

Research Article

Retrospective Analysis of Thoracic Oncology Practices: Attitudes and Beliefs about Aggressive Treatment at the End of Life

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Abstract

Few studies exist on aggressive treatment at the end of life in thoracic oncology. The objective of this study was to assess practices in this area, and to establish predictive indicators of aggressive "end-of-life care".

In this retrospective study, all patients who died over a 12-month period, who were treated for a cancer of the lung and pleura, in Pneumology Department of the French Hospital Gabriel Montpied in Clermont-Ferrand, were included. Three risk factors of aggressive end-of-life care were analyzed: anti-cancer treatments during the last month of the life, emergency hospitalization during the last month of the life and the death in hospital.

Among 189 patients, 93.6% have received at least one anti-cancer treatment. Patients receiving chemotherapy during the 4 and 2 last weeks of their life were 47.8% and 24.8% respectively. The Non-Small Cells Lungs Cancers (NSCLC) were most often treated during the last month of their life (OR=4.03 [1.41-11.54], p=0.0094). 11.6% patients were hospitalized in emergency departments during the last month of their life, the risk factor was a weight loss > 5% (OR=3.73 [1.23-11.31], p=0.02). The majority of patients (58.7%) were died during hospital stay.

Our results concur with those of the literature. In oncology, the end-of-life care is always a complex issue, which must consider different events in the end-of-life, relieve symptoms and not interfere with informed patient's choice.

Keywords: Lung cancer; Aggressive treatment; End of life; Palliative care; Analysis of practices

Introduction

Lung and pleural cancer is often diagnosed at a late stage: a patient out of 3 dies in 90 days having been taking care [1]. The last few years, the highlighting of biomolecular markers accessible to targeted therapies and immunotherapy came to change and transform the way of taking care of lung cancer and improve prognosis. Nonetheless, all patients can't be granted to targeted therapy and immunotherapy [2-4].

There is no a standardized definition of aggressive treatment at the end of life in oncology [5-8]. According to several authors, it might be defined by death at hospital [9] and hospitalization in emergency or intensive care unit in 30 days before death. This definition is incomplete that's why much often the aggressive treatment at the end of life is defined by the rate of patients who receive a specific treatment of cancer in the last four and two weeks of their life [10]. According to the American Society of Clinical Oncology (ASCO), one of the quality of life criteria is not being treated by specific oncologic treatment in the two last weeks of life.

In France, there are very few studies about aggressive treatments at the end of life, especially in thoracic oncology. That is why we did this survey.

The aim of the present work is to study within patient treated in the department of pneumology in the University Medical Center of Clermont-Ferrand, for lung cancer, the percentage of patients handled in an activate way in the last 4 and 2 weeks preceding the death and to establish the predictive factors of the aggressiveness of the care.

Materials and Methods

We included all the patients treated or followed within department of pneumology of Clermont-Ferrand for a lung cancer, histologically proven, died between January 1st, 2016 and December 31st, 2016. We collected the treatments received (number of lines, type and dates of treatments) and the date, place and cause of death.

Patients were considered in exclusive palliative care, which means a stop of the specific anti-cancer treatments, if the decision has been taken in a multidisciplinary meeting, in a medical mail of consultation, or in the report of hospitalization.

We considered criteria of aggressiveness of the care: the rate of patients receiving an anti-cancer treatment in the last 4 and 2 weeks preceding the death. We also took into account the parameters frequently associated to the aggressiveness of the care at the end of life: the rate of patients hospitalized in an emergency department,

Table 1: Characteristics of the population.

