

Cost analysis of adverse events associated with non-small cell lung cancer management in France

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Background: Adverse events (AEs) related to medical treatments in non-small cell lung cancer (NSCLC) are frequent and need an appropriate costing in health economic models. Nevertheless, data on costs associated with AEs in NSCLC are scarce, particularly since the development of immunotherapy with specific immune-related AEs.

Objective: To estimate the costs of grades 3 and 4 AEs related to NSCLC treatments including immunotherapy in France.

Methods: Grades 3 and 4 AEs related to treatment and reported in at least 1% of patients in Phase III clinical trials for erlotinib, ramucirumab plus docetaxel, docetaxel, pemetrexed plus carboplatin plus bevacizumab, platinum-based chemotherapies, nivolumab and pembrolizumab were identified. When no cost evaluation was reported in literature, estimates on standard treatments and medical resource use for each AE were obtained thanks to an expert panel. Total cost per AE was calculated from a French national health insurance perspective and updated in 2017 Euros. Hospital stay costs were estimated based on public and private weighted tariffs and data from the French Medical Information System (Programme de Médicalisation des Systèmes d'Information). Costs of tests, consultations and treatments were calculated based on national reimbursement tariffs.

Results: Overall, costs of grades 3 and 4 AEs related to treatment ranged from €46 per event to €7,742 per year. Fourteen out of 24 AEs identified had a mean estimated cost over €2,000. The highest mean costs were related to type 1 diabetes (€7,742 per year) followed by pneumonitis (€5,786 per event), anemia (€5,752 per event), dehydration (€5,207 per event) and anorexia (€4,349 per event). Costs were mostly driven by hospitalization costs.

Conclusion: Among the AEs identified, a majority appeared to have an important economic impact, with a management cost of at least €2,000 per event mainly driven by hospitalization costs. This study may be of interest for economic evaluations of new interventions in NSCLC.

Keywords: non-small cell lung cancer, adverse events, cost analysis, chemotherapy, immunotherapy

Introduction

According to the World Health Organization, lung cancer is the most common cancer worldwide with 1.8 million new cases and 1.6 million deaths in 2012 which makes it the leading cause of death due to cancer in men and the second one in women after breast cancer.¹ The prognosis of lung cancer is generally poor with a 5-year overall survival estimated at 10%–15% due to a diagnosis, generally at an advanced stage of the disease.² In France, deaths due to lung cancer were estimated at 29,949 in 2012.³

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Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers.⁴ For patients who have been diagnosed at an early stage, surgery remains the preferred treatment. At an advanced stage, first-line treatment consists of platinum-based combination therapies. Docetaxel, pemetrexed and erlotinib are considered for subsequent lines and treatment strategy takes into account histology, age and comorbidities.⁵ These therapies may be associated with toxicities:⁶ renal, neurologic and hematologic for platinum-based chemotherapy,⁷ hematologic disorders and diarrhea for docetaxel and pemetrexed,⁸ skin toxicity, diarrhea and interstitial lung disease for erlotinib.⁶ Recently, pembrolizumab and nivolumab, two monoclonal antibodies that block the interaction between PD-1 expressed on tumor cells and PD-L1 receptors expressed on T cells, became new therapeutic options for NSCLC. In recent randomized controlled trials, both pembrolizumab and nivolumab were found to significantly increase progression-free survival in patients with NSCLC expressing PD-L1 with a better tolerance profile compared to cytotoxic agents but with some adverse events (AEs) specific to immunotherapy.⁹⁻¹² However, there are very few data on costs associated with AEs in NSCLC. The objective of this study was to estimate the costs of grades 3 and 4 AEs related to NSCLC treatments including immunotherapy in France by combining literature review, expert opinions and data extraction from a French hospital discharge database.

Materials and methods

Selection of AEs of interest

The following treatments of NSCLC were considered for the analysis as representative of the main therapeutic classes of interest for first- and second-line: docetaxel, pemetrexed, bevacizumab, ramucirumab, erlotinib, nivolumab, pembrolizumab and nonpemetrexed containing platinum-based chemotherapies. After a literature review, the studies of Shepherd et al,¹⁴ Patel et al,¹³ Garon et al,¹⁵ Herbst et al¹¹ and Reck et al¹² were identified for the selection of AEs in NSCLC treatment. Grades 3 and 4 AEs (as defined by common toxicity criteria)¹⁶ related to these drugs and reported in at least 1% of patients from at least one of these pivotal clinical trials for first- or second-line NSCLC treatments were identified.

