Docetaxel in the Treatment of Non-small Cell Lung Cancer (NSCLC) – An Observational Study Focusing on Symptom Improvement

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Abstract. *Background: Results of an observational study on docetaxel-based therapy in non-small cell lung cancer (NSCLC) with focus on symptom control and therapy response, are reported. Patients and Methods: A total of 233 patients with NSCLC treated with docetaxel-containing therapy were analyzed. Results: The pre-existing symptoms of cough, dyspnea and pain markedly improved after three cycles of docetaxel-based therapy. Regression of symptoms was strongly associated with therapy response, but unexpectedly, patients with stable disease had also a substantial benefit. Alltogether, the response after three cycles was complete in 0.9% and partial in 26.6% of patients, respectively. Conclusion: Symptom control was achieved in the majority of cases, which received three cycles of docetaxel-based therapy. Thus, a clinical benefit was regularly reached shortly after initiation of chemotherapy.*

Docetaxel is an important therapeutic component in the treatment of advanced-stage non-small cell lung cancer (NSCLC), either as part of a combination therapy or as monotherapy (1). Docetaxel is an anti-mitotic drug inhibiting microtubule depolymerisation inducing cell-cycle arrest and death. In 1999, docetaxel was approved by the food and drug administration (FDA) as the first drug for second-line NSCLC therapy and afterwards also granted approval for first-line use. Approval for second-line therapy was based on the prolonged overall survival in the TAX 317 and TAX 320 trials comparing docetaxel monotherapy with best supportive care (BSC) (2) and investigator's choice (3), respectively. Afterwards, docetaxel was proven to be effective when combined with cisplatin in first-line induction therapy (TAX 326) (4). However, prospective studies addressing efficacy and tolerability of various therapies in oncology do not entirely reflect the typical cohort of tumor patients because study patients are selected by stringent inclusion and exclusion criteria. In NSCLC, there are limited data available on objective response rates and symptom control for unselected patients treated with a docetaxel-containing regimen in a routine setting. Thus, from 2005 until 2007, an observational study on the routine use of docetaxel in NSCLC was undertaken in Austria. Herein, we present the detailed results of this analysis and a comparison to previously published data.

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Patients and Methods

Patients. The TURIN survey (Taxotere Use Research in NSCLC) was undertaken between 2005-2007 in Austria including oncology and pneumology departments with expertise in the treatment of lung cancer. This was an observational study with consecutive patients treated within the licensed indication in the daily's routine clinical setting, and patients' data were documented in an anonymized matter, considering only the age and gender of each patient. The primary objectives of this analysis were to quantify symptom control, to detect a change of performance status and to analyze therapeutic response after three cycles and at the end of the docetaxel-containing therapies; secondary objectives included the analysis of symptom control and response according to clinical characteristics and prior therapies. In this observational study, data on adverse events were not collected. According to the protocol, patients were eligible for documentation if (i) they had

histologically-proven NSCLC, (ii) were over the age of 18 years, and (iii) received at least three courses of docetaxel-containing therapy, either as monotherapy or combination therapy. Docetaxel was usually given in a three-weekly cycle, at a dose of 75 mg/m^2 [n=222 (95%)]. In 11 cases, however, docetaxel was given weekly; in these cases, one cycle was usually determined to last three weeks (*i.e.* three weekly applications). As pre-specified in the protocol, patients treated neoadjuvantly with docetaxel/platinum were evaluated also if only two cycles had been administered and radical operation followed (n=3). If a combinational chemotherapy (neoadjuvant, first-line, second-line) was applied in all but one case, a platinum-docetaxel doublet was administered (n=79; docetaxel/ gemcitabine, n=1). Neoadjuvant intention of chemotherapy was defined by the following features: TNM tumor stages T1-3; clinical Union for International Cancer Control (UICC) stages I-IIIA; favourable performance status [Eastern Cooperative Oncology Group (ECOG) <2]; no prior cancer therapy; and administration of platin/docetaxel combination. Detailed clinical information on patients' characteristics including performance status (PS), nicotine consumption, symptoms prior to initiation of docetaxel, and mode and agents of prior therapies was documented. Response was evaluated according to RECIST criteria for target and non-target lesions, but no central radiogram review was conducted.

