Second Line Chemotherapy and Beyond for Non-Small Cell Lung Cancer (NSCLC)

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Key Points

- Docetaxel, pemetrexed, and erlotinib are approved for the second-line treatment of NSCLC.
- The discovery of targetable mutations, the increasing use of maintenance strategies, and the introduction of immunotherapies has made the choice of second-line agents much more complicated.
- Ramucirumab with docetaxel is the only combination regimen that has shown improved overall survival in the second-line setting.
- Erlotinib is the only agent approved in the third-line setting for EGFR wild-type patients.

First Line Treatment

In patients without targetable genetic alterations, the standard first-line therapy for advanced (stage IIIB or IV) NSCLC is chemotherapy with a platinum doublet for 4-6 cycles with or without bevacizumab.[1] Historically, a number of drugs including paclitaxel, docetaxel, gemcitabine, and vinorelbine were considered acceptable platinum partners in the first-line metastatic setting with essentially no differences in progression free survival (PFS) or overall survival (OS). More recently, additional agents have been approved in combination with platinum in this setting including pemetrexed and nab-paclitaxel.[1-3] One particular advance in the last decade has been the recognition that histology should be considered in the choice of initial chemotherapy. This was discovered after an additional

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analysis of two studies showed pemetrexed to be more effective in non-squamous histologies and less active in squamous tumors.[3-5] Based on these findings, the choice of first-line agents in metastatic NSCLC is now strongly based on presenting histology, and this initial choice affects available second-line options.

Maintenance Therapy

Historically, patients treated with first-line platinum doublet chemotherapy who had objective responses or stable disease were placed on surveillance following completion of 4-6 cycles. However, over the last decade, new data suggests that there is benefit to the addition of maintenance therapy following initial chemotherapy. There are two maintenance strategies including continuation of an agent used in the first-line setting or switching to a previously unused agent (switch maintenance). There is data supporting the use of bevacizumab, pemetrexed, and erlotinib in the maintenance setting either as single agents or in combination.[6-11] Prior maintenance therapy is of particular importance when discussing second-line chemotherapy options as the use of maintenance therapy, particularly when switch maintenance is employed, influences the availability of agents in the second-line setting and beyond.

Chemotherapy as Second-Line Treatment

Historically, nearly all patients received platinum doublet chemotherapy followed by single agent chemotherapy in the second-line setting. However, with the discovery of targetable mutations, the development of tyrosine kinase inhibitors (TKI), the increasing use of maintenance strategies, and the introduction of immunotherapies to the current list of approved medications, choosing an appropriate second-line therapy has become more complicated. In general, those patients treated with targeted therapies will receive a platinum doublet at the time of progression. For those who are wild type for exploitable mutations, immunotherapy has become an increasingly popular second-line option because of its tolerability and potential for durable responses. However, there remains a role for additional treatments following second-line platinum doublets or immunotherapy, or alternatively, a role for

second-line chemotherapy in those with contraindications to immunotherapy. This article will discuss the available data for chemotherapy in the second-line treatment of NSCLC and beyond.

Chemotherapy in the Second-Line Setting and Beyond

With the exception of immunotherapy, there are four FDA-approved agents for the second- and third-line treatment of advanced or metastatic NSCLC: docetaxel, pemetrexed, erlotinib, and ramucirumab. Docetaxel was the first agent approved for second-line treatment in 1999, and pemetrexed was approved in the second-line setting in 2004. Erlotinib was also approved in 2004 for both second- and third-line treatment of advanced NSCLC and is currently the only FDA-approved third-line therapy. Ramucirumab was approved in 2014 in combination with docetaxel following progression on platinum-based chemotherapy.

Single Agent Versus Combination Regimens

In the first-line setting, doublet chemotherapy is clearly superior to single-agent treatment in advanced NSCLC. However, it is unclear whether combination therapy in the second-line setting improves outcomes over single-agent chemotherapy. A meta-analysis of six trials compared combination regimens to single-agent therapy in the second-line setting. The combination arm showed a statistically significant improvement in response rate (RR) (15.1% vs 7.3%, p=0.0004) and median PFS (14 vs 11.7 weeks, p=0.0009, HR 0.79) compared with single-agent therapy. However, there was no difference in median OS between the two groups (37.3 vs. 34.7 weeks, HR 0.92, p=0.32). The doublet arms had significantly higher rates of both grade 3/4 hematologic (41% vs. 25%, p<0.0001) and non-hematologic (28% vs. 22%, p=0.034) toxicity. [12] Two additional meta-analyses assessing docetaxel alone versus docetaxel-based doublet chemotherapy and pemetrexed alone versus pemetrexed-based doublet chemotherapy demonstrated similar results. Both analyses showed improvements in RR and PFS with doublet chemotherapy but no improvement in OS. The doublet arms showed significant increases in hematologic toxicity for both

docetaxel and pemetrexed doublets and in non-hematologic toxicity for docetaxel doublets. [13,14] Based on these findings, current second-line treatment approaches use mainly single-agent chemotherapy.