Characteristics		Total population (N=189)	NSCLC ¹ (N=160)
		Number (%)	Number (%)
Median age (years)		65 [37-91]	65 [37-91]
Patients ≥ 65 years old		95 (50)	74 (46)
Men		137 (73)	115 (72)
Histology	Adenocarcinoma	95 (50)	95 (59.4)
	Squamous-cell	46 (24)	46 (28.7)
	Small cell lung	26 (14)	0
	Mesothelioma	3 (2)	0
	Others	19 (10)	19 (11.9)
Staging at diagnosis	I-II	12 (6)	11 (8)
	IIIA	25 (13)	23 (14)
	IIIB	28 (15)	23 (14)
	IV	124 (66)	103 (64)
Palliative care		105 (55)	84 (52)
Late palliative care		29 (15)	12 (14)
Place of death	Hospital	96 (50.2)	
	IC and RU ²	15 (7.8)	
	Palliative care unit	21 (11)	
	Rehabilitation unit	25 (15)	
	Home	27 (14)	
Cause of death	Not known	4 (2)	
	Cancer	136 (72)	
	Febrile aplasia	4 (2)	
	Sepsis	18 (9.5)	
	Other	26 (13.5)	
Number of treatment lines	Not known	7 (3)	
	Median	2 [0-7]	2 [0-7]
	0	12 (6)	12 (8)
	1	56 (30)	50 (31)
	2	59 (31)	52 (32)
	3	34 (18)	26 (16)
Last line	≥ 4	28 (15)	20 (13)
	Oral chemotherapy	12 (7)	12 (8)
	IV ³ chemotherapy	113 (63)	84 (52)
	Immunotherapy	49 (28)	49 (31)
	Chemoradiotherapy	3 (2)	3 (1)
Chemotherapy at the last 4 weeks of life	Total	90 (47.1)	84 (53)
	PC ⁴ at time of death	35 (18.3)	
Chemotherapy at the last 2 weeks of life	Total	47 (24.6)	43 (27)
	PC ⁴ at time of death	10 (5.2)	

¹NSCLC: Non-Small Cell Lung Cancer; ²IC and RU: Intensive Care and Reanimation Unit; ³IV: Intravenous; ⁴PC: Palliative Care.

in an intensive care unit or resuscitation department in thirty days preceding the death and the rate of death at the hospital.

Quantitative variables were presented as median and standard deviation and qualitative variables as a percentage. Several comparisons were made in univariate analysis using the Chi2 test or Fisher's exact test for qualitative analyzes; and the Student test or the Mann-Whitney test for quantitative analyzes.

Predictive factors were supplemented by multivariate analysis by introducing significant univariate variables ($p < 0.05$) or by clinical relevance in a logistic regression model. This multivariate analysis was performed with a Cox model if overall survival was studied. The statistical software used was SEM [11].

Results and Discussion

189 patients with lung cancer or pleural mesothelioma were included in our study and their median age was 65. At initial diagnosis, there were 66% of patients with stage IV. Median time survival was 10 months. The characteristics of the population are indicated in the (Table 1).

The median time from the interruption of anti-cancer treatments

to death was 17 days. The specific treatments were stopped for 105 patients at the time of death and were stopped at a late stage for 29 of them, that is, three days before the death. The main results are summarized in the (Table 2).

177 patients (94%) received at least one treatment regimen. The median number of treatment lines was 2 (range 0 to 7). The median time from the beginning of the last line treatment to death was 80 days and from the last cycle of treatment to death was 28 days.

47.6% patients had received the last administration of chemotherapy during their last 4 weeks of life and 24.8% in their last 2 weeks. Patients treated for a Non-Small Cell Lung Cancer (NSCLC) were more likely to receive a specific anti-cancer treatment at the last month of their life (OR=4.92, CI 95% [1.76-13.77], $p=0.0024$).

Patients who were considered in palliative care, received statistically fewer specific anti-cancer treatment at the last 4 and 2 weeks of their life, with OR=0.27 (CI 95% [0.13-0.55], $p<0.001$) and OR=0.17 (CI 95% [0.07-0.39], $p<0.001$), respectively. Conversely, late palliative care (in the last three days of life) was a risk factor to receive a specific anti-cancer treatment in the last months of life (OR=5.45; CI 95% [1.42-20.89], $p=0.013$).

Table 2: Statistical analysis for total population (N=189).

