Effect of prior immunotherapy on the efficacy of chemotherapy in advanced non-small cell lung cancer: A retrospective study

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Abstract
Background: The effect of the sequential combination of chemotherapy and immune checkpoint inhibitors (ICIs) remains unclear. Here, we evaluated the efficacy of different chemotherapy regimens administered after ICIs in advanced non-small cell lung cancer (NSCLC), compared to the same regimens administered without previous ICIs.

Methods: We retrospectively included all patients treated between 2015 and 2019 for an advanced NSCLC, receiving a salvage chemotherapy just after ICI (CAI group) comparing them to ICI naive patients (CWPI group) undergoing the same chemotherapy at Bordeaux University Hospital. The primary outcome was the time to treatment discontinuation (TTD), and secondary endpoints were overall survival (OS) and overall response rate (ORR).

Results: A total of 152 patients were included, with 34/23 (CAI/CWPI) receiving paclitaxel/bevacizumab (PB), 24/11 paclitaxel (P), 27/12 gemcitabine (G) and 6/15 pemetrexed (PE). Characteristics were comparable, except for CAI treated with PB (more patients with an ECOG PS ≤1 [p < 0.001]). Median number of lines received was higher in CAI for all groups. There was no difference between CAI and CWPI for TTD, OS and ORR. However, PB was associated with a nonsignificant increase in OS in the CAI group (HR = 0.65; 95% CI: 0.38–1.2, p = 0.17).

Conclusion: Our data showed no difference in TTD, OS and ORR regardless of chemotherapy, but a trend towards an increased OS with PB when given after an ICI, while patients received chemotherapy later in the CAI group. This suggests that a sequential combination of ICI followed by chemotherapy could be an interesting strategy in advanced NSCLC for selected patients.

KEYWORDS
angiogenesis inhibitors, immune checkpoint inhibitor, non-small cell lung cancer, salvage chemotherapy, sequential treatment

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized the management of non-small cell lung cancer (NSCLC).¹ Nevertheless, chemotherapy remains essential. Through its immunogenic properties, chemotherapy is able to potentialize the effect of immunotherapy.² Indeed, chemotherapy induces immunogenic death and modulates the immunosuppressive landscape of the tumor microenvironment. Therefore, ICIs have been successfully developed combined with chemotherapy as a first-line treatment with almost half of the patients alive at 2 years.³ The synergistic
effect of both molecules is well established. However, the potential effect of their sequential combination remains unclear. Sequential combination could be an interesting alternative, to challenge different immune populations in a complementary way.

Previous data suggest that some patients experienced an unexpected prolonged overall survival (OS) under salvage chemotherapy after nivolumab exposure. Studies frequently reported an increased antitumor effect especially for overall response rate (ORR). However, impact on treatment duration and survival exhibits controversial results from previous studies. Furthermore, most studies are retrospective, with a small number of patients and historical comparisons. The largest one including Japanese patients, showed a significant improvement in ORR (ratio 1.71; \( p = 0.004 \)) after adjustment for patient characteristics when chemotherapy was administered after ICIs. However, there was no difference in progression-free survival (PFS) or OS.

Herein, we aimed to evaluate the efficacy of different chemotherapy regimens, administered after an ICI in advanced NSCLC, compared to the same regimens administered without previous ICIs.

METHODS

Patients

We retrospectively included all consecutive patients with stage III/IV histologically proven NSCLC diagnosed between January 2015, and December 2019, inaccessible to a local therapy, treated at the Bordeaux University Hospital (France) who received at least one infusion of chemotherapy of interest. We studied four chemotherapy regimens: pemetrexed (PE), gemcitabine (G), weekly paclitaxel (P) and paclitaxel plus bevacizumab (PB). We did not study docetaxel because this chemotherapy is not commonly used in our institution due to its worse toxicity profile compared to paclitaxel.

Eligible patients could be treated after a relapse. Patients treated with more than one studied chemotherapy regimen were only included in the group of the first salvage chemotherapy. We excluded patients treated with a combination of immunotherapy and chemotherapy as first-line treatment, with pemetrexed as maintenance therapy, or treated for another cancer.

The following data were collected at inclusion: demographic and anthropometric characteristics, smoking status, histology, TNM (eighth classification), PD-L1 status, mutational status and presence of brain/liver metastasis.

