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Update on small cell lung cancer management

Educational aims

- To describe the relevance of staging, including TNM staging
- To show the clinical relevance of paraneoplastic syndromes as a presentation of small cell lung cancer
- To understand the indications for prophylactic cranial irradiation
- To describe the treatment principles in small cell lung cancer with emphasis on the relevance of staging
- To outline the second-line treatment options

Summary

Small cell lung cancers (SCLCs) account for ~15–20% of all lung cancers. Because SCLC is almost always associated with long-term tobacco smoking, abstinence from smoking and smoking cessation are crucial for primary prevention. Because symptoms are generally unspecific, the disease is often diagnosed late, with 70% of patients already in stage IIIb or IV at the time of diagnosis. Early detection of SCLC through screening is under investigation. Chemotherapy, generally a platinum-based combination, is the mainstay of therapy and is generally combined with radiation in the first-line treatment of tumours up to stage IIIb. Surgery has a place in the diagnosis and therapy of stage I SCLC, but plays no key role in advanced cancer. In patients who respond to first-line therapy, prophylactic cranial irradiation can prevent brain metastases and improve overall survival. Although the initial response to treatment is usually good, SCLC tends to relapse quickly. This makes second-line therapy quite important. Topotecan is the most studied and widely used agent in second-line therapy; however, newer agents, including biological therapies, are under study.

Statement of interest
None declared.

HERMES syllabus links:
module B. 2. 1

Introduction

Lung cancer is the leading cause of cancer deaths worldwide. In Europe, 386,000 people were diagnosed with lung cancer in 2006 and almost the same number, 330,000 people, died of the disease [1]. The advanced stage at diagnosis, high rates of systemic recurrence after surgery and resistance to systemic therapy contribute to the high mortality of this disease. Despite some recent advances in the therapy of lung cancer, the overall prognosis remains very poor, with 5-year survival rates <20%, and the need for novel treatment strategies remains great.

Historically, lung cancers have been categorised as small cell and non-small cell using conventional light microscopy. Small cell lung cancer (SCLC) accounts for ~15–20% of lung cancer cases. This figure varies regionally, and seems to be decreasing in many parts of the world. Because SCLC is strongly associated with cigarette smoking, there is great potential to reduce its incidence through smoking prevention.

Without treatment, SCLC is rapidly progressive and fatal. It is a highly aggressive tumour characterised by a rapid doubling time, high growth fraction and the early development of widespread metastases. Untreated patients with metastatic disease survive only a few weeks.

Most patients with SCLC present with unspecific symptoms, such as new cough, a change in the pattern of their chronic cough or weight loss. This delays the time to diagnosis substantially. At the time of first diagnosis, ~70% of patients with SCLC have stage IIIb or IV disease.

Epidemiology

SCLC occurs almost exclusively in smokers or ex-smokers [2]. Although only 25% of all lung cancer patients world-wide are never- or light smokers [3], the correlation between SCLC and smoking is especially strong, with a clear smoking history in the vast majority (90%) of SCLC patients [2]. The incidence of SCLC has decreased over the past several decades. GOVINDAN *et al.* [4] analysed data from the American Surveillance, Epidemiology and End Result (SEER) database, finding a clear decrease in SCLC incidence from 17.26% in 1986 to 12.95% in 2002. This observation may

be due to the introduction of low-tar filters in cigarettes or to a change in the demographics of smoking. There seem to be sex-specific factors that further increase the risk of SCLC in female compared with male smokers.

Although smoking is the most important risk factor for the development of SCLC, other risk factors have been identified. The most significant of these are work-related exposures, such as passive smoking, asbestos, arsenic, chrome, nickel, beryllium, cadmium, aromatic polycarbonates and potentially diesel dust. Passive smoking is also an important risk factor in the private sector, especially for children.

Clinical manifestation

SCLC generally originates in the central airways, in contrast to nonsquamous NSCLC, which is more often found peripherally. Radiograph and computed tomography (CT) images of SCLC typically show a large hilar mass with mediastinal adenopathy. Compression of the central airways or the superior vena may lead to post-stenotic pneumonia or superior vena cava syndrome, respectively. Other symptoms at the time of presentation are less specific and include a new cough or a change in the patients chronic cough patterns, haemoptysis, dyspnoea, fatigue and “B”-symptoms, such as weight loss, fever and night sweats. Most SCLC patients have distant metastasis at the time of diagnosis. The most common sites of metastasis are liver, adrenal glands, bones, brain and bone marrow. SCLC occasionally presents as a peripheral solitary pulmonary nodule.

Paraneoplastic syndromes, especially those causing neurological symptoms, may occur early in the course of SCLC and in the absence of other tumour-related symptoms.

Paraneoplastic syndromes

SCLC shows a high rate of neuroendocrine activity and can be associated with a wide variety of paraneoplastic syndromes, including the syndrome of inadequate antidiuretic hormone and the ectopic corticotropin syndrome [5]. In addition to endocrine paraneoplastic syndromes, neurological (*e.g.* Lambert–Eaton syndrome), haematological and dermatological syndromes have been described. The most common paraneoplastic syndromes are summarised in table 1.

