Abstract. Several new agents have been introduced in the palliative treatment of advanced and metastatic NSCLC in the recent years. In randomized trials, the new third-generation regimens showed comparable efficacy to each other, but a better response rate and time to progression combined with a remarkably improved tolerability compared to "classic schedules". In patients who are not suitable for platinum-based therapy, monotherapy could be an attractive opportunity, as shown in randomized trials. In second-line therapy, the novel antifolate Pemetrexed showed comparable activity to Docetaxel with significantly reduced toxicity. Among the new oral tyrosine kinase inhibitors, Erlotinib proved to be active in second- and third-line treatments, whereas in first-line treatment, no survival benefit has been observed to date.

Non-small cell lung cancer (NSCLC) has become a worldwide health problem. More than 60% of patients with NSCLC are not suitable for curative treatment at the time of diagnosis because of advanced or metastatic disease (1). Taking the bad prognosis of these patients into consideration, each treatment has a palliative intention.

After the impact of Cisplatin-based chemotherapy on the survival of patients with NSCLC had been confirmed by the NSCLC Collaborative Group and recently by the Big Lung Trial (2, 3), many regimens using new agents like the taxanes, the topoisomerase I inhibitors Topotecan and Irinotecan, Vinorelbine and Gemcitabine have been investigated. Furthermore, specific pathways of intracellular signal transduction in tumor cells and key points for targeted manipulations have been identified. In conclusion, several new specific therapeutic options have been developed and applied.

Combined chemotherapy

Several randomized trials have recently been conducted to compare the efficacy of new regimens. In the largest study with 1207 patients, Schiller et al. (4) found no significant difference in survival among the regimens Cisplatin/Paclitaxel, Cisplatin/Gemcitabine, Cisplatin/Docetaxel and Carboplatin/ Paclitaxel. With respect to the low rate of toxic effects, the ECOG chose Carboplatin/Paclitaxel as its reference regimen for future studies (4).

In a Southwest Oncology Study group, comparing Cisplatin/Vinorelbine with Carboplatin/Paclitaxel, there was no difference between the arms in terms of response, survival and quality of life, but significantly higher rates of toxic effects in the group of patients who received Cisplatin/Vinorelbine (5). These results were underlined by a study of Scagliotti et al. (6), comparing Cisplatin/Gemcitabine, Cisplatin/Vinorelbine and Carboplatin/Paclitaxel, who noticed an increased rate of grade 3/4 neutropenia and nausea/vomiting in the Cisplatin/Vinorelbine arm and an increased rate of thrombocytopenia in the Cisplatin/Gemcitabine arm. In agreement with the other studies, there were no differences concerning the efficacy between the arms (6).

In contrast, Fosella et al. reported a significantly higher response rate and a significantly longer survival for Docetaxel in combination with Cis-/Carboplatin combined with a improved quality of life compared to Cisplatin/Vinorelbine (7). In the last trial of Alberola et al., the three-drug combination Gemcitabine, Vinorelbine and Cisplatin failed to show any superiority regarding response or survival and was associated with a highly significant increase in toxicity (8) (Table I).

Targeting the question of the superiority of the new regimens over the old second-generation regimens, a couple of randomized trials have been published in recent years. Five
studies compared the combination Gemcitabine/Cis-
(Carboplatin) with the MIC regimen (9-11) Cisplatin/
Vindesine (12) or Cisplatin/Etoposide (13). In most studies, a
significant improvement in response (9, 10, 12, 13) and time to
progression was achieved in the Gemcitabine/Platin arm (9,
12, 13). Some studies even reported a significant increase in
survival for the experimental arm (9, 12, 13). Hematotoxicity,
especially thrombocytopenia, was pronounced in the
Gemcitabine/Platin group, whereas non hematological side-
effects appeared more frequently in the "classic" arms (9-13).

