Review

The Need for Third-line Treatment in Non-small Cell Lung Cancer: An Overview of New Options

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Abstract. *As a result of improved effectiveness of first-, second-line and maintenance therapeutic regimens in non-small cell lung cancer, there is need for new options as third-line treatment. Erlotinib and gefitinib are currently the only drugs of proven efficacy in the third-line setting. Chemotherapy drugs, such as pemetrexed, are being investigated, as are many new agents, such as cetuximab, sunitinib, sorafenib, everolimus, enzastaurin, afilbercept. These novel targeted therapies seem to improve response rates and progression-free survival and their toxicity is tolerable. In an effort to prolong survival while maintaining quality of life, large prospective studies are needed to examine the effectiveness and safety of third-line regimens in these patients.*

Lung cancer is the leading cause of cancer-related mortality. The estimate for 2010 is that new cases of lung cancer will exceed 220,000 and deaths will be more than 157,000 in the USA alone (1). Non-small cell lung cancer accounts for approximately 80% of all lung cancer cases. Nearly 70% of patients with non-small cell lung cancer (NSCLC) have inoperable locally advanced tumors or metastatic disease at time of diagnosis, with a 5-year survival rate of less than 5% (2). Moreover, a significant percentage of patients who present with local or locoregional disease will relapse with metastases, causing the low overall 5-year survival rate of 16%. Median survival for patients with advanced disease has slightly increased with the use of chemotherapy and targeted therapies alongside best supportive care (BSC) (2). A 2008 meta-analysis collected data from 16 randomized controlled trials that included 2,714 patients assigned to receive chemotherapy plus BSC or BSC alone. It showed a significant benefit for the chemotherapy plus BSC arm, increasing 1-year survival from 20% to 29%. There was no clear evidence concerning whether this improvement was to be attributed to the drugs used, or whether these drugs were used as single agents or in combination (3). Unfortunately, response to first-line chemotherapy is usually short-lived, with a median time to progression of 3 to 5 months. There are no data available regarding the percentage of patients who receive second-line therapy after first-line failure or progression during treatment but a rough estimate would be that nearly half of them receive second-line treatment. Patients with good performance status (PS), of female gender and with non-squamous histology are more likely to receive further chemotherapy (4).

Thus far, docetaxel, pemetrexed and erlotinib are established second-line agents. Docetaxel has been proven superior to BSC, vinorelbine, or ifosfamide, with improved survival and quality of life (QoL) in NSCLC patients previously treated with platinum-based chemotherapy (5, 6). However, docetaxel shows remarkable hematological toxicity. In order to improve its toxicity profile, weekly schedules of docetaxel were compared to tri-weekly schedules in randomized studies but the efficacy results were not homogenous (7-11). A meta-analysis based on data from 865 patients of 5 randomized studies showed that both schedules

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had similar efficacy but weekly docetaxel was less toxic in terms of febrile neutropenia (12). This meta-analysis suggested that weekly docetaxel represents an alternative for second-line treatment in NSCLC. Pemetrexed has been shown to be equivalent to docetaxel in terms of efficacy, but with significantly fewer side-effects in second-line treatment of patients with advanced NSCLC (13). Histology is an important factor when administering pemetrexed due to the different expression of thymidylate synthase (TS) between adenocarcinoma and squamous cell carcinoma (14). Pemetrexed was found to be superior to docetaxel in patients with nonsquamous NSCLC and docetaxel offered statistically better survival in the squamous subgroup (15). Erlotinib, the third available option, has proven superior to BSC, significantly improving survival and delaying time to symptom deterioration. The average overall response to this agent in the second-line setting is, however, less than 10% (16).

Is Second-line Treatment Beneficial for NSCLC?