Table 1 Paraneoplastic syndromes associated with lung cancer [5, 6]

| Syndrome | Patients affected % | Causative protein or antibody |
|---|---------------------|--|
| Hyponatraemia/SIADH | 15 | Arginine vasopressin or atrial natriuretic peptide |
| Ectopic corticotropin syndrome | 2–5 | Corticotropin |
| Lambert–Eaton myasthenic syndrome | 3 | Voltage-gated calcium channel antibody |
| Acromegaly | <1 | GHRH |
| Gynaecomastia | <1 | |
| Hypercoagulability | <1 | |
| Thrombocytosis | <1 | |
| Encephalomyelitis/subacute sensory neuropathy | <1 | Anti-Hu, amphiphysin, CV2 |
| Cancer-associated retinopathy | <1 | Anti-recoverin |
| Dermatomyositis | <1 | |
| Acanthosis palmaris, erythema gyratum repens | <1 | |
| Nephrotic syndrome | <1 | |

SIADH: syndrome of inadequate antidiuretic hormone; GHRH: growth hormone-releasing hormone.

Prognosis

Untreated SCLC is aggressive, with a median survival of 2–4 months after diagnosis. The prognosis correlates with the stage of disease at presentation. In stage IV disease, overall survival (OS) without treatment is only a few weeks. Although SCLC generally responds well to initial chemotherapy, resistance to chemotherapy almost invariably develops. Nevertheless, chemotherapy offers a clear survival benefit compared with best supportive care [7–9]. Patients treated for limited disease have a median survival of 16–24 months and a 5-year survival of 14%. Median survival in patients treated for extensive disease is 6–12 months, and long-term disease-free survival is rare.

The SEER data analysis by GOVINDAN *et al.* [4] and OZE *et al.* [10] came to the frustrating conclusion that OS in SCLC has not changed substantially over the last 30 years. Table 2 summarises the effects of stage at presentation and various treatment strategies on survival.

The most important prognostic factor for OS is stage at presentation [13], followed by performance status (Karnofsky or Eastern Cooperative Oncology Group (ECOG) index), weight loss, serum lactate dehydrogenase and absolute neutrophil count [6]. Age itself is not a prognostic factor. Prognostic scores should be used with caution as they seldom reflect all relevant factors, especially comorbidities. Although patients who relapse early after first-line treatment have a poor prognosis, those who are fit enough for further systemic treatment do have a survival benefit from salvage chemotherapy [14].

Staging and diagnostic work-up

The original two-stage classification of SCLC as limited disease (LD) or extensive disease (ED) was developed by the Veterans' Administration Lung Cancer Group and remains in widespread use. As shown in table 2, LD is used to describe tumours in which the

Table 2 Small cell lung cancer: survival according to extent of disease at presentation [11] modified by therapy [12]

| | LD: tumour limited to one potential irradiation field | ED: not confined to one hemithorax, malignant pleural effusion or distant metastases |
|---------------------------------|---|--|
| Median survival of all patients | 16–24 months | 6–12 months |
| 5-year survival of all patients | 14% | Rare |
| Supportive care | 3 months | 1.5 months |
| Single-agent chemotherapy | 6 months | 4 months |
| Combined chemotherapy | 10–14 months | 7–11 months |
| 5-year survival | 2–8% | 0–1% |
| Chemotherapy plus radiation | 12–16 months | 7–11 months |
| 5-year survival | 6–12% | 0–1% |

LD: limited disease; ED: extensive disease.

treatment target (generally the primary tumour and ipsilateral mediastinal or supraclavicular lymph nodes) fits into one radiotherapy field. ED refers to a tumour not confined to one hemithorax, or a tumour accompanied by malignant pleural effusion or distant metastases. Unfortunately, there are different versions of this system in use, which may lead to confusion or discrepancies between centres. Most patients have extensive disease at the time of diagnosis.

The TNM staging system, which is well established in non-small cell lung cancer (NSCLC) as well as in other solid tumours, is based on a description of the primary tumour (T), lymph node spread (N) and distant metastases (M) [15]. The 7th version of the TNM staging system has been in use since 2010 (table 3). Because TNM staging allows for a more precise description of the tumour burden than is possible using the two-stage LD/ED system, it allows for more differentiated treatment planning and trial design. This is especially true for the multimodality approaches used in stages I–IIIB. The use of TNM staging is recommended for all patients with SCLC [15].

An appropriate diagnostic workup and assessment of performance status is essential prior to therapy and during follow-up. In addition to a thorough history and physical examination, the diagnostic workup includes imaging studies (chest radiograph, CT imaging of the

head, neck, thorax and abdomen), blood tests (including blood count, electrolytes, markers of inflammation and the tumour markers pro-gastrin-releasing peptide (pro-GRP) and neuron-specific enolase (NSE)), ECG, and lung function. In some cases, exercise testing, positron emission tomography (PET)-CT or bone scintigraphy and bone marrow diagnosis may be helpful. As some of the tumours with endocrine activity express octreotide-receptors, DOTATATE/DOTATOC-PET may be helpful in finding distant metastasis which can then be treated with radiopharmaceuticals. In general, the diagnostic workup in SCLC should be carried out with little delay, as therapy should start early, ideally within 7–10 days after presentation or aggravation of symptoms [4, 6, 16, 17].

Biology of SCLC

SCLC can be distinguished from NSCLC using light microscopy. SCLC cells are small (only twice the size of lymphocytes), round or oval in form and appear bluish under light microscopy. The size and morphology of the nucleus, as well as the amount of cytoplasm, varies between subtypes. The cells are arranged in clusters, separated by fibroreticular stroma. They display a high mitotic rate and biopsies often include considerable numbers of necrotic cells. SCLC cells are fragile, resulting in typical “crush

Table 3 TNM staging of lung cancer [15]

| Occult carcinoma | Tx | No | Mo |
|------------------|---------|-------|------------|
| Stage o | Tis | | |
| Stage IA | T1a–T1b | No | Mo |
| Stage IB | T2a | No | Mo |
| Stage IIA | T1a–T2a | N1 | Mo |
| | T2b | No | Mo |
| Stage IIB | T2b | N1 | Mo |
| | T3 | No | Mo |
| Stage IIIA | T1a–T3 | N2 | Mo |
| | T3 | N1 | Mo |
| | T4 | No–N1 | Mo |
| Stage IIIB | T4 | N2 | Mo |
| | T1a–T4 | N3 | Mo |
| Stage IV | Any T | Any N | M1a or M1b |

artefacts” in biopsy specimens. SCLC may occur in combination with other histological types of lung cancer, most commonly with squamous cell carcinoma [18, 19].