Clinical endpoints

The primary outcome was the time to treatment discontinuation (TTD) (from the first day of chemotherapy to the treatment discontinuation or death). Secondary endpoints were OS (from the first day of chemotherapy of interest to death or lost to follow-up), PFS (from the first day of chemotherapy of interest until progression or death), and ORR (corresponding to a complete or partial response [RECIST 1.1 criteria]). Disease control rate (DCR) (percentage of patients achieving a complete, partial or stable disease) was also investigated.

Statistical analysis and ethical considerations

All statistical tests were performed with a type I error rate of 5%. Qualitative variables were described with numbers and percentages, and quantitative variables with numbers of nonmissing data, median with first and third quartiles or range. Survival variables were described with survival probabilities and curves using Kaplan–Meier method. The qualitative variables were compared with a Chi2, corrected Chi2 or nonparametric Fisher’s exact test. The quantitative variables were compared with a Student t-test (parametric) or a Wilcoxon test (nonparametric). The survival endpoints were compared using a log-rank test. Cox regression models were used to adjust on stratification factor.

All statistical analyses were performed using R Statistical Software (version 4.1.0; R Foundation for Statistical Computing). The study was conducted in accordance with French legislation and ethical codes. This work complies to the protection of personal health data and the protection of privacy with the framework of application provided for by article 65-2 of the amended Data Protection Act and the general data protection regulations and was registered with the following number CHUBX2020RE0270. The study was designed according to the STROBE guidelines.

RESULTS

Patient characteristics in the whole cohort

We screened 280 patients of which 152 were included (Figure 1), with 91 (59.9%) receiving chemotherapies of interest after ICI (CAI) and 61 (40.1%) the same chemotherapy regimen without previous ICI (CWPI). The most frequent chemotherapies were paclitaxel/bevacizumab (\( n = 57, 37.4\% \)), gemcitabine (\( n = 39, 29.6\% \)), paclitaxel (\( n = 35, 26.4\% \)) and pemetrexed (\( n = 21, 6.6\% \)) (Figure 1). The median number of treatment received before the different studied chemotherapies was 2. At chemotherapy initiation, 38 (25.0%) and 67 (44.1%) patients had liver and cerebral metastasis, respectively. The median OS (mOS) of the cohort was 6.5 (2.7–14.6) months. The comparison of data from the different chemotherapy subgroups, without stratifying them in CAI or CWPI, showed that PB was associated with higher TTD, PFS and OS than other chemotherapy subgroups (\( p <0.001 \)).
In the CAI group, nivolumab was the most widely used ICI (n = 44, 48.9%), followed by pembrolizumab (n = 24, 26.7%) and atezolizumab (n = 22, 24.4%). ICIs were given in the majority as second- (72.9%) or third-line (17.7%) and 82.5% of patients had an ECOG PS 0/1 before starting immunotherapy. Median TTD (mTTD) under ICI treatment was 2.7 months (1.9–6.3). There was no correlation between response duration under ICI and PD-L1 status (p = 0.71).

After failure of studied chemotherapies, 38 (42%) patients in the CAI group received subsequent therapy, with 17 (19%) ICI rechallenges with a mPFS of 3.2 (1.7–4.6) months. In the CWPI group, 24 (39%) patients received another line after, including 20 (33%) patients receiving an ICI, with a mPFS of 3.9 (1–8.1) months.

The median follow-up duration from chemotherapy initiation was 6.5 (2.7–14.6) months. At the date of the last follow-up, 35 (23%) patients were still alive: 26 (74.3%) patients (CAI) and nine (25.7%) patients (CWPI). Among them, 19 (12.5%) patients remained under treatment, with six (10.5%) patients who were still receiving the studied chemotherapy in the PB subgroup: four in the CAI and two in the CWPI groups.

Considering all patients in both groups regardless of the type of chemotherapy, there was no difference for TTD (3.0 vs 1.9 months respectively; HR = 0.88, 95% CI: 0.63–1.20; p = 0.44), PFS (3.7 vs 3.1 months; HR = 0.91, 95% CI: 0.65–1.30; p = 0.58) and ORR (23% versus 10%; p = 0.24).

ICI administration was correlated with a better outcome, with a mOS from diagnosis of 26.1 months in the cohort unexposed to ICI (HR = 0.52, 95% CI: 0.35–0.75; p < 0.001).

