TKIs not in the last month
- No treatment

(b) Patients receiving TKIs (%) *n* = 121

- Treatment in the last month of life
- No treatment in the last month of life

(c) Patients receiving chemotherapy (%) *n* = 692

- Treatment in the last month of life
- No treatment in the last month of life
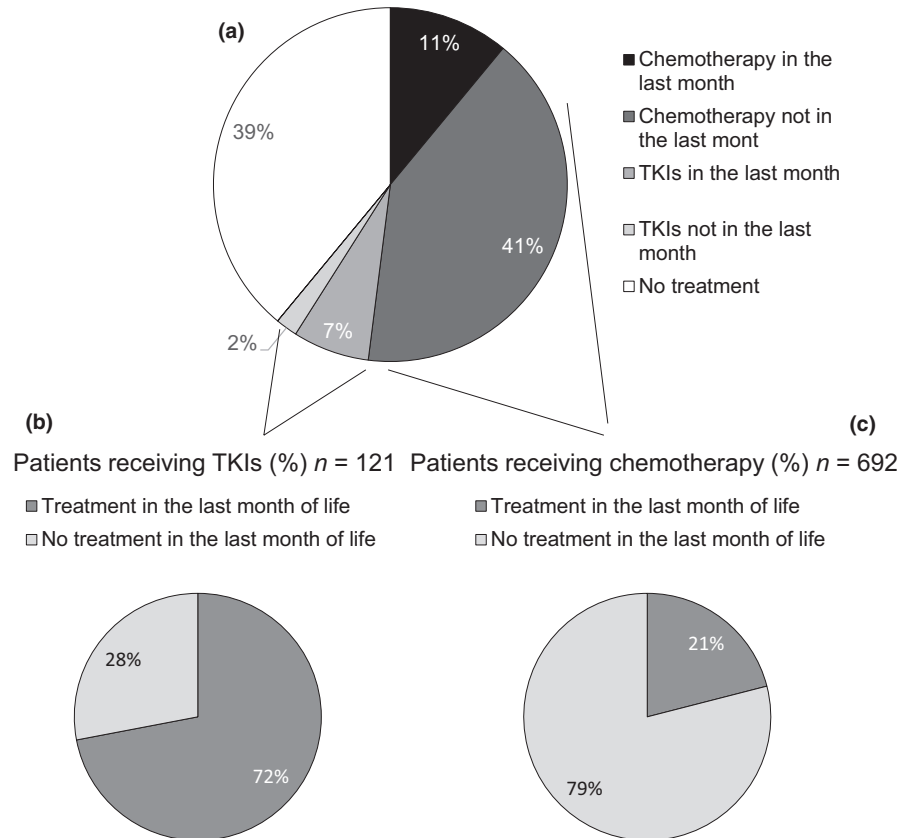
in the last month of life compared to patients with SCLC. Patients receiving TKIs had a 9.503 higher odds (*p* < .001) of receiving this treatment in the last month of life, compared to patients receiving chemotherapy (Table 2). Therefore, we decided to do a separate GEE analysis for patients receiving chemotherapy and TKIs. From these patients receiving TKIs in the last month of life, 25 patients (29%) had NSCLC− (data not shown).

3.4 | Association between the characteristics of the population and receiving chemotherapy in the last month of life

Histology of the tumour and line of treatment were associated with receiving chemotherapy in the last month of life. Patients with NSCLC− had a 0.468 lower odds (*p* = .009) of receiving chemotherapy in the last month of life compared to patients with SCLC. Patients who received third-line chemotherapy had a 2.016 higher odds (*p* = .013) of receiving chemotherapy in the last month of life compared to patients receiving first-line chemotherapy (Table 3).

3.5 | Association between the characteristics of the population and receiving TKIs in the last month of life

Tumour histology, line of treatment and age of the oncologist were associated with receiving TKIs in the last month of life. Patients

with NSCLC+ had a 2.529 higher odds (*p* = .001) of receiving TKIs in the last month of life compared to patients with NSCLC−. Patients who received TKIs in the last month of life had a 1.723 higher odds (*p* = .042) of receiving this in the second line than in the first line. From the patients who received TKIs in the second line, 15 patients (48%) had NSCLC−. From the patients who received TKIs in the third line, 19 patients (39%) had NSCLC−. Patients with a prescribing oncologist in the age range of ≤40 and 41–50 had respectively a 3.238 and 2.841 higher odds (*p* = .036; *p* = .027) of receiving TKIs in the last month of life compared to patients with a prescribing oncologist in the age range of ≥51 (Table 4).

