Rare thoracic cancers: a comprehensive overview of diagnosis and management of small cell lung cancer, malignant pleural mesothelioma and thymic epithelial tumours

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Number 3 in the Series "The world of rare lung diseases"
Edited by Michael Kreuter, Marc Humbert, Thomas Wagner and Marlies Wijsenbeek

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Shareable abstract (@ERSpublications)
SCLC, mesothelioma and thymoma are rare thoracic cancers. Diagnosis and treatment options should therefore be discussed in a multidisciplinary discussion. Although progress has been made with the entrance of ICI, novel strategies are being studied. https://bit.ly/3TTUgY9

Cite this article as: Dumoulin DW, Bironzo P, Passiglia F, *et al*. Rare thoracic cancers: a comprehensive overview of diagnosis and management of small cell lung cancer, malignant pleural mesothelioma and thymic epithelial tumours. *Eur Respir Rev* 2023; 32: 220174 [DOI: 10.1183/16000617.0174-2022].

This article has an editorial commentary: https://doi.org/10.1183/16000617.0006-2023

Received: 30 Aug 2022
Accepted: 18 Oct 2022

Abstract

Despite the progress in outcomes seen with immunotherapy in various malignancies, including nonsmall cell lung cancer, the benefits are less in small cell lung cancer, malignant pleural mesothelioma and thymic epithelial tumours. New effective treatment options are needed, guided *via* more in-depth insights into the pathophysiology of these rare malignancies. This review comprehensively presents an overview of the clinical presentation, diagnostic tools, staging systems, pathophysiology and treatment options for these rare thoracic cancers. In addition, opportunities for further improvement of therapies are discussed.

Introduction

Small cell lung cancer (SCLC), malignant pleural mesothelioma (MPM) and thymic epithelial tumours (TETs) are rare but aggressive thoracic malignancies. The prognosis of patients is frequently dismal and treatment options are limited. Despite the progress in outcomes seen with immunotherapy in various malignancies, including nonsmall cell lung cancer (NSCLC), the benefits in these rare thoracic malignancies are less for partially unknown reasons. New effective treatment options are needed, guided *via* more in-depth insights into the pathophysiology of these rare malignancies, as we have learned from recently performed studies that general principles established in other malignancies do not apply to these rare cancers.

In this review, we provide an overview of the current landscape of these rare thoracic cancers. Based on completed and ongoing clinical trials, we will suggest therapeutic options for further improvement of therapies in the (near) future.

Small cell lung cancer

According to the 2021 World Health Organization (WHO) classification of lung tumours, SCLC is part of the neuroendocrine lung neoplasms, along with large cell neuroendocrine carcinomas and carcinoid tumours [1].

Epidemiology

SCLC represents about 15% of all lung cancers. With an incidence of 1–5 per 10 000, SCLC is recognised as an orphan disease [2].

SCLC has a strong correlation with smoking. SCLC used to be more common in men than women, but the male/female ratio has become equal due to increased tobacco consumption in women. Because of a general decrease in the prevalence of cigarette smoking, the incidence of SCLC in the last two decades has progressively declined [3]. Of all SCLC diagnoses, only 2% occur in never-smokers. SCLC in never-smokers may originate from the histological transformation in oncogene driver-mutated lung cancer, *e.g.* in those with epidermal growth factor receptor (*EGFR*)-mutated lung cancer who develop resistance to targeted treatment.

Patients with SCLC usually present with small intrapulmonary lesions and bulky mediastinal lymphadenopathies. Distant metastases are most frequently seen in bone, liver, brain and adrenal glands [3]. At diagnosis, ∼70% of patients already have distant metastases.

Diagnosis

The diagnosis of SCLC is based primarily on histological appearance by light microscopy, which demonstrates small tumour cells, poorly defined cell borders, scant cytoplasm and nuclear moulding. The mitotic rate is high at >10 mitoses per mm^2 (mean 60 mitoses per mm^2; median 80 mitoses per mm^2).

The addition of immunohistochemistry (IHC) can help to distinguish SCLC from other tumours [4]. Because SCLC originates in the lung, these tumours are positive for keratin and epithelial membrane antigen staining, and the majority will also express thyroid transcription factor-1 (TTF1). This helps distinguish small cell tumours that originate in the lung or another organs like lymphomas that are negative for cytokeratins and express CD45. The most useful neuroendocrine markers include CD56, chromogranin and synaptophysin, which are best used as a panel. CD56 is present in ∼95% of patients, whereas up to two-thirds of SCLC will be negative for chromogranin and synaptophysin. In ∼10% of patients with SCLC, all neuroendocrine markers are negative. By using mainly the number of mutations per mm^2 and the proliferation marker Ki-67, which is exceptionally high in SCLC (>50%; usually 80–100%), SCLC can be separated from carcinoid tumours [5].

Staging

SCLC used to be divided by the Veterans Affairs Lung Study Group into limited stage disease (tumour confined to the ipsilateral hemithorax and regional nodes able to be included in a single tolerable radiotherapy port) *versus* extensive stage disease (tumour beyond the boundaries of limited disease) [6]. Although this staging system is still functional and easy to use in clinical practice, it has been replaced by the tumour–node–metastasis (TNM) classification [7]. The TNM classification provides a more detailed staging that better reflects outcome and prognostic information, which is extremely relevant in clinical trials.

At diagnosis, ∼10% of patients have brain metastases. Most of the patients have symptomatic brain metastases. However, in a substantial portion of asymptomatic patients, magnetic resonance imaging (MRI) detects brain metastases and these are therefore upgraded to stage IV disease [8].