Statistical considerations. Statistical analysis was performed with the SSPS software Version 20.0 (SPSS, Chicago, IL), as detailed in the results section. Due to the observational character of the study, ethical approval, in accordance with Austrian medical laws (Arzneimittelgesetz), was not required at the time the trial was initiated. Data management regulations and security as specified by law were adhered to.

Results

Patients' characteristics. In total, data from 233 patients with lung cancer treated with docetaxel-containing therapy were analyzed. Patients' characteristics and therapy modalities are detailed in Table I. The median age was 62 years (range, 29 to 88 years), 158 patients were male (68%), and 203 patients (87%) were smokers or former smokers. A total of 97% male patients, but only 76% of female patients had a history of smoking ($p<0.001$, chi-square test). Adenocarcinoma was predominant, followed by epidermoid carcinoma. Adenocarcinoma including bronchioloalveolar carcinoma (BAC) was significantly more prevalent in female patients (73% and 52%, in females and males, respectively, $p=0.002$). At initial diagnosis, the majority of patients had advanced-stage disease, with stage IIIB and IV in 43 (19%) and 126 (54%) patients, respectively. The most frequent site of distant metastasis was lung [n=80 (34%)], followed by bone [n=45 (19%)], liver [n=35 (15%)] and brain [n=21 (9%)]. Overall, 159/233 patients (68%) received any kind of prior therapy, including neoadjuvant chemotherapy, surgery, radiotherapy, adjuvant chemotherapy, and palliative chemotherapy. Seventy-two patients had not received any prior therapy, and for two patients this was unknown. Within the observational study, the median number of docetaxel-containing therapy cycles applied was four (range=2-8 cycles). Docetaxel was applied most frequently as monotherapy [n=149 (64%)], mostly in the second- and higher line of palliative therapy

Table I. *Patients' demographics and baseline charactersitics (n=233).*

Characteristic	N	%
Male gender	158	68
Median age (range), years	62 (29-88)	
Histology		
Adenocarcinoma	134	58
Epidermoid carcinoma	83	36
Large-cell	5	2
Bronchiolo-alveolar	3	1
Other*	8	3
Smoking status		
Smoker	113	49
Former smoker	90	39
Never smoker	22	9
Unknown	8	3
ECOG PS prior to observational study		
0	63	27
1	131	56
2	35	15
3	4	2
Previous therapies, setting		
None	72	31
Any	159	68
Radiotherapy†	20	9
Neoadjuvant	17	7
Radical surgery	33	14
Adjuvant	19	8
Palliative systemic	149	64
Unknown	2	1
Prior systemic therapy – agents		
Platinum compound	144	62
Gemcitabine	93	40
Vinorelbine	50	22
Taxane	9	4
Pemetrexed	6	3
Other**	10	4
Setting of docetaxel chemotherapy		
Neoadjuvant intention	12	5
Adjuvant	2	1
Palliative, first-line+	76	33
Palliative, second-line‡	136	58
Palliative, higher-line (docetaxel monotherapy)	5	2
Unknown	2	1

*NSCLC, Not otherwise specified (n=2), undifferentiated (n=4); adenosquamous (n=1), unknown subtype (n=1). **Erlotinib (n=3), bevacizumab (n=2), cetuximab (n=2), ifosfamide (n=1), experimental tyrosine kinase inhibitor (n=1); †including radiotherapy (n=3) and radiochemotherapy (n=3) in (neo)adjuvant and radiochemotherapy in palliative setting (n=14); +docetaxel monotherapy (n=16), docetaxel/ platinum (n=60); ‡docetaxel monotherapy (n=128), docetaxel/platinum (n=7), docetaxel/gemcitabine (n=1). Eastern Cooperative Oncology Group (ECOG) Performance Status (PS).