The histopathological classification of SCLC has been changed several times over the past several decades. Previously microscopic features were used to classify tumours as oat cell, intermediate or combined cell SCLC. The clinical features of these three subgroups are similar, and all may show neuroendocrine features. The new classification system, which was adopted by the World Health Organization (WHO) in 1999 (table 4) [20] classifies SCLC as a neuroendocrine tumour. This is clinically relevant, as paraneoplastic neuroendocrine symptoms are often the first sign of SCLC. Other neuroendocrine lung tumours include large cell neuroendocrine carcinoma, typical and atypical carcinoid tumours, as well as diffuse idiopathic pulmonary neuroendocrine cell hyperplasia and tumourlets. Antigen panels can be helpful in diagnosing SCLC. GUINEE *et al.* [21] analysed open-lung biopsies (OLBs) and transbronchial biopsies (TBBs), and were able to show that almost all SCLCs derive from the epithelium and can therefore be stained with vimentin, keratin or BER-EP4

(OLB and TBB). Neuroendocrine markers are positive in the majority of cases, and include chromogranin A (60% OLB, 47% TBB), NSE (60%/33%), Leu-7 (40%/21%), synaptophysin (5%/21%). Other groups have shown positive staining for dopa decarboxylase, calcitonin, CD56 (neural cell adhesion molecule), GRP, and insulin-like growth factor-I. Although most SCLCs express neuroendocrine markers, a lack of expression does not rule out the diagnosis of SCLC in cases with positive staining for epithelial markers [19, 21].

In addition to environmental risk factors, a family history of lung cancer is associated with an increased risk of developing SCLC. One genetic abnormality associated with an increased risk of SCLC was identified by BAILEY-WILSON *et al.* [22], who found that that an allelic loss in chromosome 6q correlates with an early onset of lung cancer and a poor prognosis.

Several important genetic and molecular changes have been noted in SCLC, including the identification of autocrine growth loops, proto-oncogene activation and loss or inactivation of tumour-suppressor genes. Alterations in tumour-suppressor genes are common in SCLC, and probably play a key role in the pathogenesis of the disease. The most

Table 4 WHO/IASLC Subtypes of neuroendocrine tumours [20]

| Subtype | Characteristics |
|----------------------------------|---|
| Classical SCLC | Small round, oval or spindle-shaped cells with scant cytoplasm, ill-defined borders, finely granular nuclear chromatin and absent or inconspicuous nucleoli. High mitotic count. Characteristic crush phenomena due to the soft texture of the tumour and mechanical alterations. Histomorphological grading G1 to G4 not applicable. |
| Typical/atypical carcinoid | Usually less aggressive tumour. |
| Large cell neuroendocrine tumour | Proliferation index relevant for classification. |
| Combined SCLC | Small-cell carcinoma with an additional component of any of the histological types of NSCLC |

WHO: World Health Organization; IASLC: International Association for the Study of Lung Cancer; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer.

relevant tumour-suppressor gene alterations in SCLC are listed in the work of JACKMAN *et al.* [23], and summarised in table 5.

Although most patients with SCLC respond well to initial chemotherapy, the development of early resistance limits OS. The mechanisms of resistance in SCLC have yet to be fully elucidated. One theory suggests that small populations of chemotherapy-resistant cancer stem cells repopulate the tumour following chemotherapy. There is also evidence that changes in calcium homeostasis may play a role in the development of resistance to chemotherapy. Further research, including refined cancer models and the integration of translational approaches, is needed to understand and overcome chemotherapy resistance in SCLC.

Therapeutic modalities

Chemotherapy

Because of its rapid doubling time and growth rate, SCLC is initially highly sensitive to chemotherapy [6, 7, 16], making chemotherapy the cornerstone of treatment. The standard chemotherapy regimens are listed in table 6. Although none of the standard combinations has been shown to be superior to the others in terms of long-term survival [9, 25], combined chemotherapy is superior to single-agent therapy. This is particularly true in ED but can be extrapolated to LD. The patient's performance status and the need for irradiation should be

taken into account when planning chemotherapy. Platinum-based combination therapies with etoposide are at least equal to CAV with less toxicity and less interference with irradiation.

The ACCP recommends cisplatin (60–80 mg·m⁻²) and etoposide (250–360 mg·m⁻² divided into 3–5 doses) as the standard treatment arm for comparative prospective studies [26].

Unfortunately, the survival of SCLC patients especially with extensive disease enrolled in phase III trials has not improved significantly over the years, clearly demonstrating the need for further development of novel targets, newer agents and comprehensive patient care.

Surgery

The role of surgery in SCLC is quite limited. Most patients present with metastatic disease and are clearly not surgical candidates. However, even in patients with localised tumours, the role of radical local therapy is not clear [27, 28]. In cases in which the diagnosis of SCLC is made intraoperatively, for instance during the workup of a solitary pulmonary nodule without evidence of lymph node disease, an anatomical resection should be carried out. In such cases, surgery may be considered curative, but adjuvant combined modality therapy is mandatory. Other than in stage I disease, surgical resection offers no clear benefit in SCLC.

