Chapter 3
Lung Cancer

Stefan Zimmermann, Alessandra Curioni Fontecedro, Rolf A. Stahel, and Solange Peters

Abstract Lung cancer treatment strategy relies on an accurate staging of the disease and a careful evaluation of patient characteristics, including capability of undergoing and tolerating a defined treatment plan. Therefore, a solid knowledge on all intervention-related adverse events and drug toxicities is essential for a reliable decision-making process.

Most lung cancer patients are diagnosed at an advanced stage of the disease, correlated with a dismal prognosis. Systemic therapy is the mainstay, and drug selection still strongly relies on expected toxicity profile. This chapter first

S. Zimmermann, M.D. (✉)
Centre Pluridisciplinaire d'Oncologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
e-mail: stefan.zimmermann@chuv.ch

A.C. Fontecedro, M.D.
Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland

R.A. Stahel, M.D.
Clinic of Oncology, University Hospital Zurich, Ramistrasse 100, Zurich, Switzerland

S. Peters, M.D., Ph.D.
Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

M.A. Dicato (ed.), *Side Effects of Medical Cancer Therapy,*
DOI 10.1007/978-0-85729-787-7_3,

describes the drug standard options and their respective toxicities in this context. Side effects of more complex multimodality combined treatments of early non–small-cell lung cancer as well as small-cell lung cancer, usually involving use of the same cytotoxic agents jointly with surgery and radiotherapy, are discussed in the second part of this chapter.

Keywords Non–small-cell lung cancer • Small-cell lung cancer Side effects • Tyrosine kinase inhibitor (TKI) • Platinum doublets Combined modalities

Non–Small-Cell Lung Cancer

Lung cancer is the most common malignancy and the leading cause of human cancer deaths worldwide. Lung cancer deaths have begun to decline in men, reflecting a decrease in smoking; in contrast, it has become the main cause of cancer deaths in women in developed countries [1]. Seventy-five percent of patients are symptomatic at the time of diagnosis. The majority of patients with non–small-cell lung cancer (NSCLC) present at an advanced stage of the disease, with a poor prognosis and the absence of any curative option. For earlier-stage disease, essentially stages I and II (cT1a cN0 to cT2b cN1, according to the seventh edition of the TNM staging system), upfront surgery, followed by adjuvant chemotherapy for stage II and selected IB patients, offers the best chances for long-term survival. In stage IV, systemic palliative treatment is recommended with a series of targeted agents that constitute potential new treatment options, as they have shown promising results in a subset of selected NSCLC patients.

Systemic Therapy in Advanced NSCLC

Decisions regarding systemic therapy for advanced NSCLC have traditionally been based on performance status of the patients, comorbidities, expected toxicity profile, and patient preferences. While this still holds true, recent developments mandate that one

take additional information into account, namely, tumor histology differentiating non-squamous from squamous cell lung cancer as well as molecular tumor characteristics.

First-Line Systemic Therapy for Advanced NSCLC

Adenocarcinoma

In the past few years, treatment of metastatic adenocarcinoma of the lung has changed remarkably. Until a few years ago, adenocarcinoma patients were treated with standard NSCLC chemotherapy, irrespective of any histologic consideration. Nowadays patient selection has become mandatory in order to customize treatment. For adenocarcinoma, the ESMO guidelines recommend the analysis of EGFR (epithelial growth factor receptor) mutational status before making decisions about the frontline therapy [2]. In the presence of activating mutations, tyrosine kinase inhibitors (TKIs), namely, gefitinib [3, 4] or erlotinib [5–7], are recommended, because they have been associated with a higher response rate and a significantly better progression-free survival as compared to chemotherapy.

In the absence of activating mutations, a platinum-based combination with pemetrexed is preferred. Pemetrexed combined with cisplatin was associated with a better tolerability and better overall survival compared to a gemcitabine combined with cisplatin [8]. Cisplatin, if possible, should be preferred as frontline therapy owing to improved progression-free survival and overall survival when compared to carboplatin based on large meta-analyses [9]. A platinum-based doublet regimen with the addition of bevacizumab can also be considered, particularly in combination with carboplatin and paclitaxel [10, 11].