Table II. *Effect of treatment on Eastern Cooperative Oncology Group Performance Status (ECOG PS) and symptoms after 3 cycles.*

Therapeutic setting	N patients (%)				
	Present at diagnosis	Improvement	No change	Impairment	Unknown
All patients					
PS 0	63	n.a.	42 (67)	20 (32)	1 (2)
PS ≥1	170	27 (16)	112 (66)	29 (17)	2 (1)
Cough	119	71 (60)	37 (31)	9 (8)	2 (2)
Dyspnea	132	80 (61)	36 (27)	13 (10)	3 (2)
Pain	91	54 (59)	27 (30)	10 (11)	0 (0)
Neoadjuvant					
PS ≥1	3	1 (33)	2 (67)	0 (0)	0 (0)
Cough	6	5 (83)	0 (0)	0 (0)	1 (17)
Dyspnea	5	5 (100)	0 (0)	0 (0)	0 (0)
Pain	2	2 (100)	0 (0)	0 (0)	0 (0)
First-line, palliative, docetaxel					
PS ≥1	11	0 (0)	8 (73)	3 (27)	0 (0)
Cough	8	5 (63)	2 (25)	1 (13)	0 (0)
Dyspnea	13	8 (62)	3 (23)	2 (15)	0 (0)
Pain	8	4 (50)	3 (38)	1 (13)	0 (0)
First-line, palliative, docetaxel/platinum					
PS ≥1	45	15 (33)	22 (49)	8 (18)	0 (0)
Cough	36	25 (69)	7 (19)	4 (11)	0 (0)
Dyspnea	40	31 (78)	3 (8)	6 (15)	0 (0)
Pain	30	21 (70)	3 (10)	6 (20)	0 (0)
Second-line or higher palliative					
PS ≥1	108	11 (10)	78 (72)	17 (16)	2 (2)
Cough	68	36 (53)	28 (41)	4 (6)	0 (0)
Dyspnea	72	35 (49)	30 (42)	5 (7)	2 (3)
Pain	51	27 (53)	21 (41)	3 (6)	0 (0)

[n=133 (57%)]. A docetaxel combination was most frequently applied in a first-line palliative setting and in all cases of neoadjuvant therapy. Overall, the patients analyzed in this survey reflected a classical unselected cohort treated in a 'real-life' setting (5).

Symptom control after three cycles. One major goal of systemic therapy is rapid improvement of symptoms and performance status. Thus, the effect of treatment on symptoms and performance status was evaluated in different settings (Table II). Briefly, taken together in all different therapy settings (neoadjuvant, palliative first-line or higher; mono- or combination therapy), the PS (ECOG ≥1) improved in 16% by at least one degree after three cycles. Furthermore, the pre-existing symptoms of cough, present before start of chemotherapy in 119 patients, improved after three cycles in 71 (60%), remained unchanged in 37 (31%), worsened in nine patients (8%), and the outcome was unknown in two patients (2%). Similarly, dyspnea (n=132) and pain (n=91) improved markedly after three cycles of docetaxel-containing therapy (overall in 61% and 59% of patients, respectively). Even patients with initial symptoms who after three cycles were radiologically-classified as stable disease (SD) had improvement of symptoms (in 62%, 66% and 73% for cough, dyspnea and pain, respectively), thus experiencing a clinical benefit. Likewise, out of the 82 patients with initially impaired PS and who had SD after three cycles of therapy, still 12 (15%) experienced an improvement of PS. Improvement of symptoms was strongly associated with therapy response [complete response (CR)/partial response (PR)] after three cycles of docetaxel-containing chemotherapy (*i.e.*, cough, $p=0.001$; dyspnea, $p=0.006$; and pain, $p=0.013$; respectively), and, thus, was strongly associated with the therapeutic setting.

In patients who did not suffer from cough (n=104), dyspnea (n=91), or pain (n=128) at the start of the study, these symptoms manifested after three cycles in 11 (11%), 8 (9%) and 7 patients (6%), respectively; this new occurrence of symptoms (cough and dyspnea) after three cycles of docetaxel-based chemotherapy was significantly associated with PD ($p<0.001$ for cough; $p=0.005$ for dyspnea). Patients achieved an improvement of initially impaired PS in 27 cases (16%), and this was also significantly associated with response after three cycles of chemotherapy ($p<0.001$).