Table 5 Some genetic alterations in small cell lung cancer (SCLC) [23, 24]

| Gene (locus) | Alteration | Possible drug/therapeutic targeting abnormalities |
|------------------------|--------------------------------------|--|
| FHIT (3p14.2) | Loss (80% of SCLC) | |
| RASSF1 (3p21.3) | Loss (>90% of SCLC) | |
| RARB (3p24) | Loss (72% of SCLC) | |
| TP53 (17p13.1) | Mutation and deletion (>75% of SCLC) | p53 adenoviral vector (Advexin) |
| c-Kit | Overexpressed | Tyrosine kinase inhibitor (imatinib) |
| Src | Constitutively activated | Src inhibitor (dasatinib) |
| c-Met | Amplified, overexpressed or mutated | siRNA, c-Met inhibitor SU11274 |
| RB1 | Altered (>90% of SCLC) | |
| PI3K/Akt/mTOR | Constitutively activated | PI3K inhibitor (LY294002) mTOR inhibitor (rapamycin) and its derivatives (CCI-779, RAD001, AP23576) |
| Bcl-2 | Overexpressed | Antisense oligonucleotide (oblimersen sodium) Inhibitor of Bcl-2 (ABT-737) |
| VEGF | Overexpressed | Humanised monoclonal antibody (bevacizumab) VEGFR-2 and EGFR inhibitor (ZD6474) |

FHIT: fragile histidine triad; RASSF: Ras-association domain family; RARB: retinoic acid receptor- β ; TP53: tumour protein p53; RB: retinoblastoma; PI3K: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; Bcl: B-cell lymphoma; VEGF: vascular endothelial growth factor; siRNA: small interfering RNA; EGFR: epidermal growth factor.

Radiotherapy

Radiotherapy has gained in importance over the past years. The radiosensitive nature of SCLC results in good local control in the irradiated area, and combining irradiation with chemotherapy further improves control over local tumour burden. Simultaneous conventional irradiation of the chest has been shown to increase 2-year survival rates to 41%, and irradiation twice-daily to an overall dose of 45 Gy further increased OS by 10% in 5 years (OS rate of 26%) [29]. Parallel irradiation starting with the first cycle of chemotherapy was also shown to be superior to sequential therapy [30, 31]. The use of prophylactic cranial irradiation will be discussed later in this review.

Palliative radiotherapy is intended to reduce pain and other symptoms. Bone metastasis may be irradiated to reduce pain, prevent pathological fractures and, in the case of vertebral metastases, reduce the risk of instability or spinal cord compression. Brain metastases are

irradiated to reduce symptoms and progressive mass effect; however, the prognosis following brain relapse, as shown in table 8, is poor even with the integration of new approaches such as radiosurgery [6, 12, 32].

First-line therapy

First-line therapy in stage IV (ED)

Most patients present in stage IV (ED) and should be treated with chemotherapy. Chemotherapy offers a clear survival benefit, from 4–6-week survival in untreated patients with extensive disease to 12-month survival in extensive disease with chemotherapy. The initial rate of response to chemotherapy in these patients is 50–80%, with complete response rates (CR) of 15–25%. However, due to early relapses, long-term survival is rare, with <5% of patients living beyond 2 years and a 5-year survival rate of just 2%.

Table 6 Widely used chemotherapeutic regimens with effect against small cell lung cancer [6]

| Regimen | Dosage | Application | Cycles/Precautions |
|--|--|-------------------------|--|
| CisEto | | | Every 3 weeks, or after nadir, normal renal function and diuretics are mandatory |
| Cisplatin | 80 mg·m ⁻² | <i>i.v.</i> d1 | |
| Etoposide | 100 mg·m ⁻² | <i>i.v.</i> d1–d3 | |
| ACO-I after Livingston and Seeber | | | Every 3 weeks; vincristine dosage has to be adjusted to age; >60 years reduce to 1 mg·m ⁻² |
| Adriamycin | 60 mg·m ⁻² | <i>i.v.</i> d1 | |
| Cyclophosphamide | 750 mg·m ⁻² | <i>i.v.</i> d1 | |
| Vincristine | 2 mg·m ⁻² | <i>i.v.</i> d1/d8/d16 | |
| ACE combination after Klastersky | | | |
| Adriamycin | 45 mg·m ⁻² | <i>i.v.</i> d1 | |
| Cyclophosphamide | 1000 mg·m ⁻² | <i>i.v.</i> d1 | |
| Etoposide | 80 mg·m ⁻² | <i>i.v.</i> d1–d3 | Every 3 weeks. |
| EpiCO therapy after Drings | | | Every 3 weeks; vincristine dosage has to be adjusted to age; >60 years reduce to 1 mg·m ⁻² |
| Epirubicin | 70 mg·m ⁻² | <i>i.v.</i> d1 | |
| Cyclophosphamide | 1000 mg·m ⁻² | <i>i.v.</i> d1 | |
| Vincristine | 2 mg·m ⁻² | <i>i.v.</i> d1/d8/d16 | |
| Carboplatin/etoposide | | | Every 3 weeks, or after nadir, normal renal function and diuretics are mandatory |
| Carboplatin | AUC 5 | <i>i.v.</i> d1 | |
| Etoposide | 100 mg·m ⁻² | <i>i.v.</i> d1–d3 | |
| Paclitaxel/etoposide/carboplatin | | | Every 3 weeks, steroids to prevent anaphylactic crisis after administration of paclitaxel is mandatory |
| Paclitaxel | 175 mg·m ⁻² | <i>i.v.</i> for 3 h | |
| Carboplatin | AUC 5 | d4 | |
| Etoposide | I–III: 100 mg·m ⁻² IV: 100 mg·m ⁻² | <i>i.v.</i> d4 d1–d3 | |
| Cisplatin/irinotecan | | | Atropine 0.25 mg 1/2 h before irinotecan <i>s.c.</i> Every 4 weeks and/or after nadir; diarrhoea is common |
| Cisplatin | 60 mg·m ⁻² | <i>i.v.</i> d1 | |
| Irinotecan | 60 mg·m ⁻² | <i>i.v.</i> d 1, 8,15 | |
| Topotecan (second-line) | | | |
| Topotecan | 1.25 mg·m ⁻² with subsequent dose adjustment according to haematological toxicity | <i>i.v.</i> d 1–5 | Every 3 weeks and/or after reaching normal laboratory values |

