Novel chemotherapy regimens for advanced lung cancer: have we reached a plateau?

Panagiotis Baxevanos[1], Giannis Mountzios[2]

[1]Department of Medical Oncology, Naval and Veterans Hospital of Athens, Athens, Greece; [2]Department of Medical Oncology, 251 Air Force General Hospital, Athens, Greece

Contributions: (I) Conception and design: G Mountzios; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Panagiotis Baxevanos. Department of Medical Oncology, Naval and Veterans Hospital of Athens, Athens, Greece. Email: baxpan88@hotmail.com.

Abstract: Lung cancer remains the most significant contributor of cancer-related mortality globally. Despite the significant progress over the last decade with the introduction of targeted and immunotherapeutic agents in the treatment of advanced non-small cell lung cancer (NSCLC), chemotherapy is still the appropriate treatment for the majority of patients. Based on clinical evidence, platinum-containing regimens have been established as the cornerstone of treatment as of today. Research efforts to optimize chemotherapy outcomes have led to novel chemotherapy regimens such as the combination of platinum plus pemetrexed as well as the addition of bevacizumab in patients with advanced non squamous NSCLC, and the combination of carboplatin with nanoparticle-albumin bound paclitaxel regardless of histology. In this article, we review clinical data regarding the recent evolution of chemotherapy in the advanced NSCLC setting, and critically evaluate the progress in therapeutic efficacy in terms of survival. We conclusively state that chemotherapy alone has reached a therapeutic plateau and report the current trends in clinical research combining chemotherapy with novel systemic therapies.

Keywords: Advanced non-small cell lung cancer (NSCLC); chemotherapy; pemetrexed; nab-paclitaxel; nedaplatin

Submitted Mar 18, 2018. Accepted for publication Mar 30, 2018.
doi: 10.21037/atm.2018.04.04
View this article at: http://dx.doi.org/10.21037/atm.2018.04.04

Introduction

Lung cancer remains the most common cause of cancer-related death in both sexes globally. Only in the United States a number of 154,050 deaths was estimated during 2017 (1). Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases and is divided into the following three major histological subtypes from most to less frequent: adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Importantly, more than half of patients are diagnosed with metastatic disease and the 5-year survival percentage at this stage is 5% (2).

Chemotherapy has been the mainstay of treatment in patients with metastatic NSCLC for approximately 3 decades and since no cure can be achieved, it is given with a palliative intent. Over the last decade the sequence of the human genome allowed novel biologic therapies to emerge in NSCLC, by targeting specific molecular alterations, called driver mutations. Targeted therapies were incorporated in the treatment algorithm of selected molecularly defined subgroups of adenocarcinoma in the advanced disease setting, after showing greater efficacy and less severe toxicity compared to conventional chemotherapy. Moreover, the advent of immunotherapy was accompanied by unprecedented efficacy outcomes in some patients with advanced NSCLC. The incorporation of immune checkpoint inhibitors initially in second-line and even more recently in the first-line treatment of NSCLC is ruled by strict selection criteria (e.g., PDL-1 expression) and

broadens therapeutic choices, but, on the other hand causes a greater complexity in treatment decision.

Despite the revolution in the therapeutic landscape of advanced NSCLC with targeted therapies and immunotherapy, the indication spectrum of these new treatments still includes the minority of patients, whereas the vast majority is inevitably candidates only for chemotherapy. In this article, we focus on the beneficial impact of chemotherapy in the advanced NSCLC setting and the progress that has been achieved in this field throughout the decades. Herein, we emphasize on novel chemotherapy regimens, with the aim to answer if chemotherapy has currently reached its therapeutic ceiling, and report current trends of clinical research on optimization of chemotherapy.

Platinum doublets

The first clear evidence regarding the beneficial role of chemotherapy in patients with unresectable or metastatic NSCLC, emerged 23 years ago in a historical meta-analysis conducted by the NSCLC collaborative group: by comparing systemic chemotherapy with best supportive care alone, researchers demonstrated a 10% absolute survival benefit at one year; of note, this survival improvement was exclusively based on cisplatin-containing regimens, in contrast with other alkylating agents of that era which might have had deleterious effects, especially after long term use (3). Meanwhile, the results of another meta-analysis in the 1990s suggested that combination chemotherapy regimens are more active—nearly double response rates—than single-agent treatments in advanced NSCLC, albeit with more severe toxicity. Nevertheless, in those clinical trials that evaluated monotherapy with either a platinum analogue or vinorelbine, the addition of other chemotherapeutic agents offered no significant survival gain at the end of the first year (4).