Literature review

For each AE of interest, costing in France was investigated through a literature review using MEDLINE. We selected articles in English language and gave priority to those published within the past 10 years. The studies by Banz et al¹⁷ and Nuijten et al¹⁸ about the management of AEs related to treatment in NSCLC were identified. The study by Nuijten

et al was considered as a duplicate of the study by Banz et al. The literature research was then extended to the management of AEs related to treatment in melanoma, considering that the management of grades 3 and 4 AEs does not depend on the underlying disease. Two studies were identified^{19,20} and none was excluded. French experts were asked to complete data when information was lacking. Costs available in literature were updated to 2017 Euros.

Expert panel

For AEs with no published available cost, an expert panel composed of 3 French oncologists (CC, DL and EA) completed a questionnaire on the assessment of resource use in real-life practice for selected AEs. This questionnaire was completed by the experts before the meeting and it included the following items: hospitalization (percentage of patients concerned and duration of hospitalization stay), diagnostic tests (percentage of patients concerned and types of tests), consultations of general practitioner (percentage of patients concerned and number of visits), treatments (percentages of patients concerned, drug name and dosage and treatment duration) and other resources. During the meeting, the methodology considered for identifying AEs was described. Then, experts were asked to give their insight and the answers to the questionnaire were discussed. As AEs were not reported with the same terms in each clinical trial, similar AEs or AEs requiring similar management were merged under a unique term when relevant, based on expert opinion. A consensus was then reached by discussion and the minutes of the meeting were validated by all participants.

Costing

Total cost per AE was calculated from a French national health insurance perspective. Hospital stays costs were estimated based on available tariffs and data from the French Medical Information System (Programme de Médicalisation des Systèmes d'Information [PMSI]). The PMSI database covers all French public and private hospitals, except military and psychiatric hospitals. For each stay, diagnosis, medical procedures, duration and treatment are reported in standardized discharge reports and collected in the PMSI.

PMSI database is primarily used for hospital funding and frequently used for observational research purposes. At the time the study was conducted, the PMSI database was available upon registration, agreement and payment to a habilitated provider or through collaboration with a French university hospital health information management department. Since April 2017, the PMSI database is monitored by the National Institute of Health Data. This institute

receives requests for authorization, which must then be submitted for an opinion from the expert committee for research, analysis and evaluation in the area of health. The decision of this committee is based on the relevance and the quality of the protocol submitted, the methodology chosen, the need and the public interest nature of the research.

In a first step, ICD-10 codes (lung cancer, C34; metastatic, C77, C78, C79) allowed selecting in the database patients with lung cancer (as principal, secondary or associated diagnosis); only stays for patients with an age of ≥ 18 years were kept. Each AE was then identified in 2014 using diagnosis codes (ICD-10) or DRG codes (diagnosis-related groups). Lung cancer patients with AE did not require having a treatment of interest.

For each AE, PMSI database provided mean length and cost of stay depending on the type of hospitalization (in intensive care unit or in general ward). Analyses of data extracted from PMSI database were performed with SAS v.9.3 (SAS Institute, Cary, NC, USA). Costs of tests, consultations and treatments were calculated based on national reimbursement tariffs.

Statistical analysis

Data were analyzed using SAS software (SAS Institute). Quantitative variables were described by median and quartiles or by mean and standard deviation. Qualitative variables were described by numbers and percentages.

Results

Considering relevant clinical trials,^{11–15} 38 AEs met the inclusion criteria; 22 AEs not reported with the same terms, but similar or requiring similar management, were merged under 8 unique terms based on expert opinion (Table 1). Finally, 24 AEs were considered for the cost analysis.

The costs of 17 AEs were obtained from literature and updated to 2017 Euros. These data and corresponding studies are summarized in Table 2. The study by Banz et al¹⁷ provided French costs of grades 3 and 4 AEs in NSCLC patients considering hospitalizations, supplementary diagnostic examinations, drug therapy and follow-up outpatient physician visits through structured data collection sessions with 6 lung cancer specialists. Results were provided only with total cost without further details on items distribution. The study by Wehler et al¹⁹ provided French costs of grades 3 and 4 AEs in patients with melanoma considering hospitalizations, supplementary diagnostic examinations, drug therapy and procedures through structured interviews done with physicians experienced in the fields of medical oncology or dermatology in melanoma. The costs of AEs were provided