Squamous Cell Carcinoma

The combination of a platinum-based therapy with gemcitabine can be considered as a first choice, but other doublets appear to be equally effective [12]. Molecular analysis of squamous cell lung cancer has not yet entered routine practice.

Second-Line Systemic Therapy for Advanced NSCLC

With the exception of patients with an EGFR-mutated tumor receiving first-line erlotinib or gefitinib, second-line therapy usually consists of monotherapy with either docetaxel or erlotinib or, for patients with non-squamous NSCLC, pemetrexed, if it is not administered as first-line therapy. For patients with adenocarcinoma and an ALK gene rearrangement, the tyrosine kinase inhibitor crizotinib is emerging as a promising, and probably future standard, option [13].

Palliative Radiotherapy

Palliative radiotherapy might be required to treat painful metastasis (bone, skin, soft tissue) and local complications due to metastasis (e.g., CNS or spinal cord compression) or related to the primary tumor (hemoptysis, vena cava compression, atelectasis due to bronchial obstruction). Usually, the relatively low dose delivered in this setting and the limited field extent strongly limits this strategy's toxicity, which consists mainly of local inflammation-related symptoms and fatigue. A rare side effect is the radiation recall syndrome (RRS), an inflammatory skin reaction that occurs in a previously irradiated body part following drug administration. This phenomenon may occur from days to years following exposure to ionizing radiation.

Side Effects of Agents Used for the Systemic Treatment of Advanced NSCLC

Clinical Side Effects of Tyrosine Kinase Inhibitors

The currently used EGFR TKIs, erlotinib and gefitinib, may be given for long periods in patients with sensitizing EGFR mutations and therefore might be associated with chronic side effects. The most common are cutaneous and gastrointestinal toxicities. Grade 1–2 cutaneous side effects have been reported in more than 60 % of patients, and grade 3–4 in

about 15 % of patients. These include folliculitis, which can be treated, if moderate, with topical antibiotics and systemically with tetracyclines (e.g., doxycycline 100 mg/day) in case of widespread lesions. Other typical cutaneous side effects are hair changes (as trichomegaly) and paronychial inflammation. This disorder can progress from erythema to painful lateral nail fold pyogenic granuloma-like lesion. As prevention, the patient should be advised to avoid trauma to the paronychium. In case of advanced lesions, antiseptic treatments should be applied and bacterial cultures should be sampled, if a bacterial infection is suspected. The use of steroid for cutaneous side effects remains controversial [14].

The most common gastrointestinal side effects of TKIs are diarrhea, described in about 10 % of patients and commonly treated with loperamide, and nausea [15]. Fatigue has been also reported in 5–15 % of patients [16]. Infrequent but potentially fatal complications include an acute interstitial lung disease (ILD) and acute hepatitis; treatment of these side effects includes high-dose steroids [17, 18].

Clinical Side Effects of Chemotherapy

Cisplatin

The most common side effects of cisplatin include nausea and fatigue, as well as neurotoxicity and ototoxicity, which have been known to sometimes last several weeks or months after treatment; neurotoxicity potentially can worsen after the end of treatment. Myelosuppression due to cisplatin occurs in about 50 % of patients and is generally mild, with only 10 % of patients experiencing grade 3–4 toxicity [19, 20]. To date there is no indication for prophylactic antibiotics or granulocyte colony-stimulating factor (G-CSF) therapy in patients receiving cisplatin-based chemotherapy. Nausea and vomiting occur very frequently; therefore, prophylactic therapy with a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant is recommended [21]. Ototoxicity characterized by a dose-dependent sensorineural hearing loss with tinnitus has been described to affect 15–20 %

of patients. Prevention of this complication includes a hearing assessment before treatment in order to exclude patients with hearing diseases from cisplatin-based chemotherapy. If it occurs during treatment, the recommendation is to discontinue cisplatin and to use alternative agents [22].

Nephrotoxicity may result from a direct effect of cisplatin to tubular epithelial cells as well as from vasoconstriction in the renal microvasculature and proinflammatory effects, leading to a renal function impairment and electrolyte alteration. In order to prevent this complication, intravenous isotonic saline before and after the treatment must be administered. Treatment of nephrotoxicity includes the discontinuation of cisplatin and the management of acute renal dysfunction or renal failure as for other diseases.