Until recently, the benefit of second-line treatment was controversial. The impact of first line chemotherapy on the outcome of second-line chemotherapy was retrospectively investigated within a large phase III study that compared docetaxel to pemetrexed in NSCLC patients after first-line failure. Multivariate analysis showed that gender, stage at diagnosis, PS and best response to first-line therapy significantly influenced overall survival (OS). Additionally, histology and time elapsed from first- to second-line therapy were statistically significant in univariate analysis (17). Moreover, a systematic review of the literature with meta-analysis of RCTs comparing any approach, namely chemotherapy or epidermal growth factor receptor (EGFR) blockage, with placebo showed a 1-year survival rate benefit for second-line treatment (p=0.029) (18). The main objective of a large observational European study was to monitor chemonaive, advanced NSCLC patients outside the clinical trials for eighteen months from initiation of first-line chemotherapy. This study, which enrolled 975 patients with a median age of 65 years, showed that second-line treatment was planned for 29.2% patients, the median time from initiation of first- to second-line chemotherapy was 5.8 months, the patients' PS was mainly 0 or 1, and the best response to treatment was as follows: complete response (CR) 0.4%, partial response (PR) 9.1%, stable disease (SD) 19.3%, progressive disease (PD) 48.8% and unknown 14.3% (19). These data suggests that the role of second-line treatment is beneficial in clinical trials as well as outside these settings. Di Maio *et al*. recently performed a meta-analysis of six trials in an effort to compare second-line doublet chemotherapy to monotherapy and showed that doublet regimens increase progression-free survival (PFS) but are more toxic and do not improve OS (20).

The Rationale Behind Third-line Treatment

There is no consensus as to whether patients should be offered third-line treatment after first- and second-line treatment failure. The growing availability of both chemotherapeutic and biological agents, as well as controlled toxicity and improvement in BSC, have led to increased numbers of patients requiring further treatment. Many patients who still have good PS and who have exhibited minimal toxicity from previous treatments usually receive third-line therapy. Interestingly, some recent studies show that the patients' request to receive active treatments against the disease is stronger than their fear of toxicity. Besides, the wish for survival prolongation seems to be higher than that for control of symptoms (21, 22). In clinical practice, this sometimes leads to administering active treatment up until the last weeks of the patient's life. Many patients would choose chemotherapy for a small benefit in health outcome and for smaller benefit than what their health providers perceive. Patients are concerned about adverse effects less than their physicians are (23). The desire of patients to receive active treatment until the last weeks of their life has been elucidated in an American retrospective study, which included 417 patients treated for advanced NSCLC. Within this study, 84% of patients received first-line treatment, whereas 54%, 26%, 10% and 5% received second-, third-, fourth- and fifth-line treatment, respectively. Forty-three percent and 20% of patients, received chemotherapy in the last 4 and 2 weeks of their life, respectively (24). A twelve-year Austrian retrospective study, which included 1,424 NSCLC patients, showed that 501 patients received first-line, 172 (34.3%) received second-line, 71 (14%) received third-line and 26 patients (5%) received fourth-line treatment (25). The increasing percentage of NSCLC patients receiving third-line treatment was also supported by the analysis of the randomised phase III trial that compared pemetrexed to docetaxel as second-line treatment. Over 40% of patients in this study received third-line therapy post-study. Out of those treated with pemetrexed, 32% received docetaxel post-study. OS observed in the pemetrexed arm with third-line docetaxel was not proven to be different from that observed in patients who received other third-line chemotherapy agents (26).

In contrast, a retrospective analysis was performed examining the clinical course of the disease after two or more treatment lines in NSCLC patients with good PS. Those patients who had received third- or fourth-line chemotherapy after two prior chemotherapy regimens that included platinum and docetaxel administered concurrently or sequentially were eligible. Prior regimens had failed due to disease progression within 90 days of chemotherapy or due to unacceptable toxicity. Over 700 patient records (1993-2000) were examined at one U.S. and one European cancer center and 43 patients fulfilled the inclusion criteria.

Response rates (RR) decreased with each new line of treatment: first-line, 20.9%; second-line, 16.3%; third-line, 2.3%; fourth-line, 0%. The disease control rate (response plus SD) also decreased dramatically from first- to fourth-line treatment, although it was higher for second-line treatment (74.4%) than for first-line (62.8%). Median OS from the beginning of the last treatment (either third- or fourth-line) was 4 months. Patients with stage III disease at diagnosis had longer OS than stage IV patients (p=0.02) (27). This study suggests that third-line treatment may be ineffective but the number of patients is inadequate to reach such a conclusion.

