Is chemotherapy rechallenge feasible in advanced-stage non-small-cell lung cancer?

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La ré-introduction de chimiothérapie est-elle faisable au cours du traitement du cancer pulmonaire non à petites cellules de stade avancé?

Short title: Chemotherapy rechallenge in advanced NSCLC

Titre court: La ré-introduction de chimiothérapie dans le CBNPC de stade avancé

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Abstract

Background:

Despite recent progress, non-small cell lung cancer (NSCLC) first-line treatment remains a platinum-based doublet in most cases. No guidelines exist beyond third line. Chemotherapy rechallenge is an option, but little data is available in NSCLC. Our study aims to describe patients who underwent chemotherapy rechallenge while assessing its efficacy and safety.

Methods:

Consecutive patients with advanced-stage NSCLC receiving first-line treatment in Tenon hospital in 2011 were included, with a 5-year follow-up. Patients were analyzed according to chemotherapy rechallenge or not. Chemotherapy rechallenge was defined as re-initiation of a previously administered chemotherapy agent at any point in the treatment sequence, with at least one treatment regimen between first use and rechallenge.

Results:

Of 149 patients, 18 underwent chemotherapy rechallenge (12%). They were younger (56 *vs.* 61 years, p=0.04), mostly women (61% *vs.* 30%, p=0.02), with lepidic adenocarcinoma (23% *vs.* 3.5%, p=0.03), a better general state of health (100% performance status 0–1 *vs.* 74%, p=0.04), and fewer cardiovascular comorbidities (16% *vs.* 42%, p=0.04). They were more likely to have received a receptor tyrosine kinase inhibitor treatment (89% *vs.* 43%, p=0.0003). Progression-free survival was longer at first use than at rechallenge (median 9.2 *vs.* 2.7 months, p=0.002). No increased toxicity was observed at rechallenge compared to first use. Finally, a subsequent line of treatment was given after rechallenge in 61% of the patients.

Conclusion:

Patients eligible for chemotherapy rechallenge were those with good prognostic factors. Chemotherapy rechallenge may provide a well-tolerated additional line of treatment, with decreased efficacy compared to its first application.

Keywords

NSCLC, chemotherapy, rechallenge

Résumé

Introduction:

Malgré des progrès récents, le traitement de première ligne des cancers broncho-pulmonaires non à petites cellules (CBNPC) reste majoritairement un doublet à base de platine. Il n'existe pas de recommandations après la troisième ligne. La ré-introduction de chimiothérapie est une option, mais peu de données sont disponibles. Notre étude vise à décrire les patients ayant eu une ré-introduction de chimiothérapie, ainsi que sa faisabilité et sa tolérance.

Méthodes:

Les patients consécutifs avec un CBNPC de stade avancé ayant reçu un traitement de première ligne à l'hôpital Tenon en 2011 ont été inclus. Ceux ayant eu une ré-introduction de chimiothérapie ont été comparés aux autres. Celle-ci était définie par la ré-utilisation d'un agent de chimiothérapie utilisé antérieurement, avec au moins une ligne entre la primo-utilisation et la ré-utilisation.

Résultats:

Parmi 149 patients, 18 ont eu une ré-introduction de chimiothérapie (12%). Il étaient plus jeunes (56 ans *vs.* 61, p=0.04), de sexe féminin (61% *vs.* 30%, p=0.02), avec un adénocarcinome lépidique (23% *vs.* 3.5%, p=0.03), un meilleur état général (PS 0–1: 100% *vs.* 74%, p=0.04) et moins de comorbidités cardiovasculaires (16% *vs.* 42%, p=0.04). La survie sans progression était plus longue à la primo-utilisation qu'à la ré-introduction (médiane 9.2 mois *vs.* 2.7, p=0.002). Il n'y avait pas de surcroît de toxicité à la ré-introduction. Enfin, une ligne supplémentaire était possible après ré-introduction chez 61% des patients.

Conclusion:

La ré-introduction de chimiothérapie fournit une ligne supplémentaire de traitement bien tolérée, avec une efficacité moindre par rapport à la primo-utilisation.