The role of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is less clear. ^{18}F-FDG-PET/CT has been shown to change the staging of the disease in a substantial number of patients, leading to a different treatment strategy [9, 10], and thus the recommendation to perform ^{18}F-FDG-PET/CT in staging. However, it does not seem to influence overall survival (OS) [11].

Pathophysiology

SCLC occurs through the inactivation of the tumour suppressor genes *TP53* and *RB1*, which is frequently initiated from exposure to tobacco carcinogens. Besides the loss of p53 and RB1 (in nearly all SCLC tumours), other alterations have also been reported in a subset of patients with SCLC, such as MYC amplification and inactivating mutations in, among others, *PTEN*, *KMT2D*, *CREBBP* and *NOTCH* genes [12]. So far, no mutationally defined subtypes of SCLC have been recognised. However, by using the expression of several specific transcription factors, SCLC can be divided into four biological different subtypes (NAPY classification, based on the transcription factors NEUROD1, ASCL1, POU2F3 and YAP1), which are becoming of increasing interest because of potential new therapeutic options [13]. The most common (70%) is the "classical" SCLC (SCLC-A) which is characterised by ASCL1 expression. It also has high expression of INSM1, L-MYC and Delta-like ligand 3 (DLL3), and low NEUROD1 expression. Immunohistochemically, SCLC-A is TTF1-high and c-MYC-low. This subtype can be further divided into SCLC-A and SCLC-A2, based on the expression of HES1 [14]. The SCLC-N subtype (11%) is characterised by high expression of NEUROD1. It has variable expression of ASCL1, the expression of TTF1 is low and c-MYC is high. The SCLC-P subtype (16%) is characterised by high expression of POU2F3. The expression of ASCL1 and INSM1 is low. The SCLC-Y subtype (3%) is characterised by

high YAP1 expression. The expression of ASCL1, NEUROD1 and INSM1 is low. This subtype is further characterised by wild-type/enriched RB1 [13]. SCLC-A and SCLC-N show a more neuroendocrine phenotype than SCLC-P and SCLC-Y. Within the neuroendocrine subtypes, another less frequently common subtype is described: NETF, characterised by the expression of the neuroendocrine transcription factor ATOH1 [15]. Identifying these molecular subtypes could help develop a personalised approach by distinguishing subsets of patients that are most likely to respond to different therapies. For example, it might be that the different subtypes have a different tumour micro-environment (TME). SCLC-Y is enriched for a T-cell inflamed phenotype, making it plausible that this subtype might be most sensitive for therapy with (in combination with) programmed cell death (ligand)-1 (PD-(L)1) inhibitors, while DLL3-targeted treatment is most logical for SCLC-A [16]. Furthermore, it seems that MYC-high SCLC is especially sensitive to aurora kinase inhibitors [17].

Treatment

Chemotherapy has been the backbone in the treatment of all stages SCLC. For several decades, the standard chemotherapy regimen has consisted of platinum/etoposide. In nonmetastatic SCLC, cisplatin is used with the advantage of combining it concurrently with radiotherapy. In metastatic SCLC or patients unsuitable for cisplatin, it can be replaced by carboplatin, without inferiority [18].

cT1–2N0M0, very limited stage SCLC

Little evidence is available for the management of patients with very limited stage SCLC, defined as cT1–2N0M0 SCLC. It can be considered to treat these patients with local treatment by surgery or radiotherapy, without a preference for one of them [19]. If a resection is performed, adjuvant chemotherapy should follow. Only in cases where an incomplete resection was performed (R1–2 or unforeseen mediastinal lymph nodes) is there a role for adjuvant radiotherapy. Patients not suitable for surgery or with a preference for radiotherapy should be treated with fractionated or stereotactic ablative radiotherapy, combined with chemotherapy before or after [20]. Prophylactic cranial irradiation (PCI) is not recommended in cT1–2N0M0 SCLC because of the relatively low percentages of brain metastases and the risk of neurocognitive toxicities in consideration of the predicted long-term survival [21].

Stage I–III SCLC

The recommended treatment for patients with stage I–III SCLC is chemo-radiotherapy. Although responses to chemotherapy are exceptionally high in SCLC, relapse will soon occur. By adding radiotherapy to the primary tumour and mediastinal lymph nodes, the 3-year OS can be increased by 5% [22]. The most preferred regimen consists of 4 cycles of chemotherapy combined with twice-daily concurrent 45 Gy radiotherapy [23], starting from the first or second cycle [24]. High-dose once-daily up to 66 Gy radiotherapy seemed not superior and toxicity was not significantly different in the CONVERT trial, but this trial was not designed to show equivalence [25]. Therefore, twice-daily radiotherapy remains the standard of care, although for logistic reasons, once-daily radiotherapy could be an alternative option [26]. Higher dose 60 Gy radiotherapy twice daily seemed to improve survival in a phase II trial without increasing toxicity [27]. For more frail patients, a sequential chemo-radiotherapy approach can be considered. In this scenario, the volume of the pre-chemotherapy primary tumour and the post-chemotherapy nodal volume will be irradiated [28].

PCI in limited stage SCLC reduced brain metastases and increased OS significantly. However, since MRI of the brain is more frequently used in staging, results have become controversial [29–31]. The currently recommended strategy is to offer PCI to patients with a performance status score of 0–1 who responded to chemo-radiotherapy. In patients with stage I–II SCLC, or frailer or older (>70 years) patients, the role of PCI is less clear. For these patients, MRI surveillance could be a worthy alternative and thus shared decision making is recommended [26]. The recommended dose of PCI is 25 Gy in 10 daily fractions [32]. Because of concerns about late neurocognitive effects, hippocampal avoidant radiotherapy has been investigated, although a lower probability of cognitive decline was not found [33].