Table 7 Small cell lung cancer: response to newer agents [6, 34–38]

| Agent | Response rate (%) |
|--------------|--|
| Paclitaxel | 34–41 |
| Irinotecan | 47 [#] |
| Topotecan | 39 |
| Docetaxel | 28 [#] |
| Gemcitabine | 26 |
| Vinorelbine | 12.5 [#] |
| Bendamustine | 72.7% first-line in combination with carboplatin |
| Amrubicin | 21.3 [#] (refractory patients), 44 [#] (sensitive patients) |

[#]: previously treated patients only.

Platinum-based regimens consisting of cis- or carboplatinum and one or two co-chemotherapeutic drugs are the standard of care for patients with adequate performance status. Carboplatinum combined with etoposide seems to be as effective in extensive disease as cisplatin and etoposide (PE), and may cause fewer side effects. Carboplatin is especially appropriate in patients with poor prognosis/performance status or contraindications to cisplatin. Cyclophosphamide,

adriamycin and vincristine (CAV) was the standard regimen before the advent of the platinum-based therapies. Although CAV is still in use in some areas, PE has shown similar response rates and is generally associated with less toxicity [6, 16]. The standard chemotherapy regimens are listed in table 7 [6].

The American College of Chest Physicians (ACCP) recommendation in 2007 was as follows: “Patients with extensive-stage disease should receive four to not more than six cycles of cisplatin or carboplatin-based combination chemotherapy. Cisplatin could be combined with either etoposide or CPT-11. (*Grade of recommendation, 1B*)”. CPT-11 is not licensed for use in SCLC in Europe.

Radiation therapy is generally used for palliation in extensive disease, with the exception of thoracic radiotherapy after complete response outside of the chest and good response in the chest. ACCP stated “After chemotherapy, patients achieving a CR outside the chest and complete or partial response in the chest can be offered consolidative TRTx in the chest (*Grade of recommendation, 2C*)”. The recommendations for prophylactic cranial irradiation are described below.

First-line therapy in stage I–IIIB (LD)

Only 30 % of patients have LD at the time of diagnosis. The standard therapeutic approach for limited disease is chemotherapy using cisplatinum and etoposide (EP) with concurrent thoracic irradiation. Because EP is relatively

Table 8 Treatment of brain metastases by radiotherapy modified from [32]

| First author [ref.] | Patients n | CR+PR % | CR % | Median survival months (range) |
|---------------------|------------|---------|------|--------------------------------|
| NUGENT [39] | 68 | 92 | | 3 |
| COX [40] | 40 | 75 | 38 | 4 (0–21) |
| BAGLAN [41] | 47 | 85 | 64 | 4 |
| HIRSCH [42] | 45 | 46 | | |
| LUCAS [43] | 39 | 56 | 25 | (1–28) |
| CARMICHAEL [44] | 61 | 63 | 32 | 7 (1–18) |
| GIANONNE [37] | 41 | 85 | 70 | 11 (1–24) |

CR: complete response; PR: partial response.

well tolerated in combination with radiation, it is preferred over CAV in this setting [45]. Chemotherapy alone does not offer good local control, with local failure rates of 75–90% despite good initial response rates of 80–90%. The use of thoracic radiotherapy increases local response. The effect of adding radiotherapy to chemotherapy seems to be more pronounced if radiotherapy is integrated early in the course of the treatment [30, 46]. Hyperfractionated radiotherapy improves survival in comparison to conventionally fractionated radiotherapy [29]. Combined modality therapy, consisting of chemotherapy and thoracic radiotherapy, can lead to complete response in 50–60% of patients, and has been shown to improve long-time survival by 10% compared to chemotherapy alone [30, 47].

Prophylactic cranial irradiation (PCI) (described below) is recommended for patients who achieve a good response following initial therapy.

Selected patients with very limited disease may benefit from surgery. The use of adjuvant chemotherapy following complete resection improves OS, even in patients with very limited disease.

Overall, with current forms of treatment, median survival times of 16–24 months can reasonably be expected, with 12–26% of patients surviving beyond 5 years.

Prophylactic cranial irradiation

PCI was originally introduced in the treatment of leukaemia, and was proposed for use in SCLC by HANSEN [48]. It is based on the concept that the brain is poorly accessible to chemotherapy, and therefore a site of sanctuary for cancer cells.

The goals of prophylactic cranial irradiation are the prevention of brain relapse, and therefore the avoidance of central nervous system symptoms, the improvement of quality of life (QoL) and the improvement of OS. Approximately 30–40% of SCLC patients will develop brain metastasis during the course of their disease, often within the first year. PCI reduces this risk to <15% and can increase OS [49] in patients with a complete or stable partial remission following chemotherapy. The short-term side effects of PCI include fatigue, loss of appetite, and transient hair loss.