Docetaxel

Docetaxel was the first agent approved for the second-line treatment of patients with advanced NSCLC. This approval came on the basis of two phase III clinical trials. In the TAX 317 trial, 104 patients previously treated with at least one platinum-based regimen were randomized to receive either docetaxel (100mg/m2 or 75mg/m2 every 3 weeks) or best supportive care (BSC). The primary endpoint of the study was overall survival, and this favored the docetaxel arms with a median OS of 7.0 vs. 4.6 months (p=0.047). The group treated with 75mg/m2 had a numerically better OS than those treated with 100mg/m2 (7.5 vs. 5.9 months) and demonstrated a much better toxicity profile.[15] A subsequently published quality of life analysis of this trial demonstrated a significant improvement in pain scores for the docetaxel arms and a trend toward improved overall quality of life.[16]

A second study evaluating docetaxel in the second-line setting following progression on platinum-based chemotherapy was the TAX 320 trial. This trial compared docetaxel at 75 mg/m2 or 100mg/m2 every three weeks to a control arm treated with either vinorelbine (30mg/m2 on days 1, 8, and 15) or ifosfamide (2mg/m2/d on days 1-3) repeated every 3 weeks. Response rate (p=0.002) and PFS (p=0.005) were better in the docetaxel arms. The median OS was not different between the three groups, although the 1-year OS was 32% in the docetaxel 75mg/m2 versus 19% in the control arm (p=0.025). The docetaxel 75mg/m2 arm again demonstrated much less hematologic and non-hematologic toxicity compared with the 100mg/m2 arm.[17] These two trials firmly established docetaxel 75mg/m2 as the standard second-line therapy in 1999.

A number of studies have compared weekly dosing of docetaxel compared with treatment every three weeks. A meta-analysis, published in 2007, included 865 individual patients and five trials

comparing these dosing strategies. Median OS was 27.4 weeks in the every three week treatment arm and 26.1 weeks in the weekly arm (p=0.24), suggesting no difference in efficacy. There were also no significant differences in the rates of anemia, thrombocytopenia, or non-hematologic toxicity, but there was less febrile neutropenia (p<0.00001 for both) in the weekly dosing arm.[18] Weekly dosing with docetaxel is an acceptable treatment alternative for second-line advanced NSCLC (Table 1), and both treatment schedules are frequently used in practice.

At least three phase III trials have compared alternative chemotherapy agents to docetaxel in the second-line setting. A randomized controlled trial comparing docetaxel to pemetrexed will be discussed in more detail below. The first of the other two trials compared docetaxel to vinflunine, a fluorinated vinca alkaloid, in a 1:1 randomization. This study met its non-inferiority endpoint with a median PFS of 2.3 months for both arms. Response rate, stable disease rate, and OS were numerically superior in favor of docetaxel but did not reach statistical significance, and the vinflunine arm had higher rates of several hematologic and non-hematologic adverse events.[19] Another study compared docetaxel to oral topotecan following progression on platinum-based therapy. This study also met its primary non-inferiority endpoint; however, progression-free survival at 1-year (25.1% vs. 28.7%) and median overall survival (27.9 vs. 30.7 weeks) were both higher in the docetaxel group though not statistically significant. The docetaxel arm did show a significant improvement in time to progression (TTP) at 11.3 vs. 13.1 weeks (p=0.02), and grade 3/4 toxicity was similar in the two groups.[20] Vinflunine and topotecan have activity in the second-line setting but neither has shown clear improvement over docetaxel in terms of either efficacy or toxicity. Neither agent is FDA-approved in the U.S. for the treatment of NSCLC.