These studies show that a subset of patients with acceptable PS after second-line failure seek further treatment. This review tries to highlight the need for novel therapeutic approaches for patients with recurrent NSCLC who present with disease progression after second-line treatment. At present, few options are available.

Treatment Options Available

Chemotherapy. Pemetrexed, approved as maintenance therapy, was recently evaluated by three retrospective studies as monotherapy in patients who had received more than two prior systemic therapies (median number of three regimens) (28-30). Tolerable toxicity and favorable efficacy were observed (28-30), as 16.3% of patients exhibited PR, whereas in more than 37% the disease remained stable (29). Progression-free survival was similar to that observed in the second-line setting and it is suggested as suitable third-line monotherapy (30). The efficacy of the combination of pemetrexed plus carboplatin/cisplatin in patients previously treated with platinum-based chemotherapy has also been studied and it seems that this doublet could be of benefit with tolerable toxicity (31). The gemcitabine and vinorelbine combination was recently studied in a phase II trial as second-, third-line and beyond treatment in NSCLC but no efficacy was proven (32). S-1, an oral fluoropyrimidine used primarily in gastrointestinal malignancies, shows mild toxicity and modest activity as third-line or further chemotherapy in advanced NSCLC, with an overall response and disease control rate of 5.7% and 40%, respectively (33).

Targeted therapies. Targeted therapies directed toward molecular factors critical to the pathogenesis of cancer growth and survival are the new promising field of research. The EGFR family is part of a complex signal-transduction network that takes part in several critical cellular processes. When activated by binding specific ligands, tyrosine kinase receptors (RTKs) dimerize and phosphorylate the intracellular tyrosine portions of the protein. The activated receptor molecule may then phosphorylate and trigger a diverse array of downstream signaling pathways, including the Ras-Raf-MEK (mitogen-activated and extracellular-signal regulated kinase), extracellular-signal regulated kinase 1 and 2 ERK-1 and ERK-2 pathways that lead to cell growth, the mammalian target of rapamycin (mTOR) pathway leading to protein synthesis and the phosphatidyl-inositol-2 kinase-Akt (PI3K-AKT) pathway sustaining cell survival. Since EGFR is often found in NSCLC cells (34, 35), efforts have been focused on developing new agents that target EGFR. There are two classes of EGFR antagonists that mainly used in clinical practice in NSCLC: the anti-EGFR monoclonal antibody cetuximab and the two small molecule EGFR inhibitors (TKIs), erlotinib (Tarceva®) and gefitinib (Iressa®).

Erlotinib. Erlotinib is a currently approved maintenance treatment in patients with advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy. Its role in the second- and third-line settings has been studied in several trials. A large randomized phase III trial was conducted by the National Cancer Institute of Canada Clinical Trials Group based on a phase II trial of erlotinib administration in previously treated NSCLC patients which showed response rates of 12.3% (36). The BR.21 study was designed to examine whether erlotinib would be effective in prolonging survival in chemotherapy-refractory NSCLC patients. Erlotinib was compared to placebo in stage III/IV NSCLC patients who had failed first- or second-line chemotherapy. The inclusion of a control group receiving placebo was considered ethical owing to lack of benefit from further chemotherapy after failure of standard treatment. A total of 731 patients were randomized in a 2:1 ratio to receive either erlotinib at 150 mg/day or placebo. Half of the patients in the trial were treated with erlotinib as second-line therapy and half received erlotinib as third-line treatment. Almost all patients had previously received platinum-based chemotherapy. As compared to BSC, treatment with erlotinib resulted in significantly prolonging OS (6.7 *vs*. 4.7 months; hazard ratio, HR: 0.70; p<0.001) and PFS (2.2 months *vs*. 1.8 months; HR: 0.6; p<0.001) (16). The QoL evaluation examined the time to clinically significant deterioration of three common lung cancer symptoms (cough, dyspnea and pain) and showed that patients receiving erlotinib had a significantly longer median time to deterioration for all three symptoms (cough: 4.9 *vs*. 3.7 months, p=0.04; dyspnea: 4.7 *vs*. 2.9 month, p=0.04; pain: 2.8 *vs*. 1.9 months, p=0.03). QoL response analyses showed that 44%, 34% and 42% of patients receiving erlotinib showed improvement of these three symptoms, respectively. There was a significantly greater improvement of physical function (31% for erlotinib *vs*. 19% for placebo; p=0.01) and global QoL (35% *vs*. 26%; for erlotinib and placebo, respectively p<0.0001) (37). Subgroups with greater likelihood of response to erlotinib were widely catalogued,