Stage IV SCLC

For many years the standard chemotherapy used for stage IV SCLC has been 4–6 cycles of platinum combined with etoposide. In terms of efficacy, no differences were found between carboplatin and cisplatin. However, more adverse events were seen with cisplatin, although carboplatin has more haematological toxicity [18]. Continuation of chemotherapy beyond 4–6 cycles is not recommended because of the risk of increased toxicity without improvement of OS.

In recent years, synergistic activity has been reported for the addition of immune checkpoint inhibition (ICI) to standard platinum-based chemotherapy, leading to a statistically significant benefit in

progression-free survival (PFS) and/or OS [34–37]. Although median benefits are only modest with an improvement of median OS of ∼2 months, the improvement in the tail of the survival curve suggests that a small proportion of patients have a durable benefit. For instance, atezolizumab combined with chemotherapy improved the 18-month survival rate from 20% to 33% and the 3-year survival rate for durvalumab combined with chemotherapy was improved from 6% to 18% [38]. Dependent on the reimbursement per country, chemotherapy combined with ICI is currently considered the standard first-line therapy for stage IV SCLC.

Several biomarkers were investigated to predict which patients benefit from ICI [39]. Although in NSCLC PD-L1 expression is used in deciding which therapy is preferred, no correlation was found between PD-L1 expression and efficacy in SCLC. Another biomarker is tumour mutation burden (TMB), which can be measured in the tumour or the blood (bTMB). TMB is defined as the number of somatic mutations found in the DNA of cancer cells per megabase. Because several trials have shown different correlations of (b)TMB, the role of TMB is still controversial. Currently, no predictive or prognostic biomarker has been found.

Almost half of patients with stage IV SCLC develop brain metastases after completion of standard chemotherapy. PCI reduces the risk of brain metastases significantly; however, OS seems not to be improved [40]. Active surveillance with MRI might be as effective as PCI [41].

Consolidation thoracic radiotherapy after chemotherapy in the CREST trial did not show an improvement on the primary end-point of 1-year OS and is therefore not recommended. However, in fit patients with residual intrathoracic disease who achieved response after chemotherapy, it could be considered [42].

Second-line treatment

Despite initial high response rates with chemotherapy, most patients relapse within 6 months. Second-line treatment depends on the treatment-free interval and the response to first-line therapy. In platinum-sensitive patients with a treatment-free interval of at least 3 months, rechallenge with carboplatin/etoposide can be considered, with a slightly higher PFS than topotecan [43]. Until 2020, topotecan, a topoisomerase 1 inhibitor, was the only approved second-line treatment. Despite the modest efficacy and significant toxicity, treatment using topotecan seems to improve OS and quality of life compared with best supportive care [44]. Oral and intravenous topotecan demonstrated similar efficacy [45].

Following the orphan designation granted by the European Medicines Agency (EMA) in 2019, in 2020 the US Food and Drug Administration (FDA) granted accelerated approval to lurbinectedin, a selective inhibitor of RNA polymerase II, for patients progressing on or after first-line chemotherapy. This was based on a phase II basket trial showing promising results with an overall response rate of 35%, a median duration of response of 5.3 months, a median OS of 9.3 months and a manageable safety profile [46]. A phase III trial comparing lower dose lurbinectedin combined with doxorubicin *versus* topotecan or cyclophosphamide/adriamycin/vincristine showed similar efficacy but a favourable toxicity profile [47].

The PD-1 checkpoint inhibitors nivolumab and pembrolizumab received FDA approval as monotherapy in third- or further-line therapy based on phase I/II studies [48, 49]; however, these approvals were withdrawn when the confirmatory phase III studies failed to reach OS improvement [35, 50]. Furthermore, second-line treatment with nivolumab compared with topotecan did not improve OS [50]. Another phase III trial comparing topotecan with rovalpituzumab tesirine (Rova-T), an antibody–drug conjugate containing a DLL3-targeting antibody tethered to a cytotoxic agent, showed decreased OS and increased toxicity with Rova-T [51].

Alternative treatment options without specific approval are cyclophosphamide combined with doxorubicin and vincristine (CAV), paclitaxel, docetaxel, irinotecan and temozolomide [26, 52].

Future perspectives

The introduction of ICI in several types of cancers did improve patient survival. Nonetheless, in SCLC this improvement with ICI is only modest. Although SCLC is characterised by high TMB (which has been shown to be predictive for ICI efficacy in other cancers [53]) and SCLC is extremely sensitive to chemotherapy (which results in massive tumour antigen release and potentially reduces the immunosuppressive environment of the tumour), these potentially beneficial characteristics for ICI efficacy do not result in improved outcomes in SCLC. In NSCLC, for instance, a synergistic effect between chemotherapy and ICI is seen [54]. In SCLC treated with combination chemotherapy and ICI, response rates do not rise and separation of the PFS and OS curves is seen late after several months, suggesting the absence of a synergistic effect in SCLC.