**Characteristics of chemotherapy subgroups**

Baseline characteristics of each group are summarized in Table 1. Patients were older in the CWPI group receiving P (p < 0.001). Regarding the PS, patients receiving PB had a better general condition in the CAI group compared to the CWPI group (p < 0.001). For the other chemotherapy groups, there were no statistically significant differences for PS (P: p = 1.0; G: p = 0.2; PE: p = 1.0).

Other clinical parameters were well balanced between subgroups. The median number of lines received was higher in all CAI groups.

In CAI groups, median duration between last IPI infusion and first following cycle of chemotherapy were 21 (14–28) (PB), 21 (15–26) (P), 34 (32–46) (PE) and 16 (14–22) (G) days.

**Efficacy of studied chemotherapies**

mTTD were not significantly different between CAI and CWPI in all the chemotherapy subgroups (PB: HR = 0.84, 95% CI: 0.48–1.50; p = 0.55; P: HR = 0.93, 95% CI: 0.44–1.90; p = 0.83; PE: HR = 0.91, 95% CI: 0.35–2.40; p = 0.84; G: HR = 0.74, 95% CI: 0.37–1.50; p = 0.42) (Table 2, Figure 2).

Evaluation of the response was available for 71 patients in the CAI and 49 patients in the CWPI groups. ORR was
| Type of chemotherapy | Paclitaxel-bevacizumab | Paclitaxel | Pemetrexed | Gemcitabine |
|----------------------|------------------------|-----------|------------|-------------|
|                     | n = 57                 | n = 35    | n = 21     | n = 39      |
| n = 152              | CAI (n = 34)           | CAI (n = 24) | CAI (n = 6) | CAI (n = 27) |
|                      | CWPI (n = 23)          | CWPI (n = 11) | CWPI (n = 15) | CWPI (n = 12) |
| Median age (years) (Q1–Q3) | 57.5 (53–62)          | 59 (50–65) | 63 (53.5–79) | 61 (68.5–70.2) |
|                      | 66 (60.5–72.5)         | 61 (58.5–66) | 64.5 (56.8–70.5) |
| Male Gender          | 22 (64.7)              | 15 (62.5) | 3 (50)     | 19 (70.4)  |
|                      | 16 (69.6)              | 7 (63.6) | 7 (46.7) | 5 (41.7) |
| Smoking status       | 2 (5.9)                | 0 (0)    | 0 (0)      | 0 (0)      |
|                      | 1 (4.3)                | 1 (9.1)  | 4 (26.7)   | 2 (7.4)    |
|                      | 28 (82.4)              | 19 (79.2) | 6 (100) | 20 (74.1) |
|                      | 15 (65.2)              | 9 (81.8) | 6 (40) | 6 (50) |
|                      | 4 (11.8)               | 5 (20.8) | 2 (13.3) | 5 (18.5) |
| Histologic subtype   | 8 (23.5)               | 3 (27.3) | 1 (6.7) | 12 (44.4) |
|                      | 2 (5.9)                | 2 (8.3) | 8 (53.3) | 1 (3.7) |
|                      | 21 (91.3)              | 2 (18.2) | 1 (6.7) | 4 (33.3) |
|                      | 32 (94.1)              | 2 (8.7) | 6 (100) | 26 (96.3) |
|                      | 2 (2–4)                | 1 (1–2) | 2 (1–3) | 3 (1–5) |
| Line of chemotherapy of interest | 3.5 (3–7) | 5 (53.3) | 9 (33.3) | 1 (8.3) |
|                      | 2 (2–4)                | 1 (1–2) | 5 (33.3) | 7 (25.9) |
|                      | 2 (2–4)                | 4 (3–5) | 2 (1–3) | 3 (1–5) |
|                      | <1%                    | 14 (41.2) | 6 (16.7) | 4 (14.8) |
|                      | 1%–49%                 | 8 (23.5) | 4 (66.7) | 8 (29.6) |
|                      | >50%                   | 5 (14.7) | 5 (33.3) | 8 (66.6) |
|                      | Unknown                | 7 (20.6) | 5 (53.3) | 7 (25.9) |
|                      | EGFR (%)               | 0 (0)    | 0 (0)     | 0 (0)     |
|                      | ALK (%)                | 0 (0)    | 0 (0)     | 0 (0)     |
|                      | KRAS (%)               | 14 (41.2) | 3 (13.0) | 1 (7.1) |
|                      | BRAF (%)               | 2 (5.8) | 4 (17.4) | 1 (7.1) |
|                      | ROS (%)                | 1 (2.9) | 0 (0)    | 0 (0)    |
|                      | STK11 (%)              | 2 (5.8) | 1 (14.3) | 0 (0)    |
|                      | ECOG PS                | ≤1       | 27 (79.4) | 8 (53.3) |
|                      |                       | >1       | 7 (20.6) | 8 (33.3) |