but multivariate analysis revealed that a non-smoking history was the only significant independent predictive factor for survival benefit with erlotinib (38).

The use of erlotinib as third-line therapy is supported by the fact that 50% of patients in the BR.21 study had already received two lines of chemotherapy. Moreover, this EGFR inhibitor showed positive results for patients with a PS of 0-1 as well as for those with a PS of 2-3 (8% and 11% PR, respectively). Median OS was 8.3, 4.3 and 1.9 months in the PS 0-1, PS 2 and PS 3 groups, respectively) (16, 39). It should be noted that the erlotinib toxicity profile was relatively mild, including rash and diarrhea (16).

After taking the above results into consideration, erlotinib received approval for patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Owing to lack of direct comparison of erlotinib to chemotherapeutic agents used in second-line treatment (docetaxel and pemetrexed), use of erlotinib in the second-line treatment is restricted to selected populations. Clinical predictive factors, such as never-smoking status, female gender, Asian ethnicity, adenocarcinoma or bronchoalveolar carcinoma histology, as well as molecular predictive factors, such as *EGFR* and *KRAS* mutations, should be taken into account when choosing NSCLC second-line treatment (40).

The role of erlotinib in third-line treatment seems to be completely different. The main objectives of treatment at this stage are the palliation of symptoms and QoL maintenance (41,42). As BR.21 study showed, erlotinib represents the best therapeutic option for heavily pre-treated patients with deteriorated PS, when survival and QoL determinants are considered (16, 37). Cappuzzo *et al*. (43) showed that erlotinib maintenance therapy is well tolerated and significantly prolongs PFS as compared to placebo. A recent phase II trial by Rossi *et al*. (44) confirmed the activity and efficacy of erlotinib as second and third line treatment in pretreated elderly NSCLC patients, especially in terms of OS. The pharmacoeconomic review by Lyseng-Williamson (45) concludes that erlotinib as second- or third-line treatment is cost-saving when compared to docetaxel or pemetrexed in this group of patients.

Gefitinib. Gefitinib was approved by the Food and Drug Administration (FDA) in May 2003 through an accelerated approval procedure for third-line therapy based on two double-blind, randomized phase II trials. The Iressa Dose Evaluation in Advanced Lung Cancer-1 (IDEAL-1) study enrolled 210 patients in Europe, Australia, South Africa and Japan to receive 250 mg/day or 500 mg/day of gefinitib as monotherapy. The patients had received one or two previous chemotherapy regimens and were not selected according to EGFR expression. There was no difference between the two doses in terms of RR, symptoms improvement, median PFS and median OS. However, the toxicity profile was better with the low dose and gefitinib at 250 mg/day was recommended for previously treated NSCLC patients (46). The IDEAL-2 study had been similarly designed but was conducted in the USA and included patients previously treated with at least two lines of chemotherapy. Both gefitinib doses were similar in terms of the objective RR and symptoms improvement (47). Based on these results, gefitinib was approved as single-agent treatment of patients with locally advanced or metastatic NSCLC, after failure of both platinum-based and docetaxel chemotherapy (48).