Many clinical trials using ICI are running to investigate multiple ways to convert SCLC to an immunogenic tumour [39]. While immunogenic cell death (ICD) is crucial for immune modulation by cytotoxic chemotherapies, various chemotherapeutic agents have different capacities to induce ICD. Translocation of the endoplasmic reticulum protein calreticulin to the cell membrane induces activation and maturation of dendritic cells, leading to T-cell activation and proliferation, and is thereby necessary for successful ICD [55, 56]. In etoposide-treated mice, calreticulin translocation was absent, suggesting that the lack of T-cell activation during etoposide treatment could be a reason for the reduced efficacy of etoposide in combination with ICI. Therefore, using another chemotherapy backbone in combination with ICI must be considered to reinforce tumour immunogenicity [57].

Since the classification of SCLC into different molecular subtypes, a more personalised approach is trying to be developed. ICI is logically most potent in tumour-associated T-cell immunophenotypes, which are the POU2F3 and YAP1 subtypes, with the highest $CD8^+$ T-cells in the tumours that express none of the molecular biomarkers (NAPY−) [58]. However, an exploratory analysis of the IMpower133 trial showed a higher proportion of long-term survivors in one subgroup named SCLC-I, but for both arms (chemotherapy plus placebo as well as for chemotherapy plus atezolizumab). This SCLC-I subgroup is not well defined but comprises an inflamed subgroup with a high expression of multiple immune genes, including $CD8^+$ cytotoxic T-cells, and lacking expression of NEUROD1, ASCL1 and POU2F3. The fact that the survival benefit was seen in both arms suggests that this subgroup might be prognostic [59].

Additionally, several other targets have been identified for which separate therapeutic options are being investigated [58]. One of these targets is DLL3, which is highly expressed in SCLC-A. DLL3 is regulated by transcription factor ASCL1, which is an inhibitory ligand of the Notch receptor. Notch signalling is downregulated during neuroendocrine tumour growth, thus the expression of DLL3 promotes the migration of SCLC. DLL3 is expressed in >80% of SCLC and other neuroendocrine tumours, while expression in normal tissue is limited, making it an interesting target of therapy. Although studies with Rova-T were disappointing [51, 60], other ways to use this target are being investigated, including a chimeric antigen receptor (CAR) T-cell (AMG 119 [61]) and a bispecific T-cell engager (AMG 757) for which the phase I results are promising [62].

Another target is MYC, which is amplified in ∼20% of SCLC. It is mainly seen in SCLC-N, but is also seen in SCLC-A. MYC-high SCLC is more sensitive to targeted therapy with aurora kinase inhibitors [17].

DNA damage plays a major role in SCLC. DNA damage repair inhibitors, *e.g.* poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors, and cell cycle checkpoint kinase inhibitors, *e.g.* WEE1 and cyclin-dependent kinase 7 (CDK7), are therefore of great interest [13]. SLFN11 is used as a biomarker for response to PARP inhibitors and DNA-damaging agents. It is expressed in all molecular subtypes of SCLC, but was absent in the SCLC tumours which were negative for all the four subtype markers (NAPY−) [58]. Multiple studies investigating DNA damage repair inhibitors are ongoing [63].

In conclusion, new insights into biological subtypes and immunogenicity are recognised as well as the association with some therapeutic response biomarkers. Although the current clinical approach to therapy is still independent of the molecular subtype, a large field of research is ongoing which could have major implications for clinical practice in the (near) future.

It should be noted that the best strategy is to prevent SCLC by smoking cessation. Luckily more attention is being given to smoking cessation counselling and intervention. Smoking cessation has also been shown to be beneficial during treatment [64].

Mesothelioma

Malignant mesothelioma is a rare tumour classified by the WHO as directly related to all types of asbestos exposure [65]. It is a fatal neoplasm arising from the mesothelial lining of the lungs, abdomen, heart or testes.

Epidemiology

In 2020, 30 000 patients were diagnosed with mesothelioma worldwide. The incidence is higher in males (0.7 per 100 000) than females (0.3 per 100 000) and increases with age. The median age at diagnosis is 76 years. The highest incidence is seen in countries with the greatest previous asbestos use, such as the Netherlands, UK and Australia [66].

Mesothelioma has a strong correlation with asbestos exposure. The greater the asbestos exposure, the greater the risk of developing mesothelioma. People who worked with asbestos products or worked in an environment containing asbestos are at increased risk of developing mesothelioma, but individuals who were washing the clothes of someone who worked with asbestos are also at risk. Although nonoccupational exposure to asbestos, including neighbourhood, domestic and household exposure, is associated with an increased risk for mesothelioma, a recent meta-analysis indicated that some summary relative risk estimates should be interpreted with caution because of high between-studies heterogeneity [67]. The time between exposure and the onset of mesothelioma is in general >30 years [68]. In some cases, mesothelioma occurs due to a genetic mutation in BRCA-associated protein 1 (BAP1). Patients with mesothelioma usually present with shortness of breath due to pleural effusion, chest pain or weight loss.

The prognosis of mesothelioma is poor. The median survival is only 9 months without therapy [69]. Patients with epithelioid histology have a better survival than those with the other histologies. Female sex, younger age and lower stage of cancer are also associated with a better prognosis, while higher performance status, high platelet counts, high fibrinogen levels, low albumin levels and low glucose levels in the pleural fluid represent adverse prognostic factors. In addition, mesotheliomas arising due to a germline *BAP1* mutation have a relatively favourable prognosis [70, 71].

Diagnosis

Although mesothelioma can be suspected on cytology, tissue biopsy is strongly recommended to establish the diagnosis, preferentially obtaining biopsies from three separate sites [66]. Based on morphology only, mesothelioma cannot be distinguished from metastatic lesions from another primary cancer or from atypia caused by reactive changes. Therefore, additional IHC investigation is recommended, used in a panel of three or four markers. Three histological subtypes are distinguished: epithelioid, sarcomatous and biphasic.