Mots-clés

CBNPC, chimiothérapie, ré-introduction

Introduction

Despite recent progress, mortality from non-small-cell lung cancer (NSCLC) remains high. During the last decade, therapeutic advances have included targeted therapies, mainly small-molecule tyrosine kinase receptor inhibitors (TKIs) [1]. However, these advances involve non-squamous NSCLC only, and targetable anomalies are harbored by a minority of NSCLC patients, for instance by 10 to 15% for *EGFR* [2], by around 5% for *ALK* [3], and by less than 2% for *ROS1*. More recently, immunotherapy in the form of checkpoint inhibitors, such as anti-PD-1 (Programmed Death 1) and anti-PD-L1 (Programmed Death Ligand 1) antibodies, have resulted in improved overall survival in second-line [4,5] for all comers and in first-line therapy, but only in patients with strong PD-L1 expression (>50%) [6].

In patients who are ineligible for TKIs or immunotherapy, which remains the majority of patients, standard first-line treatment consists of a platinum-based chemotherapy doublet combined with pemetrexed, paclitaxel, gemcitabine, or vinorelbine [7]. This standard is also recommended for progressive patients after first-line immunotherapy (more than 40% at six months of treatment). The use of either cisplatin or carboplatin depends on age, performance status, and comorbidities like chronic kidney or heart failure [8]. The benefit of a second-line treatment has been proven for pemetrexed [9], docetaxel [10], erlotinib [11], and immunotherapy [4]. Third-line treatment proves also effective for eligible patients [12,13], without any guidelines for treatment beyond this point.

Rechallenge with a conventional cytotoxic chemotherapy may be attempted if the disease has initially responded. Chemotherapy rechallenge is recommended in other cancer treatments. Pemetrexed rechallenge is indicated in malignant pleural mesothelioma when initial progression-free survival exceeds 12 months [14]. In disseminated relapsing small-cell lung cancer, rechallenge with a platinum doublet plus etoposide is considered an option in platinum-sensitive disease [15]. In the same manner, carboplatin rechallenge is common practice in platinum-sensitive relapsing ovarian cancer [16]. In metastatic castration-resistant prostate cancer, taxanes like docetaxel or cabazitaxel can likewise be reintroduced [17]. Following its introduction, immunotherapy became an additional treatment option; prior to its advent, chemotherapy rechallenge was practiced whenever other alternatives proved scarce. Chemotherapy rechallenge may still be worth considering, especially after progression on immunotherapy. Rechallenge with the various immunotherapy agents is presently being discussed. Little data currently exists on chemotherapy rechallenge in NSCLC. This work sought to better describe the characteristics of patients who

underwent chemotherapy rechallenge in a retrospective study, while assessing the efficacy and safety of this practice.

Patients and Methods

Inclusion criteria

All consecutive adult patients with advanced-stage NSCLC receiving first-line treatment from January 1, 2011, to December 30, 2011, in a French university hospital were included. Advanced-stage NSCLC was defined as Stage IIIB (ineligible for curative therapy) and Stage IV NSCLC according to the 7th edition of the International Association for the Study of Lung Cancer (IASLC) classification. First-line treatment consisted of either chemotherapy or TKI for patients with oncogenic addiction. Patients with metastatic relapse after previous curative surgery could be included. Neo-adjuvant or adjuvant chemotherapy as well as radiotherapy were accepted and were not considered as a first-line treatment. Patients list was generated from the chemotherapy prescription software.

Data collection

The following data were collected: age at diagnosis; gender; smoking history, namely number of pack-years, years of smoking, and current smoking status defined as never-smoker (<100 cigarettes in life), former smoker (>100 cigarettes in life but stopped >1 year) or current smoker (>100 cigarettes in life and either still smoking or stopped <1 year); performance status at diagnosis according to the ECOG scale; disease stage according to the 7th edition of the IASLC clinical TNM classification; occurrence of central nervous system (CNS) or sub-diaphragmatic metastases. Comorbidities like cardiovascular diseases (high blood pressure, stroke, myocardial ischemia, or arteriosclerosis obliterans), diabetes, neoplasms of other organs, chronic respiratory failure (CRF) or chronic obstructive pulmonary disease (COPD), chronic renal failure, HIV infection, psychiatric disorder, or alcoholism were recorded. Histological types were defined according to the 2004 WHO classification [18] as adenocarcinoma, squamous-cell carcinoma, large cell carcinoma, and sarcomatoid carcinoma. Adenocarcinoma subtypes were defined as acinar, mucinous, lepidic, papillary or undifferentiated. Oncogenic addiction was defined as *EGFR* mutation or *ALK* or *ROS1* rearrangement. *ALK* or *ROS1* rearrangements were detected by immunohistochemistry and confirmed by fluorescence *in situ* hybridization. *EGFR*, *KRAS*, *BRAF*, *HER2*, and *PI3KCA* mutations were screened by previously described techniques [19]. The number of treatment lines received by each patient, including targeted therapies, and for each line of treatment were recorded,

as well as its duration, how many cycles were administered (including maintenance if relevant), and whether the dose was reduced. Patients were treated in accordance with routine clinical care.