Table 1 Merging of adverse events (AEs) from different studies

AEs reported	Merging for analysis
Asthenia	Asthenia/fatigue
Fatigue	
Pneumonitis	Pneumonia, infiltration, pneumonitis
Pneumonia or infiltration	
Lung infection	
Lower respiratory tract infection	
Neutropenia	Neutropenia
Neutrophil count decreased	
Leukopenia	
White blood cell count decreased	
Lymphocyte count decreased	
Pancytopenia	
Thrombocytopenia	Thrombocytopenia
Platelet count decreased	
Transaminases increased	Elevated transaminases
Aspartate aminotransferase increased	
Acute kidney injury	Dehydration
Hypoalbuminemia	
Pulmonary or gastrointestinal hemorrhage	Hemorrhage
Epistaxis	
Skin rash	Rash
Rash or acne	

separately for inpatients and outpatients. Therefore, distribution was asked to French experts during the advisory board meeting in order to calculate a mean cost for 3 AEs (elevated transaminases, febrile neutropenia and hypertension). The cost of colitis in France was obtained from the study by Vouk et al, which estimated the costs associated with AEs in patients with metastatic melanoma across Europe through literature review followed by Delphi panel interviews.²⁰ The cost of type 1 diabetes was obtained from the Échantillon national témoin représentatif des personnes diabétiques [National representative sample of people with diabetes] survey performed in France in 6710 adult patients.²¹ In the particular case of type 1 diabetes, the cost was estimated on a per-year basis; moreover, the cost was weighted by the mean survival duration observed in KEYNOTE-024 according to the type of NSCLC (squamous or nonsquamous carcinoma).

The use of medical resource for 7 grades 3 and 4 AEs not reported in literature were assessed based on experts opinion. The mean costs of these AEs are summarized in Table 3. According to the experts, the occurrence of grades 3 and 4 AEs related to treatment required inpatient hospitalization, systematically for dehydration, pulmonary hemorrhage, pneumonitis and venous thromboembolism. These proportions were more variable for toxic ocular effect,

Table 2 Studies providing French costs of grade 3–4 adverse events

Reference	Resources for cost analysis	Source	AEs reported	Cost (2017)
Banz et al ¹⁷	Hospitalizations	National medical tariffs for inpatient and	Anemia	€5,752
	Supplementary diagnostic examinations	outpatient care	Anorexia	€4,349
	Drug therapy	Reference costs	Asthenia/fatigue	€586
	Follow-up outpatient physician visits	Pharmacy sales prices for drugs prescribed in the outpatient setting	Diarrhea	€2,879
			Infections	€3,483
			Nausea	€2,052
			Neuropathy	€259
			Neutropenia	€93
			Rash	€232
			Vomiting	€2,104
Wehler et al ¹⁹	Hospitalizations	Public French databases:	Dyspnea	€1,478
	Supplementary diagnostic examinations	ATIH	Elevated transaminases	€3,500 ^a
	Drug therapy	Classification Commune des Actes	Febrile neutropenia	€824 ^b
	Procedures	Table Nationale de Codage de Biologie	Hypertension	€46 ^c
Vouk et al ²⁰	Hospitalizations	Pharmacy sales prices for drugs	Colitis	€3,457
	Health care professional	ATIH for hospitalization		
	Other measures	National medical tariffs for inpatient and		
	Prescribed medication	outpatient care		
	Diagnostic/prognosis procedures	Expert opinion (Delphi panels)		
Ricci et al ²¹	Hospitalizations	Real-world data (PMSI database)	Type 1 diabetes	€7,742 ^d
	Supplementary diagnostic examinations			
	Drugs			
	Follow-up outpatient physician and			
	specialists visits			
	Transports			

Notes: ^aWith/without hospitalization: €6,972/€28 (50% of hospitalizations; expert opinion); ^bWith/without hospitalization: €2,017/€29 (40% of hospitalizations; expert opinion); ^cWith/without hospitalization: €1,633/€30 (1% of hospitalizations; expert opinion); ^dMean annual cost taking into account mean survival duration observed in KEYNOTE-024 (total cost: squamous carcinoma, €16,581; nonsquamous carcinoma, €21,960).

Abbreviations: AE, adverse event; ATIH, Agence Technique de l'information sur l'Hospitalisation [Technical Information on Hospitalization Agency]; PMSI, Programme de Médicalisation des Systèmes d'Information [French Medical Information System].

thrombocytopenia and arthralgia with 10%, 25% and 75% of hospitalizations, respectively. Other medical resources were used for the management of arthralgia and toxic ocular effect. Both required tests for 25% of concerned patients, consisting of a complete biological test and a fundus examination, respectively. Moreover, consultations with a specialist were considered relevant for the follow-up of 25% of patients concerned by arthralgia and toxic ocular effect and 100% of patients concerned by pulmonary hemorrhage. However, for many AEs, tests and treatment costs were considered nonsignificant or already included in the hospitalization costs except for venous thromboembolism which required, systematically, the administration of low-molecular-weight heparin by a nurse at home for 90 days.