Since then, many newer and highly potent cytotoxic agents such as gemcitabine, taxanes and camptothecins have been studied and incorporated in the treatment algorithm of advanced NSCLC. However, none of these third generation agents has managed to displace platinum analogues from the first line treatment as the standard of care. In the relevant meta-analysis of D'Addario *et al.*, platinum-based regimens remained more effective in terms of response, when compared with third-generation combination chemotherapies (3,204 patients in 14 trials; OR, 1.17; 95% CI, 1.01 to 1.36; P=0.042), while the comparison of 12-month survival between respective arms revealed similar efficacy [3,307 patients in 14 trials; 1-year survival, 36% (95% CI, 34 to 38) for platinum-based chemotherapy *vs.* 35% (95% CI, 33 to 38) for third-generation based combinations; OR, 1.11; 95% CI, 0.96 to 1.28; P=0.17] (5). Additionally, in a subsequent meta-analysis of phase 3 trials by Pujol *et al.*, the comparison of platinum-based doublets *vs.* third generation doublets (mainly gemcitabine-based with either taxanes or vinorelbine) demonstrated a statistically significant decrease in the risk of death at 1 year (OR, 0.88; 95% CI, 0.78 to 0.99; P=0.044) in favor of the platinum regimens (6). Therefore, the role of third generation agents in initial therapy of metastatic NSCLC, was restricted as partners in platinum-based doublets, with the exception of cases in which patients were not fit for a platinum analogue administration and consequently, third generation drugs either as a single agent or in combinations constituted a reasonable alternative.

Several randomized phase 3 clinical trials were conducted during the 2000s, trying to elucidate which platinum doublet combines the best efficacy along with the least toxicity. Regarding the right platinum compound, patients treated with cisplatin presented higher objective response rates than those treated with carboplatin (30% *vs.* 24%, respectively; OR, 1.37; 95% CI, 1.16 to 1.61; P<0.001), while the risk for mortality was increased in carboplatin-based chemotherapy, as compared to cisplatin-based [hazard ratio (HR), 1.11; 95% CI, 1.01 to 1.21] (7).

Third generation platinum-based chemotherapy doublets, namely combinations of a platinum compound (cisplatin or carboplatin) with one third generation agent (mainly vinorelbine, gemcitabine or taxanes), represented the cornerstone of standard chemotherapy as first-line treatment of advanced NSCLC for almost a decade, since the first randomized trials established the role of vinorelbine-cisplatin in this setting (8,9). In fact, most landmark clinical trials of that era demonstrated comparable efficacy among various platinum-based doublets, with the 1-year survival rate across all treatment arms ranging from 33% to 46% (10-13). As a result, the selection of the appropriate chemotherapy was mainly made on the basis of the specific toxicity profile as well as convenience of each regimen, whereas histological and molecular features of the tumor were not taken into consideration.

The first step towards a more individualized therapeutic approach in advanced NSCLC was made in 2008, in