Following the approval of docetaxel as a standard second-line option in NSCLC, at least three phase III trials have compared docetaxel with or without a targeted agent. In the ZODIAC trial, 1331 patients with advanced NSCLC were randomized to receive docetaxel plus placebo or docetaxel plus the

oral multi-kinase inhibitor vandetanib, an inhibitor of vascular endothelial growth factor (VEGF) receptor, EGFR, and rearranged during transfection (RET) tyrosine kinases. The primary endpoint was met with a median PFS in the vandetanib group of 4.0 months versus 3.2 months in the placebo group (HR 0.79, p<0.0001), and RR was also improved in the vandetanib group (17% vs. 10%, p=0.0001). OS was a secondary endpoint in this study. There was no difference between the two groups with a median OS of 10.3 months in the treatment arm vs. 9.9 months in the placebo (HR 0.95, p=0.371).[21] The LUME-Lung 1 trial compared docetaxel plus placebo to docetaxel plus nintedanib, an oral angiokinase inhibitor which blocks VEGFR 1-3, fibroblast growth factor receptors (FGFR) 1-3, and platelet derived growth factor receptors (PDGFR) alpha and beta. The combination arm met its primary endpoint of PFS at 3.4 months vs. 2.7 months (HR 0.79, p=0.0019). However, it failed to show a difference in OS between the two groups, although in a pre-specified subgroup analysis, there was an improvement in OS in patients with adenocarcinoma (12.6 vs. 10.3 months, HR 0.83, p=0.0359).[22] Based on this trial, nintedanib in combination with docetaxel was approved in Europe, but not the U.S., for the second-line treatment of NSCLC patients with adenocarcinoma.

Most recently, the REVEL trial randomized 1253 patients who had progressed after first-line platinum-based therapy to receive docetaxel plus either ramucirumab, an IgG1 monoclonal antibody against VEGF receptor 2, or placebo. The primary endpoint was overall survival. This study met its primary endpoint with a median OS of 10.5 months in the ramucirumab arm vs. 9.1 months in the placebo arm (HR 0.86, p=0.023). PFS was also improved in the treatment arm at 4.5 vs. 3 months (HR 0.76, p<0.0001). There were slightly higher rates of grade 3 neutropenia, febrile neutropenia, and leukopenia in the ramucirumab arm as well as higher grade 3 fatigue and hypertension.[23] Based on this study, the FDA approved ramucirumab in combination with docetaxel for the second-line treatment of NSCLC following progression on platinum-based chemotherapy. Although the OS advantage is relatively modest, this regimen remains a consideration for patients in the second-line setting.

Pemetrexed

Pemetrexed was evaluated in a second-line trial in which 571 patients were randomized to receive either docetaxel 75mg/m2 or pemetrexed 500mg/m2 every 3 weeks. This trial had a non-inferiority design comparing the OS of the two arms. The study showed no difference in OS between the two groups with a median of 8.3 months in the pemetrexed arm versus 7.9 months in the docetaxel arm (HR 1.0, p=0.226), and the 1-year survival rates were 29.7% in both arms. Response rates were also similar with 9.1% and 8.8% in the pemetrexed and docetaxel arms, respectively. There were, however, differences in the toxicity profile of these two drugs. The docetaxel arm had significantly higher rates of hematologic toxicity including neutropenia, febrile neutropenia, infection related to neutropenia, and hospitalizations for neutropenic fever. There were also higher rates of hospitalizations due to other drug-related adverse events, increased use of granulocyte colony stimulating factor, and alopecia in the docetaxel arm.[4]

Following this study, a re-analysis of the data detected a difference in outcomes between squamous and non-squamous histologies in patients treated with pemetrexed. Those with non-squamous NSCLC had superior OS when treated with pemetrexed with a median OS of 9.3 months versus 8.0 months (HR 0.78, p-0.48). Conversely, those with squamous cell carcinoma of the lung did significantly worse when treated with pemetrexed with a median OS of 6.2 versus 7.4 months (HR 1.56, p=0.018). [5] This differential efficacy according to histology was confirmed in other trials in the first-line and maintenance settings.[3,6] Based on these findings, pemetrexed became a standard second-line treatment option for patients with recurrent, advanced NSCLC with non-squamous histology and has been FDA-approved since 2004.