Carboplatin

Carboplatin was developed to provide a less toxic, more convenient alternative to cisplatin. However, hematologic toxicity is more pronounced than with cisplatin, including severe neutropenia, anemia, and thrombocytopenia [9, 23]. The use of prophylactic G-CSF might be considered when carboplatin is combined with taxanes. Ototoxicity, neurotoxicity, and renal toxicity occur less frequently with carboplatin compared to cisplatin, but electrolyte disorders can occur in about 5 % of patients. Nausea or vomiting are largely less intense than with cisplatin; the combination of palonosetron plus dexamethasone prophylaxis is generally sufficient for prevention. Of note is the occurrence of allergic infusion reactions reported in up to 15 % of patients; interestingly, these develop more often in patients who have been extensively treated with this medication [24]. Recurrence of such reactions at readministration of carboplatin can be successfully prevented with desensitization procedures.

Pemetrexed [8, 25, 26]

Pemetrexed is generally part of the first-line treatment for adenocarcinoma. The most common side effect of pemetrexed

is myelotoxicity. The administration of vitamin B12 concurrent with folate acid has reduced its hematotoxicity to a very moderate level, with grade 3 and 4 neutropenia occurring in only about 15 % of patients. Nausea and vomiting have been reported in less than 5 % of patients. A common grade 1–2 side effect is constipation.

Bevacizumab [11]

The most common grade 3 or higher events reported with bevacizumab are thromboembolic events (5 %), bleeding (epistaxis, hemoptysis, CNS hemorrhage, 2–3 %), gastrointestinal perforation (1 %), hypertension (5–8 %), and proteinuria (3–6 %). Myelotoxicity is almost nonexistent as monotherapy; a slightly higher rate of neutropenia, febrile neutropenia, and thrombocytopenia has been reported when it is combined with chemotherapy as compared to chemotherapy alone [27, 28].

Renal toxicity is a rare but possible fatal side effect due to renal thrombotic microangiopathy and interstitial nephritis, leading to proteinuria and acute kidney injury. Clinically, the most important side effect is hypertension due to the production of nitric oxide as well as increase of vascular resistance through the inhibition of new blood vessel formation, as observed as a drug class effect also with other antiangiogenic molecules. Hypertension has been reported as grade 1–2 in about 15 % of patients and in 2–10 % as grade 3–4 [29, 30]. To date, there are no guidelines for treatment of hypertension in these patients; however, there are controversies regarding the use of calcium antagonists in this setting [31, 32]. Determination and management of blood pressure during therapy, with a goal of less than 140/90 mmHg for most patients, in patients with specific preexisting cardiovascular risk factors is recommended.

Gemcitabine [33, 34]

Toxicity of gemcitabine is generally mild and reversible after discontinuation of medication. The most common side effects are flu-like symptoms in about 50 % of patients, with fever or

arthralgia. Edema (e.g., ankles) is also often observed and does not correlate with renal or cardiac dysfunction [35]. Grade 3–4 myelosuppression occurs frequently, including anemia (5 %), thrombocytopenia (1 %), leukopenia (7 %), and neutropenia (22 %), rarely resulting in neutropenia-related infection. Grade 3–4 liver toxicity can be detected in up to 10 % of patients. Nausea and vomiting often occur but are of low grade and can be prevented with a single antiemetic agent such as dexamethasone, a 5-HT_3 receptor antagonist, or a dopamine receptor antagonist. Of note are a few cases of severe lung toxicity, with a frequency varying in several reports from 0.1 to 5 % [36].

Docetaxel [25, 37, 38]

The most common side effects of docetaxel are myelotoxicity and fatigue. The rate of grade 3 or 4 neutropenia due to docetaxel varies from 40 to 60 % (according to dosage), and the risk of neutropenic fever is described in 3 % of patients. These results led to the consideration of adopting a prophylactic therapy with G-CSF, which to date is recommended in patients who had experienced a clinically significant neutropenic event with a previous cycle. Nonhematologic toxicities included alopecia, mild nausea and vomiting, and allergic manifestations such as skin rash and pruritus; therefore, pretreatment with steroids is recommended. Rare hypersensitivity reactions to docetaxel can be overcome with desensitization procedures.