4 | DISCUSSION

From the 1,322 patients included in this study, 39% received no treatment for metastatic lung cancer, 52% received chemotherapy and 9% received TKIs. In total, 18% received treatment in the last month of life (11% chemotherapy and 7% TKIs). When treatment was given, TKIs were (still) given more often in the last month of life than chemotherapy (72% vs. 21%). When treatment was (still) given in the last month of life, this treatment was started in the last month of life in 54% in case of chemotherapy and in 17% in case of TKIs.

Our study found a percentage of patients receiving chemotherapy in the last month of life that falls within the range of rates found for patients with lung cancer in other studies (between

N = 813 Variable (N)	Patients receiving medical treatment in the last month of life (row %)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Sex			
Female (335)	31	1.068 (0.923–1.236)	
Male (478)	27	1.0	
Age—Years			
≤60 (231)	32	1.308 (0.949–1.801)	
60–71 (318)	29	1.147 (0.827–1.590)	
≥71 (264)	25	1.0	
Marital status			
Not married (153)	26	1.0	
Married (565)	30	1.162 (0.740–1.825)	
Comorbidity			
No (238)	20	1.014 (0.657–1.566)	
Yes (573)	16	1.0	
Tumour histology			
SCLC (222)	29	1.0	1.0
NSCLC+ (159)	51	**2.212 (1.163–4.210)***	0.817 (0.284–2.350)
NSCLC− (431)	20	**0.593 (0.390–0.92)***	**0.439 (0.257–0.751)****
Line of treatment			
1st (490)	22	1.0	
2nd (185)	31	**1.560 (1.219–1.997)***	
≥ 3rd (134)	46	**2.510 (1.528–4.123)***	
Sex oncologist			
Female (196)	26	1.0	
Male (575)	29	1.105 (0.668–1.829)	
Age category oncologist			
≤ 40 (106)	33	1.129 (0.701–1.819)	
41–50 (296)	26	0.945 (0.579–1.541)	
≥ 51 (369)	29	1.0	
Hospital type			
Academic (301)	35	1.435 (0.622–3.308)	
Non-academic (512)	25	1.0	
Type of treatment			
Chemotherapy (692)	21	1.0	1.0
TKIs (121)	72	**8.182 (5.694–11.756)***	**9.503 (5.156–17.517)****

Abbreviations: NSCLC, non-small cell lung cancer; NSCLC+, NSCLC with targetable driver mutation; NSCLC−, NSCLC without targetable driver mutation; OR, odds ratio; SCLC, small cell lung cancer; TKIs, Tyrosine Kinase Inhibitors.

*p-Value of ≤.10.

**p-Value of ≤.05

5.7% and 27.7%) (Bekelman et al., 2016; Yang et al., 2013). The rate of 11% that we found for the Netherlands is somewhat lower than the one of 16.4% found by Bekelman et al. (2016). This might be due to the difference in methods; making use of administrative claims data as they did in that study gives less precise information on the exact date a treatment is started or stopped than a patient file study. The percentages found in both studies show that the Netherlands are not among the countries with the lowest

TABLE 3 Univariate and multivariate GEE analyses of factors associated with receiving **chemotherapy** within 1 month before death