parallel with the introduction of pemetrexed in the treatment algorithm. In particular, the relevant randomized phase 3 trial by Scagliotti *et al.*, compared the efficacy of the reference regimen of cisplatin plus gemcitabine (Cis/Gem) *vs.* the experimental doublet of cisplatin plus pemetrexed (Cis/Pem). The results of this non-inferiority study revealed equal effectiveness between Cis/Pem and Cis/Gem both in primary [median overall survival (OS), 10.3 *vs.* 10.3 months; HR, 0.94; 95% CI, 0.84 to 1.05] and secondary endpoints [overall response rates (ORR), 30.6% *vs.* 28.2% and median progression-free survival (PFS), 4.8 *vs.* 5.1 months; HR, 1.04; 95% CI, 0.94 to 1.15]. Additionally, the pemetrexed doublet was shown to be significantly safer regarding hematologic toxicity than the gemcitabine doublet (14). Even more intriguing were the findings of the histology subgroup analysis, according to which patients with nonsquamous NSCLC derived significantly greater OS benefit when treated with Cis/Pem rather than Cis/Gem (847 patients with adenocarcinoma, 12.6 *vs.* 10.9 months, respectively; HR, 0.84; 95% CI, 0.71 to 0.99; P=0.03; 153 patients with large-cell carcinoma, 10.4 *vs.* 6.7 months, respectively; HR, 0.67; 95% CI, 0.48 to 0.96; P=0.03; 1,000 patients with nonsquamous, 11.8 *vs.* 10.4 months, respectively; HR, 0.81; 95% CI, 0.70 to 0.94; P=0.005). Instead, the OS gain for patients with squamous NSCLC was lower (marginally significant) with Cis/Pem, as compared with Cis/Gem (473 patients with squamous carcinoma, median OS, 9.4 *vs.* 10.8 months respectively; HR, 1.23; 95% CI, 1.00 to 1.51; P=0.05) (14). Two subsequent meta-analyses also indicated the definite role of histology as predictive factor for pemetrexed effectiveness, and the significantly prolonged survival with pemetrexed plus platinum chemotherapy in patients with nonsquamous NSCLC, compared with other platinum-based chemotherapies (HR, 0.87; 95% CI, 0.77 to 0.98; P=0.02) (15,16).

Thus, platinum-pemetrexed chemotherapy emerged as the reference regimen in first-line treatment of metastatic non squamous NSCLC. Conversely, patients with squamous histology could be treated with any of the available doublets, consisting of a platinum analogue (cisplatin or carboplatin) plus one of the following third generation agents: gemcitabine, paclitaxel, docetaxel, vinorelbine. Histology-guided chemotherapy in first-line treatment of NSCLC has led to a modest but consistent improvement in OS (11–12 months median OS according to relevant trials) and is included in the current treatment European (17) and American (18) recommendations so far.

Platinum triplets: the addition of bevacizumab to platinum based combinations

Based on the rationale of synergism between cytotoxic drugs with different pharmacologic properties as well as the superior efficacy of doublet chemotherapy over single-agent treatment, many randomized clinical trials were conducted so as to investigate if triplet chemotherapy combinations could further improve outcomes in first-line treatment of NSCLC. According to the results of a recently updated Cochrane meta-analysis, no survival benefit was observed with the addition of a third chemotherapy agent to a doublet combination, despite the moderate but statistically significant improvement in response rates (19). Similarly, the more recent 2×2 factorial trial by Boni *et al.*, confirmed the equal treatment outcomes that ifosfamide confers when added to a gemcitabine-based doublet (20). With the appearance of newer targeted therapies, the concept of triplet regimens consisting of the standard platinum-based doublet plus one targeted agent emerged as a promising strategy.

Bevacizumab—a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF)—has been the first approved targeted anti-angiogenic agent against cancer (21). The normalizing effect that anti-angiogenic therapy exerts on tumor vasculature has been considered a mechanism of improved drug delivery in cancer cells, and provided a logical background for co-administration with chemotherapy (22). Regarding NSCLC, the addition of bevacizumab to the standard carboplatin-paclitaxel regimen in previously untreated patients with advanced NSCLC achieved higher response rates (31.5% *vs.* 18.8%) and prolonged time to progression, compared with carboplatin-paclitaxel alone, according to a randomized phase 2 trial with dose finding design (23). In this trial, special emphasis was given to pulmonary bleeding as a life threatening adverse effect of bevacizumab, which was mainly associated with squamous histology. Based on these findings, the Eastern Cooperative Oncology Group (ECOG) randomized phase 3 study compared the efficacy—OS as primary end point of bevacizumab plus carboplatin-paclitaxel against carboplatin-paclitaxel alone, in chemonaive patients with recurrent or advanced NSCLC and exclusively non squamous histology. While chemotherapy was given every 3 weeks for up to 6 cycles, the 3-week cycles of bevacizumab continued beyond the chemotherapy period and until the occurrence of disease progression or intolerable toxicity. The triplet regimen