Treatment of Early NSCLC

Surgery

Lobectomy and systematic lymph node dissection is considered standard therapy for early (stage I and II) NSCLC. Sublobar resection in the form of anatomical segmentectomy may lead to equivalent survival rates among patients with stage I NSCLC less than 1 cm in size, and is associated with fewer

complications and better postoperative lung function [39]. Large wedge resections may be an option for patients who cannot tolerate a lobectomy because of severely compromised pulmonary function, advanced age, or other significant comorbidity, but they do not represent a standard of care.

Thirty-day mortality rate after lobectomy is expected to be lower than 2 % in high-volume hospitals [40]. Pretreatment pulmonary functions tests are well-known predictors of surgical risk [41–43].

Anatomical resections are currently performed according to the Bolliger and Miller algorithms that are based on forced expired volume in 1 second (FEV1) and lung carbon monoxide diffusion capacity (DLCO). Percentage of predicted FEV1 and DLCO values were shown to correlate with patient outcome (hospital and overall mortality) in patients undergoing resections. Postoperative complications and mortality were also shown to be correlated, even with a large variability, to hospital volume and surgeon skills [44]. Pneumonectomy is seldom indicated in stage I and II NSCLC, but it is associated with a higher operative mortality rate, especially for right pneumonectomy [45].

Minimally invasive video-assisted lobectomy was shown to be equivalent to open lobectomy in terms of locoregional recurrences. Data suggest a reduced systemic recurrence rate and an improved 5-year mortality rate, but since most studies were not randomized, the effect of case selection is difficult to ascertain, even if highly probable [46]. Complete mediastinal lymphadenectomy adds little morbidity to a pulmonary resection for lung cancer and possesses a prognostic impact [47, 48].

A consistent proportion of patients undergoing lung resection exhibit an important postoperative worsening in their QoL: 28 % in the physical component summary and 15 % in the mental component summary. Patients with a better preoperative physical functioning and those with worse mental health scores were those at higher risk of a relevant physical deterioration. Patients with a lower predicted postoperative forced expiratory volume in 1 second (ppoFEV1) and higher

preoperative scores of social functioning and mental health were those at higher risk of a relevant emotional deterioration. Compared with the general population, nearly half of the patients displayed a depressed physical and emotional status 3 months after surgery [49]. The extent of resection, age, and adjuvant therapy was associated with a clinically relevant decline in the physical aspect of health-related quality of life 6 months after surgery [50].

Adjuvant Chemotherapy

Despite optimum surgical management, the 5-year survival rate of resected NSCLC ranges from 25 to 75 % according to pathologic stage. A large meta-analysis by the NSCLC Collaborative Group suggests an absolute improvement in 5-year survival with platinum-based chemotherapy of 5 % (2–7) for stage IB (from 55 to 60 %), 5 % (3–8) for stage II (from 40 to 45 %), and 5 % (3–8) for stage III disease (from 30 to 35 %) [51]. Another large meta-analysis showed a detrimental effect of adjuvant chemotherapy in stage IA NSCLC [52]. The most commonly used regimens are cisplatin in combination with vinorelbine or etoposide. Cisplatin and vinorelbine adjuvant chemotherapy is associated with frequent hematologic toxic effects, including high-grade neutropenia in 85 % of patients. Common nonhematologic effects include asthenia and nausea or vomiting. There are approximately 2 % treatment-related deaths, mainly from septic shock [53]. Overall, compliance and, as a consequence, dose-intensity and total dose of adjuvant chemotherapy are disappointing. Altogether, 59 % of patients receive at least 240 mg/m^2 of cisplatin, this parameter being potentially more important than the choice of the second compound [52]. Regarding chemotherapy strategy, 14 % of patients received only one cycle and 10 % only two cycles, mainly because of patient refusal (35 %), toxicity (34 %), and early death or progression (9 %). The median delay between surgery and the start of chemotherapy was 39 days (>60 days in 7 % of patients) [52].