Most mesotheliomas are positive for pan-cytokeratin, independent of subtype, while sarcomas, for instance, are pan-cytokeratin negative [72]. Epithelioid mesothelioma expresses high levels of calretinin, Wilms' tumour-1 (WT-1) and podoplanin (D2-40). The epithelial markers carcinoembryonic antigen (CEA), Ber-EP4 and MOC-31 are usually absent in mesothelioma, and claudin-4 is consistently negative, which makes them very useful biomarkers in assisting in the differential diagnosis [73]. Sarcomatous mesothelioma does not express high levels of calretinin, but is usually positive for GATA3, which is negative in sarcomatous lung carcinoma [72]. Conversely, MUC4 is highly expressed in sarcomatous carcinoma of the lung and negative in sarcomatous mesothelioma.

Recently, more investigation has been focused on the loss of nuclear BAP1 [74]. Loss of BAP1 in IHC corresponds to *BAP1* mutation and BAP1 loss is almost 100% specific for malignancy in mesothelial proliferations; however, it is not sensitive in distinguishing the different subtypes of mesothelioma [75]. Of all pleural and peritoneal mesotheliomas, 50–70% show BAP1 loss. BAP1 loss is seen in ∼70% of the epithelioid subtype and 15% of the sarcomatous subtype. In sarcomatous mesothelioma, loss of methyl-thio-adenosine phosphorylase (MTAP) staining is frequently seen, with 96% specificity and 78% sensitivity. MTAP in IHC can act as a surrogate for loss of cyclin-dependent kinase inhibitor 2A (CDKN2A, which has a prominent role in the tumour suppressor mechanism), which requires fluorescence *in situ* hybridisation [76].

Staging

Mesotheliomas are clinically and pathologically staged using the eighth revision of the Union for International Cancer Control TNM staging system [77]. At first, contrast-enhanced CT of the thorax and upper abdomen is performed to evaluate the T and N stages. Before performing extensive staging, it should be considered if the patient is eligible to undergo active treatment [66]. For patients suitable for surgery, additional investigations such as ^{18}F-FDG-PET/CT, endobronchial ultrasound or mediastinoscopy are recommended to exclude contralateral lymph nodes and distant metastases [66]. Although survival is similar for all N stages, a survival difference between single compared with multiple metastases was described [78]. Since brain metastases are very rare in mesothelioma, imaging of the brain is only recommended when there is clinical suspicion [79].

Pathophysiology

Mesothelioma arises when asbestos fibres enter the pleural or abdominal cavity, causing phagocytosis by macrophages. This can lead to an inflammatory reaction, followed by an increased risk of malignant transformation of mesothelial cells [80]. This risk is higher when the asbestos fibres are longer than 10 µm because of more difficult clearance by macrophages and thus failed attempts of phagocytosis [81]. Another potential risk factor for the development of mesothelioma is the fact that asbestos fibres can enter mesothelial cells and directly interfere with mitosis, leading to DNA mutations. Furthermore, mesothelial

cells exposed to asbestos fibres release inflammatory cytokines such as transforming growth factor (TGF) and vascular endothelial growth factor (VEGF), which generate an ideal environment for tumour growth. These factors are responsible for the increased risk and eventually the development of mesothelioma [80].

Treatment

Surgery

After adequate staging, surgery may be considered for selected patients where a complete macroscopic resection is to be expected. The overwhelming majority of those surgical cases are stage I mesotheliomas, although upstaging after surgery frequently occurs. The surgery has to be performed in a centre of expertise, as part of multimodality treatment. However, the role of surgery is controversial; in the Mesothelioma and Radical Surgery (MARS) study, extrapleural pneumonectomy failed to show a benefit to best supportive care as an addition to standard chemotherapy treatment [82]. Alternatively, pleurectomy/decortication is a less extensive lung-preserving surgical procedure with a significantly improved peri-operative 30-day survival [83]. It must be noted that positive reported outcomes of surgery most likely seem to be based on selection bias [84]. The MARS-2 study comparing pleurectomy/decortication with best supportive care as an addition to standard chemotherapy treatment is currently ongoing [85].

Systemic treatment

Due to widespread pleural metastases, most patients with mesothelioma are not suitable for surgery. For patients eligible for systemic treatment, the doublet combination of cisplatin combined with pemetrexed compared with cisplatin resulted in a survival benefit of 3 months [69]. By adding bevacizumab to pemetrexed plus cisplatin, an additional survival benefit of nearly 3 months can be achieved, although this treatment is not available in many countries [86]. The role of pemetrexed as maintenance therapy following initial pemetrexed and cisplatin did not result in better PFS [87]. Switch-maintenance gemcitabine significantly improved PFS compared with best supportive care, but did not improve OS [88].

ICI therapy has been extensively investigated as a treatment option in this setting. In the phase III CheckMate 743 trial, nivolumab combined with ipilimumab was compared with standard chemotherapy and resulted in a significantly improved OS [89], with 3-year OS of 23.2% *versus* 15.4%, respectively [90]. This benefit was higher in nonepithelioid subtypes compared with the epithelioid subtype due to the worse efficacy of chemotherapy for nonepithelioid subtypes. In addition, quality of life was better with nivolumab/ipilimumab than with chemotherapy [91]. Since 2020, nivolumab/ipilimumab has been approved by the FDA and the EMA, without histology or biomarker subtype restriction [92, 93].

