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Management of Extrapulmonary Small Cell Carcinomas

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Introduction

Extrapulmonary small cell cancer (EPSCC) is a rare entity, accounting for approximately 2.5 to 5% of small-cell carcinomas.[1,2] EPSCC primarily occurs in patients aged 50 years and older. Despite the variety of primary sites, it is frequently associated with smoking and excessive alcohol consumption[2], although the association with tobacco may not be as strong as with small-cell lung cancer (SCLC). As presented in Table 1, its most frequent primary sites are the female reproductive organs, the gastrointestinal and genitourinary tracts, and head and neck.[3-5]

Site	*Percentage*
Esophagus	18%
Other GI (stomach, colorectal, pancreas, hepatobiliary)	15-22%
Genito urinary	15%
Prostate	7%
Gynecological (mainly cervix)	17%
Breast	10%
Head and neck	11%

Table 1 : Distribution of extra-pulmonary small cell carcinoma per primary site[4,5]

Two main hypotheses have been proposed to explain the physiopathology of the disease. The first hypothesis is that it develops from a multipotent stem cell that differentiates towards a neuroendocrine phenotype. The alternate hypothesis is that it develops from a later-stage event in non-neuroendocrine carcinomas.[2]

In both lung and extrapulmonary sites, genetic alterations in *TP53* and *RB1* are present in nearly all cases.[6,7] Other genetic alterations appear to be more site-specific, such as *TERT* promoter mutations in the bladder and *ERG* rearrangements in the prostate.[8] Interestingly, these mutations are also found in cancers of more common histologies of the same organs, such as urothelial carcinoma and adenocarcinoma.

Recently, there has been renewed interest in Delta-like Ligand 3 (DLL3) expression in the context of small-cell neoplasms, including EPSCC. DLL3 is responsible for inhibition of NOTCH, a tumour suppressor. DLL3 is expressed in 85% and highly expressed in 68% of small-cell lung cancers (SCLCs), making it a target of great interest in several current bispecific T-cell engager trials.[6] Limited data on DLL3 expression exist for EPSCC, but the available data suggest comparable expression.[9-11]

Analogous to SCLC, the clinical course of EPSCC is aggressive, with a median overall survival (OS) of 1.4 to 3.5 years for localized disease and 8 to 12 months in the metastatic setting.[3,12] Due to its aggressive growth pattern, about 50% of cases present with metastases at initial diagnosis.[2] Incidence of brain metastases in EPSCC appears to be lower than in SCLC. It is seen in approximately 6% for all primary sites combined, but around 16-19% for prostate and up to 41% for head and neck.[13]

General Management

For localized disease, a combination of chemotherapy and radiotherapy is often recommended based on retrospective data, case reports, and extrapolation from SCLC.[13] Surgery can also be an option when anatomically feasible in early-stage disease, usually with consideration of adjuvant chemotherapy. There are, however, no randomized or prospective studies supporting these approaches.

The preferred chemotherapy regimen is based on SCLC experience and typically consists of a doublet of a platinum-based agent (either carboplatin or cisplatin) plus etoposide. This

strategy yields promising overall response rates (ORR), but responses are often short-lived.[14-16] For subsequent lines, options are also frequently extrapolated from lung disease, with topotecan as the most frequent second-line treatment despite a very modest efficacy in EPSCC.[17]

In case of treatment-refractory disease, the ipilimumab and nivolumab immune checkpoint inhibitor combination has demonstrated promising activity in high-grade neuroendocrine neoplasms and, if available, can be considered regardless of mismatch repair (MMR) status based on late-line basket trials.[18,19]

While single-agent immunotherapy has changed the management of SCLC over the last few years in both localized and metastatic disease, registrational phase III trials did not include extrapulmonary primary tumours.[20-22] There are very few data on single-agent immunotherapy in early lines of therapy for EPSCC, mainly consisting of case reports, so its place in EPSCC treatment remains unclear.[23-25] A notable exception is Merkel cell carcinoma, a high-grade neuroendocrine carcinoma of the skin, which is usually considered a separate entity to EPSCC and will not be discussed here.

Data on prophylactic cranial irradiation in EPSCC are retrospective in nature, and its role is probably limited. Some experts recommend discussing prophylactic pancranial irradiation for head and neck (except larynx) and prostate primaries, due to higher rates of brain metastases in case series with these primary sites.[26,27]

While the treatment principles above provide a top-line review of the recommended management of EPSCC, disease-site-specific data, including potential therapeutic options, exist and will be discussed below.