The beneficial effect of adjuvant chemotherapy on recurrences does not decrease with longer follow-up, and there is no

increase in the number of secondary malignancies potentially related to a carcinogenic effect of chemotherapy. However, the maintained beneficial effect of preventing lung cancer deaths contrasts with a probable chemotherapy-induced increase in non-lung cancer mortality after 5 years that can decrease but not nullify the beneficial effect of adjuvant therapy [54]. Statistically significant causes of non-cancer deaths after cisplatin-based chemotherapy in the non-lung cancer setting were infections and circulatory and respiratory diseases [55].

Postoperative Radiotherapy

Postoperative radiotherapy has a deleterious effect on patients with early stages I and II [56, 57]. In contrast with N2 disease, where the PORT-induced morbidity might be outweighed by the presence of residual microscopic disease, treated by radiotherapy, in patients with N0 and N1 disease, this benefit is not reproduced. With the limitation related to the availability of retrospective data only, where confounding factors in patient selection may have biased this interpretation, radiotherapy-related toxicity is probably one of the factors involved in this negative impact of PORT.

Small-Cell Lung Cancer

Small-cell lung cancer (SCLC) accounts for approximately 15 % of primary lung carcinoma. It is invariably associated with tobacco exposure and is characterized by rapid tumor doubling time and early development of metastases. Less than 10 % of patients are asymptomatic at diagnosis. Of all histologic subtypes of lung cancer, SCLC is the most sensitive to chemotherapy and radiotherapy, but prognosis remains dismal [58]. Staging of SCLC is made according to the 7th TNM classification and according to a two-stage system developed by the Veteran's Administration Lung Cancer Study Group, dividing patients into limited (stages IA to IIIB) or extensive (stage IV) stage disease. Limited disease is thus defined as

disease confined to one hemithorax (i.e., disease that can be included in a "tolerable" radiation field). Approximately one-third of patients present with clinical definition of "limited disease," but most of these patients already present with subclinical metastatic disease.

Extensive Disease

Chemotherapy is the mainstay of treatment for patients with SCLC because of this proclivity for early dissemination. Standard chemotherapy in Caucasian patients consists of cisplatin and etoposide, having been proven equivalent and more tolerable than older regimens such as cyclophosphamide, doxorubicin, and vincristine [59].

Toxicity is mainly hematologic, especially neutropenia, 30–40 % being grade 3–4. Granulocytopenia can be effectively prevented with recombinant granulocyte colony-stimulating factor (G-CSF). Nonhematologic toxicity is essentially gastrointestinal, with little high-grade nausea or vomiting. All other clinically significant nonhematologic toxicities, excluding alopecia, were present in fewer than 4 % of patients.

Limited Disease

The standard treatment for limited disease SCLC is combined-modality therapy consisting of thoracic radiotherapy and systemic chemotherapy. Two meta-analyses have shown an improvement of survival in patients who received chest irradiation in addition to chemotherapy compared to those receiving chemotherapy alone [60, 61], with an aim for long-term remission for a small fraction (15–25 %) of these patients. The optimal timing of radiotherapy, either concurrent or sequential, remains somehow unsettled, with compelling evidence that early radiotherapy concurrent with platinum-based chemotherapy is superior to sequential radiotherapy [62, 63].

The addition of concurrent radiotherapy to chemotherapy results in more increased myelosuppression than that

observed with sequential treatment, with 88 versus 54 % high-grade leukopenia, respectively [64].

G-CSF has been controversial in this setting, with some authors advocating that primary prophylaxis with G-CSF is not indicated during chemoradiotherapy to the chest due to the increased rate of bone marrow suppression associated with an increased risk of complications and death [65]. Nonhematologic toxicities are similar, with a trend toward more infections and esophagitis. The incidence of severe pneumonitis is not significantly different between early and late chest radiotherapy, ranging between 2 and 17 % in studies with platinum-based chemotherapy. Treatment of choice consists of oral corticosteroids. The fractionation of radiotherapy might also play a role, with one trial showing a survival advantage with twice-daily versus once-daily radiotherapy, albeit with unequal biologic effective dose [66]. Hyperfractionated radiotherapy resulted in significantly more esophagitis than once-daily fractionation and may occasionally mandate tube feeding.

