Chapter

A Rare but Real Entity: Bladder Neuroendocrine Cancer

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Abstract

The neuoroendocrine cancer of the bladder is a rare tumour, and from this entity the well-differentiated tumours with favourable prognosis, the paraganglioma with unfavourable prognosis, small and large cell types of tumours should be emphasised. From the methods of the anticancer therapies' operation can be eligible by itself in the first group but in the second group should form only the part of the multimodal treatment. Radiotherapy plays a role only in the treatment of the small and large cell tumours, and during the treatment of these tumours, the administration of the cytostatic drugs is also essential (mainly platina derivates). Somatostatin analogues, immune checkpoint inhibitors could be beneficial in special cases and some tumour agnostic treatment can be useful as well. Moreover, the palliative treatment should represent an important modality even in the early treatment period, but it should also be provided when no other treatment options are left.

Keywords: neuroendocrine tumour of the bladder, operation, radiotherapy and medical therapy, tumour agnostic therapy, palliative treatment

1. Introduction

Bladder cancer is not one of the most common tumours. (**Table 1**) [1–3]. The prevalence of neuroendocrine bladder cancer (NEBC) in muscle invasive processes is estimated to be 0.5–1.2% [4], while others estimate it to be less than 1% [5, 6]. The statistically expected 5700 (in Hungarian only 35) patients with various common symptoms—haematuria, pelvic pain, urinary obstruction—are detected and diagnosed in urological centres and efficient onco-teams (multidisciplinary teams) give them the chance to receive adequate treatment [7–10]. However, these tumours require special attention because they usually have a poor prognosis, undifferentiated forms are usually detected at a disseminated stage, and their treatment differs from the usual treatment for bladder cancer [8, 11].

	incidence (new cases)		mortality	
	males	**females**	**males**	**females**
all cancers (excluding non-melanoma skin cancer) [1]	4,824,700	4,110,118	1,926,292	1,552,475
of these bladder cancer [2]	440,864	132,414	158,785	53,751
bladder cancer in Hungary [3]	2393	1132	706	392

Table 1.
Incidence and mortality all cancers and bladder cancer [1–3].

2. Pathology

The WHO pathological classification is shown in **Table 2** [12]. The tumours can be differentiated in different ways, the well-differentiated form is extremely rare and, according to the literature, is usually not associated with carcinoid symptoms and has one of the best prognoses. Small cell NEBC is the most common, although the 'pure' form is rare, with more than half of cases (up to 61% according to some authors) being associated with transitional cell bladder cancer, glandular or squamous cell carcinoma, possibly with a sarcomatoid component, and is more common in women. Large cell tumours are also rare and, like small cell tumours, have a poor prognosis. Paragangliomas can also occur in the bladder, usually described in case reports; interestingly, they can be functional (producing catecholamines), with the 'usual'

(Listing neuroendrocrine tumours in details)
Urothelial tumours
Infiltrating urothelial tumours
Non-invasive urothelial tumours
Squamous cell neoplasms
Glandular neoplasms
Urachal carcinoma
Tumours of Müllerian type
Neuroendocrine tumours
Small cell neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Well-differentiated neuroendocrine tumour
Paraganglioma
Melanocytic tumours
Mesenchymal tumours
Urothelial tract haematopoietic and lymphoid tumours
Miscellaneous tumours

Table 2.
WHO classification of tumours of the urothelial tract [12].

clinical symptoms (sudden spikes in blood pressure, possibly hypertension, headache, palpitations, sweating, visual disturbances) caused by bladder distension or contractions. Survival data are relatively favourable, as far as it can be concluded from only a few patients [6, 13–18].

3. Diagnosis

Based on the symptoms, the clinical and imaging methods used to diagnose NEBC are the ones commonly used for bladder cancer and reported in other publications in this volume. Accurate pathological diagnosis is essential, but it is not within our competence. In the light of the histological findings, the need for axial imaging techniques—CT and MR—to assess the small cell form progression is highlighted in the literature, and bone scintigraphy is necessary in the case of osteoarticular complaints but should also be considered in the absence of symptoms [8, 19, 20]. In functional paragangliomas, MIBG (iodine-123 meta-iodobenzylguanidine) scintigraphy and PET/CT can indicate local expansion and possible distant metastases with up to 95% accuracy [16].

4. Treatment and prognosis

As there are only a few cases and thus clinical trial results with high evidence level are not available, the therapeutic recommendations are based on a summary of institutional experience and partly on analogies to the treatment of other neuroendocrine tumours. Early detection of the disease, its progression, accurate diagnosis and good overall patient health (ECOG PS [Eastern Cooperative Oncology Group Performance Status]) improve outcomes. In general, even with a carefully chosen and correctly executed treatment, the prognosis depends mainly on the differentiation of the tumour: favourable in well-differentiated NEBC and paraganglioma, unfavourable in small and large cell tumours [6, 11, 13, 15–17].