Characteristics	Treatment in the last 4 weeks of life (90 patients)		Treatment in the last 2 weeks of life (47 patients)		In emergency unit, intensive care or reanimation units hospitalization in the month prior to death (57 patients)		Deaths at the hospital (111 patients)	
	Univariate (p)	Multivariate OR [CI 95%]	Univariate (p)	Multivariate OR [IC 95%]	Univariate (p)	Multivariate OR [IC 95%]	Univariate (p)	Multivariate OR [IC 95%]
Age ≥ 65 years old	NS	-	NS	-	NS	-	NS	-
Sex	NS	-	NS	-	NS	-	NS	-
Weight loss > 5%	NS	-	NS	-	p=0.020	3.73 [1.23-11.31]	NS	-
NSCLC	p=0.0015	4.92 [1.76-13.77]	NS	-	NS	-	NS	-
Palliative care	p<1.10 ⁻³	0.27 [0.13-0.55]	p<1.10 ⁻³	0.17 [0.07-0.39]	p=0.005	0.91 [0.31-2.72]	p<1.10 ⁻³	0.44 [0.22-0.86]
Late palliative care	p=0.018	5.45 [1.42-20.89]	p<1.10 ⁻³	-	NS	-	p=0.046	-
≥ 2 lines	NS	-	NS	-	NS	-	p=0.044	0.81 [0.41-1.60]
Last line								
Oral	NS	-	NS	-	NS	-	NS	-
Intravenous	NS	-	NS	-	NS	-	NS	-
Immuno	p=0.039	1.79 [0.83-3.85]	NS	-	NS	-	NS	-
CRT	NS	-	NS	-	NS	-	NS	-
Intensive care and reanimation units hospitalization in the last month of life	p=0.022	1.25 [0.35-4.44]	p<1.10 ⁻³	3.15 [0.99-10.06]	-	-	p<1.10 ⁻³	2.23 [1.16-4.29]

OR: Odds Ratio; CI 95%: for a 95% Confidence Interval; NSCLC: Non-Small-Cell Lung Cancer; Immuno: Immunotherapy; CRT: Chemo Radiotherapy; NS: Non-Significant.

57 patients were admitted in emergency unit or in intensive care unit in their last month of life.

Discontinuation of specific treatment in the last month of life limited the side effects of treatment and the consequences of cancer were the leading cause of death for these patients ($p = 0.018$). Furthermore, these patients died especially outside the hospital ($p=0.017$).

These results are consistent with data from the literature, although studies show that there is wide variation in the percentage of patients receiving chemotherapy in the last 4 and 2 weeks of life (from 12 to 55% NSCLC) and predictive factors for receiving chemotherapy at the end of life (Table 3). In the literature review, we found the histological subtype NSCLC as a predictor of active treatment in the last month of life in a study conducted in France in 2015 [10], which included several histological types. Other studies showed that if situations are labeled palliative too late, it is seen as predictive factors for receiving specific treatment in the last month of life [11-14].

We have focused on NSCLC especially because they occur frequently and there are many therapeutic options for this histological subtype (targeted therapies, immunotherapy). 160 patients had non-small cell lung cancer. 25 patients had specific oncogenic mutations (44% KRAS mutations, 20% EGFR mutations and 20% EML4-ALK rearrangement). At diagnosis, the majority of patients had an advanced stage of cancer. The median between the last day of specific treatment and death was 24 days and patients receiving specific treatment in the last 4 and 2 weeks before death were respectively 52.5% and 27%.

The appropriate time for discontinuing specific care is a complex issue. ASCO recommends palliative chemotherapy only for patients with solid cancer and good general condition. Conversely, it is not recommended to treat the patient with chemotherapy when there is no clinical or symptomatic benefit expected [15]. The delay between the last day of specific treatment administered and death is not sufficient to define the aggressiveness of end-of-life care in oncology. Furthermore, patients who receive maintenance treatment in the last month of life (treatment begun earlier than death) and patients with whom a new specific treatment line is initiated in the last month of life should be distinguished.