Prophylactic Cranial Irradiation

Patients responding to first-line treatment, irrespective of stage, are usually offered prophylactic cranial irradiation (PCI), which has been shown to increase survival and markedly reduce the cumulative incidence of brain metastases both in patients with limited or extensive stage disease [67, 68].

PCI results in significantly more early and late (at 6 weeks and 3 months, respectively) fatigue, early and late appetite loss, nausea and vomiting, and early and late leg weakness [68].

Long-term toxicities and particularly cognitive deficits are difficult to assess, and trials yield conflicting results. A higher total dose of 36 Gy resulted in significant deterioration in neurologic function (defined as a decrease in any neuropsychological test) and increased chronic neurotoxicity (defined as deterioration in at least one neurocognitive test without documentation of brain metastases) as compared to a lower

total dose of 25 Gy – without any benefit in terms of mortality and a higher incidence of subsequent brain metastases [69]. Other trials reported a negative impact on early quality of life and a limited negative impact on functioning scales of PCI, with a maximum difference in role, emotional, and cognitive functioning between 6 weeks and 3 months, then decreasing [70].

Second-Line Therapy

Relapsing patients are offered second-line chemotherapy with the goal of survival improvement and preservation of quality of life. Oral and intravenous topotecan are classical compounds in the second-line setting. Oral topotecan extends overall survival even in patients with short (<60 days) treatment-free interval and delays deterioration of quality of life as compared to placebo [71]. Toxicity from oral topotecan is mainly hematologic, with 60 % of patients presenting with high-grade neutropenia. The most frequent nonhematologic toxicities are diarrhea and fatigue. There were fewer early deaths (<30 days) and greater likelihood of achieving symptom improvement for all symptoms, including shortness of breath, sleep interference, and fatigue.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69–90.
2. D'Addario G, Fruh M, Reck M, Baumann P, Klepetko W, Felip E. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v116–9.
3. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947–57.
4. Sequist LV, Martins RG, Spigel D, Grunberg SM, Spira A, Janne PA, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol. 2008; 26(15):2442–9.

5. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239–46.
6. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735–42.
7. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353(2):123–32.
8. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, 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(21): 3543–51.
9. Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans 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(11):847–57.
10. Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH, Johnson DH. Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. J Clin Oncol. 2010;28(6):949–54.
11. Crino L, Dansin E, Garrido P, Griesinger F, Laskin J, Pavlakis N, et al. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study. Lancet Oncol. 2010;11(8):733–40.
12. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002;346(2):92–8.
13. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363(18):1693–703.
14. Reck M, Gutzmer R. Management of the cutaneous side effects of therapeutic epidermal growth factor receptor inhibition. Onkologie. 2010;33(8–9):470–9.
15. Wu YL, Kim JH, Park K, Zaatar A, Klingelschmitt G, Ng C. Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: a subanalysis of the phase III, randomized SATURN study. Lung Cancer. 2012;77(2):339–45. Epub 2012 Apr 10.
16. Hesketh PJ, Chansky K, Wozniak AJ, Hirsch FR, Spreafico A, Moon J, et al. Southwest Oncology Group phase II trial (S0341) of erlotinib

(OSI-774) in patients with advanced non-small cell lung cancer and a performance status of 2. J Thorac Oncol. 2008;3(9):1026–31.
17. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, et al. Severe acute interstitial pneumonia and gefitinib. Lancet. 2003; 361(9352):137–9.
18. Lai YC, Lin PC, Lai JI, Hsu SY, Kuo LC, Chang SC, et al. Successful treatment of erlotinib-induced acute hepatitis and acute interstitial pneumonitis with high-dose corticosteroid: a case report and literature review. Int J Clin Pharmacol Ther. 2011;49(7):461–6.
19. Gronberg BH, Bremnes RM, Flotten O, Amundsen T, Brunsvig PF, Hjelde HH, et al. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2009;27(19):3217–24.
20. Spiro SG, Rudd RM, Souhami RL, Brown J, Fairlamb DJ, Gower NH, et al. Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. Thorax. 2004;59(10):828–36.
21. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010;21 Suppl 5:v232–43.
22. Rademaker-Lakhai JM, Crul M, Zuur L, Baas P, Beijnen JH, Simis YJ, et al. Relationship between cisplatin administration and the development of ototoxicity. J Clin Oncol. 2006;24(6):918–24.
23. Bally C, Fadlallah J, Leverger G, Bertrand Y, Robert A, Baruchel A, et al. Outcome of acute promyelocytic leukemia (APL) in children and adolescents: an analysis in two consecutive trials of the European APL Group. J Clin Oncol. 2012;30(14):1641–6.
24. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, et al. Clinical features of hypersensitivity reactions to carboplatin. J Clin Oncol. 1999;17(4):1141.
25. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004;22(9):1589–97.
26. Santoro A, O'Brien ME, Stahel RA, Nackaerts K, Baas P, Karthaus M, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J Thorac Oncol. 2008;3(7):756–63.
27. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542–50.

28. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, 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(8):1227–34.
29. Veronese ML, Mosenkis A, Flaherty KT, Gallagher M, Stevenson JP, Townsend RR, et al. Mechanisms of hypertension associated with BAY 43–9006. J Clin Oncol. 2006;24(9):1363–9.
30. Izzedine H, Ederhy S, Goldwasser F, Soria JC, Milano G, Cohen A, et al. Management of hypertension in angiogenesis inhibitor-treated patients. Ann Oncol. 2009;20(5):807–15.
31. Pande A, Lombardo J, Spangenthal E, Javle M. Hypertension secondary to anti-angiogenic therapy: experience with bevacizumab. Anticancer Res. 2007;27(5B):3465–70.
32. Mir O, Coriat R, Ropert S, Cabanes L, Blanchet B, Camps S, et al. Treatment of bevacizumab-induced hypertension by amlodipine. Invest New Drugs. 2012;30(2):702–7.
33. Anderson H, Lund B, Bach F, Thatcher N, Walling J, Hansen HH. Single-agent activity of weekly gemcitabine in advanced non-small-cell lung cancer: a phase II study. J Clin Oncol. 1994;12(9):1821–6.
34. Gridelli C, Cigolari S, Gallo C, Manzione L, Ianniello GP, Frontini L, et al. Activity and toxicity of gemcitabine and gemcitabine + vinorelbine in advanced non-small-cell lung cancer elderly patients: phase II data from the Multicenter Italian Lung Cancer in the Elderly Study (MILES) randomized trial. Lung Cancer. 2001;31(2–3): 277–84.
35. Aapro MS, Martin C, Hatty S. Gemcitabine – a safety review. Anticancer Drugs. 1998;9(3):191–201.
36. Barlesi F, Villani P, Doddoli C, Gimenez C, Kleisbauer JP. Gemcitabine-induced severe pulmonary toxicity. Fundam Clin Pharmacol. 2004;18(1):85–91.
37. Miller VA, Kris MG. Docetaxel (Taxotere) as a single agent and in combination chemotherapy for the treatment of patients with advanced non-small cell lung cancer. Semin Oncol. 2000;27(2 Suppl 3): 3–10.
38. Goodgame B, Viswanathan A, Zoole J, Gao F, Miller CR, Subramanian J, et al. Risk of recurrence of resected stage I non-small cell lung cancer in elderly patients as compared with younger patients. J Thorac Oncol. 2009;4(11):1370–4.
39. Kates M, Swanson S, Wisnivesky JP. Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer <=1 cm in size: a review of SEER data. Chest. 2011;139(3):491–6.
40. Cheung MC, Hamilton K, Sherman R, Byrne MM, Nguyen DM, Franceschi D, et al. Impact of teaching facility status and high-volume centers on outcomes for lung cancer resection: an examination of 13,469 surgical patients. Ann Surg Oncol. 2009;16(1):3–13.