was more effective than the doublet regimen in all efficacy parameters (median OS, 12.3 *vs.* 10.3 months, P=0.003; median PFS, 6.2 *vs.* 4.5 months, P<0.001; ORR, 35% *vs.* 15%, respectively, P<0.001), suggesting both the synergistic activity of bevacizumab with standard chemotherapy and its beneficial role as maintenance therapy (24). Later, results from the European randomised placebo-controlled phase 3 trial (AVAiL) confirmed the benefit improved PFS and response rates from bevacizumab administration (7.5 or 15 mg/kg) with a different induction regimen (cisplatin 80 mg/m^2 and gemcitabine 1,250 mg/m^2 for up to 6 cycles) and as continuation maintenance (25). Notably, this benefit was not translated into OS gain—median OS exceeded 13 months in all treatment groups according to a longer follow-up analysis and these findings were mainly attributed to the impact of subsequent-line therapies on OS (26).

As previously mentioned, chemonaive patients with metastatic non squamous NSCLC reap the greatest benefit when treated with platinum—pemetrexed chemotherapy. Additionally, pemetrexed as continuation maintenance therapy after induction therapy with cisplatin plus pemetrexed has shown significant improvement in OS, when compared with placebo (13.9 *vs.* 11 months, respectively, P=0.0195) (27). In the AVAPERL randomized phase 3 trial, patients with disease control after 4 cycles of cisplatin, pemetrexed and bevacizumab were randomly assigned to maintenance bevacizumab or bevacizumab-pemetrexed; a significant improvement in PFS was demonstrated in favor of the combination arm (median PFS, 3.7 *vs.* 7.4 months; HR, 0.48; P<0.001) (28). However, the updated survival analysis of this trial showed a numerically considerable but not statistically significant prolongation of OS with bevacizumab-pemetrexed maintenance treatment (17.1 *vs.* 13.2 months, HR, 0.87; P=0.29) (29). Similarly, in the PointBreak randomized phase 3 trial, patients were randomized from the beginning, either to the experimental arm (induction with carboplatin, pemetrexed and bevacizumab followed by maintenance with pemetrexed and bevacizumab), or to the control arm (induction with carboplatin, paclitaxel and bevacizumab followed by maintenance with bevacizumab) (30). Despite the limitation of the study design not allowing a clear distinction regarding the extent of contribution on survival outcomes by initial and maintenance treatment, the two general approaches appeared equally effective. The milder toxicity of pemetrexed regimen established this combination (carboplatin, pemetrexed, bevacizumab) as a reasonable first-line induction therapy in metastatic non squamous NSCLC. Finally, the comparison of the three different maintenance arms (pemetrexed alone, bevacizumab alone, pemetrexed plus bevacizumab) after induction therapy (carboplatin, paclitaxel and bevacizumab) is ongoing (ECOG E-5508 trial) and results will provide guidance regarding the optimal maintenance treatment in advanced non squamous NSCLC (31).

Nab-paclitaxel: registration trials and new indications

The administration of taxanes with first-line platinum-based treatment in patients with advanced NSCLC is less common, as compared to pemetrexed, gemcitabine and even vinorelbine, according to recent real-world evidence across Europe (32). This observation is somewhat justified by safety and pharmacokinetic issues regarding the special formulation of taxanes. Especially paclitaxel is characterized by limited aqueous solubility and has to be dissolved in appropriate lipid-based solvents (Cremophor EL). The high anaphylactogenic capacity which makes premedication with steroids essential, the chronic peripheral neuropathy, the need for special infusion sets and in-line filters as well as the long infusion time are some of the problems met with the use of standard Cremophor EL based paclitaxel (33).

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a newer water-soluble formulation of paclitaxel, consisting of albumin and paclitaxel reconstituted in normal saline. The absence of lipid-based solvents and their replacement by albumin-based nanoparticles in this novel formulation was accompanied by a significantly lower rate of adverse effects in phase 1 trials, while improved efficacy via enhanced drug delivery to cancer cells was suggested by preclinical studies (34,35). Indeed, high quality evidence confirming the superiority of nab-paclitaxel over solvent-based (SB) paclitaxel, was provided for the first time by the outcomes of the respective randomized phase 3 trial in metastatic breast cancer; Interestingly no hypersensitivity reactions were described in the group of patients treated with nab-paclitaxel, despite the absence of premedication and the shorter infusion time (36).