Recently, a French team highlighted, with patients with solid tumors, a decision score for the continuation of specific treatments after 2 lines of chemotherapy, or management for palliative care alone [13]. This prospective study of 64 patients allowed to establish a score based on two clinical values (PS according to ECOG and the number of metastatic sites) and two biological values (LDH and albumin). The score was used to classify patients into three risk groups (A, B or C). Patients in low-risk group A (score ≤ 3) were more likely to benefit from a new chemotherapy regimen, while palliative care alone was recommended for Group C, and discussed for Group B. However, the study population was heterogeneous as several histological types of solid cancers were included and several studies showed that it may be a risk factor for chemotherapy at the end of life [10,16]. This is particularly important when studies included solid tumors and hematological cancers [17-19]. The current prognosis scores remain imperfect. Other studies are needed to validate decision scores, and specifically in lung cancer.

Table 3: Literature review on end-of-life treatment for lung cancer.

References	Design	< 4 weeks	< 2 weeks	Factors	Histology	Number patients
USA Mack et al. (2015) [14]	P	18%	-	- Non caucasians - Early discussion on the quality of life	Metastatic lung and colorectal cancers	722
USA Murillo et al. (2006) [19]	R	43%	20%	- Oral chemotherapy - Maintenance treatment	NSCLC	417
0000	P	37%	19%	- Late palliative care	NSCLC	151
Norvège Nieder et al. (2014) [26]	R	28.6%	-	- Lake of « no resuscitation » in the medical file - Compression of the lower vena cava.	NSCLC	266
USA Pirl et al. (2015) [34]	R	-	9.9% (IV) 37.5% (PO)	- Oral chemotherapy	NSCLC	81 48
Norvège Nieder et al. (2016) [15]	R	30%	-	- Late palliative care	NSCLC	286
Japon Fujisawa et al. (2015) [14]	R	-	20%	- Oral chemotherapy - Anxiety and depression - Late palliative care	NSCLC	125
Canada Saito et al. (2011) [35]	R	12.4%	8.5%	- Urban zone (north) - Hospitalization	NSCLC	3 534
Australie. Kao et al. (2013) [23]	R	6.1%	-	- ≥ 2 lines	Pleural mesothelioma	147
France Sesé et al. (2015) [13]	R	55%	22%	- NSCLC	NSCLC SCLC	94
France Study presented	R	47.1%	24.6%	- NSCLC - Late palliative care	NSCLC SCLC Pleural mesothelioma	189

P: prospective study; R: retrospective study; NSCLC: non-small-cell lung cancer; SCLC: small-cell lung cancer.

Few studies on chemotherapy at the end of life reveal the causes of death. It is not always easy to distinguish between deaths due to treatment toxicities, or related to the course of the disease. This element deserves to be analyzed to assess the aggressive care at the end of life. In our study, patients who were not treated with specific treatment in the last month of their life died more often of cancer ($p = 0.018$), and patients treated at the end of their life would more often die from other causes (toxicity of the treatment, complications, or aggravation of a co-morbidity). This suggests that some patients would have benefited more from palliative care alone. Indeed, palliative care and supportive care must be an integral part of the standard treatment in thoracic oncology. However, there are still some barriers to the integration of supportive care in the usual care, and there is no consensus on the optimal timing for its implementation [21]. ASCO recommends palliative chemotherapy for patients eligible for a therapeutic trial, with solid cancer and general good health. In our study, all patients receiving chemotherapy had $PS \leq 2$. Weight loss was a predictor of hospitalization in an emergency department within 30 days prior to death ($p = 0.02$). At the end of life, ASCO does not recommend chemotherapy for chemotherapy-resistant symptoms. Unfortunately, our study did not reveal the symptoms of the patients. But, in advanced lung cancer, palliative care can be divided into two categories [22]: on the one hand, treatments that directly improve quality of life (such as corticosteroids, analgesics, antiemetics, transfusions and psychological treatments for example), and on the other hand, treatments that can indirectly improve the quality of life by acting on symptomatic tumor. Nieder's study found compression