However, a subsequent phase III trial (Iressa Survival Evaluation in Lung Cancer, ISEL) assigned 1,692 previously treated patients to receive gefitinib at 250 mg/day or placebo alongside BSC. It did not reveal any statistically significant difference in OS. Although this study did not meet its primary endpoint, it suggested that never-smokers and patients of Asian origin had survival benefit (49). Following this study, in June 2005, the FDA restricted use of gefitinib to patients who were already participating in running clinical trials and to those continuing to benefit from treatment. While gefitinib was not a treatment option for the vast majority of patients in U.S.A, it was approved in other countries and trials investigating its activity continued. A large open-label phase III trial (INTEREST) compared the efficacy of docetaxel (75 mg/m^2 every three weeks) to that of gefitinib (250 mg daily) in patients whose disease progressed after platinum-based chemotherapy. The primary endpoint was the non-inferiority of gefitinib as compared to docetaxel in terms of OS, whereas the co-primary endpoint was the superiority of gefitinib in patients with high *EGFR* gene copy number. Never-smokers and patients of Asian origin represent 20% of the enrolled population. Adenocarcinoma was the most frequent histological type, approximately 55% in both arms. Median OS was similar in the two treatment arms (7.6 months for gefitinib and 8.0 months for docetaxel; HR: 1.020; 96% confidence interval [CI], 0.905-1.150), demonstrating that gefitinib was not inferior to docetaxel. Superiority of gefitinib in patients with high *EGFR* gene copy number was not proven (HR: 1.09, 95% CI: 0.78-1.51; p=0.62; median survival 8.4 *vs*. 7.5 months). In a preplanned subset analysis in patients who were never smokers, of Asian descent and of adenocarcinoma histology, no statistically significant and clinically relevant difference in QoL was observed. The overall rate of adverse effects was lower in the gefitinib arm (50). One more study (IRESSA as Second-line Therapy in Advanced NSCLC, ISTANA) compared gefitinib 250 mg/day to triweekly docetaxel at 75 mg/m^2 as second-line treatment. This study enrolled 161 patients (62% male, 68% adenocarcinoma, 41% never-smokers) and the primary objective was PFS. The latter was longer for gefitinib (p=0.0441) and overall RR was better (p=0.0007). Gefitinib

Table I. *Results from new targeted agents in previously treated NSCLC patients.*

	Ref	Drug	No. pts	Line	PR %	OS (weeks)	PFS (weeks)	Toxicity (grade 3, 4, 5)
Hanna *et al*.	(52)	Cetuximab	60	2/3/4	4.5	35.6	9.2	Rash, anaphylactic reactions, diarrhea
Socinski *et al*.	(53)	Sunitinib	63	2/3/4	11	23.4	12.0	Fatigue, asthenia, pain, myalgia, dyspnea, vomiting, 3 hemorrhage-related deaths
Brahmer *et al*.	(54)	Sunitinib	47	2/3	2	38.1	12.3	Fatigue, asthenia, HT, dyspnoea, hemoptysis, CHF, hypomagnesemia, RF, gastrointestinal
Gatzemeier *et al*.	(55)	Sorafenib	52	2/3/4	0	29.3	11.9	bleeding HFS, hypertension, elevated lipase, MI
Soria *et al*.	(56)	Everolimus	85	2/3	7.1	-	11.3	Stomatitis, mucositis, cough, dyspnea, fatigue, anorexia, anemia, diarrhea
				3/4	2.3	-	11.6	
Oh *et al*.	(57)	Enzastaurin	55	2/3	0	33.6	7.2	Fatigue, thromboembolism, ataxia, anemia
Leighl *et al*.	(58)	Aflibercept	98	3	6	24.8	10.8	Dyspnea, hypertension, proteinuria, hemoptysis, fatigue, headache, anorexia
Govindan *et al*.	(59)	Bexarotene	146	3/4/5	-	20	-	Hypertriglyceremia/skin rash; 14% patients discontinued therapy because of toxicity
Dragnev *et al*.	(60)	Bexarotene plus erlotinib	40	3/4	5	21	7	Pulmonary hemorrhage, rash/mouth sores, cough, hypereosinophilic syndrome, abdominal pain
Hainsworth *et al*.	(61)	AZD6244	84	2/3	5	-	9.6	Dermatitis acneiform, diarrhea, nausea, vomiting

No. pts: Number of patients; PR: partial response; OS: overall survival; PFS: progression-free survival; CHF: congestive heart failure; HT: hypertension; RF: respiratory failure, HFS: hand-foot syndrome, line: line of chemotherapy, MI: myocardial infarction.

was well tolerated and had similar QoL improvement rates as docetaxel, suggesting that gefitinib is a valid option as second-line therapy (51).