N = 692 Variable (N)	Patients receiving medical treatment in the last month of life (row %)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Sex			
Female (270)	22	1.085 (0.814–1.445)	
Male (422)	20	1.0	
Age—years			
≤60 (188)	22	1.204 (0.756–1.918)	
61–70 (270)	22	1.198 (0.824–1.741)	
≥71 (234)	19	1.0	
Marital status			
Not married (136)	21	1.018 (0.660–1.572)	
Married (472)	22	1.0	
Comorbidity			
No (191)	19	1.0	
Yes (501)	22	1.208 (0.702–2.080)	
Tumour histology			
SCLC (222)	29	1.0	1.0
NSCLC+ (79)	24	0.563 (0.238–1.329)	0.664 (0.216–2.043)
NSCLC– (390)	16	**0.442 (0.277–0.704)***	**0.468 (0.265–0.828)****
Line of treatment			
1st (451)	18	1.0	1.0
2nd (154)	21	1.243 (0.831–1.861)	1.050 (0.646–1.709)
≥ 3rd (85)	34	**2.072 (1.287–3.336)***	**2.016 (1.157–3.513)****
Sex oncologist			
Female (178)	20	1.0	
Male (484)	21	1.095 (0.764–1.571)	
Age category oncologist			
≤ 40 (91)	24	1.205 (0.775–1.873)	
41–50 (263)	19	0.885 (0.576–1.360)	
≥ 51 (307)	22	1.0	
Hospital type			
Academic (242)	25	1.357 (0.605–3.042)	
Non-academic (450)	19	1.0	

Abbreviations: NSCLC: non-small cell lung cancer; NSCLC+: NSCLC with targetable driver mutation; NSCLC–: NSCLC without targetable driver mutation; OR: odds ratio; SCLC: small cell lung cancer; TKIs: Tyrosine Kinase Inhibitors.

*p-Value of ≤.10.

**p-Value of ≤.05

percentages such as Canada (5.9%) or Norway (5.7%) (Bekelman et al., 2016).

To our knowledge there are no studies with which we can compare our finding of 7% of patients who died with metastatic lung cancer that had TKIs in the last month of life. This percentage seems low, but this is for a large part due to TKIs not being given so often to this patient group (9% TKIs and 52% chemotherapy). We found that patients who received TKIs had an odds ratio of 9.5 to still receive therapy in the last month of life compared to patients receiving chemotherapy. A salient finding is that from patients receiving TKIs in their last month, 71% did not have a targetable driver mutation. However, these patients did not receive their TKIs in the first line. Knowing the rate of success is low in this group, it is debatable whether this should be considered good practice (Corallo

N = 121 Variable (N)	Patients receiving medical treatment in the last month of life (row %)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Sex			
Female (65)	65	0.436 (0.201–0.945)*	
Male (56)	80	1.0	
Age—Years			
≤60 (43)	74	1.033 (0.317–3.361)	
61–70 (48)	69	0.773 (0.282–2.116)	
≥71 (30)	73	1.0	
Marital status			
Not married (17)	65	1.0	
Married (93)	73	1.496 (0.426–5.253)	
Tumour histology			
NSCLC+ (80)	79	2.211 (1.242–3.934)*	2.529 (1.448–4.639)**
NSCLC− (41)	61	1.0	
Comorbidity			
No (47)	70	1.0	
Yes (72)	72	1.102 (0.586–2.071)	
Line of treatment			
1st (39)	72	1.0	1.0
2nd (31)	81	1.670 (1.025–2.719)*	1.723 (1.019–2.912)**
≥ 3rd (49)	67	0.836 (0.343–2.047)	1.188 (0.520–2.712)
Sex oncologist			
Female (18)	83	1.775 (0.846–3.723)	
Male (91)	73	1.0	
Age category oncologist			
≤ 40 (15)	87	3.553 (1.106–11.414)*	3.238 (1.081–9.698)**
41–50 (33)	85	2.848 (1.068–7.599)*	2.841 (1.123–7.184)**
≥ 51 (62)	66	1.0	1.0
Hospital type			
Academic (59)	75	1.374 (0.712–2.641)	
Non-academic (62)	70	1.0	

Abbreviations: OR: odds ratio; TKIs: Tyrosine Kinase Inhibitors; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; NSCLC+: NSCLC with targetable driver mutation; NSCLC−: NSCLC without targetable driver mutation.

*p-Value of ≤.10.

**p-Value of ≤.05

et al., 2017). This result resonates with findings of Choi et al. that the time between stopping TKIs and death is shorter compared to the time between stopping chemotherapy and death: being 19 days compared to 35 days respectively (Choi et al., 2015). Burgers et al also found a higher odds (OR = 1.3) of TKIs compared to chemotherapy with regard to 30-day mortality after the start of the initial treatment (Burgers & Damhuis, 2018).