of the superior vena cava as a predictive factor of active treatment in the last month of life in patients treated for advanced NSCLC [23]. In this case, palliative chemotherapy prescribed at the end of life, which could be considered as aggressive treatment, aims to improve the quality of life [24]. In this situation, receiving active treatment at the end of life is not an isolated criterion sufficient to judge the aggressiveness of a care. For this reason, palliative chemotherapy should be discussed in a multidisciplinary way. In our study, the median time between cessation of specific active treatments and death was 17 days but the median time between the last chemotherapy received and death was 28 days. The difference in time between these two medians is probably a reflection of the time required for the "palliative approach", which requiring a collegial discussion and an exchange with the patient and his family. The choice of patient must be made clear. The Silvestri study, based on questionnaires completed by patients, after failure of prior platinum based chemotherapy for an advanced NSCLC, showed that only 22% of patients accepted chemotherapy toxicities for a survival benefit of 3 months, while 68% accepted chemotherapy if it helped reduce symptoms [25]. In a more recent prospective study, among patients with lung cancer, only 19% chose an intensive chemotherapy for a 3-month survival gain, while 70% chose chemotherapy, and accepted side effects, to reduce the symptoms [26]. The British study by the Slevin team found that patients were willing to accept a high degree of toxicity for a new line of chemotherapy, only if there was even a minimal possibility of cure [27]. These results suggest that patients who wish to receive chemotherapy may be insufficiently informed about the

prognosis of their disease, and on the sole objective of palliative treatment. It is sometimes easier for the physician to prescribe a new line of “aggressive” treatment, which is always a source of hope for the patient [28], but to the detriment of quality of life in most cases [29]. The prescription of a treatment because there is hope from the patient is inappropriate, and if the doctor suspects a death in the following months, he should not prescribe active treatment if the objective is not to improve the symptoms [30]. These findings highlight several points: the importance that patients attribute to quality in relation to the duration of life, the importance of symptomatic status to assess the need for palliative chemotherapy, and the place of exchange between the oncologist and the patient in this situation. Thus, the delay between the last administration of chemotherapy and death is no longer sufficient to define the aggressiveness of care in oncology, which cannot be reduced to a date.

The cessation of specific treatments becomes a process spread over time [31] and this process takes into account other events occurring at different times of the end of life, such as hospitalizations. We also analyzed hospitalizations in the last month of life in emergency or intensive care units. In our study, 57 patients (30%) had been hospitalized in an emergency or intensive care units within 30 days before their death. The statistically significant risk factor was weight loss > 5% ($p = 0.02$). Similarly, the significant risk factor identified in patients who died in hospital was hospitalization in an emergency department, intensive care units in the last month of life ($p = 0.016$). Some authors describe them as indicators of the aggressiveness of end-of-life care in oncology [9]. Patients in palliative care were less likely to die in hospital (OR = 0.44 CI 95% [0.22-0.86], $p = 0.017$). Home, which was largely dominant in 1950, remained the majority until the mid-1970s before giving way to the institutions and especially to the hospital. But dying in the hospital does not mean that the whole end of life took place in the hospital. Although the places of death have been the subject of several studies, the circumstances of the end of life remain largely unexplored in France. Some authors propose not to consider only the place of death, but to evaluate the multiplicity of trajectories at the end of life (usually from the home to the hospital), which considers other parameters such as autonomy, for example to evaluate the aggressiveness of end-of-life care [32].

Conclusion

Discontinuation of specific end-of-life treatments in thoracic oncology is a major problem, with ethical and economic issues.

This retrospective study analyzed the management over the last month of life of 189 patients treated for lung cancer or the pleura over a period of 12 months. We focused on aggressive care at the end of the life. Patients treated for non-small cell lung cancer were more likely to receive specific treatment in the final weeks of life. This result is probably a reflection of therapeutic advances (with the use of targeted therapies and immunotherapy). These new anti-cancer treatments, better tolerated, contribute to complex situations, where the benefit-risk balance is more favorable for a new line for patients considered fragile. But the definition of the aggressiveness of care at the end of life cannot be reduced to the time between the last administration of the specific treatments and the death. Other parameters to consider include quality of life and symptoms experienced by the patient. This requires new prognostic tools to aid in the medical decision of a new

specific treatment or of supportive care alone. These tools must take into account the specific difficulties and symptoms of lung cancer, assessing the purpose of a new line, individual frailty and informed choice of the patient.

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