Site Specificities

Gastropancreatic

For localized gastropancreatic tumours, neoadjuvant chemotherapy may be offered to facilitate surgery and improve OS compared with upfront surgery.[28-30] Adjuvant treatment may also be appropriate, either with chemotherapy alone or in combination with radiation. The preferred chemotherapy regimen is 4 to 6 cycles of platinum and etoposide. When surgery is not possible, chemoradiation is the primary treatment option.[31]

For metastatic disease, the same chemotherapy backbone of a platinum agent and etoposide is favoured, but cisplatin-irinotecan and alternatives used in gastrointestinal adenocarcinomas, such as FOLFOX (folinic acid, fluorouracil, and oxaliplatin)and FOLFIRINOX (folinic acid, fluorouracil, oxaliplatin and irinotecan), have also been studied.[32-35] There is limited data on the use of immunotherapy in this setting. Although its primary endpoint was not met, the NICE-NEC phase II study demonstrated favourable outcomes with the addition of nivolumab to the chemotherapy regimen and with maintenance immunotherapy for a year in treatment-naïve patients with advanced grade 3 neuroendocrine neoplasms. After a median follow-up of 30 months, the median progression-free survival (PFS) and OS were 6 and 14 months, respectively, with an ORR of 57% and 38% of patients alive at 2 years of follow-up.[36] More data will likely be needed before changing official treatment recommendations.

Second-line treatment depends on tumour characteristics. In cases of deficient MMR/high microsatellite instability (dMMR/MSI-H), representing about 5% of cases, immunotherapy is prioritized, whether with pembrolizumab or dostarlimab.[37,38]

Data support tumour-agnostic treatment with dabrafenib and trametinib in patients with tumours harbouring *BRAF* V600 mutations[39], with selpercatinib in the presence of a *RET* fusion[40], and with larotrectinib, entrectinib, or repotrectinib in the presence of *NTRK* fusions.[41,42] However, use of tyrosine kinase inhibitors (TKI) in high-grade neuroendocrine carcinomas is controversial. It remains unclear whether such alterations, considered driver mutations in most settings, act as such in the setting of small-cell carcinoma. It has been shown that *EGFR*-mutant non-small cell lung cancer (NSCLC) that transforms to small-cell lung cancer loses EGFR protein expression and thus becomes resistant to EGFR TKIs.[43] Despite this, at least one case report suggests potential activity of BRAF inhibition in SCLC[44], and digestive neuroendocrine carcinomas were not excluded from most tumour-agnostic trials. As such, after the use of available cytotoxic chemotherapy regimens, use of TKIs in the presence of an activating mutation can be considered.

For patients without an actionable mutation, if the disease progresses within 6 months of the first-line regimen, alternative first-line options listed above can be used. Other options include

FOLFIRI (folinic acid, fluorouracil, and irinotecan) and temodal with or without capecitabine[45,46], or, as noted above, topotecan in an SCLC-inspired approach. If the disease progresses more than 6 months after a platinum agent and etoposide, rechallenge with the same regimen is recommended.[32]

Bladder and Upper Urinary Tract

Small-cell carcinoma of the bladder represents less than 1% of bladder and upper urinary tract cancers.[47] The standard approach for localized disease involves neoadjuvant chemotherapy, which improves OS compared with the adjuvant approach.[48,49] The preferred regimen is cisplatin and etoposide, but carboplatin and etoposide can be used in cases of cisplatin ineligibility. A regimen of cisplatin-etoposide alternating with doxorubicin and ifosfamide was studied in a prospective phase II study, but the added benefit of this approach remains unknown in the absence of comparative studies.[48-50] After the initial systemic approach, either consolidation radiotherapy, chemoradiation, or radical cystectomy can be performed with similar outcomes depending on the patients' preferences and comorbidities.[51,52]

For patients undergoing upfront surgery, adjuvant chemotherapy consisting of 4 to 6 cycles of a platinum agent and etoposide can be offered, as it has suggested to improve OS in retrospective data.[53] There is no established role for immunotherapy in the adjuvant setting, as the CheckMate-274 trial with adjuvant nivolumab did not include small-cell histology.[54]

Metastatic disease is managed globally as SCLC, with cisplatin and etoposide as the standard first-line treatment.[50] Later-line options studied in this setting include topotecan, lurbinectedin, nivolumab plus ipilimumab, or monoimmunotherapy.[55-60]

Prostate

Primary small-cell carcinoma of the prostate is a rare entity, whereas small-cell transformation in the setting of pretreated, metastatic castration-resistant prostate cancer is observed slightly more often. It should be suspected in the setting of disease progression with very low or negative prostate-specific antigen (PSA) levels, especially if a neuroendocrine component was described in initial prostate biopsies. The recommended first-line treatment is the combination of a platinum-based agent (cisplatin or carboplatin) with etoposide. Addition of carboplatin to taxanes used in prostate adenocarcinoma (docetaxel or cabazitaxel) can also be considered.[61]

