Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

The most common cause of cancer-related deaths in Europe in 2006 is lung cancer (estimated 334 800 deaths). After prostate cancer, lung cancer is the most frequent type of cancer in men. Age-standardized incidence and mortality rates in 2006 are estimated to be 75.3 and 64.8/100 000/year, respectively, in men, and 18.3 and 15.1/100 000/year in women. Small-cell lung cancer (SCLC) accounts for 15%–18% of all cases. In recent years the incidence of SCLC has decreased. SCLC is strongly associated with tobacco smoking.

diagnosis

Pathological diagnosis should be made according to the WHO classification. Biopsies can be obtained by flexible bronchoscopy, mediastinoscopy, endoscopic ultrasound, transthoracic needle aspiration and thoracoscopy depending on the localization of the tumour. A biopsy from a metastatic lesion can substitute for a biopsy from the primary tumour. The least invasive approach should be used [V, D].

staging and risk assessment

Staging procedures should include medical history, physical examination, chest X-ray, complete blood count including differential count, liver, lung and renal function tests, lactate dehydrogenase (LDH) and sodium levels, and a CT scan of the chest and abdomen including the liver and adrenal glands. In patients with symptoms or abnormal physical examination suggesting metastasis, additional tests may include bone scintigraphy, CT scan with intravenous contrast or MRI of the brain, and bone marrow aspiration and biopsy. If extensive disease is detected by one test, further staging can be omitted. Brain CT/MRI is recommended if chemoradiation with curative intent is under consideration [V, D]. The role of combined FDG-PET/CT scanning is yet to be completely defined but if available, it may be useful in certain cases that require accurate staging.

Staging has been performed according to a two-stage system developed by the Veteran’s Administration Lung Cancer Study Group (VALSG) in the USA dividing patients into limited and extensive disease. Limited disease was defined as tumour tissue that could be encompassed in a single radiation port and extensive disease was defined as any tumour that extended beyond the boundaries of a single radiation port.

In 1989, the International Association for the Study of Lung Cancer (IASLC) revised the VALSG staging system and defined limited disease as tumour tissue confined to one hemithorax with regional lymph node metastasis including both ipsilateral and contralateral hilar, supraclavicular and mediastinal nodes, as well as ipsilateral pleural effusion. In most clinical trials with limited disease, patients with contralateral hilar or supraclavicular lymphadenopathy as well as malignant pleural or pericardial effusions have been excluded. The relevance of disease involvement at these sites remains controversial with respect to treatment planning.

The IASLC proposed to apply the seventh edition of the TNM classification in the staging of SCLC. This proposal is based on analysis showing that survival of limited-disease patients with N2 and N3 involvement differs significantly from N0 and N1 disease. Patients with pleural effusion have an intermediate prognosis between limited and extensive disease patients with haematogenous spread. Furthermore, conformal radiation techniques and IMRT require more precise nodal staging.

first-line treatment

limited disease

Limited-disease patients should be treated with etoposide/platinum [I, C], preferably etoposide/cisplatin, in combination with thoracic radiotherapy [I, A].
Patients with limited disease are potentially curable as evidenced by a 5-year survival rate of between 20% and 25% in large meta-analyses and randomized trials using early concurrent platinum-based chemoradiotherapy.

The evidence regarding the use of chemotherapy is addressed in the section concerning extensive disease as most trials investigating chemotherapy tend to include both limited and extensive disease.

Thoracic radiotherapy increases local control and survival in limited-disease patients. A meta-analysis of 13 randomized trials including individual data from 2140 patients concluded that thoracic radiotherapy increased 3-year survival from 8.9% to 14.3%.