Chemotherapy rechallenge was defined as the re-use of a drug that had been administered earlier in the course of treatment and stopped due to disease progression or toxicity. At least one line of treatment had to have been received between first use and re-use. Resuming treatment after a break was not considered rechallenge, even if treatment was halted for a long period. The same agent had to be used, except for platinum-derived products like cisplatin or carboplatin. Re-using an agent as monotherapy when it was first used in a platinum-based doublet was considered as a rechallenge (Fig. 1). Rechallenge with targeted therapy was not taken into account for this study.

The following data were collected for each chemotherapy rechallenge: treatment duration, performance status at rechallenge, number of previous lines, use as maintenance or not, progression-free survival at first-use and at rechallenge, line of treatment after rechallenge, and toxicity (hematological, gastrointestinal, or other) graded according to the WHO classification. Rechallenged patients were divided into five groups: platinum-based doublet or triplet (cisplatin/carboplatin + other agent ± bevacizumab), or pemetrexed, gemcitabine, paclitaxel and vinorelbine monotherapy.

Statistical analyses

Patients were analyzed according to whether they received chemotherapy rechallenge or not. Continuous variables were expressed as median and associated range [min–max]. Categorical variables were expressed as percentages. Comparisons between non-parametric continuous variables were conducted using the Mann-Whitney test. Comparisons between categorical variables were conducted by means of the the Chi-squared test or Fisher's exact test when the number of observations was less than 5. Progression-free survival rates at first use and at rechallenge were compared with the Wilcoxon test. Toxicity at first use and at rechallenge were compared using McNemar's Chi-squared test. Results were considered statistically significant when $p < 0.05$. Analyses were performed with SPSS 20.0 (IBM France) software. Data were reviewed by a statistician.

Ethics and regulations

The local database was declared, and it obtained authorization from the bodies that monitor the application of data privacy laws according to French guidelines.

Results

Patients characteristics

In 2011, 149 patients underwent first-line treatment for advanced-stage NSCLC, in our French university hospital. Median age was 60 years [36–87]. Overall, 66% of the patients were men, 47.5% were smokers, 39% were former smokers, and 8.5% were never-smokers. Histology showed 66.5% had adenocarcinoma, 21% squamous-cell carcinoma, 10.5% large cell carcinoma, and 2% sarcomatoid carcinoma. Among non-squamous NSCLCs, 6.5% were *EGFR* mutated, 16% *KRAS* mutated, 0.5% *BRAF* mutated, and 5% harbored *ALK* rearrangement. No *ROS1* rearrangement was observed. The mutation status of 11 patients (7.5%) was unknown. Regarding comorbidities, 39% of the patients had at least one cardiovascular comorbidity, 11.5% had diabetes, 14.5% had a current neoplasm or had had a prior neoplasm in another organ, and 11.5% had either CRF or COPD. Most patients were in good general condition (77% had a performance status of 0–1) at first-line treatment. Patients received a mean of 2.8, or a median of 2.0 [1–11], treatment lines, and almost half of them received TKI (regardless of mutation status) in accordance with current guidelines.

Characteristics of chemotherapy rechallenge

Altogether, 18 of 149 patients (12%) underwent chemotherapy rechallenge: 13 had asingle rechallenge and five two rechallenges with different agents. Hence, 23 distinct rechallenges were noted across our five groups, namely eight rechallenges with a platinum-based doublet (carboplatin, *n=5;* cisplatin, *n=3*), seven with pemetrexed, four with gemcitabine, three with paclitaxel and one with vinorelbine. No rechallenge with docetaxel was observed.