Initial studies of pemetrexed showed the maximum tolerated dose (MTD) to be 500-600mg/m2. It was later demonstrated that the addition of vitamin B12 and folic acid could ameliorate the hematologic toxicities, and subsequent studies utilizing these vitamins reported MTDs of 900-1000mg/m2. Therefore,

two clinical trials assessed whether higher doses of pemetrexed would improve outcomes in second-line NSCLC. The first was a phase III trial comparing pemetrexed 500mg/m2 vs. 900mg/m2 every 3 weeks. This trial was stopped early after an interim analysis showed a low likelihood of improved OS and a numerically higher rate of adverse rates in the 900mg/m2 arm.[24] The second trial was a phase II trial from Japan comparing pemetrexed 500mg/m2 versus 1000mg/m2. This trial showed no difference in RR, disease control rate, or median PFS between the two arms, and the 500mg/m2 was numerically superior for each of these endpoints.[25] Based on these trials, 500mg/m2 has remained the standard dose of pemetrexed with vitamin B12 and folic acid support.

Two large phase III trials have also looked at the combination of pemetrexed with additional agents in the second-line setting in patients with non-squamous histologies. The LUME-Lung 2 trial compared nintedanib with placebo in combination with pemetrexed with a primary endpoint of PFS. The study was stopped early for futility following accrual of 713 of a planned 1300 patients based on investigator-assessed PFS. However, a central review of enrolled patients actually reported a statistically significant improvement in median PFS (4.4 vs. 3.6 months, HR 0.83, p=0.04) in favor of the combination arm. OS (HR 1.03) and RR (9%) did not differ between the two arms.[26] A second phase III trial (ZEAL) randomized patients to receive pemetrexed in combination with either vandetanib or placebo. The combination arm failed to improve either PFS (HR 0.86, p=0.108) or OS (HR 0.86, p=0.219) compared to placebo.[27] Based on these studies, neither nintedanib nor vandetanib are approved for use in combination with pemetrexed.

EGFR Tyrosine Kinase Inhibitors

Erlotinib was initially approved for the second and third-line treatment of advanced NSCLC based on the results of the BR.21 trial which randomized 731 unselected patients to receive erlotinib or best supportive care (BSC) following progression on first-line platinum-based chemotherapy. Erlotinib

demonstrated improved RR (8.9% vs. <1%, p<0.001), PFS (2.2 vs. 1.8 months, HR 0.6, p<0.001), and OS (6.7 vs. 4.7 months, HR 0.7, p<0.001) compared with BSC alone (Table 2).[28] A subsequent analysis of this trial revealed that patients treated with erlotinib had a longer time to deterioration and improved physical function and quality of life compared to BSC.[29]

A number of trials have also compared erlotinib to chemotherapy (either docetaxel or pemetrexed) in either unselected or purely EGFR wild-type (EGFRwt) populations. No major trial in unselected or EGFRwt patients has shown erlotinib to be statistically superior to chemotherapy. The TITAN, HORG, and PROSE trials all failed to demonstrate any difference in RR, PFS, or OS between the two groups.[30-32] There have, however, been two trials which suggest that chemotherapy in the second-line setting may be superior to erlotinib in EGFRwt patients. The TAILOR trial was a comparison of docetaxel vs. erlotinib in a purely EGFRwt population. This study demonstrated improved RR (15.5% vs. 3%, p=0.003) and PFS (2.9 vs. 2.4 months, HR 0.71, p=0.02) favoring the docetaxel arm. It also showed a non-significant but numerically superior OS advantage of 2.8 months (8.2 vs. 5.4 months, adjusted HR 0.73, p=0.05) for the chemotherapy arm.[33] The DELTA trial compared erlotinib to docetaxel as second- or third-line therapy. In the overall group, there was no difference in RR, PFS, or OS, but in the subgroup of EGFRwt patients, the docetaxel arm had a higher PFS (2.9 vs. 1.3 months, p=0.01) although no difference in OS (10.1 vs. 9 months, p=0.907).[34] Lastly, a meta-analysis including six trials with a total of 990 EGFRwt patients demonstrated improved PFS for second-line chemotherapy compared with EGFR-TKIs (HR 1.37, p<0.00001) but no difference in OS (HR 1.02, p=0.81).[35] Based on these findings, many practitioners prefer chemotherapy over erlotinib for fit patients receiving second-line therapy.