timing of radiotherapy. Timing of radiotherapy has been addressed in at least eight individual trials and in a number of meta-analyses. The analyses differ with respect to the definition of early and late radiotherapy. Thirty days or 9 weeks after the initiation of chemotherapy have been the most common time points for the discrimination between early and late radiotherapy. Fried et al. reported a significant survival benefit at 2 years, which disappeared at the 3-year time point. In a Cochrane meta-analysis, 2- and 5-year survival rates were not significantly different when all trials were taken into account. However, when excluding one trial using non-platinum-based chemotherapy the odds ratio of survival at 5 years significantly favoured early chest radiotherapy with 5-year survival rates of 20.2% for early versus 13.8% for late radiotherapy. One meta-analysis suggested that early radiotherapy only increases survival when delivery of the intended doses of chemotherapy is achieved. Finally, completing radiotherapy in <30 days after initiating chemotherapy was associated with a significantly higher 5-year survival (RR: 0.62, 95% CI 0.49–0.80, \( P = 0.0003 \)) in one meta-analysis. In conclusion, the bulk of the evidence suggests that early radiotherapy concurrent with platinum-based chemotherapy is superior to the delivery of late radiotherapy [II, B].

fractionation of radiotherapy. Fractionation and the overall treatment time of chest radiotherapy have been explored in the North American intergroup trial 0096 comparing twice-daily with once-daily radiotherapy. This trial achieved the longest 5-year survival ever reported in a large randomized study, i.e. 26% using 45 Gy in twice-daily fractions delivered over 3 weeks compared with 16% in patients receiving once-daily fractions to a total of 45 Gy in 5 weeks. However, twice-daily fractionation has not been uniformly implemented as standard treatment presumably because of its inconvenience. The nominal dose of 45 Gy on the once-daily arm corresponds to a lower biologic effective dose and the two treatment arms were not equitoxic as reflected by a rate of severe oesophagitis of 27% compared with 11% on the once-daily arm. Indeed, the maximal tolerable dose of twice-daily and once-daily concurrent radiochemotherapy has been determined to be 45 Gy in 30 fractions over 3 weeks and 70 Gy in 35 fractions over 7 weeks, respectively. A trial performed by the North Central Cancer Group failed to show any survival benefit of twice-daily radiotherapy in 32 fractions to a total of 48 Gy compared with once-daily radiotherapy in 28 fractions to a total of 50.4 Gy with an identical overall treatment time of 5.6 weeks in both arms. However, the late delivery of radiotherapy and the introduction of a 2.5 week split on the twice-daily arm might compromise the effectiveness of the twice-daily regimen. In conclusion, it remains to be determined whether twice-daily fractionation is superior to once-daily using biologically equivalent doses. Phase III studies that compare 45 Gy in twice-daily fractions over 3 weeks with once-daily schedules with a higher total dose (e.g. 66 Gy in 33 fractions in 6.6 weeks) are ongoing. The North American intergroup trial 0096 suggests that the overall treatment time of chest radiotherapy may be important for long-term survival.

dose of radiotherapy. The optimal dose of radiotherapy is still to be established as no direct comparisons of delivered dose have been performed in randomized trials. However, retrospective analyses suggest that increasing dose is associated with increased local control. Consequently, doses in the range 60–70 Gy delivered in 6–7 weeks have been explored in recent feasibility studies. Phase III trials investigating both the total dose and the overall treatment time are ongoing, both in Europe and in the USA, but presently, no data support the use of high-dose thoracic radiotherapy outside a clinical trial.

target volume of radiotherapy. The optimal target volume remains to be defined as mainly retrospective studies are available making definitive recommendations inappropriate. Omission of elective node irradiation based on CT scans should be used with caution [III, C] as this strategy resulted in three isolated nodal failures in 27 patients. In contrast, recent prospective data from the same group indicate that elective node irradiation based on pretreatment FDG-PET scans resulted in a low rate of isolated nodal failures, i.e. two nodal failures in 60 patients.

surgery. In patients with very limited disease (i.e. T1–2, N0), surgical resection may be considered followed by adjuvant chemotherapy and prophylactic cranial irradiation. Preoperative staging should include mediastinoscopy [III, D]. No randomized trials have compared this strategy with concurrent chemo-radiotherapy.

extensive disease

Extensive disease patients should be treated with cisplatin or carboplatin in combination with etoposide [I, C].

The prognosis of extensive disease is poor with a median survival of 10 months and a 2-year survival rate of 10%. Long-term survivors are extremely rare.