Therapeutic response. Data on response were available for 233 patients, as detailed in Table III. Taking the different settings of docetaxel-containing therapy together, response after three cycles included CR in two (0.9%), PR in 62 (26.6%), SD in 100 (42.9%) and PD in 53 patients (22.7%). In 16 patients (6.9%), response evaluation after three cycles of therapy was not performed. In the neoadjuvant setting (n=12), a therapeutic response upon the combination platinum-docetaxel after 2-3 cycles was observed in 11 patients (91.7%); eight of these patients were subsequently subjected to radical surgery. In first-line palliative therapy, response after three cycles was highly dependent on whether a platinum-docetaxel doublet was administered. Thus, for patients treated with combination therapy (n=60), response after three cycles was as follows: PR, 32 patients (53.3%), SD, 18 patients (30%), PD, 10 patients (16.7%). Response to combination therapy after three cycles was significantly associated with pre-treatment PS (ECOG grade 0-1 *vs*. 2-4, p=0.013), and not associated with the following characteristics: gender; age; histology (adenocarcinoma *vs*. non-adenocarcinoma), stage at initial diagnosis; and prior radical surgery. Patients who received docetaxel in first-line monotherapy (n=16) were characterized by an inferior PS when compared with those who received the platinum-docetaxel combination (p=0.027). After three cycles, the response rate (RR) in these patients was only 13%. In the 141 patients who received docetaxel in second- or higher line therapy, the drug was given as monotherapy in all but eight cases. Taken together, the reponse after three cycles in this cohort was as follows: PR in 18 (13%); SD in 71 (50%); PD in 40 (28%) and not available in 12 (9%) patients, well in line with published data (2, 3).

Table III. *Therapeutic efficacy (response) in NSCLC patients with docetaxel-based therapy (n=233).*

Therapeutic setting*	After 3 cycles	End of therapy
	N patients (%)	
All patients (n=233)		
CR	2 (1)	5 (2)
PR	62 (27)	64 (28)
SD	100 (43)	74 (32)
PD	53 (23)	87 (37)
NE	16 (7)	3 (1)
Neoadjuvant† (n=12)		
CR + PR	11 (92)	12 (100)††
SD	0	0
PD	0	0
NE	1 (8)	0
First-line palliative, docetaxel (n=16)		
CR + PR	2 (13)	2 (13)
SD	10 (63)	9 (56)
PD	3 (19)	5 (32)
NE	1 (6)	0
First-line palliative, docetaxel/ platinum (n=60)		
CR + PR	32 (53)	33 (55)
SD	18 (30)	11 (18)
PD	10 (17)	14 (23)
NE	0	2 (3)
Second-line or higher palliative‡ (n=141)		
CR + PR	18 (13)	20 (14)
SD	71 (50)	52 (37)
PD	40 (28)	68 (48)
NE	12 (9)	1 (1)

CR: Complete remission, PD: progressive disease, SD: stable disease, NE: not evaluable. *In 233 patients, therapeutic setting was neoadjuvant (n=12), adjuvant (2), first-line palliative (76), second-line palliative (136), third-line palliative (3), forth-line palliative (2) and unknown (2). †In three patients subjected to radical surgery, therapeutic outcome was documented after two cycles of neoadjuvant docetaxel/platinum. ††One patient with SD after three cycles continued on chemotherapy to six cycles overall and achieved PR. ‡In second-line palliative therapy, 128/136 patients (94%) received docetaxel as monotherapy (the remainder, docetaxel/platinum combination). In third- and fourth-line palliative therapy (n=5) all patients received docetaxel as monotherapy.

