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Treatment and Outcome of Patients with Palliative Non-small Cell Lung Cancer (NSCLC) in Routine Outpatient Care Over Two Decades

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Abstract

Objectives: We evaluated the practice in our outpatient setting to analyze and study the outcomes of patients with palliative lung cancer.

Methods: All consecutive patients with palliative non-small cell lung cancer (NSCLC) treated between June 1995 and December 2016 were analyzed retrospectively.

Results: 736 patients with a median age of 66 (37-88) could be evaluated. All patients had a primary lesion in the lung and 71% metastatic disease at the time of presentation. Adenocarcinoma (61%) was the most common histological subtype followed by squamous cell cancer (28%). The majority (93%) received at least one line of chemotherapy. A mean of 2.5 lines of treatment per patient (1-11) was delivered with platin doublet chemotherapy being the most common therapeutic choice (479/650; 74%). 93% of patients died, mostly due to tumor (76%) during the observation period.. The median overall survival (OS) was 13.5 months (0.4-194.6). Patients with disease limited to the lungs without metastases had an OS of 16.9 months (1.2–188.5+) compared with 11.6 months (0.4-194.6) for patients with metastases (p=0.003).

Conclusions: Good quality care can be delivered closer to home in an outpatient setting with the help of a competent multidisciplinary framework. Our results are comparable to that of clinical trial and cancer registry data.

Keywords: Non-small cell lung cancer; Palliative treatment; Chemotherapy; Carcinoma; Metastasis

Introduction

Lung cancer is the second most common solid tumor and the leading cause of cancer related deaths across both genders worldwide [1,2]. Unfortunately, the majority of patients are diagnosed at an advanced stage where a curative option is not feasible. Lung cancer mainly comprises of two different subtypes small cell and non-small cell; the latter accounting for around 85% of all lung cancers. The recent advent of immunotherapy agents has further revolutionized the available therapeutic options [3]. The knowledge of driver mutations and the availability of tyrosine kinase inhibitors targeting these mutations has significantly improved the prognosis of this small sub-cohort of NSCLC patients [4-6].

Despite the advances in the treatment options, only 4% of the patients diagnosed with palliative NSCLC survive more than 5 years [7]. Data obtained from clinical trials do not reflect the day-to-day reality of older patients, with multiple comorbidities deemed unfit as per inclusion and exclusion criteria. We retrospectively analyzed data on patients with palliative NSCLC in our community-based outpatient practice over the last two decades. The aim of our study was to analyze the impact of various treatment modalities on an unselected, unbiased population. We demonstrate the importance of a multidisciplinary team in the treatment of this patient cohort and the impact of changing therapeutic options on day-to-day clinical practice.

Methods

The treatment and outcome of all consecutive patients diagnosed with palliative NSCLC in our community-based oncology group practice between June 1995 and December 2016 was retrospectively analyzed. No patient could be offered a curative therapy i.e. surgery or curative radiochemotherapy. Patients with disease limited to one lung but inoperable or ineligible for a curative radiochemotherapy were defined as having locally advanced lung disease. Patients with a primary lesion in the lung and metastases were defined as having metastatic lung disease. All patients with locally advanced lung disease and metastatic lung disease were identified as having advanced stage palliative NSCLC and included in the study. The primary endpoint was OS and the secondary endpoints were response rates and toxicity. Informed consent was obtained from all patients. Patients were identified by searching the practice's electronic files for relevant codes of the international classification of diseases. A computerized data collection tool was used to extract the relevant data. In addition to data from our personal files, information was also obtained from our cooperation partners involved in the care of the patient i.e. hospitals and primary care physicians.

Performance status was evaluated using the Eastern Cooperative Oncology Group (ECOG) criteria [8]. Toxicity was analyzed based on the National Cancer Institute CTC version 3 [9]. The Charlson comorbidity index (CCI) has been widely used to predict the mortality rate based on the comorbidities [10]. We used the age adapted Charlson comorbidity index (aaCCI) to analyze the influence of age as well as comorbidities on the disease specific outcome [11]. The anonymized data were collected from patient files into a database and analyzed statistically using SPSS 19. Statistical analyses were descriptive, specific hypotheses were not tested. Survival analyses were performed according to the method of Kaplan and Meier.

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Results

Patient demographics

736 patients with advanced stage palliative NSCLC were identified during the study duration. Patient demographic data is shown in Table 1. The majority were male (n=490, 67%) with a median age of 66 (range 37-88) at the time of diagnosis. 46% of the patients (n=335) were under 65. Language posed no barrier to good communication in the majority of patients (96%, n=704).