One of the largest and most recent randomized trials including both limited and extensive disease patients favours cisplatin and etoposide with respect to survival. However, meta-analyses including studies with both limited and extensive disease patients from the last three decades have reached conflicting results. A meta-analysis of 19 randomized trials with a total of 4054 patients showed that patients treated with a cisplatin-containing regimen had higher response rates and prolonged survival. In contrast, a recent Cochrane review of 29 randomized studies reported no statistically significant differences in 6-, 12- and 24-month survival rates when comparing platinum- with non-platinum-based chemotherapy although the risk ratios numerically favoured the platinum-based regimens. The rate of complete response was significantly higher following platinum-containing treatments. A meta-
analysis of 36 trials compared etoposide- and/or cisplatin-containing regimens with regimens that did not contain one of the two drugs. A survival benefit in favour of etoposide alone or in combination with cisplatin was reported. Thus, most evidence supports the recommendation of etoposide/platinum as the standard of care although inconsistence exists [I, C]. Carboplatin is an acceptable option in the non-curative setting of extensive disease, whereas cisplatin is recommended when cure is intended in limited disease [II, C].

Trials comparing etoposide with either topotecan or irinotecan in combination with platinum have reached conflicting results. A study performed by the Japanese Cooperative Oncology Group (JCOG) was prematurely stopped due to a pre-planned interim analysis reporting an encouraging 3.4-month survival benefit favouring irinotecan/cisplatin compared with etoposide/cisplatin. However, two confirmative studies failed to reproduce the Japanese data. Hanna et al. used a slightly modified schedule, whereas the SWOG study was a true replicate of the JCOG study using the exact same schedule. Both confirmative studies were substantially larger (n = 331 and n = 651) than the Japanese study (n = 152). No significant differences were seen in overall survival, time to progression or response rates. Etoposide induced more myelotoxicity and irinotecan caused more gastrointestinal toxicity. A Norwegian trial of 210 patients using oral etoposide in combination with carboplatin as the comparator arm reported a slight but significant increase in survival from 7.1 to 8.5 months favouring irinotecan/carboplatin. Both oral and intravenous topotecan have been compared with etoposide in combination with cisplatin in two recent large randomized trials. No increase in survival was reported in either study but both oral and intravenous topotecan were deemed non-inferior to etoposide with respect to survival according to pre-specified non-inferiority criteria. Time to progression in the intravenous topotecan arm was inferior to etoposide. However, the opposite was true in the oral study, where time to progression was inferior to etoposide. Neither irinotecan nor topotecan are recommended as part of first-line treatment [II, C].

A substantial number of frail patients with extensive disease do not tolerate aggressive chemotherapy due to low performance status and high incidence of co-morbidity. Therefore, less intensive regimens have been developed including oral etoposide. However, two randomized trials comparing single-agent oral etoposide with standard multidrug intravenous chemotherapy both found that oral etoposide was inferior with respect to survival, symptom control and quality of life. First-line oral single-agent etoposide is not recommended [I, A].

The addition of a third drug to a standard two-drug platinum-based regimen has not uniformly been proved beneficial in either limited or extensive disease. Two randomized studies evaluating the addition of ifosfamide reached conflicting results. One study reported a survival benefit while the other study was negative. In both studies, ifosfamide increased myelotoxicity. The addition of paclitaxel to cisplatin and etoposide failed to improve survival in a large randomized study (n = 587). Paclitaxel resulted in more non-haematological toxicity and increased the toxic death rate. Another randomized study using a similar schedule was prematurely closed after 133 patients were enrolled due to a high toxic death rate of 13%.