Tyrosine Kinase Inhibitors are believed to extend survival with less toxicity and a higher quality of life in patients with a specific targetable protein driver mutation. If effective, they usually show a rapid response which makes it suitable for patients with a poor performance score. Therefore, oncologists may be reluctant to stop this medication even when it is close to the end of life. Another reason of reluctance to stop might be that a disease flare after TKIs discontinuation may occur (Chaft et al., 2011). Although nausea, vomiting, myelosuppression and alopecia generally occur less frequently than with chemotherapy, TKIs are associated with side effects such as skin problems, chronic diarrhoea, fatigue and electrolyte imbalances

that should not be ignored (Guevremont, Alasker, & Karakiewicz, 2009). The risk of side effects may also increase closer to the end of life due to altered metabolism and interaction with other prescribed medication (Burotto, Ali, & O'Sullivan Coyne, 2015). On the other hand, in a study of Shaw et al. (2013), patients reported greater reductions in symptoms of lung cancer and greater improvement in global quality of life with crizotinib (a TKI) than with chemotherapy (Shaw et al., 2013). However, even with a five-year survival of >50%, timely discontinuation of these treatments may be essential to patients for a dignified leave of their loved ones and life itself (Adam et al., 2014). Therefore, more research is needed about the consequences of continuation of TKIs shortly before death. Only then it is possible to consider whether not giving TKIs shortly before death should be a quality indicator for appropriate end-of-life care, as is not giving chemotherapy shortly before death (De Roo et al., 2014). Our result, that in 54% of patients who received chemotherapy in the last month of their life this treatment also had started in the last month of life, is an indication of overtreatment and supports the relevance of this quality indicator and the recommendations of ASCO (Schnipper et al., 2012).

Patients who received third-line chemotherapy had higher odds (OR = 2.084) of receiving chemotherapy in the last month of life compared with patients receiving first-line chemotherapy. In this case, it might play a role that patients with already a poor performance status were given chemotherapy as a final option for maintaining hope and therefore died shortly after the last chemotherapy cycle. SCLC patients may have received chemotherapy for attempted symptom control, which might explain the lower odds of NSCLC patients receiving chemotherapy. Patients with a prescribing oncologist aged ≤50 had a higher odds of receiving TKIs in the last month of life compared to patients with a prescribing oncologist aged ≥51. A possible explanation might be that younger oncologists are better up to date compared to their older colleagues when it comes to TKIs.

The high number of patients analysed in this study (1,322) among ten different hospital sites makes the results robust and generalizable. Since all patients diagnosed with metastatic lung cancer were included in this study, there is no selection bias. However, this study has some potential limitations. First, the inevitable limitation of a patient file study is that we are not able to discover the rationale of the patient and the oncologist behind starting and stopping of chemotherapy or TKIs. Second, data on performance status could not always be retrieved from medical records due to the absence of documentation. Third, we only documented the last treatment line; therefore, we do not know what treatments patients received in earlier treatment lines.

In conclusion, our study gives indications of overtreatment at the end of life. An indicator is that more than half of patients who received chemotherapy in the last month of life also started this treatment in the last month of life. Also that the choice of the treatment among others depends on non-patient-related factors such as age of the oncologist might be an indication of overtreatment. Additionally, a high percentage of patients treated with TKIs did not

fulfil appropriate criteria for starting this type of treatment, which might indicate overtreatment of negative driver mutation patients. Especially when chemotherapy is started shortly before death, this can be seen as aggressive care. TKIs are said to have less side effects and do not lead to many hospital visits. Therefore, it is debatable whether TKIs started shortly before death should be considered as aggressive treatment. However, when still receiving it until shortly before death, this might influence preparing for death in a negative way. It is important to study whether this is the case. Although this study describes the Dutch situation, the percentages of receiving a medical treatment for metastatic lung cancer are informative for other countries.

CONFLICT OF INTEREST

ORCID

Adinda Mieras https://orcid.org/0000-0002-5446-0569

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