The median number of cycles was 4 [1–16] at both first use and rechallenge. For platinum-based doublets, the median cycle number at rechallenge was 4 [2–5] *versus* 4 [4–5] at first use. The median cycle number was lower at rechallenge than at first use for pemetrexed (3 [2–8] *vs.* 7 [1–16]) and for gemcitabine (2 [1–16] *vs.* 5.5 [4–8]). At rechallenge, patients were mostly at their fourth line of treatment (4 [3–6]) and mostly (78%) with a favorable PS (0-1). A subsequent line of treatment was feasible in 61% of patients. Pemetrexed and gemcitabine were initially used as maintenance therapy in respectively 43 and 50% of the patients (Table 1).

Characteristics of patients according to chemotherapy rechallenge

In univariate analyses, rechallenged patients were younger (median age 56 *vs.* 61 years, p = 0.04), were more often women (61% *vs.* 30.5%, p = 0.021), had fewer cardiovascular comorbidities (16.5% *vs.* 42%, p = 0.039), and had a better PS (100% 0–1 performance status at diagnosis *vs.* 74%, p = 0.043). Rechallenged patients tended to smoke less (median smoking duration of 30.5 *vs.* 40 years, p = 0.086). They received a higher number of treatment lines (median 5.0 *vs.* 2.0, p <0.0001) and received a targeted therapy (TKI) more often (89% *vs.* 43.5%, p = 0.0003), regardless of the presence or absence of oncogenic addiction. A higher proportion of adenocarcinomas was noted in rechallenged patients (72% *vs.* 65% other histology, p = 0.57) particularly of the lepidic subtype (23% *vs.* 3.5%, p = 0.037). No difference was found according to *EGFR* or *ALK* status. *KRAS*-mutated patients tended to be less rechallenged than others (1/24 rechallenged *vs.* 23/24 not rechallenged, p = 0.18) (tables 2 and 3). Regarding overall survival, patients with chemotherapy rechallenge had a longer overall survival (median 32.7 months *vs*. 13.4 months, p = 0.0002).

Progression-free survival at first use and rechallenge

Progression-free survival was shorter at rechallenge than at first use, namely 2.7 months [0.2–22.5] *versus* 9.2 months [2.7–31.6] (p = 0.0021). Progression-free survival by drug is given in Table 4.

Toxicity at first use and rechallenge

During the 23 rechallenges, at least one Grade-3 or -4 toxicity was observed in seven cases (30%) at first use and in five cases (24%) at rechallenge (p = 0.62). No toxicity gain was found at rechallenge compared to first use, except one case of Grade-4 neutropenia during paclitaxel rechallenge. Toxicity was mostly hematological. There was no Grade-3 or -4 neurological or renal toxicity (data not shown) nor iatrogenic death.

Discussion

Of 149 patients with advanced NSCLC, 18 underwent at least one chemotherapy rechallenge during treatment, with five being rechallenged twice. Hence, we recorded a total of 23 distinct rechallenges. The most commonly used drugs for rechallenge were pemetrexed and platinum-based doublets, which were given in, respectively, 7 and 8 cases. Rechallenge was carried out with gemcitabine in four cases, with paclitaxel in three cases, and with vinorelbine in one case.

Those who received chemotherapy rechallenge were characterized as patients exhibiting favorable prognostic factors. Younger age, female gender, better general condition, fewer comorbidities, and lepidic histological subtype have previously been shown to be associated with longer overall survival [20],[21],[22]. Our results are consistent with the study of Girard *et al.*, in which patients who benefited the most from third-line therapy were those with good prognostic factors [13].

KRAS-mutated patients received chemotherapy rechallenge less than others (1 patient rechallenged *vs.* 23 non-rechallenged, p = 0.18). *KRAS* mutation seems to be associated with worse survival for patients with advanced NSCLC [23], but its involvement in chemotherapy resistance is still debatable [24].

Progression-free survival at rechallenge was 2.7 months for all treatments, which was significantly shorter than progression-free survival at first use (9.2 months). For platinum-based doublets, progression-free survival at rechallenge was non-significantly shorter (3.0 months) than at first use (7.4 months), which might be due to lack of statistical power. For pemetrexed, progression-free survival was significantly shorter at rechallenge (2.5 months) than at first use (7.7 months). The longest progression-free survival at rechallenge was obtained with paclitaxel (5.4 months) and the shortest with gemcitabine (1.8 months).