Radiotherapy

The role of radiotherapy in mesothelioma is limited. Prophylactic irradiation was not beneficial in tract metastases rate, chest pain, analgesia requirements, quality of life or OS and is therefore not recommended. Radiotherapy as part of multimodality treatment, before or after surgery, did not result in a longer relapse-free survival and is therefore not standard of care. Radiotherapy can be considered as palliative treatment in the case of mesothelioma-induced pain [66].

Second-line treatment

Based on phase II studies, patients can be treated with vinorelbine or gemcitabine in the second or later line, although the impact on survival is questionable and responses are rare [94, 95]. In the phase II second-line PROMISE-meso study, ICI monotherapy (pembrolizumab) was compared with vinorelbine or gemcitabine, which showed an improved response rate; however, the study failed to show an additional benefit in PFS or OS [96]. The phase III CONFIRM study compared ICI monotherapy (nivolumab) to best supportive care, which resulted in improved outcomes with significantly higher OS, PFS and response rates with ICI [97].

Future perspectives

Mesothelioma can be classified as a cold tumour characterised by low T-cell infiltration into the tumour, which is caused by a low mutational load and an immunosuppressive TME consisting of increased amounts of myeloid-derived suppressor cells, M2 macrophages and regulatory T-cells. This may result in impaired immune activation.

Several strategies could potentially lead to the activation of the antitumour immune system [98]. In NSCLC, the addition of chemotherapy causes cell death leading to the release of tumour neoantigens. In addition, chemotherapy itself can result in a less suppressive TME. After promising results of two phase II studies [99, 100], combination chemotherapy with durvalumab as a first-line treatment is currently being investigated in the phase III DREAM3R study [101]. Furthermore, the phase III BEAT-MESO trial comparing bevacizumab with standard chemotherapy with or without atezolizumab is ongoing [102].

Another strategy to overcome immune suppression in mesothelioma considers the potential of dendritic cells to activate T-cells. Dendritic cells have the capacity to recognise tumour antigens following presentation to T-cells. The immunosuppressive TME of mesothelioma prevents the maturation and activation of dendritic cells. This obstacle can be bypassed by the administration of activated and tumour lysate-loaded dendritic cells. Several phase I/II trials have been performed using dendritic cell vaccination therapy. The long-term follow-up of these separate phase I/II trials showed a promising signal, with a 2-year OS of >50% and a 5-year OS of >20% [103]. These studies have led to the currently active randomised phase III DENIM trial; the accrual is completed and the results are awaited [104].

CAR T-cell therapy is an alternative way to overcome the issue with inactivated T-cells. Using this strategy, genetically engineered T-cells are administrated against a specific tumour-associated antigen such as mesothelin. This strategy has been investigated in several phase I studies, mainly in combination therapies such as ICI [105, 106].

Alternative treatment strategies are currently being investigated. Pegargiminase (ADI-PEG 20) is an enzyme degrading arginine, an amino acid on which mesothelioma cells are dependent. In the ATOMIC phase II/III study, this drug is being investigated in addition to first-line chemotherapy compared with placebo [107].

Notably, in the last decades more attention has been given to the prevention of mesothelioma, but currently there is no indication for a systematic early detection programme in the exposed population. Asbestos use is currently forbidden or heavily regulated in most Western countries [108].

Thymic epithelial tumours

TETs are rare neoplasms originating from the thymus.

Epidemiology

TETs have an incidence of 1.3–3.2 cases per million worldwide [109]. TETs are the most frequent tumours of the anterior mediastinum in adults, with a mean age at diagnosis of 50–60 years.

Approximately 30% of patients diagnosed with thymoma are asymptomatic; however, pain, dyspnoea or cough can occur due to local tumour growth. Rarely, superior vena cava syndrome or phrenic nerve paralysis may occur at presentation, while stridor or dysphagia are late symptoms. Pleural or pericardial effusion suggests metastatic spreading. Up to 35% of patients with thymoma are diagnosed with myasthenia gravis. Among other potential paraneoplastic syndromes associated with thymomas, pure red cell aplasia and hypogammaglobulinaemia are the most frequent (2–6%) [110].

Different from thymomas, thymic carcinomas are more aggressive tumours, often presenting with symptoms due to local or distant growth, as well as aspecific complaints such as weight loss or fever [111]. Only few patients with thymic carcinoma are diagnosed with paraneoplastic syndromes [110].

Diagnosis

According to the fifth edition of the WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, thymomas represent 75–85% of all TETs, and are classified as type A (11.5%), AB (25%), B1 (17.5%), B2 (26%), B3 (16%), micronodular thymoma with lymphoid stroma (1%) and metaplastic thymoma (0.1%) [112]. As most thymomas have nonneoplastic immature T-cell components, terminal deoxynucleotidyl transferase immunostaining could be useful for diagnostic purposes, even in metastatic sites. Thymic carcinomas encompass 14–22% of TETs. Although their morphology is that of conventional carcinomas, they often show immunostaining for CD5 and KIT (CD117).

Pre-treatment biopsy is not required when TETs are highly suspected based on imaging and upfront surgical resection is feasible. In all other cases, biopsy (respecting pleural spaces to avoid tumour cell seeding) should be performed to inform treatment decisions.

Staging

For more than 40 years, the Masaoka–Koga classification has been used for TET staging. Currently, the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer TNM classification, developed by the International Association for the Study of Lung Cancer/International Thymic Malignancy Interest Group, is effective and should be adopted for staging purposes [113]. This classification is based on a retrospective database of more than 8000 cases provided by major global thymic organisations. CT scan is the primary imaging modality that should be used in evaluating TETs.