(Continues)
The most important challenge in advanced NSCLC is the first-line setting, to rapidly and sustainably control cancer disease. With combinations arising in first-line, there is a crucial need to study efficient therapeutic strategies for subsequent lines, to improve survival while preserving quality of life. However, chemotherapy responses commonly used as first-line treatment are historically associated with low response rates. Here, we investigated clinical reports of seemingly increased responses to chemotherapy in a post-immunotherapy setting.

Our "real-life" study, evaluating all available ICIs in France, showed no significant differences in terms of TTD, PFS, and OS when comparing CAI and CWPI patients. Nevertheless, PB chemotherapy administered after ICI tended to increase OS and TTD, although these results were not significant. Interestingly, OS were comparable between groups, while CAI patients experienced this treatment in a more advanced line. This could be partly explained by the 30% crossover rate to ICI in the CAI group. This suggests that chemotherapy is associated with low OS, particularly in the absence of contraindications without compromising its outcome.

Our discussion emphasizes the importance of chemotherapy in advanced NSCLC. However, the addition of prior immunotherapy does not significantly affect the outcome. There was no evidence of a prolonged response to chemotherapy due to immunotherapy, but these swimmers plots showed that some patients could experience an unexpected prolonged response to chemotherapy even in unresponsive tumor for immunotherapy.
comparison between all these studies is difficult due to the heterogeneity between chemotherapy and ICI regimens. Furthermore, most of them were performed on Asian and/or small cohorts.

The question of a potential “post-immunotherapy effect” has also been raised in head and neck carcinoma, where Saleh et al. have reported an ORR of 30%, three to five times higher than historical trials. In metastatic

TABLE 2  Survival and response in the different chemotherapy subgroups

| Chemotherapy | Treatment | mTTD (months) | mOS (months) | mPFS (months) | ORR (%) | DCR (%) |
|--------------|-----------|---------------|--------------|---------------|---------|---------|
| Paclitaxel-Bevacizumab | CAI (n = 34) | 5.5 | 18.3 | 6 | 43 | 90 |
| | CWPI (n = 23) | 3.3 | 6.6 | 4.1 | 39 | 78 |
| Paclitaxel | CAI (n = 24) | 1.45 | 4.5 | 3.25 | 24 | 59 |
| | CWPI (n = 11) | 2.8 | 5.8 | 3.1 | 10 | 60 |
| Pemetrexed | CAI (n = 6) | 2.25 | 8.6 | 2.95 | 33 | 50 |
| | CWPI (n = 15) | 1.4 | 3.8 | 2.1 | 18 | 54 |
| Gemcitabine | CAI (n = 27) | 1.6 | 5.7 | 2 | 18 | 59 |
| | CWPI (n = 12) | 1.5 | 4.05 | 2.35 | 10 | 33 |

Abbreviations: CAI, chemotherapy of interest after ICI; CWPI, chemotherapy regimen without previous ICI; mTTD, median time to treatment discontinuation; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; DCR, disease control rate.
urothelial carcinoma, Szabados et al. have found an ORR of 64% for patients experiencing chemotherapy after immunotherapy versus 21% for patients experiencing chemotherapy after failure of first-line platinum-based therapy.\textsuperscript{16} However, all these studies were performed on small cohorts, with different chemotherapy regimens, and with probably an effect according to tumor type.