ECOG performance status and body mass index (BMI) was available for 383 patients and 680 respectively (52%; 92%). The majority (297/383, 78%) had an ECOG performance status ≤ 1 and around half (312/680, 46%) a normal BMI (18.5-24.9). History of nicotine abuse could be obtained on the majority of patients (n=615, 84%); of these 53% were smokers and 35% continued to smoke despite the diagnosis. 13% never smoked. An occupational hazard could be established in 11% (n=41) of patients. Based on the available documented evidence, 83% (n=34) of these patients were reported to the respective authorities and in 12% (n=5) an occupational hazard could be confirmed. In our patient cohort, the aaCCI was <8 and ≥ 8 in 18% (136/736), and 82% (600/736) respectively Table 1.

151/736 (21%) had surgery as first line therapy and 59/151 (39%) adjuvant or neoadjuvant chemotherapy prior to recruitment into this study and were in a follow-up program. Information on patients who received curative radio chemotherapy was not available.

Tumor location

61% (n=451) of patients had an adenocarcinoma whereas 28% (n=205) had a squamous etiology. Majority of the tumors were located in the upper lobe (48%, n=353) followed by lower lobe (23%, n=166) and middle lobe (10%, n=75). 216 patients (29%) suffered from locally advanced lung disease. 520 (71%) had metastatic lung disease. 27%, 20% and 15% (n=138, n=106, n=76) of patients with metastasis had only lung, bone or brain metastases respectively at the time of diagnosis. Patients with metastatic disease had on average 1.5 metastases (range 1-5). 8% had brain and bone +/- lung metastases (n=42), 4% had lung and bone metastases (n=21) and 26% (n=137) had metastases in other sites such as adrenal glands and liver.

Treatment

The majority of patients (93%, n=685) were considered fit for a palliative therapy whereas 7% (n=51) of the patients were offered best supportive care alone. Therapy consisted of chemotherapy with or without palliative radiation in 95% of patients, 5% had radiation only. 1,622 chemotherapy lines were administered to 650 patients (mean 2.5 per patient; range 1-11). A platin doublet chemotherapy was the most common therapeutic option in 479/650 patients (74%) and in 619/1,622 (38%) therapy lines respectively. 433 patients (67%) received a second and 260 (40%) a third line treatment. A platin doublet was administered as first, second and third line treatment in 411 (63%), 124 (29%) and 44 (17%) lines respectively Figure 1. 146 (22%) received more than 3 lines of chemotherapy. 8% (50/650) of patients were offered a triple therapy with a platin, a taxane or pemetrexed in combination with bevacizumab. 23% (n=147) received a single agent treatment as first line. Immunotherapies with nivolumab or pembrolizumab were offered to 46 (7%) patients.

Supportive therapy and toxicity

Supportive therapy played a major role in the treatment. 633 patients (86%) were offered a palliative support therapy in addition to chemotherapy or radiotherapy. 58 (8%) patients received a palliative surgery such as kyphoplasty or resection of a metastasis, 2 (0.3%) received chemoembolization, 4 (0.5%) radiofrequency ablation and 4 (0.5%) an intraperitoneal chemotherapy. 24% (n=178) received a bisphosphonate or a monoclonal antibody directed against RANKL. 72% (n=532) required pain management. 41% (n=303), 17% (n=127) and 11% (n=81) were given blood and blood products, erythropoietic stimulating agent and or a granulocyte stimulating colony factor following chemotherapy. 93% of the patients tolerated the treatment very well. In 9% of all applied chemotherapies and in 19% of patients grade 3-4 neutropenia, thrombocytopenia and anaemia could be observed.

Age	Median (Range)	66 (37-88)
	N	%
Age groups		
- <65 years	335	46
- 65-69 years	144	20
- 70-75 years	152	21
- >75 years	105	14
Gender		
- male	490	67
- female	246	33
Stage		
- metastatic disease	520	71
- advanced stage disease	216	29
Year of diagnosis		
- 1995 - 2000	140	19
- 2001 - 2004	130	18
- 2005 - 2008	129	18
- 2009 - 2012	133	18
- 2013 - 2016	204	28
ECOG performance status *(n=383)*		
- ECOG ≤1	297	78
- ECOG ≥2	86	22
Age adjusted Charlson Comorbidity Index (aaCCI)		
- aaCCI <8	136	18
- aaCCI ≥8	600	82
Occupational hazard *(n=390)*		
- occupational hazard identified	41	11
Identified occupational hazard *(n=41)*		
- reported to the authorities	34	83
- confirmation of hazard	5	12
Marital status *(n=566)*		
- married or in a relationship	442	78
- widowed	46	8
- living alone	78	14
Body Mass Index		
- underweight	38	6
- normal	312	46
- overweight	251	37
- adipose	79	12
History of nicotine abuse		
- never smoked	78	13
- still smoking	214	35
- smoked prior	323	53

Table 1: Demographic data.