Discussion

In this observational study of NSCLC, including different settings such as neoadjuvant or palliative therapy, encouraging results with docetaxel as monotherapy or in combination with a platinum compound were observed, which is in line with already published data [as reviewed in (1)]. Studies with intent of market authorization of a drug include strict inclusion criteria, which often do not reflect the standard patient cohort. Therefore, we aimed to define the role of docetaxel in 233 consecutive patients with NSCLC who were treated within licensed approval, with a focus on symptom improvement and response. The strength of an observational study is to evaluate the efficacy of anti-neoplastic drugs in unselected patients, often compromised by comorbidities and unfavorable PS. This study is part of the Authors' ongoing efforts to study effects of various treatments on different malignancies in a 'real-life' setting (5-11). To highlight this fact, the presented study cohort included 39 patients with ECOG PS of ≥2 (17%), which is a patient population mostly excluded from clinical studies. Furthermore, a high proportion of patients were treated in higher therapy lines, including third- and fourth-line settings. With respect to response, we were able to demonstrate that therapeutic results observed in prospective studies usually translate well into the routine situation (4, 12, 13). In second-line therapy, the pivotal studies TAX 317 and TAX 320 (2, 3) revealed objective RR for the docetaxel arms of 7.1% and 6.7%, and SD of 47.3% and 36%, respectively; in our study, the RR in second and higher lines were comparable,

with PR in 14% and SD in 37%. In the first-line setting with platinum-docetaxel doublet, response after three cycles and at end of therapy was comparably high, with CR/PR in 53% and 55%, respectively (Table III). This demonstrates rapid therapy response and symptom benefit. This favorable RR may be partly explained by selection in that only patients who received at least three cycles were recruited into this observational study. In the prospective TAX 326 study, in which a "best response analysis" was presented, the objective response was 31.6% (4).

The results of neoadjuvant therapy showed a high RR after two to three cycles (Table III), with a subsequent resectabiliy in 8/12 patients. In our prospective neoadjuvant study (INN06 trial), two scheduled cycles of chemo-immunotherapy were applied in 36/38 patients, generating an RR of 58% (14). Betticher *et al*. in 2003 reported that neoadjuvant docetaxel and cisplatin is effective and tolerable for stage IIIA pN2 NSCLC (15), with a 66% overall RR. This demonstrates that the vast majority of patients can receive two or three cycles of neoadjuvant chemotherapy without major problems with encouraging RR and resection rates supporting the concept of neoadjuvant treatment.

Symptom improvement is a major goal of palliative therapy and this was achieved concerning cough, dyspnea and pain relief in 69%, 78% and 70% of the analyzed patients, who had received platinum/docetaxel in the first-line setting. The present study found improvements of cough, dyspnea and tumor pain to be significantly associated with response. Improvements were observed even in patients achieving disease stabilization. By this, it is highlighted that a clinical benefit of chemotherapy in NSCLC does not necessarily require an objective response, comparable to the situation in pancreatic carcinoma (16). In a previous study in NSCLC using gemcitabine and low-dose carboplatin in elderly patients (n=88), improvement with respect to pain, dyspnea and asthenia was demonstrated in 51.7%, 50% and 61.5% of patients, respectively (17). To enter our observational trial, patients had to receive at least three cycles of docetaxel-based chemotherapy. We are convinced that palliative chemotherapy terminated after one or two cycles might not add any benefit to patients. Since the primary objective of the present study was to determine the effect of chemotherapy on symptom control or improvement, the predefined selection of patients was necessary. It was our aim to draw conclusions on patients who received a significant amount of therapy; this makes sense when the primary objective of the study is the analysis of symptom control and improvement, and the effect of chemotherapy can be studied reliably only in patients who undergo at least three cycles. In our *Tyrol* lung cancer registry, we found that 30% and 36% of patients received fewer than three cycles of first- and second-line palliative therapy, respectively, with early termination due to PD or toxicity (5). Thus, patients analyzed in this observational trial showed a certain degree of a favorable course of disease during the first months of chemotherapy. On the other hand, a remarkable proportion of patients in this study were characterized by unfavorable clinical features and certainly did represent a real-life patient cohort.

In conclusion, we have shown that rapid symptom control can be achieved in the majority of cases of NSCLC patients treated with docetaxel-based therapy. This is a strong argument to initiate chemotherapy even in difficult clinical situations, highlighted by the fact that symptom improvement is often achieved even in cases with disease stabilization only.

Conflicts of Interest

AP, IKW, MM, GG, EU, AMS and WH have no conflicts of interest to disclose. MF has received honoraria from Sanofi Vienna for analysis of data.

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