Overall, costs of grades 3 and 4 AEs related to treatment ranged from €46 per event to €7,742 per year (Tables 2 and 3). Fourteen out of 24 grades 3 and 4 AEs identified had an estimated mean cost over €2,000. The highest mean costs per patient were related to type 1 diabetes (€7,742 per year) followed by pneumonitis (€5,786 per event), anemia

(€5,752 per event), dehydration (€5,207 per event) and anorexia (€4,439 per event). The costs of AEs more specifically reported with immunotherapy treatments were €3,457 for colitis, €3,500 for elevated transaminases and €7,742 per year for type 1 diabetes.

Discussion

AEs associated with medical treatment in lung cancer are frequent and their management represent a significant cost. This cost varies according to countries.^{17,19} For example, Banz et al reported that the management of grades 3 and 4 anemia in NSCLC patients varied from €1,526 in Spain to €5,228 in France.¹⁷

The total costs of grades 3 and 4 AEs are, generally, driven by hospitalization. Therefore, the estimation of hospitalization rates and length of stay must be accurate in cost analysis. In their study comparing treatment costs of grades 3 and 4 AEs in NSCLC patients from different countries, Banz et al reported that cost variations were primarily due to differences in clinician's estimate of hospitalization referral rates.¹⁷ An

Table 3 Resource use for grades 3–4 adverse events and mean costs (according to experts and PMSI database)

Adverse events (number of stays identified from the PMSI database)	Type (n) ^a	Patients (%) ^b	Mean (SD) length of stay ^c (days)	Mean (SD) cost of stay ^d (euros, 2017)	Unit costs (euros, 2017)	Estimated mean costs (euros, 2017)
Arthralgia (n=6)						
(ICD-10: M255)						
Hospitalization	In general ward	75	2.2 (4.4)	1132.22 (673.80)	514.65 per day	849.17
Examinations	Complete biological test (n=1)	25			32.05	8.01
Follow-up consultations ^e	Specialist consultations (n=3)	25			30.28	22.71
	Total					879.89
Dehydration (n=396)						
(ICD-10: E86)						
Hospitalization	In general ward	75	6.2 (6.4)	3170.82 (1866.17)	511.44 per day	2378.20
	In ICU	25	15.1 (16.8)	5485.66 (4196.91)	363.30	1371.46
	Total					3749.66
Ocular toxic effect (n=51) (DRG: 02M08)						
Hospitalization	In general ward	10	4.3 (6.7)	2268.86 (2388.58)	527.66 per day	226.89
Examinations	Fundus examination (n=1)	100			28.46	28.46
Follow-up consultations	Ophthalmologist consultations (n=3)	25			33.93	25.45
	Total					280.80
Pulmonary hemorrhage (n=13) (ICD-10: R048)						
Hospitalization	In respiratory ICU	25	13.5 (13.7)	3485.38 (911.71)	258.18 per day	871.36
Follow-up consultations	In ICU	75	8.4 (11.6)	3809.00 (2947.59)	453.46 per day	2856.80
	Lung specialist consultation (n=1)	100			26.24	26.24
	Total					3754.40
Pneumonitis (n=3,529) (DRG: 04M05)						
Hospitalization	In general ward	60	8.8 (7.8)	461.50 (2884.62)	524.62 per day	2760.00
	In respiratory ICU	20	10.8 (8.9)	6067.31 (3059.66)	561.80 per day	1213.49
	In ICU	20	16.5 (16.3)	9012.38 (4026.19)	546.96 per day	1804.97
	Total					5778.46
Thrombocytopenia (n=85) (ICD-10: D695)						
Hospitalization	Platelet transfusion	25	1	830.25 (42.25)	830.25	207.56
	Total					207.56
Venous thromboembolism (n=1,441) (ICD-10: I26, I802)						
Hospitalization	In general ward	29	8 (8.1)	4288.35 (2316.25)	536.10 per day	1243.75
Treatment	In ICU	5	13.1 (11.4)	6249.99 (6552.79)	477.12 per day	312.51
	Low-molecular-weight heparin administered at home by a nurse	100	90		19.64 per day	1767.60
	Total					3323.86

Notes: ^aType and quantity of resource use per type of AE were assessed according to expert opinion; ^bPercentage of patients concerned were assessed based on expert opinion; ^cMean durations of hospitalization were estimated according to the PMSI database; ^dHospital stay costs were estimated based on public and private weighted tariffs and 2014 PMSI database; costs of diagnostic examinations, follow-up consultations and treatments were calculated based on national reimbursement tariffs; ^eComplete blood cell count, serum creatinine, serum electrolytes and rheumatoid factor blood test.