4.1 Surgery

A biopsy during cystoscopy is almost always necessary [8, 13]. For well-differentiated NEBC and paraganglioma, adequately radical surgery (partial or radical cystectomy) may be a solution in itself but for functionally active tumours, pre-operative endocrinological consultation and medication are essential. In small- and large-cell forms, surgery (depending on the dissemination status) may be considered as part of a complex treatment, and although significance is questionable due to the small number of cases in these studies, it seems that surgery in selected cases may improve survival [13, 15–17].

4.2 Radiotherapy

It can be an alternative to surgery in exceptional cases of well-differentiated forms and paragangliomas and applied to treat local recurrences. In paraganglioma, ^{131}I MIBG treatment has a beneficial effect on symptoms. For small and large cell NEBC, radiotherapy is an essential part of multimodality treatment. The recommendation of the Canadian Association of Genitourinary Medical Oncologists (CAGMO) includes

prophylactic cranial irradiation and—as appropriate—irradiation of symptomatic metastases [5, 6, 8, 11, 13, 15, 21].

4.3 Somatostatin receptor analogues

In functional forms of differentiated NEBC—their use, as in other neuroendocrine tumours—is logical and results in symptom relief (due to the small number of cases, anti-tumour effects cannot be assessed) [22–24].

4.4 Cytostatic treatment

Its role is minor in well-differentiated tumours. In this regard, small- and large-cell NEBC can be grouped together in practice, since in these cases cytostatic treatment is considered both as neoadjuvant or adjuvant treatment and as part of radiochemotherapy, and in disseminated disease it is almost the only option. Whether used alone or as part of a multimodal regimen, from cytostatics cisplatin (or possibly carboplatin) and etoposide, ifosfamide-doxorubicin, cisplatin (or carboplatin) and irinotecan are recommended, and in mixed tumours, methotrexate, vincristine, cyclophosphamide and taxanes may be added. The poor general condition of the patient sometimes only allows monotherapy [5, 8, 11, 13, 16, 17, 21, 25–29].

4.5 Immune checkpoint inhibitors

PD-1 (programmed cell death protein 1) and PD-L1 (programmed death-ligand 1) inhibitors have also been tested in this disorder, and although they have generally not been successful, positive results have been described in case reports. Clinical trials with adequate evidence are ongoing [11, 30–32].

4.6 Tumour-agnostic treatment

The 'classical' knowledge of tumours includes the organ origin, histological structure, tumour infiltration, differentiation, prognostic and predictive markers, etc., while the agnostic approach does not consider these as essential but focuses on the genetic target of treatment. Drugs acting on targets in tumour-agnostic treatment have a convincing anti-tumour effect regardless of the organ of origin, meaning that detection of the target (often by genetic testing) is highly likely to predict treatment success. Currently, three drugs and three targets in NEBC can meet these requirements, as specified by the European and North American Medicines Agency. These: pembrolizumab (EMA [European Medicines Agency] and FDA [U. S. Food and Drug Administration] for PD-L1, MSI-H [Microsatellite Instability high] and dMMR [DNA mismatch repair deficiency]), larotrectinib, (both EMA and FDA for NTRK [Neurotrophic tyrosine receptor kinase] gene fusion) and entrectinib EMA and FDA for NTRK gene fusion or ROS-1 (Proto-oncogene tyrosine-protein kinase 1) positive non-small-cell lung cancer [33–42].

5. Palliative and terminal care

According to the WHO (World Health Organisation) definition, 'Palliative care is a crucial part of integrated, people-centred health services. Relieving serious

health-related suffering, be it physical, psychological, social, or spiritual, is a global ethical responsibility. Thus, whether the cause of suffering is cardiovascular disease, cancer, major organ failure, drug-resistant tuberculosis, severe burns, end-stage chronic illness, acute trauma, extreme birth prematurity or extreme frailty of old age, palliative care may be needed and must be available at all levels of care' [43]. This includes curative anticancer treatment and symptomatic therapy (drugs, physiotherapy, psychosocial support, terminal care, ensuring a dignified death and dealing with the grief response if needed). In well-established oncology centres, some elements of early palliation have always been used and are still used, but the biggest problem is the period after active treatment options run out when due to limited capacity, a large proportion of patients are discharged from the care system. For NEBC, in addition to the necessary pain relief, management of functioning tumour symptoms, management of catheters and drains, athropia, anaemia, incontinence, bleeding from the bladder, painful, crampy urination, possible pelvic compression symptoms and body image changes and depression after advanced surgery are also problems to be addressed [44–47].

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Conflict of interest

The authors declare no conflict of interest.

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