41. Brunelli A, Refai M, Salati M, Xiume F, Sabbatini A. Predicted versus observed FEV1 and DLCO after major lung resection: a prospective evaluation at different postoperative periods. Ann Thorac Surg. 2007;83(3):1134–9.
42. Barnett SA, Rusch VW, Zheng J, Park BJ, Rizk NP, Plourde G, et al. Contemporary results of surgical resection of non-small cell lung cancer after induction therapy: a review of 549 consecutive cases. J Thorac Oncol. 2011;6(9):1530–6.
43. Ferguson MK, Vigneswaran WT. Diffusing capacity predicts morbidity after lung resection in patients without obstructive lung disease. Ann Thorac Surg. 2008;85(4):1158–64; discussion 1164–5.
44. Otake H, Yasunaga H, Horiguchi H, Matsutani N, Matsuda S, Ohe K. Impact of hospital volume on chest tube duration, length of stay, and mortality after lobectomy. Ann Thorac Surg. 2011;92(3):1069–74.
45. Wahi R, McMurtrey MJ, DeCaro LF, Mountain CF, Ali MK, Smith TL, et al. Determinants of perioperative morbidity and mortality after pneumonectomy. Ann Thorac Surg. 1989;48(1):33–7.
46. Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. J Clin Oncol. 2009;27(15):2553–62.
47. Allen MS, Darling GE, Pechet TT, Mitchell JD, Herndon 2nd JE, Landreneau RJ, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg. 2006;81(3):1013–9; discussion 1019–20.
48. Saji H, Tsuboi M, Yoshida K, Kato Y, Nomura M, Matsubayashi J, et al. Prognostic impact of number of resected and involved lymph nodes at complete resection on survival in non-small cell lung cancer. J Thorac Oncol. 2011;6(11):1865–71.
49. Pompili C, Brunelli A, Xiume F, Refai M, Salati M, Sabbatini A. Predictors of postoperative decline in quality of life after major lung resections. Eur J Cardiothorac Surg. 2011;39(5):732–7.
50. Moller A, Sartipy U. Predictors of postoperative quality of life after surgery for lung cancer. J Thorac Oncol. 2012;7(2):406–11.
51. Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, Le Chevalier T, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010;375(9722):1267–77.
52. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552–9.
53. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzales-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus

observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7(9):719–27.
54. Arriagada R, Dunant A, Pignon JP, Bergman B, Chabowski M, Grunenwald D, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol. 2010;28(1):35–42.
55. Fossa SD, Gilbert E, Dores GM, Chen J, McGlynn KA, Schonfeld S, et al. Noncancer causes of death in survivors of testicular cancer. J Natl Cancer Inst. 2007;99(7):533–44.
56. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol. 2006;24(19):2998–3006.
57. Postoperative radiotherapy for non-small cell lung cancer. PORT Meta-analysis Trialists Group Cochrane Database Syst Rev. 2005; (2):CD002142.
58. Kelly K. New chemotherapy agents for small cell lung cancer. Chest. 2000;117(4 Suppl 1):156S–62.
59. Roth BJ, Johnson DH, Einhorn LH, Schacter LP, Cherng NC, Cohen HJ, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol. 1992;10(2): 282–91.
60. Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med. 1992;327(23):1618–24.
61. Arriagada R, Pignon JP, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. Effect of thoracic radiotherapy on mortality in limited small cell lung cancer. A meta-analysis of 13 randomized trials among 2,140 patients. Anticancer Res. 1994;14(1B):333–5.
62. Pijls-Johannesma MC, De Ruysscher D, Lambin P, Rutten I, Vansteenkiste JF. Early versus late chest radiotherapy for limited stage small cell lung cancer. Cochrane Database Syst Rev. 2005;(1):CD004700.
63. Spiro SG, James LE, Rudd RM, Trask CW, Tobias JS, Snee M, et al. Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. J Clin Oncol. 2006;24(24):3823–30.
64. Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol. 2002;20(14):3054–60.

65. Crawford J, Caserta C, Roila F. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. Ann Oncol. 2010;21 Suppl 5:v248–51.
66. Turrisi 3rd AT, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med. 1999;340(4):265–71.
67. Auperin A, Arriagada R, Pignon JP, LePechoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med. 1999;341(7): 476–84.
68. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. 2007;357(7):664–72.
69. Wolfson AH, Bae K, Komaki R, Meyers C, Movsas B, Le Pechoux C, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2011;81(1): 77–84.
70. Slotman BJ, Mauer ME, Bottomley A, Faivre-Finn C, Kramer GW, Rankin EM, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol. 2009;27(1):78–84.
71. O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cucevia B, Juhasz G, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006;24(34):5441–7.