The favorable results of nab-paclitaxel in the treatment of breast cancer prompted research about its therapeutic value in the field of other malignancies, including NSCLC. Initially, nab-paclitaxel was tested as single agent treatment in chemotherapy naïve patients with advanced NSCLC. The relevant phase 2 trials evaluated safety and efficacy across a range of doses and schedules (every 3 weeks or

weekly) and showed encouraging single-agent activity. No need for premedication was also confirmed, as no hypersensitivity reactions occurred (37,38).

Aiming to define the optimal dose and schedule of nab-paclitaxel in combination with carboplatin, a dose finding phase 2 trial was conducted with patients enrolled consecutively in seven cohorts (25 patients in each one). Patients in cohorts 1 to 4 received nab-paclitaxel every 3 weeks with a dose ranging from 225 to 340 mg/m^2 while those in cohorts 5 to 7 had weekly doses of 100, 125 and 140 mg/m^2 respectively. The dose of carboplatin [area under the curve (AUC) 6] was the same across all cohorts and was given on day 1 of every 3-week cycle. Antitumor activity was evident in all cohorts, though weekly nab-paclitaxel administration was associated with more frequent responses (36–56%) than the every 3 weeks administration (24–40%). It was conclusively reported that weekly nab-paclitaxel at the dose of 100 mg/m^2 achieved the most favorable clinical benefit-risk ratio (39). On the basis of these findings, the combination of carboplatin (AUC 6 on day 1) plus weekly nab-paclitaxel (100 mg/m^2 on days 1, 8 and 15) was selected as the experimental regimen for comparison with the control regimen of carboplatin (AUC 6) plus SB-paclitaxel (200 mg/m^2) every 3 weeks, in the multicenter randomized phase 3 trial by Socinski *et al.* (40). This trial met its primary endpoint (ORR) showing significantly higher ORR in favor of nab-paclitaxel regimen (33% *vs.* 25%; response rate ratio, 1.313; 95% CI, 1.082 to 1.593; P=0.005). Despite its greater efficacy, carboplatin plus nab-paclitaxel in first line did not appear to delay progression, compared with carboplatin plus SB-paclitaxel (median PFS 6.3 *vs.* 5.8 months, respectively; HR, 0.902; P=0.0214). Additionally, the nab-paclitaxel regimen prolonged OS by 1 month compared with SB-paclitaxel regimen (median OS, 12.1 *vs.* 11.2 months, respectively; HR, 0.922; P=0.271) but this moderate clinical effect was not statistically significant.

Quite interesting findings were reported in the subgroup analysis of the aforementioned study. Particularly, in the subset of patients with squamous NSCLC, the nab-paclitaxel regimen achieved much higher ORR than did SB-paclitaxel regimen (41% *vs.* 24%; response rate ratio, 1.680; 95% CI, 1.271 to 2.221; P<0.001). However, no significant difference in survival was found among histology subgroups. A significant OS benefit in favor of nab-paclitaxel was found for patients enrolled in North America (12.7 *vs.* 9.8 months, P=0.008) and in elderly patients, namely over 70 years old (19.9 *vs.* 10.4 months; P=0.009). Regional differences in patient baseline characteristics may have an impact in the OS advantage seen in North America. In elderly patients, apart from the possible intrinsic superiority of nab-paclitaxel over SB-paclitaxel, another suggested explanation for this survival advantage refers to the improved tolerability profile of nab-paclitaxel which enables increased dose administration and intensity, especially among older patients (41).

The United States Food and Drug Administration (FDA) first approved in October 2012 the combination of carboplatin plus nab-paclitaxel in chemotherapy naïve patients with advanced NSCLC, and after 3 years this regimen was also approved by the European Medicines Agency (EMA). This was an important advance of chemotherapy in first-line treatment, especially for patients with squamous histology, where the therapeutic landscape was unchanged for many years. The amelioration of symptoms and the positive impact on quality of life has always been a constant pursue and nab-paclitaxel in combination with carboplatin significantly contributed to this direction through its high response rates.