Several trials have shown a survival benefit for PCI in patients with SCLC. A meta-analysis of PCI in patients with complete remission after systemic treatment demonstrated a slight

survival benefit of above 5% with PCI [42]. In addition, a more recent phase III trial performed by SLOTMAN *et al.* [50] in patients with extensive disease and performance status 0–2 showed that, in patients who responded to chemotherapy (not only patients with complete response), PCI decreased the incidence of brain metastases from 40.4% at 1 year to 14.6% (hazard ratio (HR) 0.27, 95% CI 0.16–0.44; $p < 0.0001$) and gave a survival and symptomatic benefit with a 1-year survival rate of 13.3% in the control group and 27.1% in the treated group (HR 0.68, 95% CI 0.52–0.88; $p = 0.003$).

A Cochrane review showed brain metastases in 29% of patients who received PCI and 57% of patients without PCI (HR 0.38, 95% CI 0.23–0.64). The survival HR was 0.77 (95% CI 0.54–1.11) [51].

Relapse and further-line therapy

Despite a generally good response to initial therapy, patients with SCLC almost invariably go on to develop progression [6, 9, 14, 27, 28], and should be considered for second-line chemotherapy. The choice of second-line chemotherapy depends on the first-line therapy regimen, the initial response, the time to relapse and the overall performance status of the patient. In general, second-line therapy is less effective than first-line, resulting in a relatively small survival benefit when compared with best supportive care (5.5 *versus* 2.2 months). This is particularly true in patients with early relapse or primarily refractory/progressive or resistant disease (progression within 3 months of primary therapy). If the remission following first-line therapy was stable for >6 months, more aggressive second-line therapy, even using the systemic agents used in first-line therapy, can be considered. In relapses with a shorter interval, an alternative chemotherapy should be discussed. One of the most studied options in second-line chemotherapy is topotecan. Topotecan is a topoisomerase-I inhibitor that can be given orally or intravenously. In a prospective study of 170 patients (73.2% in stage IV, 63.4% having received platinum-based first-line therapy), the overall response rate was 14.1%, with one complete remission. Moreover, 28.8% of the patients had stable disease, with a median duration of response of 13.6 weeks and median survival of 23.4 weeks. In this trial, topotecan was used with a starting dose of 1.25 mg·m⁻² *i.v.* and dose-adjusted according to the haematological toxicity. This reduced the haematological

toxicity significantly without impairing efficacy [6]. In a randomised phase III trial, topotecan demonstrated a survival advantage against best supportive care [31]; and in a randomised trial against CAV, topotecan was at least equally effective [52]. Other substances which have demonstrated at least some efficacy in trials are listed in table 7, and include paclitaxel, gemcitabine and pemetrexed [17, 35, 37, 38, 43, 54].

In the setting of relapse, irradiation should only be used to reach defined palliative goals, such as the prevention of pathological fractures or the treatment of brain metastases. Brain metastases that develop after PCI should be assessed in light of the time span after PCI and the systemic tumour situation. Stereotactic radiotherapy may be possible, and, in cases of brain relapse after a longer progression-free period, re-irradiation of the brain may be considered. Depending on the patient's general medical condition, symptomatic treatment with dexamethasone and/or systemic (chemo)therapy should be considered.

Although primary chemotherapy resistance can occur in SCLC, patients who do not achieve a significant remission under first-line therapy should be carefully considered for alternative diagnoses, such as the presence of combined histologies. In such cases, the SCLC portion of the combined tumour may respond differently than the NSCLC portion. The presence of a second tumour should be considered in cases of apparent relapse after a long progression-free interval. The tumour in question should be (re)biopsied and the chemotherapy adjusted accordingly.

Approaches for improvement of systemic therapy

As OS in SCLC remains poor, efforts to improve the effectiveness of systemic therapy have been the focus of much attention. These approaches involve the escalation of chemotherapy, the use of newer chemotherapeutic agents and the integration of targeted therapies.

Escalation of chemotherapy

Dose escalation

An escalation of chemotherapy can be achieved by increasing the dose or by reducing the interval between cycles. The feasibility of these

approaches is often limited by the morbidity and mortality associated with the myelodepressive side-effects of chemotherapy.

The use of colony-stimulating factors (CSFs) allows chemotherapy to be given at higher or denser dosages. Earlier evidence suggested that dose intensification in patients with a good prognosis may improve survival [55]. Unfortunately, despite higher response rates, this strategy was not shown to significantly improve OS [56]. In addition, there have been some reports of harm associated with the use of granulocyte CSF (G-CSF). The Southwest Oncology Group reported more severe and prolonged neutropenia and severe thrombopenia under G-CSF, especially in patients who received combined-modality therapy [57].

Maintenance therapy

In contrast to recent evidence for the use of maintenance therapy in NSCLC, this approach is not generally accepted in the treatment of SCLC. Studies have examined various agents in the maintenance setting in SCLC, including chemotherapeutics, interferon and other biological agents. Some of these trials were able to show a progression-free survival (PFS) benefit with maintenance therapy. For example, the ECOG E7593 trial used topotecan (four cycles of $1.5 \text{ mg}\cdot\text{m}^{-2}$ for 5 days) as switch maintenance treatment in extensive disease and demonstrated a difference in PFS of 1.4 months (2.3 *versus* 3.7 months; $p < 0.001$), with no significant difference in OS (8.9 *versus* 9.3 months; $p = 0.43$) [58].