New Targeted Therapies

Newer targeted agents that are being examined in the third-line setting are presented in Table I.

The monoclonal chimeric antibody against EGFR, cetuximab, which has not yet received approval in combination with cisplatin/vinorelbine for first-line treatment of NSCLC, has already been evaluated in patients with recurrent or progressive disease after receiving at least one prior chemotherapy regimen. In this study, 66 NSCLC patients were enrolled to receive weekly infusions of cetuximab until disease progression or treatment intolerance. The RR was 4.5%, the median PFS was 2.3 months (95% CI, 2.1 to 2.6 months) and the median OS was 8.9 months (95% CI, 6.2 to 12.6 months) (52).

Sunitinib malate (Sutent®) is an oral, multitargeted TKI with antiangiogenic and antitumour activities. In a phase II clinical trial, 63 patients were assigned to receive sunitinib (50 mg/day for 4 weeks followed by 2 weeks of no treatment in 6-week cycles) after platinum-based chemotherapy failure. Results were promising showing overall RR of 11.1% (95% CI, 4.6% to 21.6%), median PFS of 12.0 weeks (95% CI, 10.0 to 16.1 weeks) and median OS 23.4 weeks (95% CI, 17.0 to 28.3 weeks). The 1-year survival rate was 20.2% and the treatment was well tolerated (53). One more phase II study evaluated sunitinib malate at a continuous oral dose of 37.5 mg/day. Forty-seven NSCLC patients who had received of one or two previous chemotherapy regimens were evaluated. The RR was 2.1% whereas the disease remained stable in 19.1% of cases. The median PFS was 12.3 weeks, median OS was 38.1 weeks and toxicity was tolerable (54).

One more oral multi-kinase inhibitor that targets the Raf/MEK/ERK pathway, sorafenib, was evaluated in a phase II clinical trial. A number of 52 previously treated patients with relapsed or refractory advanced NSCLC received 400 mg *bid* of sorafenib continuously. Fifty-nine percent of patients presented with SD. The median PFS was 11.9 weeks and the median OS was 29.3 weeks with acceptable toxicity (55). Furthermore, a randomised, double-blind, placebo controlled phase II study evaluated the role of sorafenib in third-line and beyond in NSCLC. This study used a randomized discontinuation design in order to enrich for patients with slowly growing disease who are theoretically more likely to benefit from sorafenib. Preliminary results suggest sorafenib prolongs PFS in heavily pre-treated patients, while toxicity is mild with symptoms including rash, hand-foot syndrome, fatigue, INR abnormalities and hemoptysis (62).

AZD6244 is a selective MEK inhibitor that was recently studied by Hainsworth *et al*. (61) in second- and third-line settings. AZD6244 showed clinical activity but its advantage over pemetrexed is yet to be proven. The authors suggested it be further studied taking the status of *BRAF* or *RAS* mutation into account.

Several agents that inhibit mTOR kinase, an important mediator of tumour growth and proliferation, are currently studied in clinical trials. Everolimus (RAD001) was evaluated in a phase II trial comparing patients who failed ≤2 lines of chemotherapy, one platinum-based (arm 1) to those who failed second line chemotherapy combined with an EGFR antagonist (arm 2). Eighty-five patients were enrolled in this study. The median PFS was 2.6 months in arm 1 and 2.7 months in arm 2, while toxicity was moderate (56).

Enzastaurin, an oral serine/threonine kinase inhibitor, represents one more agent under evaluation for recurrent NSCLC. In a phase II study, 55 patients who had previously failed one or two systemic regimens (including one or more platinum-based chemotherapy regimens) received 500 mg/day of enzastaurin. Median OS was 8.4 months (95% CI, 6.0 to 13.6 months) and median PFS was 1.8 months (95% CI, 1.7 to 1.9). Toxicity was mild (57).