Moreover, MRI has proved to be superior to CT in discriminating TETs from thymic hyperplasia and cysts, and so should be used in equivocal cases [114]. ^{18}F-FDG-PET in thymoma diagnosis and staging can lead to false-negative results, as low-grade tumours may lack glucose uptake. At the same time, the differential diagnosis of ^{18}F-FDG-PET-positive mediastinal masses includes other tumours such as primary mediastinal germ cell tumours and lymphomas as well as nonneoplastic diseases (*e.g.* infections, thymic hyperplasia and fibrosing mediastinitis). On the other hand, ^{18}F-FDG-PET is an essential test to rule out distant metastases in thymic carcinoma patients with localised disease at CT scan.

Treatment

Surgery

Surgery is the mainstay of treatment of localised TETs. Complete thymectomy is considered the standard approach for patients diagnosed with thymoma and myasthenia gravis, while thymomectomy can be considered in nonmyasthenic patients with stage I disease. Minimally invasive surgery should be considered an option only in early stages and carried out by experienced surgeons. Robot-assisted thoracic thymectomy has proved to be safe and feasible, with two meta-analyses suggesting less operative blood loss and better short-term post-operative outcomes compared with the video-assisted procedure [115, 116]. In locally advanced tumours, *en bloc* removal of all affected structures should be carried out, also including pleural deposits, whenever feasible. N1 lymphadenectomy is recommended in all TETs, while N2 sampling should be added in stage III/IVA thymomas and in thymic carcinomas and neuroendocrine tumours irrespective of clinical stage [117]. In selected cases, debulking resection of thymomas can be performed to facilitate subsequent radiotherapy (with or without chemotherapy) with radical intent. Such an approach should be not pursued in thymic carcinoma. Surgery also has a role in recurrences, as complete resection of recurrent lesions, such as pleural metastases, is a major predictor of favourable outcomes in thymomas [118, 119]. It should be emphasised that, especially in thymoma management, multidisciplinary discussion is mandatory to optimise the patient's outcomes.

Radiotherapy

Prospective, multicentre evidence on the role of post-operative radiotherapy (PORT) in TETs is scarce and all available data are based on the Masaoka–Koga staging system. As patients with stage I Masaoka–Koga thymoma should not undergo PORT, stage II patients may receive PORT in the presence of aggressive histology (type B2/B3) or extensive trans-capsular invasion according to the European Society for Medical Oncology guidelines [117]. However, PORT is recommended in stage III and IVA thymoma as well as in R1 and R2 resection, despite the stage. For thymic carcinoma, PORT is recommended from stage III to IVA, should be considered for stage II and is optional for stage I radically resected patients [117]. In unresectable patients with limited disease, radiotherapy can be considered the standard approach as a part of a sequential chemo-radiotherapy strategy [117, 120].

Systemic treatment

Historically, chemotherapy has been considered the backbone of advanced, unresectable TETs. However, chemotherapy could be also considered as adjuvant therapy in stage II, III and IVA radically resected thymic carcinoma, and in all TETs after R2 resection. Moreover, some experts suggest also discussing adjuvant chemotherapy in R1 resected B3 thymomas [121].

In patients with locally advanced TETs, primary/induction cisplatin-based chemotherapy is usually proposed after multidisciplinary discussion. These multidrug regimens led to a 70–80% response rate and up to 50% of radical resections [122]. Usually, re-evaluation to assess resectability is carried out after 2–4 cycles. Unfortunately, no prospective comparative trials of neoadjuvant chemotherapy *versus* chemo-radiotherapy are available, therefore this latter approach is rarely proposed.

Chemotherapy is the standard of care for unresectable or metastatic TETs. No randomised trials have been conducted to compare different regimens. However, the combination of cisplatin, doxorubicin and cyclophosphamide (PAC) is considered the favoured approach for thymomas based on its efficacy and tolerability, while carboplatin plus paclitaxel is usually administered to patients with thymic carcinomas [123]. Second-line treatment of advanced thymomas could be based on platinum doublets, the combination of capecitabine plus gemcitabine or single-agent chemotherapy (including etoposide, pemetrexed and ifosfamide), with response rates of 15–40%. Patients not eligible for chemotherapy may be treated with octreotide alone or in combination with prednisone upon *in vivo* demonstration of somatostatin receptors [124]. Second-line chemotherapy for thymic carcinomas is based on similar regimens as for thymomas, although the expected response rate is lower (5–26%).

Among biological agents, the most promising appear to be the mammalian target of rapamycin inhibitor everolimus, which has been evaluated in a phase II study of patients with platinum pre-treated TETs, including both thymomas and thymic carcinomas [125]. The treatment led to a disease control rate and median PFS of 93.8% and 16.6 months, respectively, in 32 patients affected by thymomas, while the disease control rate and median PFS were 61.1% and 5.6 months, respectively, in thymic carcinoma patients.

Multi-tyrosine kinase inhibitors with antiangiogenic activity such as sunitinib and lenvatinib showed interesting results in thymic carcinomas. Sunitinib as second-line treatment showed a response rate of 26% and median PFS of 7.2 months in 23 patients affected by thymic carcinoma in a phase II trial, while lenvatinib achieved a 38% response rate and a median PFS of 9.3 months in 42 patients with advanced thymic carcinoma who had progressed to at least one platinum-based regimen in the REMORA phase II study [126, 127]. Currently, sunitinib represents the second-line treatment of choice in advanced/metastatic thymic carcinomas.