A recent meta-analysis of 21 published randomised trials (11 using chemotherapy, six interferon and four other biological agents), including a total of 3,688 patients, demonstrated no overall statistical advantage in OS (HR 0.93, 95% CI 0.87–1.00; $p = 0.05$) or in PFS (HR 0.98, 95% CI 0.91–1.06; $p = 0.63$) [59] with maintenance therapy. However, there was a reduction in mortality in those studies using chemotherapy (HR 0.89, 95% CI 0.81–0.98; $p = 0.02$) or interferon- α (HR 0.78, 95% CI 0.64–0.96; $p = 0.02$). Clearly, further clarification of the utility of maintenance therapy in SCLC through well-designed randomised trials to address specific questions is needed.

Newer chemotherapeutic agents

The alkaloid topotecan is a topoisomerase inhibitor approved by the US Food and Drug

Educational questions

- 1) Standard treatment of stage IIIA SCLC consists of
 - a. Surgery
 - b. Radiotherapy
 - c. Chemotherapy
 - d. Chemoradiotherapy
 - e. Chemoradiotherapy and prophylactic cranial irradiation
- 2) Standard treatment of stage IV SCLC consists of
 - a. Monochemotherapy
 - b. polychemotherapy
 - c. Polychemotherapy and thoracic radiotherapy
 - d. Palliative radiotherapy
 - e. Polychemotherapy and prophylactic cranial irradiation
- 3) Prophylactic cranial irradiation is indicated
 - a. As first step of treatment in stage IV SCLC
 - b. Only after chemotherapy of stage II SCLC
 - c. Only after radiochemotherapy in stage I – III SCLC with complete remission
 - d. Only after chemotherapy in stage IV SCLC with complete remission
 - e. After treatment of SCLC of stage II – IV with good response to treatment

4.) Relapse of SCLC can be treated (two answers are correct)

- a. With reexposure to 1st line therapy 6 weeks after completion of 1st line therapy
- b. With topotecan
- c. With reexposure to 1st line therapy 6 months after completion of 1st line therapy
- d. With pemetrexed
- e. With erlotinib

Administration for the second-line therapy of SCLC [45, 61]. It has also been investigated for use as a first-line agent. Some first-line studies have shown a slightly better OS following cisplatin plus topotecan compared with carboplatin plus etoposide [61, 62]. One study in extensive disease compared cisplatin and topotecan to cisplatin and etoposide, showing a benefit with the topotecan combination (OR 55.5 *versus* 45.5%, $p=0.01$). Median time to progression was 7 *versus* 6 months (log-rank $p=0.004$) and median OS 10.5 *versus* 9.5 months) [63].

Irinotecan, another topoisomerase-I inhibitor, has not yet found its place in the treatment of Caucasian populations with SCLC. In a randomised Japanese trial of 154 patients with extensive disease, irinotecan and cisplatin resulted in significantly better survival than cisplatin and etoposide [64]. This survival advantage has not been reproduced in trials in Caucasian populations [65, 66]. Irinotecan can be administered sequentially or parallel to irradiation. It should be avoided in patients with diarrhoea and requires intensive patient monitoring.

The taxanes docetaxel and paclitaxel have also been tested in SCLC. There are few data concerning docetaxel [67]. Paclitaxel, in combination with etoposide and platinum, has given encouraging results in phase II studies. The data from phase III trials is somewhat inconsistent, and varies between trials with cisplatin and those with carboplatin. Two phase III studies comparing paclitaxel–etoposide–cisplatin (TEP) and EP showed comparable efficacy, but an increased number of toxic deaths in the TEP arm [57, 68]. However, a phase III trial comparing paclitaxel/etoposide/carboplatin (TEC) to carboplatin/etoposide/vincristine (CEV) in patients with both ED and LD showed a significant survival benefit in favour of TEC. A median OS of 12.5 months following TEC, compared to 11.7 months in the CEV arm (HR 1.21, 95% CI, 1.02–1.43; $p=0.030$), was found [69]. The 5-year survival rates were 14% for the experimental *versus* 6% for the CEV arm. A significant survival benefit was also observed in the subgroup of patients with stage IV disease (HR 1.27, 95% CI, 1.00–1.60; $p=0.047$). In addition, patients in the TEC arm reported less grade 3/4 toxicity, and showed improvements in several relevant QoL parameters including global overall QoL and physical functioning [70].

Gemcitabine is a nucleotide analogue that disturbs protein biosynthesis by replacing cytosine in the DNA backbone. The faulty nucleic acid cannot be processed and apoptosis is induced. A study of poor prognosis SCLC (mostly ED) showed a benefit of cisplatin plus gemcitabine *versus* cisplatin and etoposide plus gemcitabine, mainly on the basis of less haematological toxicity. Survival was similar in both arms [6, 34].

Pemetrexed is an antimetabolite with a similar chemical structure to folic acid. It inhibits enzymes involved in purine and pyrimidine synthesis, and therefore interferes with DNA synthesis. In a randomized phase II study in SCLC, pemetrexed was combined with carboplatin or cisplatin, resulting in good response rates for both arms, with fewer grade 3–4 haematological toxicities [71]. However, a phase III trial comparing pemetrexed–carboplatin with etoposide–carboplatin in chemotherapy-naïve patients with ED SCLC showed pemetrexed–carboplatin to be inferior to etoposide–carboplatin for both OS (median 8.1 *versus* 10.6 months; HR 1.56, 95% CI 1.27–1.92; log-rank $p<0.01$) and PFS (median 3.8 *versus* 5.4 months; HR 1.85, 95% CI 1.58–2.17; log-rank $p<0.01$) [72].