Nedaplatin

Nedaplatin is a second-generation platinum derivative, characterized by a more favorable toxicity profile—lower rates of associated emesis and renal toxicity compared with cisplatin. Nedaplatin has been developed, studied and widely applied in the Japanese population. Notably, the first assessment of nedaplatin efficacy in NSCLC was made almost 3 decades ago and reported marginal activity of this agent as monotherapy (42). Since then, a plethora of mostly phase 1 and phase 2 clinical trials, have investigated safety and efficacy of various nedaplatin-based regimens (mainly with gemcitabine, irinotecan or a taxane) in NSCLC. According to a recent meta-analysis of these trials, a significant interaction was confirmed between the histological type of NSCLC and the observed response rates by nedaplatin-based chemotherapy (ORR, 55.6% in squamous histology tumors *vs.* 34.4% in non-squamous histology), suggesting a more potent activity of nedaplatin against squamous NSCLC. Regarding survival, this meta-analysis reported that combinations of nedaplatin with a taxane led to promising survival outcomes, with a median OS of at least 10 months and a median PFS of at least 5 months (43).

Based on the remarkable efficacy results of the nedaplatin-docetaxel regimen in 21 patients with advanced squamous NSCLC (ORR, 62%; median PFS, 7.4 months;

median OS, 16.1 months), researchers conducted a Japanese randomized phase 3 study in advanced squamous NSCLC setting, comparing nedaplatin (100 mg/m^2) plus docetaxel (60 mg/m^2) *vs.* cisplatin (80 mg/m^2) plus docetaxel (60 mg/m^2) and investigating OS as primary endpoint (44,45). Regimens were given every 21 days for up to 6 cycles. Nedaplatin-based chemotherapy achieved significantly prolonged OS compared to cisplatin-based chemotherapy (median OS 13.6 *vs.* 11.4 months, respectively; HR, 0.81; P=0.037). No significant differences were observed between nedaplatin and cisplatin arms in terms of PFS (median PFS, 4.9 *vs.* 4.5 months; HR, 0.83; P=0.050) and response rates (56% *vs.* 53%).

It is conceivable that this trial provided compelling evidence on substitution of cisplatin with a more potent and less toxic chemotherapeutic agent. Nevertheless, the fact that the overwhelming proportion of subjects in this trial originated from East Asia sets a serious limitation for the introduction of nedaplatin in first-line treatment of advanced squamous NSCLC in western populations, because of possible genomic differences in drug metabolism.

Comment on the plateau of chemotherapy

The beneficial effect of chemotherapy in the supportive care setting has been repeatedly proven across all patient subgroups with advanced NSCLC (3,46). Platinum-based doublets have been the backbone of first-line treatment and lead to a median OS that does not exceed one year in the first landmark trials (10,13). Over the last decade, several successful clinical trials in this field have been conducted and respective changes in the treatment paradigm have been adopted, though offering a modest prolongation of OS beyond this plateau. The development of pemetrexed was associated with the need for histological distinction of NSCLC into squamous and nonsquamous types, when designing therapeutic strategy.

Since then, the landscape of chemotherapy in nonsquamous NSCLC evolved more rapidly. Initially the addition of bevacizumab to platinum-based chemotherapy extended median OS just beyond the historical 1-year benchmark, and later the continuation of pemetrexed as maintenance treatment was accompanied by a median OS of 13.9 months (23). Conversely, chemotherapy in squamous NSCLC was characterized by lack of progress, until the advent of nab-paclitaxel, which despite the impressive increase in responses when added to platinum-based therapy, did not manage to show significant differences in survival (40). Nedaplatin-based chemotherapy in patients with advanced squamous NSCLC led to a remarkable median OS of 13.6 months, with the reproducibility of these outcomes being limited to East Asia.