Petrelli *et al.* reported a progression-free survival of 3.9 months with platinum/pemetrexed rechallenge in a pooled analysis of 11 studies [25]. In a retrospective study, when pemetrexed rechallenge was given as monotherapy or as combination therapy with a platinum salt, it showed a progression-free survival of 3.8 months in a second-line setting only [26]. Median age was similar and patients were in good general condition (97% had a performance status of 1). In both studies, patients were rechallenged earlier than in ours (second line *vs.* fourth), which may explain why they observed longer progression-free survival. In another retrospective study, 25 patients had pemetrexed rechallenge [27]. Progression-free survival was shorter (1.5 month). The patients were

mostly men (64%) and mostly had a performance status of 2 (60%). The discrepancies between all these studies may be due to their retrospective design and small sample sizes.

In our study, Grade-3 or -4 toxicities did not increase at rechallenge except for one patient with paclitaxel (Grade-4 neutropenia). A rise in toxicity could have been expected, since chemotherapy rechallenge is practiced on heavily pre-treated patients. For example, docetaxel rechallenge in metastatic castration-resistant prostate cancer is risky, owing to cumulative neurotoxicity [17]. No cumulative toxicity was found in our study, especially no renal toxicity.

A further line of treatment was administered after rechallenge in 61% of our patients. The rechallenge was not, therefore, their last line of treatment, which suggests that their general condition permitted them to receive the additional treatment line. PFS was shorter at rechallenge than at first-use in our study. These results are coherent with other studies describing a decreased disease control between first-line and subsequent lines [28]. This retrospective study does not answer the question of whether rechallenge proves cost-effective or of benefit in terms of quality of life. Our study reflects the realities of routine practice in this patient population. Immune checkpoint inhibitors are considered a new option and may delay the need for chemotherapy rechallenge in the course of the disease. Our study's limitations were its retrospective design, single-center data, small sample size, and heterogeneity of administered treatments (including those administered twice). However, our findings may further improve our understanding of chemotherapy rechallenge.

Conclusion

Of 149 patients with advanced NSCLC, 18 (12%) underwent chemotherapy rechallenge. These patients had good prognostic factors. Progression-free survival was shorter at rechallenge than at first use. No toxicity gain was noted at rechallenge. Thus chemotherapy rechallenge should be considered a treatment option in suitable patients.

Acknowledgments

The authors wish to thank Dr. Pierre Levy for his review of the statistics, Mr. J. Rose for his help generating the list of patients, Ms. V. Poulot and Ms. L. Pinon for their help with molecular and histological data, and Ms. N. Mathiot and Ms. G. Pontdeme for their overall contribution to this work.

Figure 1: Illustration of chemotherapy rechallenge in the course of treatment

Figure 1: The x-axis represents treatment course. Re-use of a platinum salt was considered as platinum salt rechallenge, regardless of the drug it was combined with. Re-use of an agent as monotherapy when it was first used in a platinum-based doublet was considered as a rechallenge.

307 **Table 1: Description of chemotherapy rechallenge**

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Variable	Characteristics of rechallenge according to drug					
	All ***n=23***	**Platinum + X** ***n=8***	**Pemetrexed** ***n=7***	**Gemcitabine** ***n=4***	**Paclitaxel** ***n=3***	**Vinorelbine** ***n=1***
Number of cycles at first use						
Median	4	4	7	5.5	4	5
[range]	[1–16]	[4–5]	[1–16]	[4–8]	[4–4]	[5–5]
Initially used as maintenance	NA*	NA	3 (43)	2 (50)	NA	NA
Performance status at rechallenge						
0 - 1	18 (78)	7 (87.5)	5 (71)	3 (75)	100 (0)	0 (0)
2	5 (22)	1 (12.5)	2 (29)	1 (25)	0 (0)	1 (100)
Histology						
Adenocarcinoma	17 (74)	6 (75)	6 (86)	2 (50)	3 (100)	0 (0)
Squamous cell carcinoma	4 (17)	2 (25)	0 (0)	1 (25)	0 (0)	1 (100)
Large cell carcinoma	1 (4.5)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)
Sarcomatoid carcinoma	1 (4.5)	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)
Number of lines at rechallenge						
Median	4	4	5	4.5	3	5
[range]	[2–6]	[2–6]	[2–6]	[3–5]	[2–4]	[5–5]
Number of cycles at rechallenge						
Median	4	4	3	2	6	2
[range]	[1–16]	[2–5]	[2–8]	[1–16]	[5–7]	[2–2]
Subsequent line of treatment after rechallenge	14 (61)	6 (75)	4 (57)	2 (50)	2 (67)	0 (0)