The alkylating agent bendamustine is best known for its use in haematological malignancies; however, it also has demonstrated efficacy in SCLC. A phase II trial in combination with carboplatin in patients with extensive disease showed good tolerability and activity comparable with that of other platinum-based regimens [36].

The anthracycline amrubicin has been licensed for use in SCLC in Japan since 2002. Amrubicin acts by inhibiting topoisomerase II, and is often compared with the topoisomerase I inhibitor topotecan in clinical trials [54]. The efficacy of amrubicin in Caucasian patients remains unclear, a difference which may be due to ethnic variations in enzymatic metabolism [73]. There are phase II data in both second-line [37, 38] and first-line in Caucasian patients with extensive disease [74]. One randomised trial in second-line therapy, which compared amrubicin to topotecan, has been presented in abstract form [75] and appears to suggest activity in Caucasian patients.

Targeted therapies

New targets for systemic therapy at the genetic level offer the hope of improved survival. The

enthusiasm for targeted therapies in SCLC has been fuelled by successes in other areas of oncology, including the treatment of NSCLC.

However, positive trial results in SCLC have been relatively sparse, and currently only a few novel agents continue to show promise in SCLC. Nevertheless, improvements in our understanding of tumour biology and efforts to integrate targeted therapies in the treatment of SCLC have the potential to improve patient survival [76]. As targeted therapies remain experimental in SCLC, they have to be tested in an appropriate window of opportunity and are often combined with conventional cytotoxic chemotherapy.

The most promising agents are listed here. However, it should be emphasised that there are currently no phase III data showing a benefit with these targeted agents in SCLC. Further trials and new combinations are certainly necessary.

Mammalian target of rapamycin inhibitors

Rapamycin, also known as Sirolimus, is an immune modulator normally used in transplanted patients to reduce organ rejection. Blocking mammalian target of rapamycin (mTOR) blocks the translation of cell cycle-regulating genes and is, therefore, antiproliferative and also antiangiogenic.

Vascular endothelial growth factor inhibitors

Vascular endothelial growth factor (VEGF) is a potent endothelial promoter of neoangiogenesis.

Bevacizumab

A monoclonal antibody against VEGF, bevacizumab, has been tested in combination with chemotherapy (irinotecan and carboplatin) and as continuation maintenance therapy, showing PFS at 1 year in 63% and at 2 years in 54% of patients.

Tyrosine kinase and tyrosine kinase receptor inhibitors

Tyrosine kinases (TKs) are enzymes that catalyse the phosphorylation of tyrosine residues, and can be divided into receptor-coupled TKs and cellular or nonreceptor TKs. They are involved in cellular signalling pathways, and regulate cell growth, proliferation, differentiation and antiapoptotic signalling.

Unregulated activity seems to be a hallmark of many cancer cells [77, 78].

Imatinib

Imatinib is a small-molecule inhibitor of several TKs, including c-Kit (CD117), and has shown considerable effect in patients with chronic myeloid lymphoma. Because SCLC cells also can show CD117 positivity, they may provide a target for imatinib. Unfortunately, clinical data have not shown much promise for imatinib in this setting [79].

Matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are zinc metalloendopeptidases and belongs to the MB clan of metallopeptidases, which are enzymes capable of degrading the extracellular matrix. They are involved in physiological and pathological processes, including tumour growth and migration. Recent studies have not shown a benefit for the use of MMP inhibitors in the treatment of SCLC [80].

Vaccine therapy

SCLC cells display antigens that distinguish them from normal cells. KRUG *et al.* [81] reported on an anti-idiotypic vaccine against the GD3 ganglioside and BEC-2. The vaccines were tested in a phase III trial in 2004. Unfortunately, there was no survival benefit with these immune therapies compared with standard multimodality therapy.

Antisense oligonucleotides

This new approach targets specific RNA sequences and interferes in protein expression at the level of mRNA translation. Oblimersen is an antisense nucleotide currently under investigation. Because tumour cells often show increased activity of the antiapoptotic B-cell lymphoma protein (Bcl)-2 compared with proapoptotic Bax (Bcl-2-associated X), blocking Bcl-2 should reactivate physiological cell cycle regulation and sensitise tumour cells for chemotherapy. Bcl-2 may also play a role in triggering tumour resistance against chemotherapy [82].

Conclusion

The prognosis of SCLC has not improved significantly over the past decades. This seems

to be due in part to the biology of the tumour and its rapid development of resistance to conventional systemic treatments. For this reason, there is much interest in the integration of biology in clinical trials, including targeted therapies and stem cell approaches.

Outside of trials, treatment should be guided by algorithms based on exact staging of the tumour, taking individual patient factors into account. In stage I–III, a multimodality approach including PCI should be used. In

stage IV, systemic therapy, with PCI in responders, is recommended. The intensity of systemic treatment in stage IV depends on the clinical situation and individual patient prognosis. In second-line therapy, the choice of systemic treatment depends on the progression-free interval following first-line treatment.

Treatment in centres with ready access to respiratory physicians, thoracic oncologists, thoracic surgeons, radiation oncologists and palliative care is recommended.

Key points

- Systemic treatment improves the prognosis of patients with small cell lung cancer.
- The treatment of small cell lung cancer depends on the extent of disease and the performance status at presentation.
- Paraneoplastic syndromes can be the first sign of small cell lung cancer.
- In patients who respond to first-line treatment, prophylactic cranial irradiation should be considered.

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Suggested answers

1. e.
2. e.
3. e.
4. b and c.