In general, the efficacy of chemotherapy in terms of survival remains in a plateau, with the only exception being a slight survival gain in nonsquamous NSCLC with the introduction of pemetrexed and bevacizumab in first-line or maintenance treatment. We could say that the major therapeutic advancements regarding chemotherapy have to do with increased response rates and better tolerability, so purely chemotherapeutic regimens seem insufficient to further improve the treatment course of advanced NSCLC, as we know it today.

Following the successful paradigm of combining chemotherapy with bevacizumab, a variety of clinical trials are currently investigating combinations of chemotherapy with other targeted agents such as EGFR TKIs (erlotinib, gefitinib) or next generation anti-angiogenic agents (aflibercept, ramucirumab). Even more promising seems the clinical research on combinations of chemotherapy with immunotherapy. We selectively report the multi-cohort phase 2, KEYNOTE-021 study with its outcomes underlining the manageable safety profile and significant antitumor activity of the triplet pembrolizumab (an anti-PDL-1 agent) plus carboplatin and pemetrexed in previously untreated patients with advanced non-squamous NSCLC (47). In two phase 3 studies, KEYNOTE-189 and KEYNOTE-407, the addition of pembrolizumab to platinum-based chemotherapy is currently being tested in non-squamous and squamous NSCLC, respectively. Similarly, nivolumab—an anti-PD1 agent plus platinum doublet chemotherapy constitutes one of the three experimental arms compared with a platinum doublet alone, in the first-line treatment of patients with recurrent or metastatic NSCLC (Checkmate 227, NCT02477826). Finally, the combination of chemotherapy with durvalumab (anti-PDL1 agent) alone or plus tremelimumab (an anti CTLA-4 agent) is being evaluated as experimental arm in two different phase 2 clinical trials (NCT03057106, NCT02250326).

Conclusions

Chemotherapy still remains the standard of care for the majority of patients diagnosed with advanced NSCLC. Despite the development of novel chemotherapeutic agents, such as pemetrexed and nab-paclitaxel, as well as

the addition of bevacizumab to current regimens, there is a modest extension of survival, with a therapeutic plateau in OS ranging from 12 to 14 months according to results of most clinical trials. Combinations of chemotherapy with targeted agents and especially with immunotherapy may hold the key for maximizing survival benefit and clinical research is already moving towards that direction.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
2. National Cancer Institute. Browse the SEER Cancer Statistics Review 1975-2014. Available online: https://seer.cancer.gov/csr/1975_2014/browse_csr.php?sectionSEL=15&pageSEL=sect_15_table.14.html
3. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899-909.
4. Lilenbaum RC, Langenberg P, Dickersin K. Single agent versus combination chemotherapy in patients with advanced nonsmall cell lung carcinoma: a meta-analysis of response, toxicity, and survival. Cancer 1998;82:116-26.
5. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol 2005;23:2926-36.
6. Pujol JL, Barlesi F, Daures JP. Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. Lung Cancer 2006;51:335-45.
7. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst 2007;99:847-57.
8. Le Chevalier T, Brisgand D, Douillard JY, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. J Clin Oncol 1994;12:360-7.
9. Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. J Clin Oncol 1998;16:2459-65.
10. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-24.
11. Kelly K, Crowley J, Bunn PA Jr, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001;19:3210-8.
12. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002;20:4285-91.
13. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8.
14. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.
15. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. J Thorac Oncol 2011;6:64-70.
16. Li M, Zhang Q, Fu P, et al. Pemetrexed plus platinum as the first-line treatment option for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials. PLoS One 2012;7:e37229.
17. Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v1-27.
18. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. 2018. Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf
19. Delbaldo C, Michiels S, Rolland E, et al. Second or third additional chemotherapy drug for non-small cell