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310 *NA= not applicable

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Table 2: Histological subtypes according to rechallenge of treatment

Variable	Overall *n=99* n (%)	Rechallenged *n=13* n (%)	Not rechallenged *n=86* n (%)	Univariate analysis (p)
Adenocarcinoma histologic subtype				
Acinar	26 (26.5)	3 (23)	23 (26.5)	p = 0.74
Mucinous	14 (14)	3 (23)	11 (13)	p = 0.42
Lepidic	6 (6)	3 (23)	3 (3.5)	**p = 0.037**
Papillary	3 (3)	0 (0)	3 (3.5)	p = 1.0
Undifferentiated	34 (34.5)	3 (23)	31 (36)	NC*
Unknown	16 (16)	1 (8)	15 (17.5)	NC

*NC = not calculated

Comparisons between categorical variables were conducted with the Chi-squared test or Fisher's exact test when n < 5.

Table 3: Characteristics of rechallenged and non-rechallenged patients

Variable	Rechallenged *n = 18* n (%) or median [range]	Not rechallenged *n = 131* n (%) or median [range]	Univariate analysis (p)
Age (years)	56 [42–72]	61 [36–87]	**p = 0.04**
Gender			
Male	7 (39)	91 (69.5)	**p = 0.021**
Female	11 (61)	40 (30.5)	
Smoking history			
Non-smoker	2 (11)	11 (8.5)	p = 0.87
Former smoker	8 (44.5)	50 (38)	
Current smoker	8 (44.5)	63 (48)	
Pack-years	39 [0–92]	40 [0–150]	p = 0.21
Smoking duration (years)	30.5 [0–53]	40 [0–64]	p = 0.086
Histology			
Adenocarcinoma	13 (72.5)	86 (65)	p = 0.57
Squamous cell carcinoma	3 (16.5)	28 (21.5)	p = 0.77
Large cell carcinoma	1 (5.5)	15 (12)	p = 0.69
Sarcomatoid carcinoma	1 (5.5)	2 (1.5)	NC
Mutations (*)			
EGFR mutation	2 (11)	8 (6)	p = 0.61
ALK rearrangement	1 (5.5)	6 (4.5)	p = 1.0
KRAS mutation	1 (5.5)	23 (17.5)	p = 0.18
BRAF mutation	0 (0)	1 (1)	NC
No mutation	10 (55.5)	55 (42)	NC
Initial stage			
IA–IIIA	2 (11)	18 (14)	p = 1.0
IIIB/IV	16 (89)	112 (86)	
Metastases at diagnosis			
CNS	3 (16.5)	32 (24.5)	p = 0.56
Subdiaphragmatic	6 (33.5)	47 (36)	p = 0.84
Comorbidities			
Yes/No	9 (50)/9 (50)	85 (65)/46 (35)	p = 0.22
Cardiovascular comorbidities	3 (16.5)	55 (42)	**p = 0.039**
Diabetes	1 (5.5)	16 (12)	p = 0.7
Other neoplasm	2 (11)	20 (15.5)	p = 1.0
CRF/COPD	2 (11)	15 (11.5)	p = 1.0
Chronic renal failure	0 (0)	3 (2.5)	p = 1.0
HIV	1 (5.5)	1 (1)	p = 0.23
Psychiatric comorbidity	4 (22)	8 (6)	**p = 0.04**
Alcoholism	0 (0)	5 (4)	p = 1.0
Performance status at diagnosis			
0–1	18 (100)	97 (74)	**p = 0.043**
2–4	0 (0)	23 (17.5)	
Number of treatment lines			
Mean	5.5	2.4	**p < 0.0001**
1–3 lines	2 (11)	99 (76)	
> 3 lines	16 (89)	32 (24)	
Targeted therapy (TKI) received	16 (89)	57 (43.5)	**p = 0.0003**
No oncogenic addiction	13 (72)	44 (34)	**p = 0.044**

Comparisons between non-parametric continuous variables were conducted with the Mann-Whitney test. Comparisons between categorical variables were conducted with the Chi-squared test or Fisher' exact test when n < 5. **(*)** Mutational status research doesn't include patients with squamous histology (*n=31*). Among patients with non-squamous histology, 11 have unknown mutational status.a

Table 4: Progression-free survival according to first use and rechallenge for each drug