Duration of chemotherapy. Two trials have shown that maintenance chemotherapy beyond six cycles of induction therapy was unable to increase survival in patients responding to induction therapy. Likewise, seven additional cycles of maintenance chemotherapy in non-progressing patients after five cycles of induction chemotherapy did not improve survival. A modest and non-significant survival benefit has been reported after six cycles compared with three cycles. In a four-arm randomized study, four cycles of chemotherapy was inferior to eight cycles in terms of survival. However, this disadvantage in survival disappeared for those randomized to second-line therapy at relapse. Four cycles of topotecan maintenance did not increase survival after four cycles of cisplatin and etoposide induction therapy. Maintenance therapy improved progression-free survival in some trials. However, the clinical relevance of this improvement is questionable. Targeted maintenance treatment has failed to improve survival including anti-GD3 immunization, anti-angiogenic treatment with thalidomide and metalloproteinase inhibition with marimastat. Four to six cycles of chemotherapy are recommended in extensive as well as in limited disease [II, B]. Maintenance therapy has failed to achieve a relevant clinical advantage and is not recommended in either extensive or limited disease [II, B].

Dose intensity. The role of increased dose intensity remains unresolved. A number of studies have evaluated dose-dense therapy by the use of colony stimulating factors and blood-progenitor-cell support. In most trials, dose intensification was achieved by decreasing intervals between cycles. A decade ago, two large randomized trials (n = 300 and n = 403) reported a survival benefit favouring dose intensification. However, the two most recent larger trials (n = 318 and n = 244) were unable to confirm these results in good-prognosis patients despite the achievement of a 1.7- to 1.8-fold increase in dose intensity compared with the standard dose arm. In contrast, a very recent trial with an identical study design and schedule did in fact show an impressive survival benefit of ~1 year. However, this study was a single institution study of only 83 patients. Of note, one study was prematurely terminated due to decremental survival in the dose-dense arm. Dose-intense treatment is not recommended outside a clinical trial in extensive as well as in limited disease [II, C].

Prophylactic cranial irradiation. Patients with any response to first-line treatment irrespective of stage should be offered prophylactic cranial irradiation (PCI) after the completion of first-line treatment [I, A].

A meta-analysis based on individual data from 987 patients with mainly limited disease in complete remission showed that PCI increased 3-year survival from 15.3% to 20.7%. The risk reduction for brain metastases was 54%. Increasing doses of radiation from 8 to 40 Gy was associated with a decreased risk of brain metastases. Recently, the benefit of PCI in extensive disease was demonstrated in a randomized trial. PCI resulted in a 73% reduction in the risk of brain metastases and prolongation of survival in patients with extensive disease.
second-line treatment

Relapsing patients should be considered for second-line chemotherapy as survival benefit and maintenance of quality of life are achievable in selected patients [II, B].

Candidates for second-line chemotherapy should be selected on the basis of response to first-line therapy, time interval since the discontinuation of first-line therapy, residual toxicity to first-line therapy and performance status, as the likelihood of response to second-line chemotherapy is dependent on these factors [III, C].

Symptomatic patients with a low likelihood of benefit from second-line chemotherapy should be considered for palliative radiotherapy [III, C].

Recently, a survival benefit was demonstrated for patients treated with second-line chemotherapy in a small randomized study (n = 141). Oral topotecan extended median survival from 14 to 26 weeks compared with best supportive care. Of note, significant survival benefit was maintained in the subgroup of patients with a treatment-free interval of <60 days. There were fewer early deaths (<30 days from randomization), better symptom control and slower deterioration of quality of life in the chemotherapy arm. In two randomized studies no differences in overall survival were seen comparing oral and intravenous topotecan. Furthermore, in a randomized phase III trial, equivalent survival rates were observed when comparing single-agent intravenous topotecan with combination chemotherapy with cyclophosphamide, adriamycin and vincristine.

The available data from randomized studies do not justify the recommendation of a specific regimen of chemotherapy as no regimen has proved superior to others. With the lack of evidence with regard to efficacy, the choice of second-line therapy should be based on patient preference and convenience as well as toxicity patterns.

response evaluation

Response evaluation is recommended during and at the completion of therapy. Initial positive imaging should be repeated [V, D].

follow-up

There is no evidence that follow-up of asymptomatic patients is needed. Specific examinations should be as clinically indicated. For patients who achieve long-term survival, monitoring for development of a second primary cancer may be considered. Smoking cessation is recommended.

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

literature

16. Bogart JA, Hendron JE 2nd, Lyss AP et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis...