Cervix

Small cell tumours of the cervix account for approximately 2% of cervical cancers.[62] The disease tends to be bulkier and presents at a higher stage than standard cervical cancer.[63] Tumours <4 cm can be approached surgically upfront with adjuvant treatments, whereas tumours >4 cm receive chemoradiotherapy, potentially followed by surgery depending on the response. The benefit of surgery after chemoradiation remains unclear. The preferred chemotherapy regimen is 4 cycles of a platinum-based agent and etoposide.[64]

For metastatic disease, the standard approach of combining a platinum-based agent with etoposide also applies.[64] For recurrent disease, a combination of topotecan, paclitaxel, and bevacizumab demonstrated encouraging activity in this difficult-to-treat setting and may be considered for fit patients who can tolerate the toxicity.[65]

Unknown Primary

Unknown primary small cell tumours are a very rare entity. For high-grade undifferentiated tumours of unknown primary origin, platinum and etoposide are recommended, with an ORR of around 70%, similar to that in primary NECs.[66,67] The phase II NICE-NEC trial with nivolumab, discussed above, included 6 patients with EPSCC of unknown primary.[36] Considering the relative frequency of SCLC compared with other primary sites of small cell carcinoma, if no convincing site of origin is found, many clinicians will approach this type of disease as they would SCLC.

MiNENs

Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) are a rare and aggressive cancer type characterized by the presence of distinct neuroendocrine and non-neuroendocrine components within the same tumour. According to the World Health Organization (WHO) classification, each component must constitute at least 30% of the tumour to be classified as MiNEN.[68] The most frequent non-neuroendocrine and endocrine components are adenocarcinoma and carcinoma, respectively. The general guideline is to treat the most aggressive component in the tumour, namely neuroendocrine carcinoma,

regardless of its percentage within the tumour.[69] A combination of platinum and etoposide is the most often used regimen, but approaching the disease like a digestive neoplasm with FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) is also feasible in selected patients.[70,71]

DLL3-Targeted Therapy

With the emergence of DLL3-targeted therapy such as tarlatamab in SCLC, there is excitement about whether the practice-changing benefits of these therapies could translate to the setting of EPSCC. Fortunately, there is a growing body of phase I and II data on the role of DLL3-specific therapies (mostly bispecific T-cell engagers) in EPSCC across multiple tumour sites. The ORR ranges from 20% to 56%, and the disease control rate is up to 75%, depending on DLL3 expression level, tumour site, and drug used.[9,72-77] The DLL3 expression level seems to correlate with response to these therapies. Responses appear to be durable, with a median duration of approximately 6 to 12 months. The safety profile of such molecules, including a risk of cytokine release syndrome (CRS), is generally low-grade and manageable. Grade 3 CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) are rare and concordant with known SCLC literature. Based on these emerging data, experts recommend utilization of DLL3-directed therapy in refractory EPSCC after chemotherapy if such therapies are available. Clinicians should still use caution in directly extrapolating results of large, phase 3 clinical trials in SCLC to the EPSCC population as larger trials and retrospective series are expected.

Specifically for tarlatamab in prostate EPSCC, a phase 1b trial has shown an ORR of 22.2% and PFS of 27.7% at 6 months for DLL3-positive (IHC >=1 %) tumors. Interestingly, and in contrast to what is observed in SCLC, the ORR for DLL3-negative tumors was 0%.[78]

As for antibody-drug conjugates (ADCs) targeting DLL3, there is a paucity of data regarding EPSCC. While development of this drug has since been terminated, rovalpituzumab tesirine (Rova-T), one of such ADCs with a pyrrolobenzodiazepine (PBD) payload, has shown an ORR of 17% in DLL3-positive tumors (50% or more DLL3+ cells).[79] More recently, ABBV-706, an ADC targeting SEZ6 with a topoisomerase-1 payload, has shown in a phase 1 including SCLC and EPSCC an ORR of 43.8%.[80]

There is currently no published data for other molecules proved to be active in SCLC, such as risvutatug-rezetecan and tambotatub-pelitecan.

Conclusion

In summary, EPSCC is an aggressive entity that shares some clinical and molecular characteristics with the more frequent and better-known SCLC, but also has some significant nuances. While tumour-site-specific management exists for some primary sites, first-line systemic therapy typically consists of platinum-based chemotherapy plus etoposide. The role of immunotherapy and prophylactic whole-brain radiation remains unclear across different primary sites. DLL3-targeted therapies are currently being studied prospectively in this setting and may offer significant benefits to patients with EPSCC in the near future. It is expected that other promising therapies for SCLC, including antibody-drug conjugates, will also be further investigated in the context of EPSCC in the next few years.

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