Variable	Rechallenge according to drug					
	All ***n=23***	**Platinum+X** ***n=8***	**Pemetrexed** ***n=7***	**Gemcitabine** ***n=4***	**Paclitaxel** ***n=3***	**Vinorelbine** ***n=1***
PFS at first use (months) Median [min–max]	9.2 [2.7–31.7]	7.4 [4.3–15.7]	7.7 [2.7–12.8]	9.2 [8.7–11.5]	7.1 [4.3–31.7]	15.7 [NA]
PFS at rechallenge (months) Median [min–max]	2.7 [0.25–22.5]	3.0 [1.0–22.5]	2.5 [1.0–6.6]	1.8 [0.25–12.1]	5.4 [4.5–6.3]	4.5 [NA]
Wilcoxon test	**p = 0.002**	p = 0.16	**p = 0.027**	NA*	NA	NA

*NA = not applicable; PFS = progression-free survival

Progression-free survival at first use and at rechallenge were compared with the Wilcoxon test.

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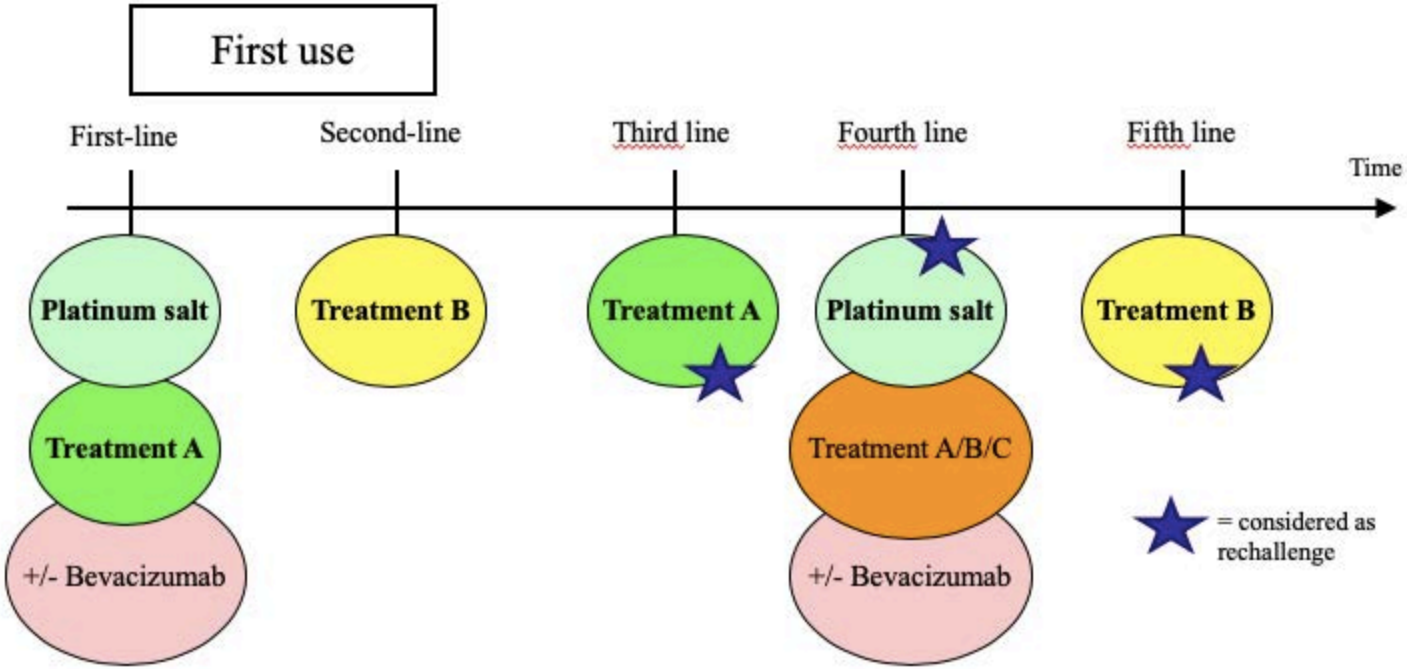

Figure 1: Representation of chemotherapy rechallenge in the course of treatment

The x-axis represents treatment course. Re-use of a platinum salt was considered as platinum salt rechallenge, regardless of the drug it was combined with. Re-use of an agent as monotherapy when it was first used in a platinum-based doublet was considered as a rechallenge.