Vascular endothelial growth factor (VEGF) is the dominant growth factor controlling angiogenesis. Tumour cells, like normal cells, require a blood supply with subsequent access to several nutrients in order to grow and survive. VEGF blockage by bevacizumab binding, a humanized monoclonal antibody against VEGF-A, has an established role alongside chemotherapy in first-line treatment of NSCLC (63, 64) and seems to be effective in the second-line setting as well (65) even in case of brain metastases as long as they are treated (66). Another angiogenesis inhibitor, Aflibercept (VEGF Trap), is a recombinant fusion molecule with great affinity for binding to VEGF and placentar growth factor (PGF) and it has been evaluated in a phase II trial in cases of lung adenocarcinoma who have failed platinum-based chemotherapy and erlotinib. It was well tolerated but had minor single-agent activity in heavily pretreated lung adenocarcinoma (58).

Bortezomib is a selective proteasome inhibitor that was recently evaluated by Scagliotti *et al*. in combination with pemetrexed or alone in NSCLC pretreated patients but there was no significant clinical efficacy proven (67). Vandetanib is an oral multi-kinase inhibitor that was shown to improve PFS when added to docetaxel after first-line treatment failure (68).

There is evidence that inactivated retinoid receptors in the cell nucleus may play a role in the development of lung tumours. Bexarotene is a selective retinoid acid receptor (RXR) modulator that binds RXR alpha, beta and gamma (69, 70). Bexarotene was evaluated in NSCLC patients who had received at least two regimens including platinum and taxane. A total of 146 patients were enrolled in this phase II trial that showed that median OS was 5 months (95% CI, 8 to 15 months) and 1-year survival 23% (95% CI, 16% to 31%). Bexarotene given as third-line treatment did not reach the intended median survival of 6 months (59). One more study evaluated the concomitant administration of bexarotene and erlotinib in heavily pre-treated NSCLC patients. From 40 enrolled patients, 2 patients showed partial response. Median PFS and OS were 7 and 21 weeks, respetively. Toxicity was tolerable (60).

Selecting Second- and Third-line Treatment

Treatment options for NSCLC patients with metastatic disease who have received two lines of treatment are evolving. Currently, there are no data from phase III trials supporting the routine use of chemotherapy as third line treatment. It is very important to be able to identify patients who are most likely to benefit from third line treatment and to take their *EGFR* mutation status into account (Figure 1). A retrospective analysis by Girard *et al*. (71) demonstrated that the best candidates can be selected using standard prognostic factors (age, pack-years, weight loss, tumour spread). Disease control after first- and second-line treatment was the best predictor of survival after third-line treatment (71).

Large clinical trials have significantly changed standard first- and second-line treatment and have influenced options available as third-line therapy. Moreover, maintenance treatment after response to first-line therapy is increasingly being used in clinical practice leading to early use of agents potentially active in a second- or third-line setting. Apart from docetaxel that can be used in a platinum-based regimen, the combination of cisplatin and pemetrexed represents an attractive combination for non-squamous lung cancer in the first-line setting (72). The randomised phase III Iressa Pan Asia Study (IPASS) evaluated the role of gefitinib *versus* chemotherapy (carboplatin/paclitaxel) in chemotherapy-naive, light or non-smokers, Asian patients. The most notable finding was the benefit shown in EGFR tyrosine kinase mutation-positive patients in terms of RR. The primary end point, PFS, was met but no difference in OS was shown, probably because of the post-study use of EGFR inhibitors in most patients in the chemotherapy arm (73).