Comparing Paclitaxel/Cis-(Carboplatin) with Etoposide
(Teniposide)/Cis-(Carboplatin), Giaccone et al. observed a
significant increase in response rate and quality of life for the
Paclitaxel arm (14), and Bonomi et al. a significantly superior survival with comparable quality of life data (15).
Le Chevalier et al. showed a significantly better response rate and survival for Cisplatin/Vinorelbine compared to
Cisplatin/Vindesine (16, 17). Finally, Negoro et al. reported a
clear trend in survival for Cisplatin/Irinotecan versus
Cisplatin/Vindesine, without reaching a significant level (18). Analyzing the toxicity, there was a high rate CTC
Grade 4 neutropenia in the Vindesine arm, but also a
remarkably high rate of CTC 3/4 diarrhea in the Irinotecan arm (18) (Table II).

**Monotherapy**

Despite the superiority of combination therapy versus
monotherapy regarding survival, which has been underlined by
two meta-analyses and several randomized trials for the
combinations Carboplatin/Paclitaxel, Carboplatin/ Gemcitabine,
Cisplatin/Docetaxel, Cisplatin/ Vinorelbine and Cisplatin/
Irinotecan (19-23, 16-18), many patients with NSCLC are not
suitable for combination therapy because of age, bad
performance status or comorbidity. An attractive alternative with a significantly reduced toxicity is monotherapy with one of
the new agents. Gridelli observed no difference in survival
comparing Gemcitabine/Navelbine with Gemcitabine or
Navelbine in patients who were at least 70 years old (24). Other
randomized studies suggested that monotherapy with Paclitaxel,
Docetaxel, Vinorelbine or Gemcitabine might be a convenient
alternative for patients with a bad performance status, leading
to a significant increase in survival compared to best supportive
care (BSC) (25-27) and to a better control of tumor-related
symptoms combined with an improvement of quality of life (25-
28). Another attractive prospective for palliative treatment is
the new oral application of Vinorelbine, which was active in
stage IV NSCLC and showed comparable efficacy to
intravenous Vinorelbine in a randomized trial (29, 30).
The gold standard in second-line treatment of NSCLC, which has proven activity in a randomized trial, remains Docetaxel (31). In recent years, a couple of phase II studies with weekly applications of Docetaxel (32, 33) or Paclitaxel (34) in order to increase the dose density were performed. Besides encouraging efficacy data with response rates of 10-37.5% and median survival times of 4.5-8 months, low toxicity profiles were observed especially with low hematotoxic side-effects (32-34).

This year Hanna et al. published a randomized phase III trial of Pemetrexed, a novel multitargeted antifolate, versus Docetaxel in second-line therapy of NSCLC. They reported comparable efficacy data between Pemetrexed and Docetaxel, with response rates of 9.1 versus 8.8%, median time to progression of 2.9 versus 2.9 months and median survival of 7.9 versus 8.3 months. Furthermore, hematotoxic...
side-effects appeared much more frequently in the Docetaxel arm (neutropenia CTC 3/4 5.3% versus 40.2%, febrile neutropenia: 1.9% versus 18.7%), which led to a higher rate of hospital admissions due to toxicity (1.9% versus 13.9%) (35). Meanwhile, Pemetrexed is approved by the FDA and EMEA for second-line therapy in NSCLC.

**Targeted therapies**

Among the wide spectrum of new substances in targeted tumor therapy, to date most clinical data are available for the oral Tyrosine Kinase Inhibitors (TKI) Gefitinib (ZD 1839, Iressa) and Erlotinib (Tarceva™). In two randomized phase II trials, Iressa was applied in two dosages (250 mg / 500 mg) in patients with recurrent or progressive NSCLC and at least one prior treatment. With objective response rates between 9-19%, median overall survival times of 5.9-7.9 months and estimated 1-year survival rates of 24-35% without any difference concerning the dosage, the "traditional" efficacy data were similar to data for second-line chemotherapy in NSCLC (36, 37). Furthermore, an early symptom improvement in 35-43% of the evaluable patients and an improvement in quality of life in 24-34% of the evaluable patients were observed (36, 37).