ICI has been also evaluated in TETs. However, thymomas are characterised by complex interactions with the immune system, as underlined by the frequent coexistence of autoimmune diseases and paraneoplastic immune-mediated syndromes. Trials with ICI showed promising activity in patients affected by thymomas but at the cost of severe toxicities, especially in patients with thymomas [128]. Results from cohort 1 of the phase II NIVOTHYM trial in patients with previously treated TETs (n=55; 78% with thymic carcinoma) showed a 6-month PFS rate of 35% and overall response rate of 12% with nivolumab [129]. Notably, 20% of patients discontinued treatment due to adverse events, including three grade 4 events. A second cohort investigating the combination of nivolumab plus ipilimumab is currently enrolling patients (ClinicalTrials.gov: NCT03134118). Recently published results from a phase II study in the same population (n=32; 84% with thymic carcinoma) exploring the combination of the tyrosine kinase inhibitor axitinib with the anti-PD-L1 monoclonal antibody avelumab showed an overall response rate of 34%, with a 12% rate of serious adverse events, including grade 3 or 4 polymyositis [130].

Future perspectives

Ongoing clinical trials registered at ClinicalTrials.gov are currently evaluating different systemic approaches in TETs.

Two phase II trials are evaluating the activity and safety of the combination of carboplatin plus paclitaxel and the anti-VEGF receptor 2 monoclonal antibody ramucirumab as first-line treatment of advanced and metastatic TETs (NCT03921671 and NCT03694002), while another single-arm trial is evaluating carboplatin plus paclitaxel or nab-paclitaxel with pembrolizumab in the same setting (NCT04554524).

Ongoing trials in second or further treatment lines include those exploring anti-PD-(L)1 agents alone (NCT03134118, NCT03076554 and NCT04321330) or in combination with lenvatinib (PECATI: NCT04710628) or sunitinib (NCT03463460).

Another trial is currently investigating the bispecific inhibitor of PD-L1 and CTLA-4 monoclonal antibody KN046 in thymic carcinomas patients who already received anti-PD-(L)1 drugs (NCT04925947). Finally, bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, is also being investigated in advanced, pre-treated TETs in a phase II trial (NCT04417660).

Points for clinical practice

- SCLC arises due to exposure to tobacco carcinogens, which initiate the inactivation of the tumour suppressor genes *TP53* and *RB1*. Due to this correlation with cigarette smoking, patients with SCLC often have smoking-related comorbidities such as COPD, cardiac disease and hypertension. The diagnosis is based primarily on histological appearance by light microscopy. IHC can play a role in dividing SCLC into four neuroendocrine subtypes. SCLC is staged according to the TNM classification. Chemotherapy is still the backbone therapy in all stages of SCLC.
- Mesothelioma arises due to exposure to asbestos fibres, which can lead to an inflammatory reaction and thus an increased risk of malignant transformation of mesothelial cells. In some cases, mesothelioma occurs due to a germline *BAP1* mutation. The diagnosis is preferentially made based on histology; additional IHC can be used to distinguish three histological subtypes. Mesotheliomas are staged according to the TNM classification. Most patients with mesothelioma are not suitable for surgery due to widespread pleural metastases; however, surgery can be considered for selected patients where a macroscopic complete resection can be expected. Since 2020, nivolumab/ipilimumab has to be considered standard first-line therapy, independent of histological subtype.

- TETs are the most frequent tumours of the anterior mediastinum in adults. The diagnosis is frequently based on imaging; MRI has proved to be superior to CT in discriminating thymoma from thymic hyperplasia and cysts. Up to 35% of patients with thymoma are diagnosed with myasthenia gravis. The TNM classification has replaced the Masaoka–Koga staging system for TETs. Surgery is the mainstay of treatment of localised TETs, followed by post-operative radiotherapy dependent on stage or if not fully resected.

Provenance: Commissioned article, peer reviewed.

Previous articles in this series: No. 1: Simonneau G, Fadel E, Vonk Noordegraaf A, *et al.* Highlights from the International Chronic Thromboembolic Pulmonary Hypertension Congress 2021. *Eur Respir Rev* 2023; 32: 220132. No. 2: Buschulte K, Cottin V, Wijsenbeek M, *et al.* The world of rare interstitial lung diseases. *Eur Respir Rev* 2023; 32: 220161.

Conflict of interest: D.W. Dumoulin reports personal fees from Roche, BMS, MSD, Pfizer, AstraZeneca and Novartis. P. Bironzo declares honoraria from AstraZeneca, BMS, BeiGene, Roche and Takeda; an institutional research grant from Roche and Pfizer; and virtual meeting registration from Amgen and Daiichi Sankyo. F. Passiglia declares advisory/consultant fees from MSD, AstraZeneca, Janssen, Amgen, Sanofi, Beigene and Thermofisher Scientific. G.V. Scagliotti declares honoraria from AstraZeneca, Eli Lilly, MSD, Pfizer, Roche, Johnson & Johnson and Takeda; consulting or advisory roles for Eli Lilly, Beigene, AstraZeneca and Verastem; institutional research funding from Eli Lilly, MSD and Tesaro; and travel and accommodation from Bayer. J.G.J.V. Aerts declares honoraria and nonfinancial support from MSD, BMS, Boehringer Ingelheim, Amphera, Eli Lilly, Takeda, Bayer, Roche and AstraZeneca, outside the submitted work. In addition, J.G.J.V. Aerts has a patent allogenic tumour cell lysate licensed to Amphera, a patent combination immunotherapy in cancer pending, and a patent biomarker for immunotherapy pending.

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