89% (n=657) of the patients required hospitalization following the onset of therapy. On average patients were hospitalized 3 times (range 1-17). The majority of hospitalizations (63%, 1,160 hospitalizations) were due to tumor related problems with only 57 (3%) admissions resulting from treatment related toxicities. The remaining patients were hospitalized for the delivery of chemotherapy or palliative procedures such as radiofrequency ablation, intraperitoneal chemotherapy and chemoembolization. The median duration of hospitalization was 22 days (range 1-179 days). In patients for whom the information was available (79%, n=493); 50% (245/493) died in hospital, 40% (198/493) at home and 10% (50/493) of patients in a hospice or old age home.

Survival analyses

The median OS of the whole cohort was 13.5 months (range 0.4 – 195). 7% (n=53) of the patients are still alive. Men had an inferior median OS in comparison with women 12.5 *versus* 15.4 months (p=0.12). Younger age was associated with a better OS; 15 months if ≤ 65 *versus* 12 months if >65 (p<0.001). The OS of patients who received best supportive care only was 5.1 months (0.4 - 120). Patients with advanced lung disease had a better OS of 16.9 months compared to 11.6 months in patients with metastatic lung disease (p=0.003) (Figure 2). Amongst the patients with metastatic disease, those who had brain metastases had an inferior OS compared to those without (10.2 months *versus* 14.4 months) (p=0.002). A statistically significant difference in survival was not observed between the patients with or without liver metastases.

Patients who received more therapy lines had a better prognosis which was statistically significant (p<0.001). The median OS varied from 5.4 months (range 0.5-100) to 11.0 months (1.3-195) to 20.4 months (range 2.6-188) in patients who received 1, 2 or more than 2 therapy lines respectively.

Survival analysis of patients with aaCCI scores <8 and ≥ 8 show a significantly different outcome (17.2 months vs. 12.5 months; p<.001) (Figure 3). Patients with an ECOG performance score ≤ 1 survived 13.0 months (0.4 - 195) in comparison to a median of 8.0 months (0.7 - 189+) if the ECOG was ≥ 2 (p=0.004).

Patients with driver mutations

In the last decade, tyrosine kinase inhibitors became available for patients with driver mutations. Molecular genetic analysis for possible mutations or translocations on EGFR, ROS-1, ALK or BRAF genes were performed in 29% (n=214), 8% (n=61), 18% (n=129) and 6% (n=42) of the total number of patients. 10% of the patients tested (44/446) had a genetic aberration in the analysis. PD-L1 expression was not analyzed until 2016 and hence the data on PD-L1 testing was not obtained.

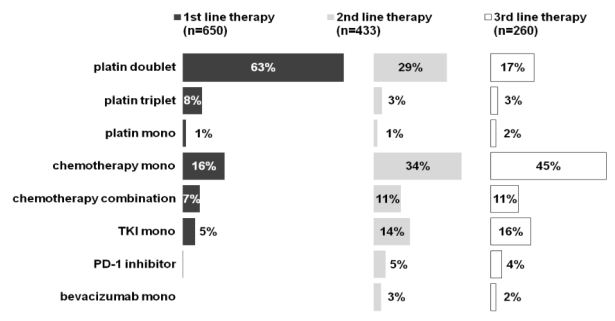

Figure 1: Administered therapies in 1st, 2nd and 3rd line treatment.

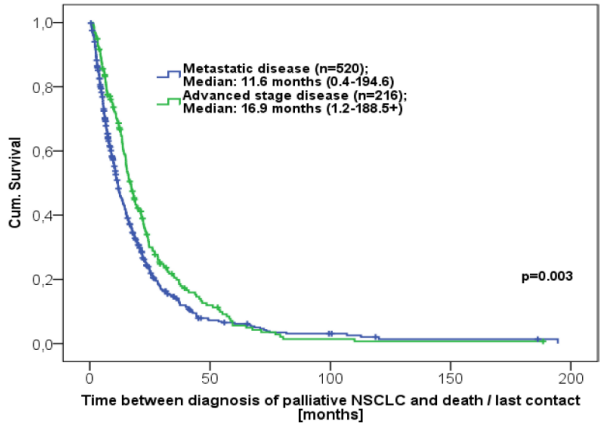

Figure 2: Overall Survival - comparison of patients with metastatic disease *vs.* advanced stage disease.