Other Therapeutic Agents

The utility of other chemotherapeutic agents has been investigated but only in phase I and II trials. These agents include gemcitabine, vinorelbine, paclitaxel, and irinotecan. These trials have demonstrated

varying degrees of efficacy and toxicity.[36-40] Gemcitabine is the most studied agent with multiple phase II studies suggesting that it has efficacy in the second-line setting both as a single-agent[41,42] and in combination.[43]

Conclusions

The landscape for the second- and third-line treatment of advanced NSCLC has changed dramatically over the last two decades. Immunotherapeutic agents have become a preferred choice following progression on platinum-based first-line chemotherapy. However, there remains a role for cytotoxic chemotherapy and both pemetrexed and docetaxel (with or without ramucirumab) are approved for single-agent use in the second-line setting. Furthermore, the EGFR TKI, erlotinib, is approved for either second- or third-line use in unselected patients, though many experts feel it is less effective than chemotherapy in EGFRwt patients. With the discovery of new genetic alterations and the development of novel targeted drugs, the treatment of advanced NSCLC following progression on first-line therapy will likely continue to become more complicated as new treatment algorithms evolve.

Table 1- Select trials of single agent and combination chemotherapy in second-line advanced NSCLC

Select Cytotoxic Chemotherapy Trials							
Author	Trial	Treatment	N	RR	PFS or TTP	OS (mo)	1-yr Survival
Shepherd[15]	TAX 317	Doc 100 mg/m2	49	6.3%	10.6 wk	5.9	19%
		Doc 75 mg/m2	55	5.5%	10.6 wk	7.5	37%
		BSC	100	NR	6.7 wk	4.6	19%
Fossella[17]	TAX 320	Doc 100 mg/m2	125	10.8%	19%*	5.5	21%
		Doc 75 mg/m2	125	6.7%	17%*	5.7	32%
		Vinorelbine/Ifosfamide	123	0.8%	8%*	5.6	19%
Hanna[4]	JMEI	Pemetrexed	265	9.1%	2.9	8.3	29.7%
		Docetaxel	276	8.8%	2.9	7.9	29.7%
Di Maio[18]	Meta-Analysis	Weekly Doc	432	6.7%	NR	26.1 wk	27%
		Q3 Week Doc	433	8.1%	NR	27.4 wk	24.8%
Select Trials of Combination Therapy							

Garon[23]	REVEL	Docetaxel Docetaxel + Ramucirumab	625 628	14% 22%	3.0 4.5	9.1 10.5	NR NR
Reck[22]	LUME-Lung 1	Docetaxel Docetaxel+ Nintedanib	659 655	3.3% 4.4%	2.7 3.4	9.1 (10.3)** 10.1 (12.6)**	44.7% 52.7%
Hanna[26]	LUME-Lung 2	Pemetrexed Pemetrexed +Nintedanib	360 353	9% 9%	3.6 4.4	HR 1.03	NR NR
Herbst[21]	ZODIAC	Docetaxel Docetaxel + Vandetanib	697 694	10% 17%	3.2 4.0	9.9 10.3	41.2% 44.7%
Di Maio[12]	Meta-Analysis	Single-Agent Chemo Doublet Chemo	428 419	7.3% 15.1%	11.7 wk 14.0 wk	34.7 wk 37.3 wk	31.8% 34.4%

*Percent survival at 26 weeks.

**OS for adenocarcinoma subgroup in parentheses.

Table 2- Select trials of EGFR TKIs in EGFR wild type patients

Select EGFR TKI Versus Chemotherapy Trials							
Author	Trial	Treatment	N	RR	TTP or PFS	OS (mo)	1-yr Survival
Shepherd[28]	BR.21	Erlotinib BSC	488 243	8.9% <1.0%	2.2 1.8	6.7 4.7	31.2% 21.5%
Karampeazis[31]	HORG	Erlotinib Pemetrexed	166 166	9.0% 11.4%	3.6 2.9	8.2 10.1	39.5% 43.6%
Garassino[33]	TAILOR	Erlotinib Docetaxel	112 110	3.0% 15.5%	2.4 2.9	5.4 8.2	31.8% 39.6%
Kawaguchi[34]	DELTA	Erlotinib Docetaxel	150 151	17% 17.9%	2.0 (1.3)* 3.2 (2.9)*	14.8 (9.0)* 12.2 (10.1)*	NR NR
Ciuleanu[30]	TITAN	Erlotinib Pem or Doc	203 221	7.9% 6.3%	6.3 wk 8.6 wk	5.3 5.5	26% 24%

*PFS and OS for subgroup of EGFRwt patients in parentheses.

BSC = Best Supportive Care, EGFR = Epidermal Growth Factor Receptor, TKI = Tyrosine Kinase Inhibitor, RR = Response Rate, TTP = Time to Progression, PFS = Progression Free Survival, OS = Overall Survival, NR = Not Reported

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