There is a strong rationale to study the combination between chemotherapy and ICI, due to the important interplay between these therapeutic modalities. Indeed, immunotherapy sensitizes tumors to chemotherapy by prior activation of the immune system, which will be able to better react to chemotherapy-induced antigen release.\textsuperscript{17} However, chemotherapy could also resensitize to further ICI therapy. Indeed, chemotherapy agents can modulate immune cells, increasing antitumor response while inhibiting some immunosuppressive cells.\textsuperscript{2} The optimal timing of PD-1/PD-L1 blockade and chemotherapy, concomitant or sequential, remains unknown beyond the first-line setting. Some preclinical data comparing both strategies in mouse models reported an increased antitumor activity for chemotherapy when given before ICIs, compared to concomitant chemoimmunotherapy.\textsuperscript{18} More investigations have to be done to study such a strategy in a human setting and to determine which patient would benefit from a sequential treatment.

Our study showed that the association PB after immunotherapy tended to increase OS. VEGF, which mediates angiogenesis, inhibits antitumor immune cells while promoting immunosuppressive cells.\textsuperscript{19} Some studies in small cohorts assessing combination of antiangiogenic drugs with docetaxel after ICI showed an ORR between 36%\textsuperscript{20} and 50%.\textsuperscript{21} There are few data on the specific efficacy of PB following ICI. In a cohort of 33 patients, Bilger et al found an ORR of 42%, a PFS of 6.2 months and a 1-year OS not reached, consistent with our results.\textsuperscript{22} In comparison, the phase III trial Ultimate evaluating the association between paclitaxel and bevacizumab showed an ORR of 22.5%, a PFS of 5.4 months and an OS of 9.9 months.\textsuperscript{13} Our study, which is the first to compare PB administered after or without an

\begin{figure}
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\caption{Kaplan–Meier estimates of overall survival (OS) according to the different types of chemotherapy regimen. HR, hazard ratio; CAI, chemotherapy of interest after ICI; CWPI, chemotherapy regimen without previous ICI; mOS, median overall survival.}
\end{figure}
ICI, confirms that this combination is a valuable strategy after ICI failure.

The “post-immunotherapy effect” could also be explained by a transient concomitant effect due to the long-term binding of antibodies to lymphocytes,\textsuperscript{23} and extended half-life of ICI (25–27 days according to molecule).\textsuperscript{24} Immunotherapy antibodies are still circulating at the beginning of chemotherapy. Another strategy could be to continue immunotherapy beyond progression, associated to a new line of chemotherapy, to maintain an immunological pressure on tumor cells, chemotherapy being effective on tumor clones that are resistant to the immune response. Such strategies have been evaluated in Hodgkin’s lymphoma ($n = 30$) showing an effect of continuing immunotherapy with chemotherapy.\textsuperscript{25} This continuation strategy is currently being evaluated in NSCLC (NCT03656094, NCT03083808).

With the improvement of patient survival, some of them benefit from a rechallenge of immunotherapy alone. Therefore, knowing the efficacy of chemotherapy after ICI as monotherapy remains topical. Finding the better sequential strategy to prioritize one drug among others is challenging. In patients with melanoma, such strategies were studied, using ipilimumab combined to nab-paclitaxel/bevacizumab\textsuperscript{26} with a 1-year improvement in mOS. However, the difference was not significant because of the small number of patients ($n = 24$). These sequential strategies are highly relevant, due to the reciprocal interactions between immunotherapy and chemotherapy mechanisms of action, highlighting the importance of considering multiple rechallenges. In this sequential strategy, determining specific resistances to ICI of each tumor could help to identify the most appropriate chemotherapy to be administered.

There are some limitations in our findings. First, it is a retrospective study, with small groups with a lack of power not allowing multivariate nor subgroup analysis. Moreover, given its “real-life” nature, the first scanographic evaluation under chemotherapy was not performed at the same time. This could have affected the PFS, and we preferred TTD as the primary endpoint. Finally, even if both groups were statistically comparable for most of the clinical features, ECOG was significantly lower in the CAI groups treated with PB or G, which may lead to a bias in survival analysis.

In conclusion, this study, including all the approved ICIs and the main chemotherapy regimens for the management of NSCLC showed no difference in TTD, OS and ORR regardless of chemotherapy but a trend towards an increased OS with paclitaxel/bevacizumab when given after an ICI. This
could be a valuable option in advanced NSCLC for selected patients. However, our data have to be confirmed in larger cohorts, specifically studying paclitaxel/bevacizumab regimens. Sequential combination strategies need further investigation, and the place of such therapeutic strategy has to be determined since combinations are validated as first-line treatment.

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CONFLICT OF INTEREST
None.

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