Interestingly, a single-institution retrospective study evaluated the benefit from the administration of erlotinib as first-, second- and third-line treatment. In 137 consecutive patients treated with erlotinib for 2 years, erlotinib was used as first-line treatment in 27%, second-line in 45% and third-line in 28%. There was no significant difference in median OS between these settings (74). Moreover, two studies evaluated the efficacy of erlotinib or gefitinib when compared to docetaxel in the second- and third-line setting. A retrospective review of the NSCLC database at Princess Margaret Hospital in Toronto identified 74 patients out of which 52 (70%) received docetaxel as second-line and 22 (30%) as third-line therapy. Twenty-two and 31 of these patients received second- and third-line EGFR TKI, respectively. In both second- and third-line settings, PFS and OS were not significantly different between the two groups

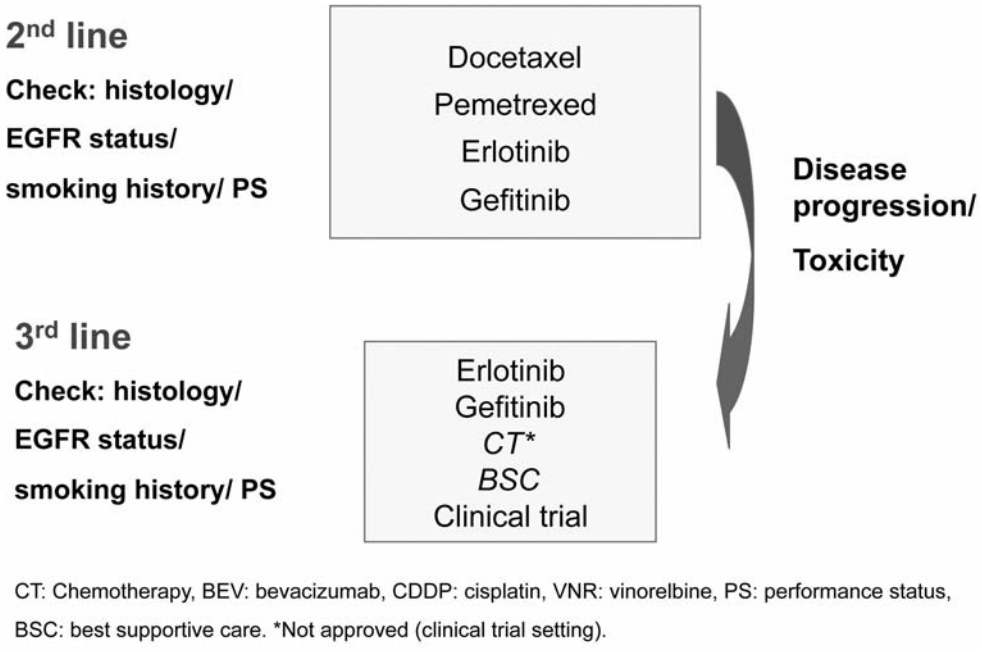

Figure 1. *Treatment algorithm for second- and third-line treatment of unresectable, locally advanced and metastatic NSCLC.*

(75). One more retrospective study evaluated the effectiveness of erlotinib and gefitinib in patients with relapsed NSCLC in second- and third-line settings, and compared this with that of docetaxel. No statistically significant difference in OS between these three drugs in either setting was present (76).

However, based on the BR.21 trial, erlotinib should be administered as second-line treatment in patients considered unfit for chemotherapy, or in a subgroup of patients with positive predictive clinical and/or molecular factors especially in never-smokers, and as third-line therapy. The positive results of the INTEREST trial conducted in patients who were fit for further chemotherapy after the failure of one or two previous chemotherapy regimens support the consideration of EGFR inhibitors as a reasonable alternative to second-line chemotherapy and especially in third-line treatment after pemetrexed or docetaxel failure (77).

Regarding the comparative differences between erlotinib and gefitinib in terms of efficacy, Kim *et al*. (78) recently retrospectively studied 467 patients who had received either of these EGFR inhibitors after progression on prior therapies. There was no statistically significant difference with regards to OS and PFS.

Conclusion

Although gefitinib and erlotinib are the only drugs of already proven efficacy in third-line therapy, there are also many other new agents under investigation. As new therapeutic targets are identified, options for further treatment in previously treated NSCLC patients are increasing. Effectiveness and safety of targeted therapies is associated with specific histological subtypes. Large prospective studies are needed in order to examine the effectiveness of treatment beyond second-line in NSCLC patients, in an effort to maintain a reasonable QoL as well as to increase OS.

Conflict of Interest

None.

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