Two large randomized double-blinded placebo-controlled phase III trials investigated Gefitinib in combination with Gemcitabine/Cisplatin (Intact I) or Carboplatin/Paclitaxel (Intact II) in first-line therapy of NSCLC. Both studies failed to show survival benefits for the Gefitinib-containing arms (38, 39). It is unclear why the combination of Gefitinib with standard doublet chemotherapy failed to show survival benefits in the first-line setting. Possible explanations include a pharmacodynamic antagonism between the drugs, or that treatment with chemotherapy sensitizes tumors to EGFR-targeted therapy, so that Gefitinib is more effective in pretreated patients.

These results were confirmed by two additional double-blinded placebo-controlled Phase III trials which evaluated, in a similar design, the Erlotinib versus Placebo in combination with first-line chemotherapy in NSCLC (TALENT, TRIBUTE). Again, no increase in survival or progression-free survival by addition of the TKI could be detected (40, 41). On the other hand, the placebo-controlled phase III trial of the TKI Erlotinib in second/third-line treatment of NSCLC showed a highly significant increase in survival (median survival: 6.7 versus 4.7 months, one-year survival 31% versus 21%, Erlotinib versus Placebo), as well as progression-free survival (median progression-free survival: 9.7 versus 8.0 weeks, Erlotinib versus Placebo) (46). These data led to approval of Erlotinib in second/third-line therapy of NSCLC by the FDA last autumn.

Blocking the endothelial growth factor receptor by a monoclonal antibody is another opportunity to inhibit the intracellular signal cascade. Schiller et al. observed good efficacy data with a median survival of 10.1 months and a 1-year survival of 42% for the combination Trastuzumab and Carboplatin/Paclitaxel (42), while Gatzemeier et al. failed to show a difference in time to progression for Trastuzumab and Cisplatin/Gemcitabine versus Cisplatin/Gemcitabine (43). Preliminary data of a randomized phase III study indicated an improved response rate for Cetuximab and Cisplatin/Vinorelbine versus Cisplatin/Vinorelbine (44).

Further mechanisms of targeting the intracellular signal pathways include the synthesis of protein kinase c alpha by antisense proteins. Despite encouraging phase II data, ISIS (Affinitac) failed to show a survival benefit in combination with chemotherapy versus chemotherapy alone in a large phase III trial and was associated with more systemic and local side-effects (45).

Other randomized trials to define the role of the modern "Biologics" like the farnesyl transferase inhibitor Lonafarnib are in progress.

**Conclusion**

Platin-based chemotherapy remains the standard therapy in advanced or metastatic NSCLC. With the third-generation agents Gemcitabine, Docetaxel, Paclitaxel, Vinorelbine, Irinotecan and Topotecan, we have reached a new plateau of efficacy. Comparative trials with second-generation trials have shown an increase in response and time to progression and, in some trials, also an increase in survival for the "new" regimens. In general, the third-generation agents were better tolerated than the second-generation agents (9-18). Among the "new" regimens, only small differences in efficacy and toxicity could be detected in randomized trials. The regimen Cisplatin/Vinorelbine showed a relatively high toxicity (4-7). A significantly longer survival was proven for two drug regimens compared to monotherapy which, on the other hand, caused significantly more toxic side-effects (19-23). Nevertheless, monotherapy with Paclitaxel, Docetaxel, Vinorelbine or Gemcitabine is an attractive alternative for patients with bad performance, with significantly improved survival and quality of life in comparison with "Best Supportive Care" (24-28). Looking at second-line therapy, weekly application of taxanes offered attractive efficacy data and low toxicity rates (32-34). Furthermore, second-line therapy with Pemetrexed showed equal survival and time to progression compared with Docetaxel, but a significantly reduced hematotoxicity (35).

Among the modern "Biologics" the oral Tyrosine Kinase Inhibitor Erlotinib (Tarceva™) demonstrated...
significant activity in second-/third-line treatment with an increase in survival and progression-free survival (46). In first-line treatment, no additional benefit of Gefitinib or Erlotinib in combination with chemotherapy could be shown (38-41). Other principles of EGFR-inhibition, like the monoclonal antibody Cetuximab (Erbitux™) or other targeting therapies, are currently under investigation.

References