lung cancer in patients with advanced disease. Cochrane Database Syst Rev 2007;(4):CD004569.
20. Boni C, Tiseo M, Boni L, et al. Triplets versus doublets, with or without cisplatin, in the first-line treatment of stage IIIB-IV non-small cell lung cancer (NSCLC) patients: a multicenter randomised factorial trial (FAST). Br J Cancer 2012;106:658-65.
21. Jenab-Wolcott J, Giantonio BJ. Bevacizumab: current indications and future development for management of solid tumors. Expert Opin Biol Ther 2009;9:507-17.
22. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7:987-9.
23. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184-91.
24. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50.
25. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009;27:1227-34.
26. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010;21:1804-9.
27. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final Overall Survival Results of the Phase III Study of Maintenance Pemetrexed Versus Placebo Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non–Small-Cell Lung Cancer. J Clin Oncol 2013;31:2895-902.
28. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized Phase III Trial of Maintenance Bevacizumab With or Without Pemetrexed After First-Line Induction With Bevacizumab, Cisplatin, and Pemetrexed in Advanced Nonsquamous Non–Small-Cell Lung Cancer: AVAPERL (MO22089). J Clin Oncol 2013;31:3004-11.
29. Barlesi F, Scherpereel A, Gorbunova V, et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. Ann Oncol 2014;25:1044-52.
30. Patel JD, Socinski MA, Garon EB, et al. PointBreak: A Randomized Phase III Study of Pemetrexed Plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab Versus Paclitaxel Plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients With Stage IIIB or IV Nonsquamous Non–Small-Cell Lung Cancer. J Clin Oncol 2013;31:4349-57.
31. ClinicalTrials.gov. Bevacizumab or Pemetrexed Disodium Alone or In Combination After Induction Therapy in Treating Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer. Available online: https://ClinicalTrials.gov/show/NCT01107626
32. Moro-Sibilot D, Smit E, de Castro Carpeño J, et al. Outcomes and resource use of non-small cell lung cancer (NSCLC) patients treated with first-line platinum-based chemotherapy across Europe: FRAME prospective observational study. Lung Cancer 2015;88:215-22.
33. Gelderblom H, Verweij J, Nooter K, et al. Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. Eur J Cancer 2001;37:1590-8.
34. Desai N, Trieu V, Yao Z, et al. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clin Cancer Res 2006;12:1317-24.
35. Nyman DW, Campbell KJ, Hersh E, et al. Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. J Clin Oncol 2005;23:7785-93.
36. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005;23:7794-803.
37. Green MR, Manikhas GM, Orlov S, et al. Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol 2006;17:1263-8.
38. Rizvi NA, Riely GJ, Azzoli CG, et al. Phase I/II trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage IV non-small-cell lung cancer. J Clin Oncol 2008;26:639-43.
39. Socinski MA, Manikhas GM, Stroyakovsky DL, et al. A dose finding study of weekly and every-3-week nab-Paclitaxel followed by carboplatin as first-line therapy

in patients with advanced non-small cell lung cancer. J Thorac Oncol 2010;5:852-61.
40. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 2012;30:2055-62.
41. Socinski MA, Langer CJ, Okamoto I, et al. Safety and efficacy of weekly nab(R)-paclitaxel in combination with carboplatin as first-line therapy in elderly patients with advanced non-small-cell lung cancer. Ann Oncol 2013;24:314-21.
42. Fukuda M, Shinkai T, Eguchi K, et al. Phase II study of (glycolate-O,O') diammineplatinum(II), a novel platinum complex, in the treatment of non-small-cell lung cancer. Cancer Chemother Pharmacol 1990;26:393-6.
43. Tian Y, Liu Q, Wu K, et al. Meta-analysis comparing the efficacy of nedaplatin-based regimens between squamous cell and non-squamous cell lung cancers. Oncotarget 2017;8:62330-8.
44. Naito Y, Kubota K, Ohmatsu H, et al. Phase II study of nedaplatin and docetaxel in patients with advanced squamous cell carcinoma of the lung. Ann Oncol 2011;22:2471-5.
45. Shukuya T, Yamanaka T, Seto T, et al. Nedaplatin plus docetaxel versus cisplatin plus docetaxel for advanced or relapsed squamous cell carcinoma of the lung (WJOG5208L): a randomised, open-label, phase 3 trial. Lancet Oncol 2015;16:1630-8.
46. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008;26:4617-25.
47. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497-508.

Cite this article as: Baxevanos P, Mountzios G. Novel chemotherapy regimens for advanced lung cancer: have we reached a plateau? Ann Transl Med 2018;6(8):139. doi: 10.21037/atm.2018.04.04