Abbreviations: DRG, diagnosis-related group; ICD-10, The International Classification of Diseases, Tenth Edition; ICU, intensive care unit; PMSI, Programme de Médicalisation des Systèmes d'Information [French Medical Information System]; SD, standard deviation.

advantage of our study was that the estimations concerning hospitalization (duration of stay, admission to intensive care unit or general ward) were based not only on expert opinion but also when necessary on objective real-life data from the PMSI database. In contrast with Wehler et al, who separately reported outpatient and inpatients costs of grades 3 and 4 AEs, we estimated the proportions of inpatients and outpatients, when necessary, and a mean cost was calculated. This approach was also adopted by Banz et al who reported mean total costs of AEs by taking into account country-specific estimates of admission rates and length of stay at hospital.¹⁷

Immunotherapy is a new paradigm in NSCLC therapy and pembrolizumab or nivolumab acts on cancer through the anti-tumor activity of T cells. As a consequence, different safety profiles can be expected in comparison with cytotoxic agents.

In pivotal trials, AEs were less frequent in immunotherapy arms. Thus, in KEYNOTE-024 study, treatment-related AEs of any grade were less frequent in pembrolizumab 200 mg group compared with the chemotherapy group (73.4% versus 90.0% of patients) as were treatment-related grades 3 and 4 AEs (26.6% versus. 53.3%). In KEYNOTE-010 study, grades 3 and 4 AEs attributed to study treatment were reported in

only 12.3% of patients in pembrolizumab 2 mg/kg group versus 35% in docetaxel group.¹¹ The same trends were observed in clinical trials for nivolumab. For this reason, taking into consideration AEs reported in at least 1% of patients of at least 1 pivotal clinical trial appeared to be more relevant than the usual threshold at 5% or 10%.

Then, the present article shows that the costs of management of some AEs are significant. More than half of the identified grades 3 and 4 AEs had a mean estimated cost of >€2,000. Moreover, the costs of AEs specifically reported with immunotherapy treatments were estimated at €3,457 for colitis, €3500 for elevated transaminases and €7,742 per year for type 1 diabetes.

There are some limitations to our study. Costs were calculated in the setting of French healthcare system and extrapolations to other countries should be cautious. Moreover, the assessment of medical resources was not obtained prospectively, but was based, in part, on literature data and expert opinion. Literature data were extracted from clinical trials and reporting of AEs is not standardized; sometimes only AEs of interest are reported. Moreover, the description of some AEs, for example, “infection,” was imprecise and could recover heterogeneous clinical situations.¹⁷ A possible criticism is the use of data from the study by Wehler et al who included patients with metastasis melanoma. Indeed, it could be argued that AEs have different medical impacts and costs according to the underlying disease. An additional limitation of literature data is the report of the rates and costs for grade 3 or 4 AEs only as a unique category. Indeed, some grade 4 AEs are potentially life-threatening with most probably an increase of the associated costs. Finally, the estimations of the management schedules of AEs rested on the opinions and experience of the 3 oncology experts who coauthored this article. Their point of view may be not representative of practices in France for the management of AEs in NSCLC. Moreover, the experts represented only a limited number of medical specialties and some costs could have been over- or underestimated. Nevertheless, possible discrepancies that would appear with a larger group of experts should be minimized. Indeed, the 3 experts agreed that the management of the AEs under discussion was rather standard and a consensus was easily achieved.

These limitations must be kept in mind and costs reported, in the present study, must be considered as an indication of the cost that payers have to consider for each AE. For future studies, it could be very helpful to prospectively record medical resource associated with predefined AEs in NSCLC.

Despite these limitations, the specific values reported in the present article for the most frequent grades 3 and 4 AEs in trials

with NSCLC patients should be useful for future economic analyses. Indeed, both incidence and costs of hospitalization of these AEs were taken into account. Moreover, immunotherapy, which involves higher costs in comparison with previous treatments, was also considered. Modeling the overall burden of the management of AEs in NSCLC will allow comparisons between treatments with various safety profiles.

In conclusion, this study may be of interest for economic evaluations of new interventions in NSCLC. Among the identified AEs, a majority appeared to have an important economic impact, with a management cost of at least €2,000 mainly driven by hospitalization costs.

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