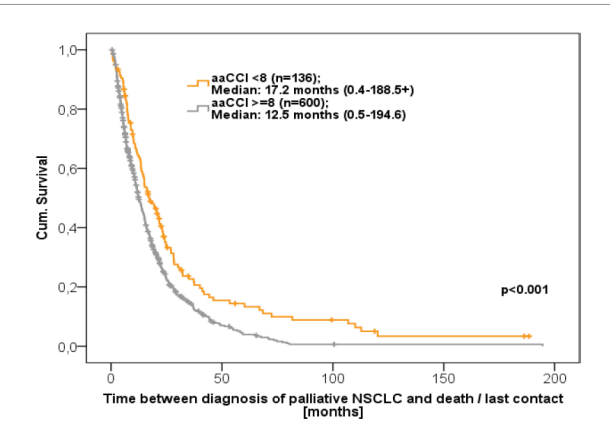

Figure 3: Overall Survival - comparison of patients with an age adapted Charlson comorbidity index (aaCCI) ≥8 *vs.* aaCCI <8.

39 patients were diagnosed with a mutation (ALK; ROS; EGFR) and received a targeted therapy. OS of this patient subgroup was not significantly longer than patients without a driver mutation, 16.5 months (1.8 - 186+) *versus* 13.4 months (0.4 - 195) (p=0.342). 4 patients (9%) had best supportive care only as they died shortly after or before the driver mutations were established or had radiation or chemotherapy mostly due to comorbidities and a reduced performance status. The patient with BRAF mutation had an ALK-translocation as well and hence was commenced on crizotinib.

Discussion

Lung cancer remains the most important cause of cancer related deaths despite the advances in the available therapeutic options. Our own previous analysis from June 1995 to June 2006 published in 2009 showed a median OS of 10 months [12]. In comparison with the analysis published in 2009, the current study comprises a bigger cohort (736 *versus* 212) with metastatic disease in a bigger proportion (71% *versus* 51%). The current study had a greater subgroup of elderly patients 70 or above (35% *versus* 26%) but a smaller proportion with an ECOG of 2-4 (22% *versus* 43%). Even after taking these factors into account the improvement in OS in our current study is probably due to the improvement in the therapeutic options and supportive care provided.

Our 1, 3- and 5-year OS data surpasses the data obtained from the Rhineland-Palatinate or Munich, SEER or NHS England cancer registries. This suggests that the advent of new therapeutic options has resulted in an improvement in the OS of this patient cohort and that we can successfully deliver this care in a community practice.

Around one fifth of the patients had a curative therapy with surgery and or adjuvant chemotherapy prior to enrolment in the study, implying that these patients were possibly identified prior to the onset of symptoms during the follow-up period. This cohort of patients might have contributed to our admirable results. We analyzed this cohort with the rest of the subset which had no prior surgery and found as expected an improved OS (20.3 months *versus* 12.5 months, p<.001). The lack of data on patients who received curative radio chemotherapy is also a drawback of our study with respect to the possible influence of this treatment on subsequent therapeutic decisions as well as their tolerability and also the prognosis of this subset of patients.

Age, gender, ECOG performance status and metastases, especially brain metastases, are established risk factors which influence the outcome of patients with lung cancer [13]. Our own experience confirmed the impact of these confounding variables on survival outcome. 4% (n=29) of the patients were above 80. In the time period between 1995-2000 8% (n=11) of the patient cohort were above 75 whereas between 2011-2016 they accounted for 17% (n=46) of the study group. We need more clinical studies which recruit elderly patients in order to understand the dose limiting toxicities in this cohort of patients [14]. The statistically significant impact of aaCCI on outcome highlights the influence of comorbidities. The recently suggested tools to predict chemotherapy toxicities should be incorporated into our day-to-day practice to alleviate the impact of comorbidities on outcome [15-17].

Despite the ECOG status of ≥ 2 in 22% (n=86) of patients, 93% could be offered a chemo or radiotherapy and the majority tolerated the treatment with minimal toxicity. Our data shows minimal limitation with respect to grade 3 and 4 toxicity secondary to chemotherapy. A drawback of our study is the lack of grade 1 and 2 toxicity data. A significant proportion (89%, n=657) of the patients required multiple hospital admissions and mostly (63%, 1,160 hospitalizations) due to tumor related events. In many patients (40%, n=198) death at home could be facilitated highlighting the value of multidisciplinary teams in the community setting. In the future we should invest in resources to facilitate end of life care at home [18].

Conclusion

We conclude that with the advances in cancer therapy the outcome of patients with palliative lung cancer has improved. This patient group benefits from palliative chemotherapy which can be accomplished successfully in an outpatient setting with outcomes comparable to randomized controlled trials and contemporary data available from regional and international cancer registries. Appropriate follow-up of patients with lung cancer who have received a curative therapy results in the early detection of relapse and hence improved outcome. A good comprehensive multidisciplinary team is mandatory in the delivery of care for this patient cohort with multiple comorbidities.

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